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Original Paper

Improving Survival of Melanoma Patients in Europe Since 1978

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Within the EUROCARE study 45 cancer registries have contributed survival data on 3.5 million cancer sufferers within 17 countries in Europe. This paper reports on survival in 16 113 cutaneous malignant melanoma cases diagnosed between 1985 and 1989. Relative survival rates were calculated according to the Hakulinen computer program with data stratified according to country, age group and period of diagnosis. Relative 5-year survival was higher in women (81%) than in men (69%) but there was wide variation in relative survival across Europe at both 1 and 5 years, ranging at 5 years between 54 and 89%. At both 1 and 5 years, survival was lowest in the Eastern countries. Between 1978 and 1989 there was an improvement in survival rates probably attributable to the detection of increasing proportions of better prognosis, thinner tumours. In the younger age groups, this may be related to public awareness campaigns. The discrepancy in survival between men and women also narrowed. The single most important prognostic factor is the depth of invasion at diagnosis and there is some evidence that underlying variation in stage at presentation as well as histological type accounts for much of the observed variation in survival. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: primary cutaneous melanoma, survival, prognostic factors, Europe
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INTRODUCTION

COLLABORATION ACROSS Europe in the EUROCARE study [1] has now been extended to 45 registries in 17 countries that have accumulated data currently on 3.5 million new patients, most diagnosed between 1978 and 1992. Since no data on malignant melanoma were presented in the first EUROCARE report [1], this is the first report on survival from malignant melanoma across Europe. We describe variation in relative survival of adult patients from 1985 to 1989 and explore major trends in survival since 1978 for most countries.

Malignant melanoma is a tumour which arises in the melanocytes, the pigment producing cells in the basal cell layer of the epidermis. There are four main types of melanoma occurring in the skin: superficial spreading, thin tumours commonly on the legs in women; nodular, rapidly growing deeply pigmented nodules; acral, on the soles of the feet or the nail area of feet and hands; lentigo maligna, slow growing over many years commonly on the face of older people.

Malignant melanoma accounts for less than 10% of all skin cancer and less than 3% of all malignant disease in Europe [2]. The incidence has been rising rapidly at a rate of approximately 30% over 5 years during the time period of this study [3]. Melanoma is very rare before the age of 20 years, but the incidence increases thereafter. The number of cases is as great amongst adults in their thirties [4], when it is the third most common cancer, as those in their sixties. In Europe, malignant melanoma is more common in women than men, although the ratio varies between countries, whereas in Australia and America the rates are slightly higher for men [2]. Mortality from malignant melanoma in European countries has also been increasing with an average increase of 4% per year. The increase is slightly higher in men and is greater in Southern than in Northern European countries [5].

There is a well documented, though complex, association between the incidence of malignant melanoma and sun exposure. The risk from sun exposure is presumed to come

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from the ultraviolet component of sunlight which is known to be damaging to tissue [6]. Therefore, latitude of residence should be important in determining melanoma risk. This is the case when comparing Australia and New Zealand with Europe, but not within Europe. There is some evidence that those with long term occupational exposure are at lower risk than those with intermittent high level exposure and that episodes of severe sunburn, particularly in childhood, increase risk [7].

The single most important prognostic indicator is the depth to which a melanoma invades the dermis, known as the Breslow thickness and differences in stage of disease at presentation account for wide survival differences. Variation in both incidence and survival across Europe in recent years may be explained by population differences and, in part, by different healthcare systems with different levels of investment in public health campaigns. (See Discussion for a full account of these factors). The mainstay of treatment is surgery.

