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CUTANEOUS MALIGNANT MELANOMA IN EUROPE

Esther de Vries, Jerzy E. Tyczynski and D. Maxwell Parkin

Introduction

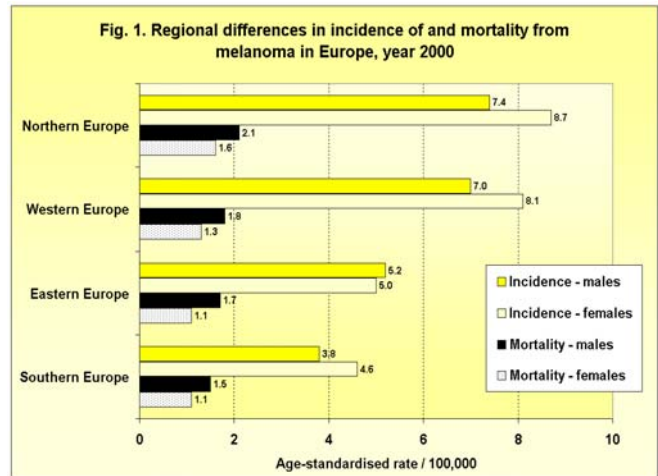
Melanoma¹ is less common than the familiar basal and squamous cell tumours of the skin, but much more fatal. In Europe, approximately 26,100 males and 33,300 females are diagnosed each year with melanoma, and around 8,300 males and 7,600 females die of it (Ferlay et al., 2001). It is the 8th most commonly diagnosed cancer in females and 17th in males.

Melanoma has shown some of the fastest rates of secular increase in incidence in white populations, and has a complicated relationship with sun exposure, that is not completely understood. When melanomas are detected at early stages they are curable, but once advanced they are very difficult to treat.

Light skin type, large numbers of naevi and excessive sun exposure, mainly in childhood, are the major modifiers of melanoma risk.

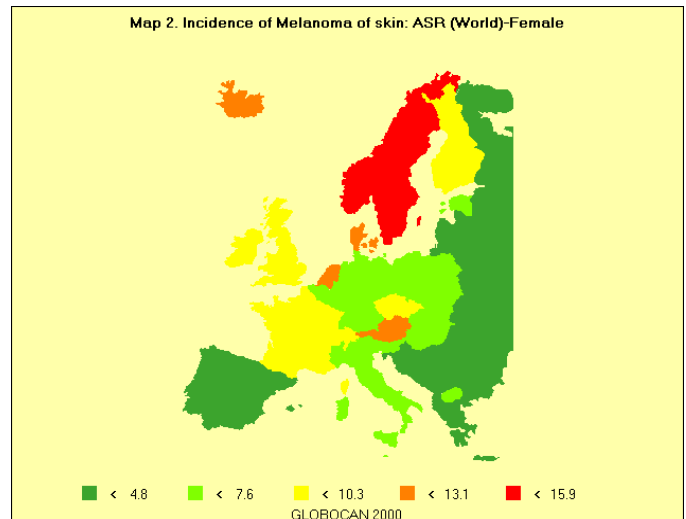
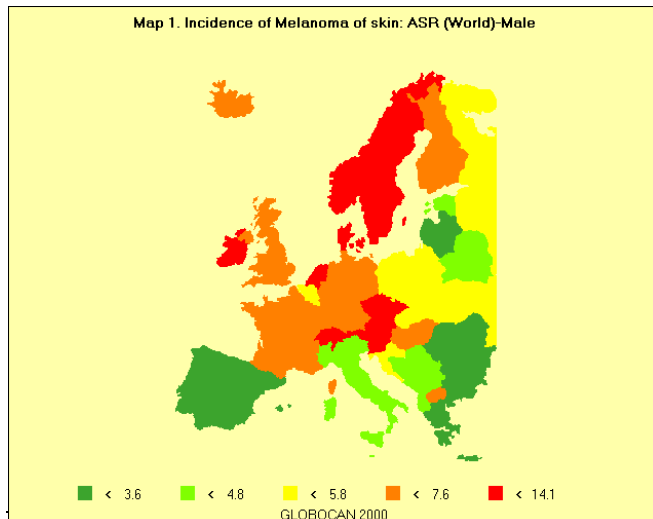
Regional Differences in Melanoma

