EUROPEAN JOURNAL OF CANCER 48 (2012) 1167–1175

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

Descriptive epidemiology of malignant mucosal and uveal melanomas and adnexal skin carcinomas in Europe

S. Mallone [a,*], E. De Vries [b,c], M. Guzzo [d], E. Midena [e,f], J. Verne [g], J.W. Coebergh [b,h], R. Marcos-Gragera [i], E. Ardanaz [j], R. Martinez [k], M.D. Chirlaque [l,m], C. Navarro [l,m], G. Virgili [n], The RARECARE WG

[a] Cancer Epidemiology Unit, National Center for Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy
[b] Department of Public Health, Erasmus Medical Centre, Rotterdam, The Netherlands
[c] Unit of Descriptive Epidemiology, IARC, Lyon, France
[d] Fondazione IRCCS 'Istituto Nazionale dei Tumori', Milan, Italy
[e] Department of Ophthalmology, University of Padova, Italy
[f] Fondazione IRCCS 'GB Bietti', Rome, Italy
[g] South West Public Health Observatory, Bristol, United Kingdom
[h] Eindhoven Cancer Registry, Comprehensive Cancer Center South, Eindhoven, The Netherlands
[i] Unit of Epidemiology and Girona Cancer Registry, Pla Director d'Oncologia, Departament de Salut, Girona, Spain
[j] Navarra Cancer Registry, Instituto de Salud Pública de Navarra, Pamplona, Spain
[k] Basque Country Cancer Registry, Subdirección de Sanidad de Araba, Gobierno Vasco, Vitoria, Spain
[l] Department of Epidemiology, Murcia Regional Health Authority, Murcia, Spain
[m] CIBER Epidemiología y Salud Pública (CIBERESP), Spain
[n] Department of Ophthalmology, University of Florence, Florence, Italy

ARTICLE INFO

Article history:
Available online 25 November 2011

Keywords:
Rare cancers
Mucosal melanomas
Uveal melanomas
Adnexal skin carcinomas
Incidence
Survival
Complete prevalence

ABSTRACT

This work provides descriptive epidemiological data of malignant mucosal and uveal melanomas and adnexal skin carcinomas in Europe as defined as in the RARECARE project. We analysed 8669 incident cases registered in the period 1995–2002 by 76 population-based cancer registries (CRs), and followed up for vital status to 31st December 2003. Age-standardised incidence to the European standard population was obtained restricting the analysis to 8416 cancer cases collected by 64 not specialised CRs or with information available only for some anatomical sites. Period survival rates at 2000–2002 were estimated on 45 CRs data. Twenty-two CRs which covered the period 1988–2002 were analysed to obtain the 15-year prevalence (1st January 2003 as reference date). Complete prevalence was calculated by using the completeness index method which estimates surviving cases diagnosed prior to 1988 ('unobserved' prevalence). The expected number of new cases per year and of prevalent cases in Europe was then obtained multiplying the crude incidence and complete prevalence rates to the European population at 2008. We estimated 5204 new cases per year (10.5 per million) to occur in Europe, of which 48.7% were melanomas of uvea, 24.8% melanomas of mucosa and 26.5% adnexal carcinomas of the skin. Five-year relative survival was 40.6% and 68.9% for mucosal and uveal melanomas, respectively. Adnexal skin carcinomas showed a good prognosis with a survival of 87.7% 5 years after diagnosis. Northern Europe, United Kingdom (UK) and Ireland showed the highest 5-year

* *Corresponding author:* Address: Istituto Superiore di Sanità, Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Epidemiologia dei tumori, Viale Regina Elena 299, 00161 Roma, Italy. Tel.: +39 06 49904295; fax: +39 06 49904285.
E-mail address: sandra.mallone@iss.it (S. Mallone).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.10.004

survival rate for uveal melanomas (72.6% and 73.4%), while Southern Europe showed the lowest rate (63.7%). More than 50,000 persons with a past diagnosis of one of these rare cancers were estimated to be alive at 2008 in Europe, most of them (58.8%, $n = 29,676$) being patients with uveal melanoma. Due to the good prognosis and high incidence of uveal melanomas, these malignancies are highly represented among the long-term survivors of the studied rare cancer types. Therefore, maximising quality of life is particularly important in treatment of uveal melanoma. As regards mucosal melanomas, the centralisation of treatment to a select number of specialist centres as well as the establishment of expert pathology panels should be promoted. The geographical differences in incidence and survival should be further investigated analysing the centre of treatment, the stage at diagnosis and the treatment.