PATIENTS AND METHODS

Survival analysis was carried out on 16 113 malignant melanoma cancer cases diagnosed between 1985 and 1989 from 17 countries, recorded in 38 population-based cancer registries. Some of these (Finland, Denmark, Estonia, Slovenia, Scotland, Slovakia) cover the whole country; some a large proportion (England) and the rest up to 20% (Italy, Spain, France, The Netherlands, Germany, Sweden). Cases discovered at autopsy, patients first diagnosed with another tumour or known on the basis of death certificate only (DCO) were not included. The protocol specified a minimum follow-up of 5 years (unless death intervened). Iceland and Austria were excluded because of small numbers. Variables corresponding to age, gender, period of diagnosis and sub-site of lesion were available, but not stage of disease.

Relative survival rates were computed according to the Hakulinen computer program [8], with relative survival computed as the ratio between the observed (crude) survival and the expected survival, derived from the general mortality

Table 1. *Percentage of adult registrations by gender and age diagnosed with malignant melanoma between* 1985 *and* 1989 *in Europe (EUROCARE* II*)*

			Age group (years)				
		No. cases overall	% 15–44	% 45–74	% 75+	% DCO	% Lost to follow-up
Northern Europe							
Iceland	M	15	40	47	13	0	0
	F	35	26	46	29		
Finland	M	1043	28	62	10	0.1	0
	F	1089	30	52	18		
Sweden*	M	560	22	63	15	0	0
	F	658	28	53	19		
Denmark	M	1309	27	60	13	0	0
	F	1813	32	52	15		
U.K.							
Scotland	M	805	30	57	14	0.1	0
	F	1348	32	50	18		
England	M	3052	31	56	13	2.0	0.12
	F	5559	32	53	15		
Western and Central Europe							
The Netherlands*	M	110	37	52	11	0	6.94
	F	176	45	49	5		
Germany*	M	194	28	62	10	2.2	0
	F	252	22	63	15		
Austria*	M	70	36	49	16	2.8	0
	F	135	36	53	12		
Switzerland*	M	230	25	59	17	0	5.12
	F	255	29	55	16		
France*	M	156	34	53	13	0	0.93
	F	268	32	53	15		
Southern Europe							
Spain*	M	205	27	57	16	2.4	0
	F	311	30	50	20		
Italy*	M	574	25	65	10	1.0	0.69
	F	713	25	55	20		
Eastern Europe							
Slovenia	M	231	28	64	9	1.1	0.94
	F	293	33	54	13		
Slovakia	M	556	26	63	11	1.9	0
	F	673	31	55	14		
Poland*	M	124	23	65	11	1.6	5.99
	F	188	32	53	15		
Estonia	M	117	28	66	6	0	0.59
	F	218	23	58	18		

* < 20% of the national population covered. M, male; F, female.

data. The data were stratified into country, five age groups (15–44, 45–54, 55–64, 65–74 and 75+ years) and four diagnosis periods (1978–1980, 1981–1983, 1984–1986 and 1987–1989). Age-standardised survival rates were computed from age-specific rates directly, taking the age distribution of the whole European population as the standard. A European estimate of survival was calculated for comparative purposes by pooling the data from contributing countries and applying weights according to the estimated national incidence to compensate for the variation in population sizes [1].

In addition to these data, an additional database was maintained at the South and West Cancer Intelligence Unit in England, utilising data collected within the framework of the EUROCARE Study. Results from this database are not presented here, but information regarding stage and morphology has been extracted to facilitate explanation of survival differences.

RESULTS

The number of registrations in each age group and gender is presented by country in Table 1, with the proportion of DCOs and lost to follow-up cases and an indication of where there was less than 20% national coverage by the data. The proportion of DCOs and lost to follow-up cases was low overall, except in Switzerland, The Netherlands and Poland where the lost to follow-up rate was high. These factors are, therefore, unlikely to be the major reason for the wide variation in survival.

