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Survival probabilities and hazard functions of malignant melanoma in Germany 1972–1996, an analysis of 10 433 patients. Evolution of gender differences and malignancy

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Abstract

The evaluation of the impact of prevention activities on the course of survival in conjunction with the individual hazard rate of dying is described using data from a follow-up study of 10 433 melanoma patients during three observation periods (1972–1980, 1981–1988, 1989–1996). Kaplan–Meier survival curves combined with hazard functions were calculated. At all observation periods, survival of men was lower compared with women and their maximum dying risk was earlier (70 versus 100 months after removal of the primary tumour). In 1989–1996, differences in the survival rates were approximately halved compared with those for 1972–1980 or 1981–1988, respectively. This improvement was predominantly seen in young men. There was a lower survival rate of men compared with women with identical thickness categories. The maximum dying risk for those men with tumours >4 mm peaked at approximately 60 months, the other thickness categories showing a lower and later maximum; in women, the maximum dying risk for tumours >4 mm was also seen at approximately 60 months, but less pronounced. Over time, the influence of Breslow thickness on the survival rates remained constant in women; in men, with the exception of thick tumours, there was a trend towards a better survival. Melanoma awareness campaigns conducted in Germany since the late 1980s have resulted in a trend towards a remarkable increase of thin tumours in recent years, whereas the number of new cases with thick tumours has remained constant.

Keywords: Melanoma; Prevention; Survival; Hazard function; Gender

1. Introduction

The ultimate goal of malignant melanoma prevention is a reduction in incidence and mortality. In recent decades, there has been a global continuous increase within the Caucasian population in both genders, mostly with a lower incidence and higher mortality in men compared with women [1–4]. However, recently there have been reports showing a lower increase and even decrease in the incidence of malignant melanoma in women resulting in equal incidences for both genders and a plateauing or decreasing mortality amongst females in younger age groups [5–13]. This positive development is generally interpreted to result from prevention campaigns but, since there was little effect on males, preventive health programmes were designed to exclusively target men in some regions [4].

Unfortunately, a population-based register on malignant melanoma allowing a reliable observation and evaluation of incidence and mortality is still in its initial stages in Germany. Hence, in the following study, we describe the evaluation of the known parameter of the survival rate completed by the corresponding risk of dying represented by a hazard function. The latter allows the assessment of the actual 'death risk' at any time point and is independent of past events. These epidemiological data can be used to evaluate prevention effects.

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As a result, the following questions are posed:

- How did survival rates and actual risks of dying develop from 1972 until 1996?
- How does gender determine the survival rates and actual risks of dying?
- Which age group shows the greatest improvement in survival?
- Is there a change in the ''biological behaviour'', i.e. the characteristics of the tumour over time?

Three centres participated in this study representing West (Münster), Central (Göttingen) and East (Dresden) Germany in order to obtain a demographically balanced distribution of patients.

2. Patients and methods

2.1. Patients and follow-up

The case notes of 10 433 patients who were treated and followed-up between 1972 and 1996 by the Department of Dermatology of the Göttingen University, the Hornheide Clinic near Münster, and the Department of Dermatology of the Dresden-Friedrichstadt Hospital were collected and evaluated. In total, 97% all melanoma patients were registered by these institutions. They are regional centres that specialise in the treatment of melanoma. Patients were referred mainly by dermatologists and general practitioners, to a minor degree by physicians of other specialities. In all geographical regions, the referral pattern remained constant during the whole observation period.

Patients are distributed as follows: Münster: $n = 7666$; Göttingen: $n = 1337$; Dresden: $n = 1430$.

Patients with ocular melanoma and *in situ* melanoma were not included. For the latter, a 5-year survival rate of 100% is presumed. In many cases, insufficient follow-up data had to be completed using information obtained from general practitioners, patient's relatives, health insurances, parishes, registration offices and other sources. Patients who did not complete the ten year follow-up until 31 December 1996, patients who died of other causes besides melanoma during the follow-up period time and those lost to follow-up were included in the survival calculation as censored data.