There are some differences in the occurrence of melanoma across Europe. Figure 1 shows rates of incidence and mortality for both sexes in four different areas. Incidence rates vary substantially between the regions, with highest rates in Northern and Western Europe, whereas mortality rates are more similar between regions (Figure 1). The estimates for individual countries are



Temporal Changes in Incidence of and Mortality from Melanoma

Trends in rates of incidence of and mortality from melanoma differ across Europe. In Northern Europe, where incidence rates are high, the rates seem to be levelling off since the mid-1990's, especially in younger age groups. In contrast, in Southern and Eastern Europe rates are increasing steeply in all age categories (de Vries et al, 2003) (Figures 4 & 5).

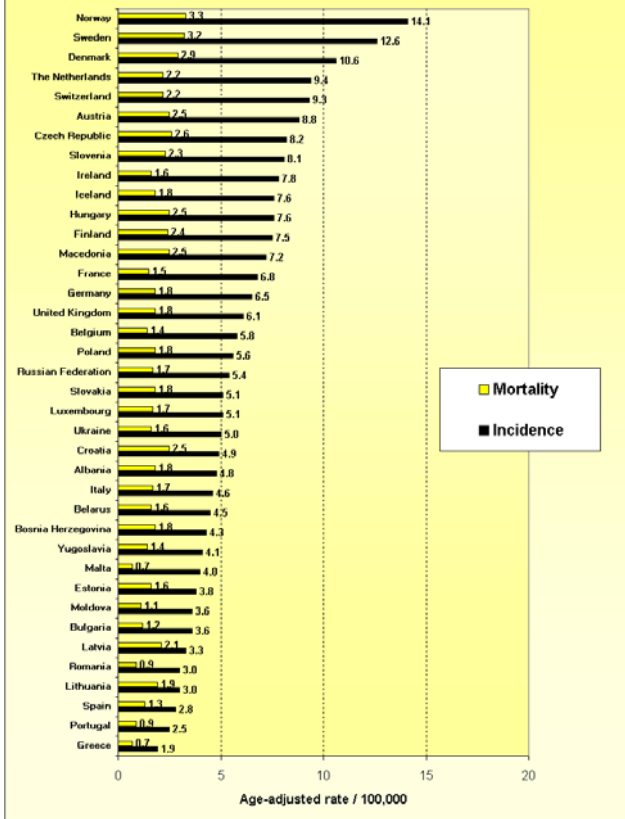


In this fact sheet 'melanoma' refers to cutaneous malignant melanoma.

Geographical Differences across Europe

As can be seen in the maps (Map 1 & 2), melanoma incidence follows a distinct North-to-South gradient, with the highest rates in Northern Europe. In other parts of

Figure 2. Melanoma incidence and mortality in Europe, year 2000 estimates, by country, males



tralia) increase with increasing proximity to the equator (Tucker et al, 2003). The inverse pattern is observed in Europe. This is probably related to lighter skin types and a higher intermittent sun exposure in many Northern European countries. Many Northern Europeans spend their summer holidays in the Mediterranean area, increasing their amount of sun exposure without being used to the amount of sun received during this period.