Intercountry variation in survival

In Figure 1, 1-year and 5-year relative survival rates from cutaneous malignant melanoma in adults are presented for the participating European countries for the registration period 1985–1989. These were age-standardised to ensure comparability between countries. Relative survival for Europe overall was 93% at 1 year and 77% at 5 years, but there were wide variations across Europe in relative survival from malignant melanoma. As shown in Figure 1 at both 1 and 5 years, survival was lowest in the Eastern countries. The variation was broad at 5 years, with a range between the best and worst results of 35%. This diversity was less at 1 year, with a range of 15%. The pattern of variation was the same for both men and women, (Figure 1a and b), although survival for women was higher than that of men.

Effect of age on survival

Table 2 shows the 5-year relative survival rates by age group. There were some surprising results, particularly in

Table 2. Five-year relative survival rates (%) in adult European malignant melanoma patients diagnosed between 1985 *and* 1989*, according to age at diagnosis (EUROCARE* II*)*

	Age at diagnosis (years)				
Country	15–44 %	45–54 %	55–64 %	65–74 %	75–99 %
Northern Europe					
Finland	87	86	80	78	67
Sweden*	92	92	88	87	72
Denmark	86	81	79	76	64
U.K.					
Scotland	88	82	80	82	79
England	84	81	78	74	68
Western and Central Europe					
The Netherlands*	85	86	90	80	52
Germany*	77	87	73	72	74
Switzerland*	89	92	86	92	86
France*	84	71	73	89	65
Southern Europe					
Spain*	80	76	83	67	84
Italy*	78	76	67	59	52
Eastern Europe					
Slovenia	68	60	54	59	53
Slovakia	65	64	63	56	65
Poland*	62	50	54	45	46
Estonia	72	72	53	52	68
Europe	81	80	76	73	64

* < 20% of the national population covered.

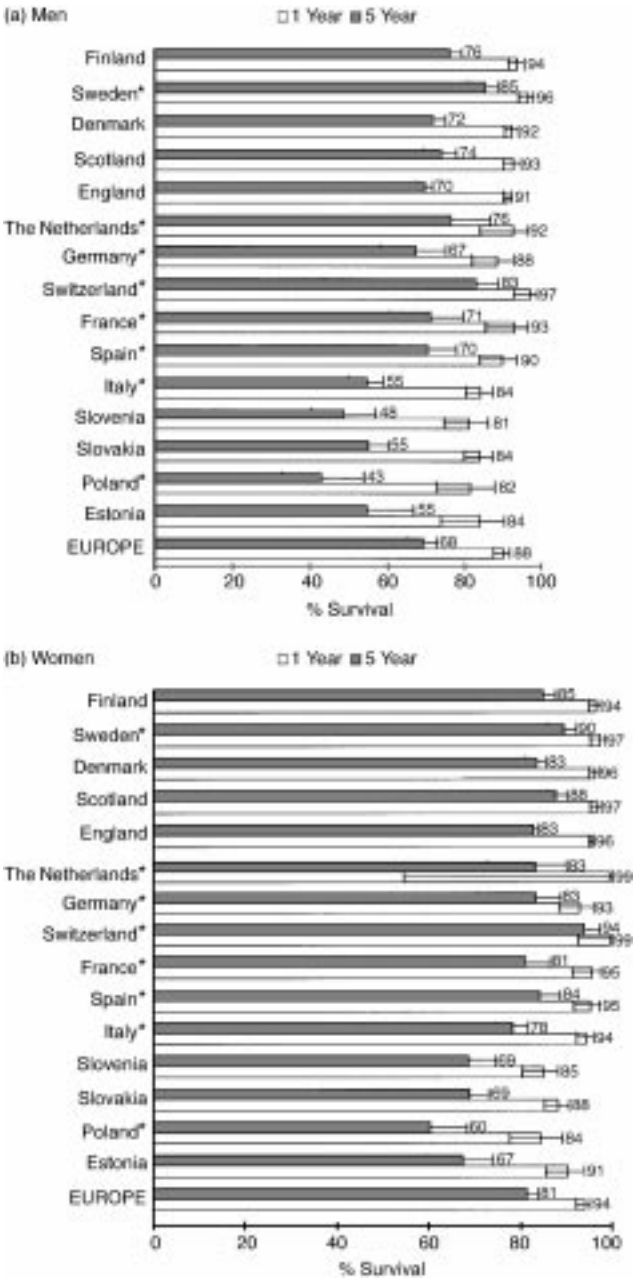

Figure 1. Age-standardised relative survival rates in 15 European countries for adult (a) men and (b) women with malignant melanoma between 1985 and 1989 (EUROCARE II). Bars, 95% confidence intervals. * < 20% of the national population covered. Countries with only a small number of cases are not shown.