2.2. Calculations

Data comparability of the participating centres was verified by a structural analysis with descriptive statistical methods (frequency tables, distributions, cross tables) and confirmed by Chi-square tests. The following parameters were tested: Age, gender, site of primary tumour, Breslow thickness, Clark's level, histological subtype.

Firstly, in order to demonstrate the evolution over time, three observation periods (OP) were compared: 1972–1980 (OP1), 1981–1988 (OP2), and 1989–1996 (OP3). Secondly, to gain information about survival development for different ages, three age groups were established: 0–44, 45–74, 75–99 years. Thirdly, with regard to Breslow tumour thickness, four categories according to International Union Against Cancer (UICC) (1987) were used: <0.75 mm (T1), 0.76–1.5 mm (T2), 1.51–4 mm (T3) and >4 mm (T4).

Survival analysis was performed according to the Kaplan–Meier method. Estimate curves of the survival time starting with primary tumour excision were calculated, as well as the 5-, 7- and 10-year survival rate. Differences between the curves were confirmed or rejected by the log-rank test. Additionally, the hazard function giving the actual dying risk, i.e. the immediate chance for the event of death to occur, were determined. Different hazard rates were compared by its ratios. For the estimation of the hazard functions, non-parametric smoothing methods based on kernel functions [14] and the software KEHaF were used [15].

3. Results

Whereas the age distribution of the samples showed no substantial differences between the observation periods (OP1: mean value 52.8, OP2: mean value 54.3, OP3: mean value 54.0), the absolute number of recruited patients, as well as the male/female ratio (mfr), were continuously increasing: OP1: $n = 1617$, mfr 0.62; OP2: $n = 3765$, mfr 0.70; OP3: $n = 5051$, mfr 0.78.

During the complete observation period, 2111 patients died from melanoma. Table 1 shows the 5-, 7- and 10-year survival rates of this period and separately for the time periods of OP1, OP2 and OP3. At all times, survival of women exceeded that of the men, but in recent times, the differences were approximately halved.

The overall survival estimates for women and men within the total observation period with its corresponding hazard rate analysis are depicted in Fig. 1. As also demonstrated in Table 1, at all times the survival rates for men were lower compared with those for women. Additionally, the hazard curves indicated by the peak values a maximum risk of dying for men at approximately 70 months and for women approximately 30 months later.

Figs. 2 and 3 show survival estimates with its corresponding hazard functions for men and women for the several observation periods. The survival curves are shorter for patients having their primary tumour removed within OP3 than for those operated upon earlier because there was less follow-up data available for the more recent observation period. In men, differences between the Kaplan–Meier curves were significant for a

better survival in OP3 compared with OP1 ($P<0.0001$) and OP2 ($P<0.0001$), respectively, whereas differences between OP1 and OP2 were not significant ($P=0.076$). In the hazard function, the maximum dying risk in OP1 was more pronounced and somewhat earlier (approximately 55 months) compared with that of OP2 (approximately 75 months). Afterwards the actual dying risk was lower with time. In women, differences between the Kaplan–Meier estimates were significant between OP1 and OP3 ($P<0.0001$), between OP1 and OP2 ($P=0.031$) and OP2 and OP3 ($P=0.013$). In contrast to men, the maximum dying risk indicated by the corresponding hazard functions was roughly identical at approximately 80 months. Near the end of the timescale, the observed actual dying risks approach each other. In contrary to men, the hazard ratio was always greater than 1 for chronologically later time periods in comparison to earlier ones. In both Figs. 2 and 3, a comparison with the hazard function of OP3 although feasible should be analysed with caution since within this period there were still too few patients at risk of dying.

Table 2 shows the 5-year survival rates of the age groups 15–44, 45–74 and 75–99 years. Survival improvement was mainly seen in men below 45 years of age.

The most influential factor for survival and/or dying risk is the Breslow tumour thickness. In Fig. 4, the time course of the median Breslow thickness is shown for both genders. There was a continuous decline starting from 2.30 mm in men, 1.80 mm in women, and ending at 1.10 mm in men, 0.90 mm in women. In men, the decline was more impressive so that an equal median for both genders can be expected in the near future.