Biology of Melanoma

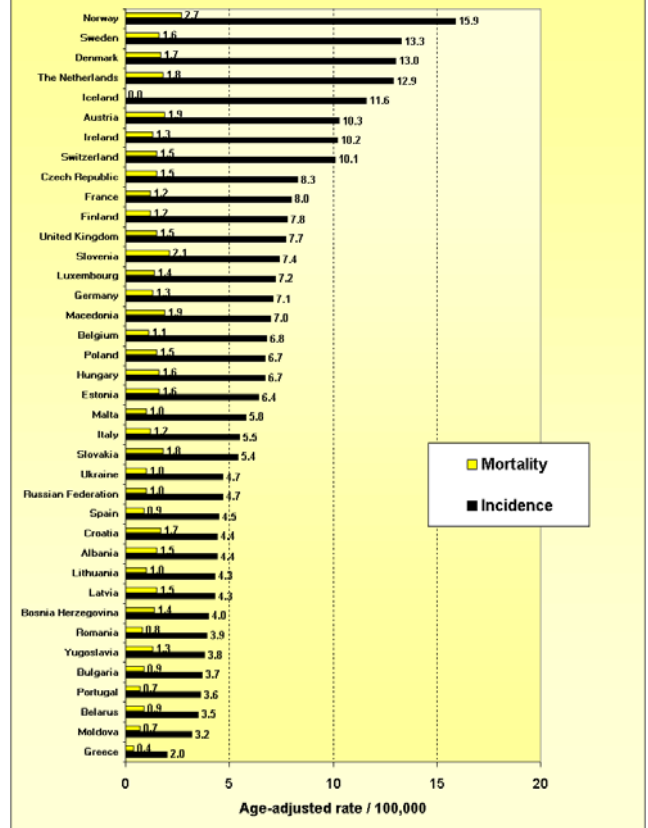
Melanoma is thought to develop by the malignant transformation of melanocytes, cells in the basal layer of the epidermis which synthesise melanin, a pigment with a photoprotective function. Ultraviolet (UV) radiation can promote the limited proliferation capacity of melanocytes (Armstrong et al, 1983). The most common types of melanoma are superficial spreading melanoma, nodular melanoma and lentigo maligna melanoma. The latter type is most prevalent in older age groups, whereas superficial spreading and nodular melanomas are more common among younger patients (Van der Spek-Keijser et al, 1997).

Aetiology of Melanoma

Risk factors for melanoma include both endogenous and exogenous factors. The endogenous factors: skin phototype, number of nevi, having clinical atypical nevi, and having a family history of skin cancer, are the most important predictors of melanoma risk (Tucker et al, 2003).

The most important exogenous risk factor is exposure to UV radiation (Armstrong et al, 1993; Gilchrest et al 1999), although its association with melanoma depends on skin characteristics, with highest risks in those with a sun-sensitive skin. Mutations found in melanomas are often

Figure 3. Melanoma incidence and mortality in Europe, year 2000 estimates, by country, females



radiation exposure (Giglia-Mari et al, 2003). Individuals with DNA repair deficiencies, such as Xeroderma Pigmentosum, are at higher risk of developing melanoma (Giglia-Mari et al, 2003). Exposure to psoralens is also a risk factor for the development of melanoma (Autier et al, 1997).

Exposure to ultraviolet radiation

The relative risk of UV exposure for the development of melanoma is around 2, but when skin characteristics are taken into account, the relative risks increase markedly for those with a sun-sensitive skin (Tucker et al, 2003; Brenner et al, 2002).

Most melanomas are thought to be caused by intermittent (not chronic) sun exposure to UV radiation, especially during childhood, although exposure in adulthood certainly also plays a part (Armstrong et al, 1993; Gilchrest et al, 1999). The characteristics of melanomas among the elderly, more melanomas on the chronically exposed body sites and more lentigo maligna melanomas, suggest that melanomas among elderly patients are more related to chronic sun exposure (Van der Spek-Keijser et al, 1997).