Table 3. *Percentage of cases in each sub-site for adult European malignant melanoma patients diagnosed between* 1978 *and* 1989—*both sexes, by country (EUROCARE* II*)*

	Sub-site									
	Head and neck		Trunk		Upper limb		Lower limb		Other	
Age	15–44	75+	15–44	75+	15–44	75+	15–44	75+	15–44	75+
Northern Europe										
Finland	8	33	44	30	15	13	29	19	3	7
Sweden*	7	39	36	24	14	16	33	18	11	4
U.K.										
Scotland	9	50	27	7	18	10	41	31	3	3
England	7	36	26	11	19	12	41	32	7	10
Western and Central Europe										
The Netherlands*	10	29	20	24	22	14	48	29	1	5
Germany*	5	25	26	14	16	18	33	13	21	31
Switzerland*	4	5	25	10	8	13	17	10	56	63
France*	13	44	29	10	17	15	34	23	6	10
Southern Europe										
Spain*	5	38	21	13	13	6	30	16	31	28
Italy*	11	10	38	13	13	14	29	36	8	7
Eastern Europe										
Slovenia	9	25	1	2	40	20	14	16	38	40
Slovakia	11	33	46	21	14	11	26	28	4	8
Poland*	7	23	30	16	20	9	33	33	10	19
Estonia	7	37	45	21	13	15	31	25	4	2

* < 20% of the national population covered.

respect of the oldest age group. The very high relative survival for the age 75+ in Spain (84%), which is the highest of any age group for that country suggests that this may not be an accurate reflection of the situation. Italy has low survival overall compared with Spain, but the divergence in the rates between these two countries is apparent from the middle age group. The Netherlands had a very low relative survival for the oldest age group, but this is probably a reflection of the high proportion of male cases.

Table 3 illustrates the percentage of cases by sub-site by country, for the oldest and youngest age groups. In the 15–44 age group, the commonest sub-sites were the trunk and the lower limb; whilst in the oldest age group, the highest percentage of registrations were for the head and neck for most countries.

Time trends in survival

Tables 4 and 5 indicate time trends by gender and age between 1978 and 1989. The trend across this period was generally one of improvement in survival and the discrepancy between male and female survival rates also generally decreased over time.

DISCUSSION

Various prognostic indicators of survival, and factors to be considered when interpreting differences in survival between different populations, i.e. between countries or males/females, have been discussed in detail in the EUROCARE monograph [1]. Improvements in survival are, as stated above, related to earlier diagnosis and may be affected by such factors as socio-economic characteristics (affecting distribution of stage of disease), screening programmes and other preventative measures, therapeutic procedures and artefactual changes.

With regard to artefactual changes, it is difficult to eliminate selection bias completely, but this is minimised by the use of standardised classification systems. The inclusion of a different proportion of *in-situ* tumours would give an apparent increase in survival, but it is unlikely that this would happen in the absence of a higher proportion of patients with early stage disease at diagnosis, which would also increase survival. Hence the effect may be exaggerated, but not untrue. The effect of emigration on survival in Switzerland is described in the EUROCARE monograph [1] and is probably responsible in part for some of the high survival, as cases lost to follow-up are censored from the analysis. There is also low national coverage by the registries in Switzerland and the observed survival may not be truly representative of the country as a whole.