Figs. 5 and 6 demonstrate the survival curves for the several thickness categories in men and women with the corresponding hazard functions. The curves confirm the finding of an inverse relationship between tumour thickness and survival. Moreover, there was a lower survival rate of men with identical thickness categories compared with women. Differences were significant for

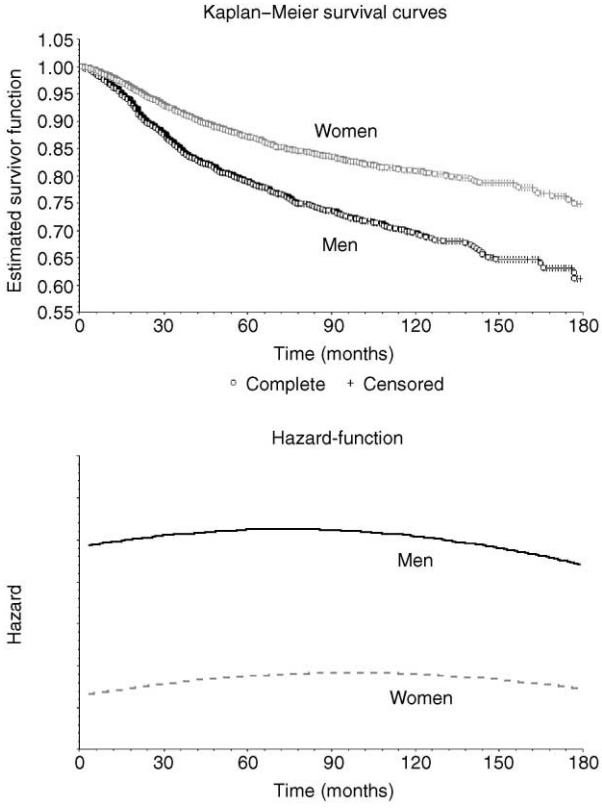

Fig. 1. Overall survival estimates for woman and men ($n=10\,433$) within the complete observation period with its corresponding hazard rate analysis.

Table 1
5-, 7- and 10-year survival rates for men and women

	5 years (%)	Standard deviation	7 years (%)	Standard deviation	10 years (%)	Standard deviation
1972–1996						
Women ($n=6044$)	85.24	0.51	81.78	0.57	78.66	0.65
Men ($n=4389$)	75.59	0.72	71.03	0.80	65.97	0.92
Total ($n=10433$)	81.20	0.42	77.30	0.48	73.44	0.54
1972–1980 (OP1)						
Women ($n=999$)	82.33	1.23	79.37	1.32	76.23	1.41
Men ($n=618$)	69.82	1.90	65.37	1.98	61.05	2.06
Difference	12.51		14.00		15.18	
1981–1988 (OP2)						
Women ($n=2212$)	84.98	0.78	81.73	0.85	78.55	0.93
Men ($n=1553$)	73.49	1.16	68.92	1.23	63.73	1.33
Difference	11.49		12.81		14.82	
1989–1996 (OP3)						
Women ($n=2833$)	86.62	0.80	82.38	1.08	–	
Men ($n=2218$)	79.60	1.05	76.17	1.22	–	
Difference	7.02		6.21		–	

T1, T2, T3 $P<0.0001$, and T4 $P=0.001$. For men, the hazard function of thickness category T4 indicated a pronounced maximum dying risk at approximately 50 months followed by a steep decline and a hazard cross with the category-T3 function at approximately 180 months. Maximum dying risks for categories T2 and T3 were less pronounced and occurred later at approximately 80 months. For category T1, a maximum dying risk was not visible. Compared with men, in women the maximum dying risk of the thickness categories T4, T3 and T2 was approximately 1–2 years later. In T4, the decline following the maximum was less pronounced and did not cross the other curves.

In order to get an impression of the possible changes in the tumour characteristics over time, we compared the influence of Breslow thickness on the 5-, 7- and 10-year survival rates for the different observation periods (Table 3). In women, the rates remained remarkably steady whereas in men the results were not homogeneous: With the exception of thick tumours (T4), there was a trend towards a better survival in all other categories over the time periods observed concerning the 5- and 7-year, but not the 10-year, survival rates.