Sunbeds

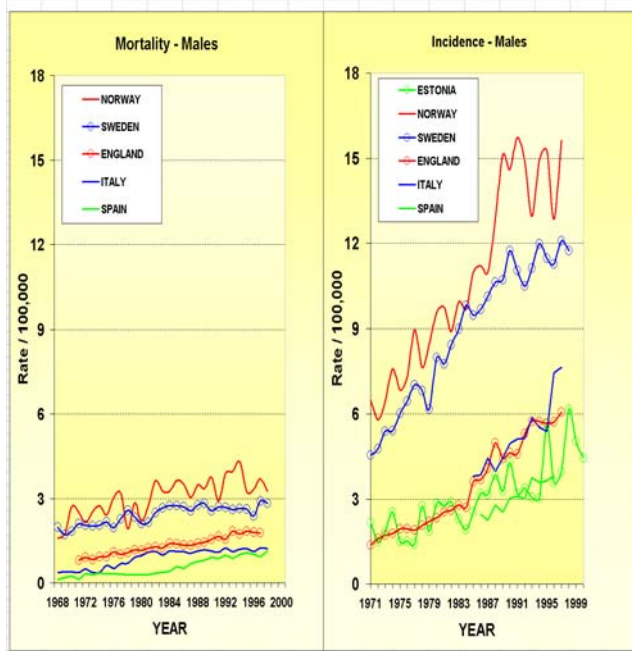
Based on epidemiological studies performed so far, it is not clear whether exposure to UV-radiation from sunbeds conveys a risk for the development of melanoma (Westerdahl et al, 2000; Swerdlow et al, 1998; Autier et al, 1994; Bataille, 2003). However, it seems reasonable to assume that – based on lab results – UV radiation from sunbeds has similar effects on the skin as UV radiation

from the sun. Therefore, very frequent use of sunbeds does not seem to be a smart thing to do, especially for children and people with a sun-sensitive skin.

Genetic factors

In melanoma families, two genes, *CDKN2A* and *CDK4* have been discovered, of which *CDKN2A (p16)* is the most prevalent. Germline mutations in this gene have been found in up to 25% of melanoma families worldwide. Its penetrance varies with population incidence rates, indicating that the same factors that affect population incidence of melanoma may also mediate *CDKN2A* penetrance. Both

Figure 4. Time trends - malignant melanoma - Males



CDKN2A and *CDK4* are important in controlling cell division. Other genes, such as *MC1R* are likely to play a role in susceptibility to melanoma. This gene is involved in skin and hair pigmentation and in senescence and immunity (Bataille, 2003; Bishop et al, 2002; Tucker et al, 2003)

Socio-economic status

Melanoma is more common among people with a higher socio-economic status, probably due to a higher excessive intermittent exposure to UV radiation (outdoor sports, winter sports, sunbathing, getting a tan) in this group.

Melanoma Prevention

The main way to prevent skin cancer, including melanoma, is to advise people to limit their exposure to the sun by avoiding the sun during the hottest hours of the day, wearing protective clothing, and preventing sunburn. Protection from the sun is especially important in children. As a tanned skin is still considered beautiful and a sign of good health, limiting sun exposure is a difficult message to convey.

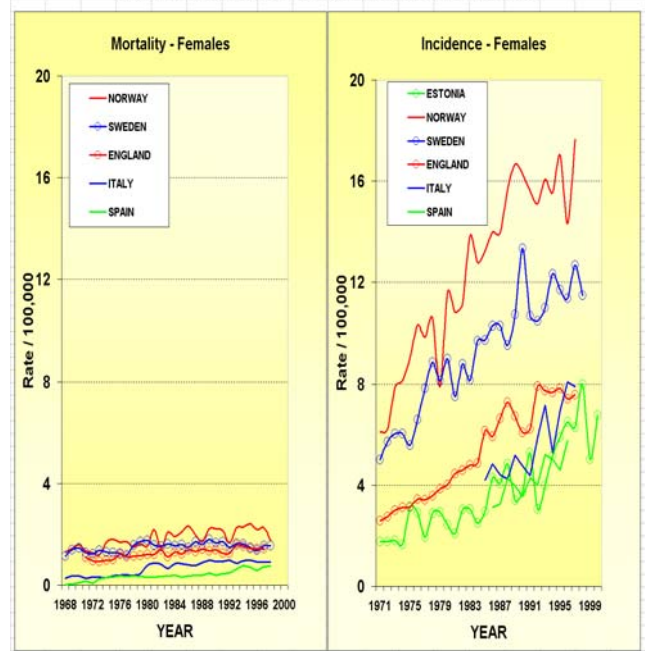
Because early detection of melanomas dramatically improves survival, and the incidence of skin cancers is expected to keep increasing for a while, early detection of melanomas remains an important part of every strategy to combat the disease. Messages about the need to visit the doctor when suspected skin lesions are found have been spread in North-western Europe since the 1980s (Koh et al, 1995), and have probably resulted in a decrease in the average thickness of melanomas and a stabilisation in