The single most important prognostic factor known to influence survival is Breslow thickness. Over 90% of patients with tumours of Breslow thickness less than 1.5 mm are expected to survive for five years, whereas those with tumours greater than 3.5 mm have an expected 5-year survival of less than 40% [9]. This is because small tumours can be effectively treated by local surgery, but for more advanced disease, few patients show prolonged responses to chemotherapy and radiotherapy also has little part to play in primary treatment [10]. Survival is better for women than for men and for patients with superficial spreading melanoma than for those with nodular melanoma [11]. However, these associations are probably because of differing average thickness at presentation. In spite of possible differences in factors such as artefactual changes, therefore, it seems likely that the depth of invasion at diagnosis is the major underlying reason for the survival variation. We have access to the EUROCARE database held at the South and West Cancer Intelligence Unit in England (see Methods) and used this to explore the likely

Table 4. *Five-year age-standardised relative survival rates for adult European malignant melanoma patients, according to country, registered between* 1978 *and* 1989, *by diagnosis period (EUROCARE* II*)*

Country		Period				Absolute difference in survival between 1978 and 1989
		1978–1980	1981–1983	1984–1986	1987–1989	
Northern Europe						
Finland	M	66	72	70	79	13
	F	78	82	85	85	7
Sweden*	M	78	76	80	88	10
	F	90	88	91	90	0
Denmark	M	70	70	71	73	3
	F	79	83	84	83	4
U.K.						
Scotland	M	63	63	64	78	15
	F	79	77	82	91	12
England	M	56	59	66	71	15
	F	76	78	80	84	8
Western and Central Europe						
The Netherlands*	M	48	57	65	84	36
	F	85	70	82	87	2
Germany*	M	68	70	75	63	−5
	F	67	75	83	85	18
Switzerland*	M	89	85	79	86	−3
	F	91	85	85	93	2
France*	M	64	63	60	77	13
	F	84	83	89	82	−2
Southern Europe						
Italy*	M	36	43	48	54	18
	F	70	65	76	77	7
Eastern Europe						
Poland*	M	Unknown	Unknown	36	48	–
	F	60	55	56	75	15
Estonia	M	30	39	53	47	17
	F	60	62	56	70	10

M, male; F, female. * < 20% of the national population covered.

Table 5. *One- and* 5*-year age specific relative survival rates for adult European malignant melanoma patients, diagnosed between* 1978 *and* 1989, *by age group (EUROCARE* II*)*

Age (years)	Rate	Period				Absolute difference in survival between 1978 and 1989
		1978–1980	1981–1982	1983–1985	1987–1989	
15–44	1 year	91	95	95	96	5
	5 year	75	78	80	84	9
45–54	1 year	87	96	95	96	9
	5 year	70	77	80	81	11
55–65	1 year	89	91	93	94	5
	5 year	66	69	70	74	8
65–74	1 year	88	88	91	89	1
	5 year	55	53	63	66	11
75+	1 year	72	76	78	79	7
	5 year	37	35	42	39	2

impact of stage of disease at presentation on the observed variation in survival. Although up to 70% of cases are unstaged, for those which are staged, tumour thickness corresponds well to the EUROCARE survival figures. For example, Switzerland and Sweden have 73 and 66% respectively of staged cases with a Breslow thickness of < 1.5 mm, compared with only 15% in Poland and 27% in Slovenia < 1.5 mm.

Nodular melanoma has also been indicated as a factor related to shortened survival from malignant melanoma [10, 11]. Again, no information about this is available in the EUROCARE dataset, but data from the database held at the South and West Cancer Intelligence Unit in England show that the morphology of the tumour corresponds well with the EUROCARE survival rates. When comparing the ratios of nodular to superficial spreading, Poland has 90 and 10%, respectively and Slovakia 70 and 30%, respectively. However Switzerland has 34 and 66% and The Netherlands 20 and 80%, respectively.