The impact of melanoma awareness campaigns in Germany from approximately 1988 until the present time is demonstrated in Table 4. Whereas in OP2 compared with OP1, the amount of patients with thickness categories T3 and T4 paralleled the general increase of recruited patients, in OP3 (1989–1996), the absolute number of T3 and T4 patients remained constant or slowly decreased although there were around 1000 additional patients diagnosed with malignant melanoma during this time period. This reflects a trend towards a proportional decrease of thick melanomas in recent years.

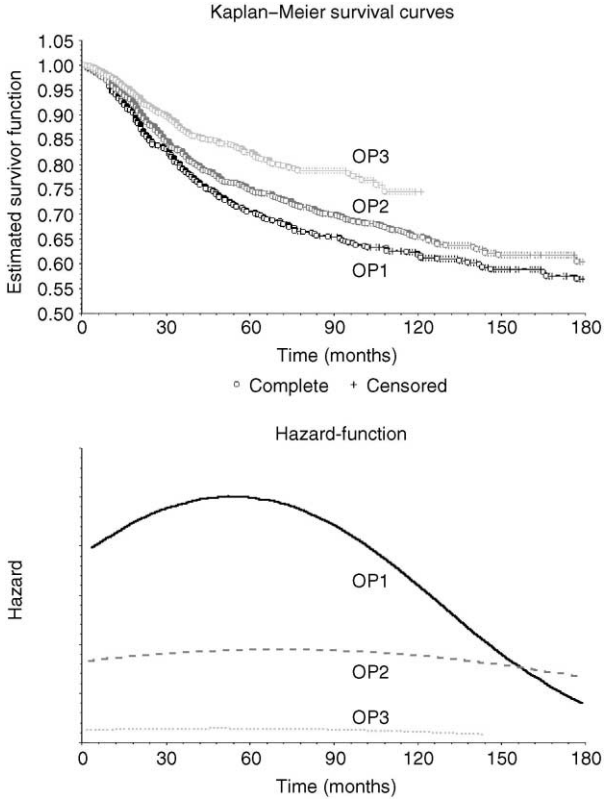

Fig. 2. Survival estimates for men ($n=4389$) with corresponding hazard functions for the different observation periods.

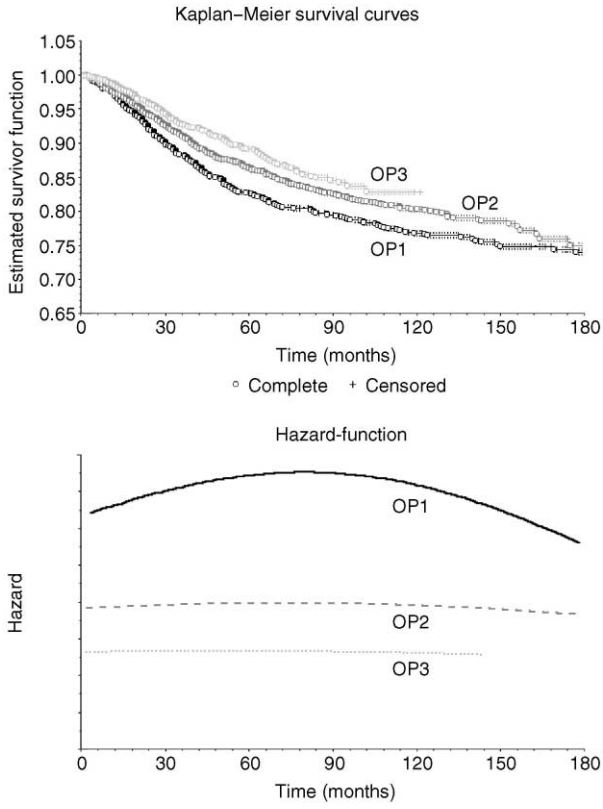

Fig. 3. Survival estimates for women ($n=6044$) with corresponding hazard functions for the different observation periods.