melanoma mortality in young people (Mansson-Brahme et al, 2002; MacKie et al, 2002; Kolmel et al, 2002).

Sunscreen use

Sunscreens are often recommended as a sun protection method because they can reduce sunburns and other UV-induced skin lesions. Their preventive impact on melanoma incidence is, however, obscure. Several case-control studies have suggested that sunscreen use is associated with an *increased* risk of melanoma. The conclusions of a meta-analysis studying the methodology of 11 case-control studies were that the available epidemiological data

Figure 5. Time trends - malignant melanoma - Females



do not support the existence of a relationship between sunscreen use and either an increased or decreased risk (Huncharek, 2002).

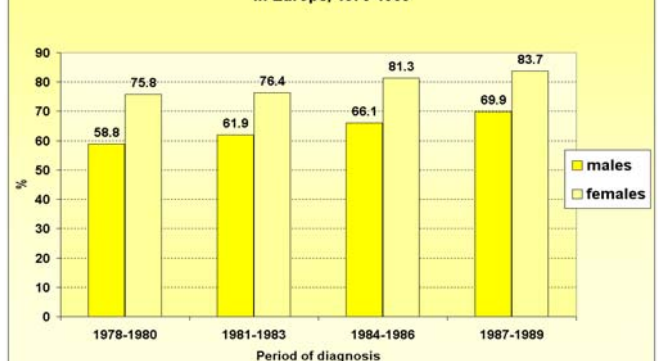
Survival of Melanoma Patients

Stage

Melanoma survival rates are strongly correlated with the stage of disease at diagnosis. When the melanomas are still localised, they can be excised and survival rates are generally very favourable. If, however, the melanomas are in more advanced stages, treatment is very difficult and survival rates are rather poor.

There are substantial differences across Europe in staging of melanoma at the time of diagnosis. The percentage of cases diagnosed in stages 0 and I (localised) varies in European countries from about 10% to 70%.

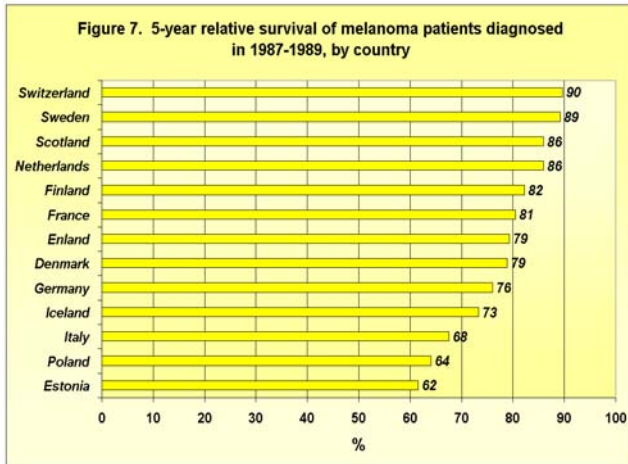
Figure 6. Average 5-year relative survival of melanoma patients in Europe, 1978-1989



Survival

Although women generally have a higher incidence of melanoma, their survival is better. The average 5-year survival of patients diagnosed with melanoma in Europe throughout the period 1978-1989 increased in males from 59% to 70% and in women from 76% to 84% (Figure 6).