Public awareness of the disease and other measures aimed at early detection are therefore important issues. With respect to malignant melanoma, as stated above, this means detection of

Table 6. *Data comparisons—5-year relative survival figures for malignant melanoma from other published data series*

Study	Country	Period	5-year relative survival figures					
Thorn and associates [18]	Sweden (population based)	1960–1984	Overall for 1980–1984 (81%)					
Mackie and associates [19]	Scotland	1979–1994	Actuarial by period					
				1979/1990	1979/1981	1982/1984	1985/1987	1988/1990
			M	69	60	59	69	76
			F	82	75	79	83	89
SEER data [20]		1983–1988	White patients		83%			
			Black patients		68%			
SEER data [20]	Northern California	1987–1993	All stages:		89%			
			Localised:		96%			
			Regional:		64%			
			Distant:		16%			

M, male; F, female.

thin (Breslow thickness < 1.5 mm) tumours [12, 13]. Although population-based screening programmes are impractical, publicity campaigns to encourage self-screening and, therefore, earlier referral and treatment have been shown to produce a shift towards less advanced lesions [14, 15]. Public health campaigns have been conducted in the middle, Northern and Western countries and Scotland, where survival rates are high, and in some cases improving. This may account for some variation in survival rates between countries. However, it was pointed out in the first EUROCARE monograph [1] that in practice there are few reliable data to quantify the level of opportunistic screening. The differences in staging in Europe described above may provide indirect information about this.

Another biological factor which can affect survival is subsite. Drzewiecki and associates [16], in a study of patients with localised disease, found that patients with foot melanoma had the worst prognosis, followed by patients with melanoma of the trunk. In the EUROCARE study, there was some difference between the proportions with melanoma of the trunk (front and back combined) with 18% in Switzerland compared with 39% in Slovakia and this may also influence the survival differences. Caution, however, is needed in interpretation because of the high proportion with an unknown sub-site in Slovenia, Spain, Germany and Switzerland.

Survival can also be affected by demographic and socioeconomic characteristics of the general population of a country and possible selection with respect to these characteristics [1]. A study by Mackie and Hole [17] found that good prognosis tumours were most common in the most affluent men and women (possibly as a result of better awareness leading to earlier self-referral and thus earlier diagnosis and treatment). However, even after controlling for tumour thickness, socio-economic status remained a major indicator affecting survival and they hypothesised that this was as a result of poor nutrition leading to low levels of anti-oxidants or immunological defects or both. This could, therefore, be a factor in the poorer survival within the less affluent eastern countries shown in the EUROCARE study.

The results of the comparisons with other data series seen in Table 6 are comparable with the EUROCARE data. The SEER data demonstrated a difference in survival by skin type and it would be useful to know the mix of ethnicity in the EUROCARE regional data.

Finally, with respect to trends in survival in the EUROCARE data, results show there has been a general improvement in the survival rates across Europe between 1978 and 1989. This improvement has occurred despite the documented increase in mortality rates [5]. A study in Denmark [16] conducted a time trends analysis for the years 1964–1982 and also found that over that time there was a significant decrease in tumour thickness and in the proportion of ulcerated tumours. The authors concluded that the distribution of these significant prognostic factors shifted over time in the direction of improved prognosis.

In conclusion, survival was higher in females than males and there was wide variation in survival across Europe at both 1 and 5 years, ranging at 5 years between 54% (Poland) and 89% (Switzerland). At both 1 and 5 years, survival was lowest in the Eastern countries. Between 1978 and 1989 there was an improvement in survival rates and additionally the discrepancy in survival between men and women narrowed. The single most important prognostic factor is the depth of invasion at diagnosis and it is possible that underlying variation in stage at presentation accounts for much of the observed variation in survival.

Further evaluation of public health campaigns and their effect on survival would be valuable. Further research should also be undertaken to describe the distribution of known prognostic factors such as sub-type, site and thickness of tumour at presentation in relation to the observed variation in survival.

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APPENDIX

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