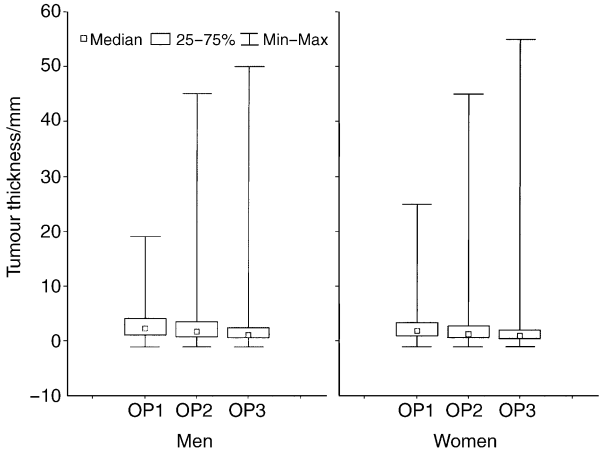

Fig. 4. Median Breslow thickness over the observation periods for males and females.

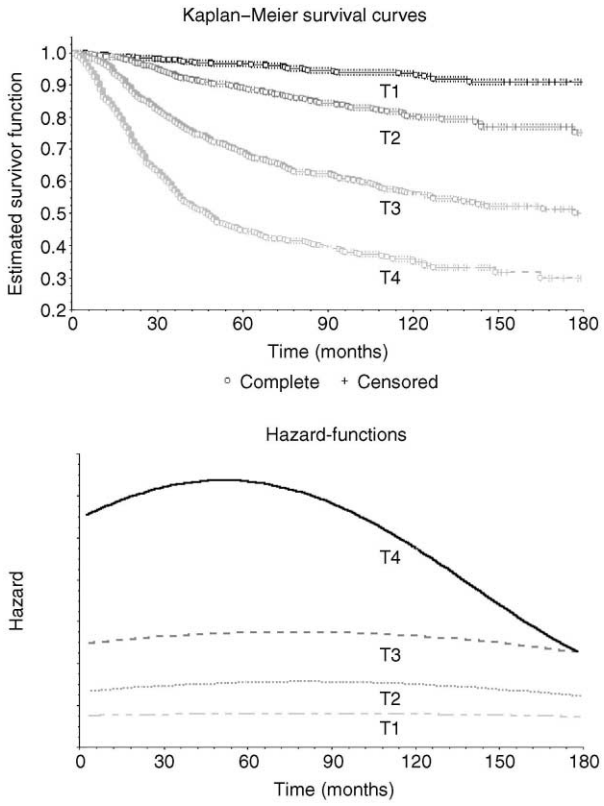

Fig. 5. Survival estimates for men ($n = 3882$) for the several thickness categories with corresponding hazard functions.

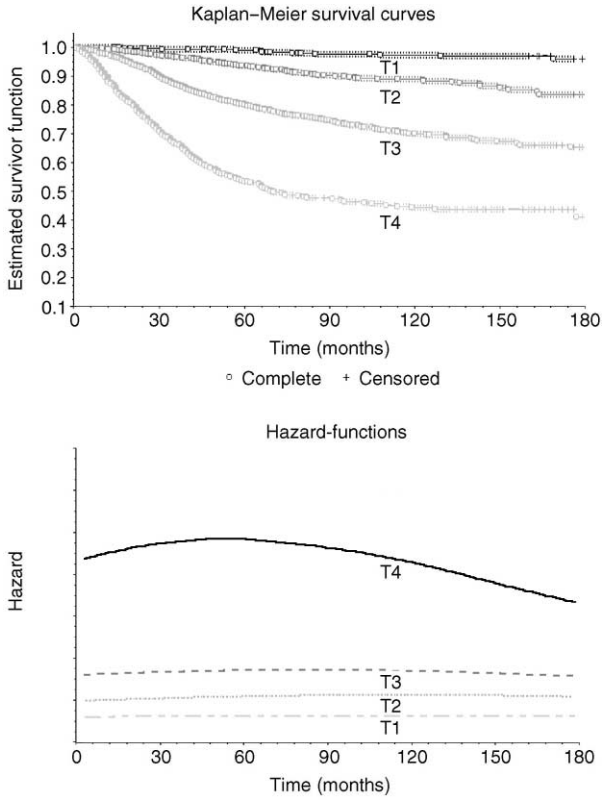

Fig. 6. Survival estimates for women ($n = 5428$) for the several thickness categories with corresponding hazard functions.