There are substantial differences in survival among European countries. The EURO CARE II study has shown that the highest 5-year relative survival rates among patients diagnosed in 1987-1989 were in Switzerland (90%), Sweden (89%), Scotland and the Netherlands (both 86%), Finland (82%), France (81%), England (79%), Denmark (79%), Germany (76%), Iceland (73%), Italy (68%), Poland (64%), and Estonia (62%) (Figure 7). Note



that the countries with the highest incidence rates also have the highest survival rates, whereas in those countries where incidence is low, survival rates are relatively poor. This is probably due to a higher awareness in high incidence countries, resulting in earlier detection of melanomas and therefore better survival.

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Table 1. Estimates of melanoma incidence and mortality in Europe in 2000

Country (region)	Incidence				Mortality			
	Males		Females		Males		Females	
	ASR (World)	Cases	ASR (World)	Cases	ASR (World)	Deaths	ASR (World)	Deaths
Eastern Europe	5.2	9253	5.0	10983	1.7	3000	1.1	2736
Belarus	4.5	258	3.5	271	1.6	94	0.9	74
Bulgaria	3.6	214	3.7	239	1.2	72	0.9	66
Czech Republic	8.2	564	8.3	645	2.6	181	1.5	134
Hungary	7.6	498	6.7	539	2.5	165	1.6	149
Moldova	3.6	80	3.2	87	1.1	25	0.7	21
Poland	5.6	1251	6.7	1722	1.8	403	1.5	420
Romania	3.0	417	3.9	579	0.9	134	0.8	140
Russian Federation	5.4	4327	4.7	5024	1.7	1394	1.0	1252
Slovakia	5.1	158	5.4	201	1.8	56	1.8	71
Ukraine	5.0	1487	4.7	1675	1.6	474	1.0	407
Northern Europe	7.4	4688	8.7	6085	2.1	1437	1.6	1293
Denmark	10.6	388	13.0	472	2.9	114	1.7	85
Estonia	3.8	32	6.4	69	1.6	13	1.6	20
Finland	7.5	264	7.8	300	2.4	87	1.2	56
Iceland	7.6	12	11.6	19	1.8	3	0.0	0
Ireland	7.8	175	10.2	249	1.6	36	1.3	33
Latvia	3.3	44	4.3	88	2.1	28	1.5	33
Lithuania	3.0	63	4.3	119	1.9	41	1.0	34
Norway	14.1	422	15.9	481	3.3	109	2.7	92
Sweden	12.6	874	13.3	895	3.2	230	1.6	142
United Kingdom	6.1	2398	7.7	3375	1.8	769	1.5	795
Southern Europe	3.8	3667	4.6	5053	1.5	1535	1.1	1382
Albania	4.8	68	4.4	63	1.8	25	1.5	21
Bosnia Herzegovina	4.3	99	4.0	102	1.8	40	1.4	37
Croatia	4.9	151	4.4	150	2.5	81	1.7	64
Greece	1.9	131	2.0	172	0.7	57	0.4	43
Italy	4.6	1813	5.5	2408	1.7	737	1.2	649
Macedonia	7.2	84	7.0	90	2.5	31	1.9	26
Malta	4.0	9	5.8	13	0.7	2	1.0	2
Portugal	2.5	158	3.6	277	0.9	59	0.7	60
Slovenia	8.1	102	7.4	107	2.3	30	2.1	34
Spain	2.8	774	4.5	1383	1.3	370	0.9	306
Yugoslavia	4.1	272	3.8	286	1.4	101	1.3	106
Western Europe	7.0	8498	8.1	11215	1.8	2348	1.3	2222
Austria	8.8	465	10.3	640	2.5	141	1.9	143
Belgium	5.8	381	6.8	521	1.4	103	1.1	105
France	6.8	2488	8.0	3363	1.5	625	1.2	615
Germany	6.5	3732	7.1	4767	1.8	1114	1.3	1048
Luxembourg	5.1	15	7.2	23	1.7	6	1.4	5
The Netherlands	9.4	956	12.9	1334	2.2	239	1.8	208
Switzerland	9.3	458	10.1	561	2.2	121	1.5	99