4. Discussion

In this study, we were able to demonstrate the development of survival rates from 1972 until 1996 on a large scale for over 10 000 melanoma patients. Additionally, we produced data relating to the actual risk of dying during this time period.

With every observation period, a steady increase of new cases was seen reflecting the general increase of melanoma in Germany. The overall survival increased especially after 1989, possibly as consequence of the melanoma awareness campaigns that started in Germany around this time. This improvement was mainly seen in younger men.[1] Furthermore, at any time period, survival of women was better, but recently the differences between the genders were less impressive. The shorter survival of males can be attributed to circumstances at presentation: tumour thickness of males always exceeded that of women; however, as demonstrated in Fig. 4, the decrease of median tumour thickness over the whole time period was more pronounced in males (males: 2.3→1.1 mm; females: 1.8→0.9 mm), leading to almost equal thicknesses nowadays. Nevertheless, for identical tumour thickness categories, there were still better survival rates for women as has been found by other authors [4–6]. In particular, this finding justifies prevention campaigns that are particularly targeted at men, although the above outlined decrease of tumour thickness could still render any evaluation difficult. We also confirmed the finding of an increase of thin melanomas and a stable incidence of thick melanomas [16].

In contrast to the Kaplan–Meier survival-curves, which give an indication of the probability to survive after removal of the primary tumour, the hazard rate analysis which does not depend on previous events focuses on the actual risk of death—the hazard rate. In addition, the hazard function determines periods of the patient's greatest risk for death. Customarily, the results of such analyses are taken as prerequisites to determine the length and the intensity of patients' follow-up [17–19].

We found men to be at an earlier and higher risk of dying compared with women in all observation periods and for all tumour thickness categories. In men, the time period of maximum dying risk varied between 50

[1] Nevertheless, there are some doubts as to whether the marked worse 5-year survival of men after 75 years of age as seen in Table 2 can be attributed solely to melanoma. Probably many patients with metastases died from other causes, including senility. We categorised all patients with metastases who died suddenly without a known cause due to melanoma; a procedure there is justified for the younger age groups, but dubious for the older patients. This is a general problem for all such comparable investigations.

Table 2
5-year survival rates in percent for three age groups

	15–44 years ($n=1206$)		45–74 years ($n=2795$)		75–99 years ($n=388$)	
	5-year survival	Standard deviation	5-year survival	Standard deviation	5-year survival	Standard deviation
Men						
1972–1980 (OP1)	61.6	3.51	62.2	2.64	56.9	7.88
1981–1988 (OP2)	67.5	2.38	61.7	1.69	64.2	5.03
1989–1996 (OP3)	75.5	2.69	72.8	1.80	63.5	7.96
Difference OP3−OP1	13.9		10.6		6.6	
	($n=1814$)		($n=3521$)		($n=709$)	
	5-year survival	Standard deviation	5-year survival	Standard deviation	5-year survival	Standard deviation
Women						
1972–1980 (OP1)	79.7	2.34	75.2	1.82	67.6	6.68
1981–1988 (OP2)	83.7	1.59	78.0	1.22	63.1	3.64
1989–1996 (OP3)	84.4	2.18	79.2	1.67	73.8	4.34
Difference OP3−OP1	4.7		4.0		6.2	

Table 3
Influence of Breslow tumour thickness on 5-, 7- and 10-years survival rates for three periods

Survival rates (%)		5 years	Standard deviation	7 years	Standard deviation	10 years	Standard deviation
Tumour thickness 0–0.75 mm							
1972–1980	Females ($n=173$)	100	0.00	100	0.00	100	0.00
(OP1)	Males ($n=82$)	91.25	3.16	89.88	3.40	88.05	3.79
1981–1988	Females ($n=631$)	97.86	0.61	97.45	0.68	96.50	0.88
(OP2)	Males ($n=351$)	95.43	1.15	92.85	1.48	90.70	1.91
1989–1996	Females ($n=1127$)	97.93	0.74	96.86	1.05	–	
(OP3)	Males ($n=721$)	97.16	0.90	96.38	1.18	–	
Tumour thickness 0.76–1.5 mm							
1972–1980	Females ($n=195$)	90.46	2.14	88.81	2.30	88.09	2.39
(OP1)	Males ($n=112$)	82.25	3.70	80.30	3.86	76.13	4.18
1981–1988	Female ($n=516$)	94.21	1.04	91.63	1.25	89.74	1.43
(OP2)	Males ($n=312$)	87.80	1.91	82.90	2.23	78.76	2.57
1989–1996	Females ($n=636$)	91.08	1.49	87.56	2.14	–	
(OP3)	Males ($n=473$)	88.28	1.99	87.39	2.16	–	
Tumour thickness 1.51–4 mm							
1972–1980	Females ($n=312$)	77.01	2.45	74.01	2.58	69.19	2.76
(OP1)	Males ($n=192$)	60.84	3.62	54.72	3.74	52.70	3.78
1981–1988	Females ($n=627$)	77.68	1.72	73.52	1.84	68.58	2.05
(OP2)	Males ($n=500$)	64.55	2.24	59.87	2.32	51.92	2.52
1989–1996	Females ($n=585$)	77.09	2.27	71.06	3.08	–	
(OP3)	Males ($n=535$)	69.36	2.50	66.66	2.75	–	
Tumour thickness >4 mm							
1972–1980	Females ($n=140$)	49.14	4.57	47.17	4.59	43.92	4.64
(OP1)	Males ($n=117$)	49.33	4.99	44.67	5.03	37.28	5.19
1981–1988	Females ($n=264$)	49.53	3.29	44.95	3.32	43.27	3.41
(OP2)	Males ($n=253$)	38.96	3.26	35.01	3.21	31.08	3.33
1989–1996	Females ($n=222$)	49.57	4.64	49.57	4.64	–	
(OP3)	Males ($n=234$)	42.50	4.12	39.10	5.00	–	

and 80 months after diagnosis. Men also died earlier when they had thick tumours and the time of diagnosis dated back to the earlier observation period. In women, the greatest risk to die was somewhat later—at approximately 80–90 months—and lower. A difference between the observation periods was indistinguishable. In addition, in men we found a hazard cross for observation periods 1 and 2 at approximately 160 months (Fig. 2) and for tumour thickness categories T4 and T3 at approximately 180 months (Fig. 5). After these time points, the risk of death was smaller for OP1 patients than those of OP2 and for Breslow thickness category

Table 4
Distribution of tumour thickness up to 1.5 and >1.5 mm in absolute numbers and percentage, separated by gender and three observation periods

		Low risk ⩽1.50 mm		High risk 1.51–>4.00 mm		Total
		n	%	*n*	%	
1972–1980 (OP1)	F	368	44.88	452	55.12	820
	M	194	38.57	309	61.43	503
	Σ	562	42.48	761	57.52	1323
1981–1988 (OP2)	F	1147	56.28	891	43.72	2038
	M	663	46.82	753	53.18	1416
	Σ	1810	52.40	1644	47.60	3454
1989–1996 (OP3)	F	1763	68.60	807	31.40	2570
	M	1194	60.83	769	39.17	1963
	Σ	2957	65.23	1576	34.77	4533

T4 in comparison to T3, respectively. This means, the less favourable prognosis for patients with tumours of more than 4 mm thickness and for those recruited in 1972–1980 appears to reverse after 180 or 160 months, respectively; patients still living thereafter are at a lower risk of dying compared with those recruited in 1981–1988 or with a tumour thickness of 1.51–4 mm, respectively. In contrast, for tumours with thickness <1.5 mm, the individual risk of dying remained fairly constant. Follow-up recommendations should take these facts into consideration.

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