1. Introduction

This work is focused on three tumour types which are rare and understudied, thus, poorly understood: uveal and mucosal melanomas, adnexal skin carcinomas. Uveal melanoma is the most common adult intraocular tumour, arising from melanocytes in the uvea. Mucosal melanoma develops in the mucous membrane that lines the nose, mouth, oesophagus, anus, urinary tract and vagina. Adnexal skin tumours are extremely diverse group of neoplasms, arising from cutaneous appendages particularly the sebaceous, apocrine and eccrine glands. Because of their rarity, even the basic descriptive epidemiology of these three tumour types is sparse, restricted to specific anatomic sites and confined to case reports or clinical series. To estimate the cancer burden, the most appropriate data are provided by population-based cancer registries (CRs) which include all cases diagnosed in a well-defined population. The Surveillance of Rare Cancers in Europe[1] (RARECARE) is a large collaboration project of population-based CRs across Europe funded to deal with the issue of rare cancers. The RARECARE working group produced a new list of both rare and common tumours, and developed a new operational definition of rarity. In this work we describe incidence, prevalence and survival patterns in Europe for malignant melanomas of mucosa and uvea, and adnexal skin carcinomas as defined in the RARECARE list of rare tumours.

2. Materials and method

2.1. Data and tumours definition

The RARECARE project extracted data on patients registered by 89 CRs in the period 1978–2002 and followed up for vital status at least to 31st December 2003, from the EUROCARE-4 database.[2] The mean population covered was about 162,000,000 corresponding to 32% of the European population (EU27). Malignant melanoma of mucosa, of uvea and adnexal carcinomas of the skin were drawn from the RARECARE list of tumours defined on the base of morphology and topography codes, according to the third revision of the International Classification of Diseases for Oncology (ICD-O-3).[3] These cancer entities were conceived to be meaningful for clinical decision-making and clinical studies, and identified as rare cancers on the base of their annual incidence rate of less than 6/100,000 per million person-years (pyr). Incidence, which is not affected by variations in life expectancy was considered as a better criterion than prevalence of the burden posed on organisation of health care by rare cancers.

2.2. Statistical analysis

The study was done on 9844 incident malignant cases diagnosed in the period 1995–2002 and registered in 76 CRs. Crude incidence by age as the number of new cases occurring in 1995–2002 divided by the total pyr in the general population (male and female) was obtained restricting the analysis to 8416 cases collected by 64 CRs since we excluded specialised CRs or other not specialised with information available only for some anatomical sites. The European standard population was used to estimate the age-standardised incidence (ASR), overall, by sex and by the following European regions: Northern Europe, Central Europe, Eastern Europe, Southern Europe, United Kingdom (UK) and Ireland.

Relative survival rates were estimated by the period approach[4] in 2000–2002 as the ratio of absolute survival to the expected survival in the general population of the same age and sex. For this analysis, 45 CRs contributing to the considered period were used.

The counting method was applied to 22 CRs which covered the period 1988–2002, choosing 1st January 2003 as reference date, to obtain the observed prevalence[5] of cases diagnosed within 2, 5 and 15 years of the index date. A completeness index was used to estimate the complete prevalence by adding the estimated surviving cases diagnosed prior to 1988 ('unobserved' prevalence) to those counted in 1988–2002[6] (15-year observed prevalence). The completeness indices were obtained by modelling 1985–1999 incidence data with a logistic exponential or polynomial function on age and 1988–1999 survival data with parametric cure models.[7] The expected number of new cases per year and of prevalent cases in Europe (EU27) was calculated by multiplying the incidence and complete prevalence to the 2008 European population (497.5 million) provided by EUROSTAT.[8]

The incidence, survival and prevalence rates and their corresponding standard errors and 95% confidence intervals have been calculated by using SEER*Stat software.[9] We used the SAS software[10] to model incidence and survival data, and the ComPrev software[11] to calculate the completeness index.

Table 1 – Quality indicators of malignant uveal and mucosal melanomas, adnexal skin carcinomas. Cases diagnosed in 76 RARECARE cancer registries[a], between 1995 and 2002.

Cancer entity	Cancer cases (N)	Data quality indicators (%)				Topography codes	Morphology codes
		Death certificate only	Autopsy	Microscopic verification	Cases 1995–1998 censored before 5 years follow-up		
Malignant melanomas							
Mucosa	2335	0.2	0.0	97.3	0.6	All cancer sites except C7–C8, C22, C25, C37–C50, C54, C55.9, C56, C57.0–57.9, C58.9, C60.0–C66.9, C68.1, C68.9, C69.1–C80.9	8720–8780
Uvea	4103	0.3	0.0	77.2	1.0	C69.3–C69.4	8720–8780
Adnexal skin carcinomas	2231	0.0	0.1	99.7	1.2	C44, C63.2	8100–8110, 8200, 8211, 8390–8420, 8480, 8542, 8940

[a] National population covered: Austria, Iceland, Ireland, Malta, Norway, Northern Ireland, Slovakia, Slovenia, Sweden, Scotland and Wales. Variable proportion of national population covered: Belgium, England, France, Germany, Italy, Netherlands, Poland, Portugal, Spain, Switzerland

3. Results

3.1. *Data quality*

Overall, 0.2% of cases were based on death certificate only, while the proportion of cases diagnosed by autopsy was very low, with a maximum of 0.3% for malignant melanomas of uvea (Table 1). About 88.4% of all cases (7664) were microscopically verified, of these 41.3% were uveal melanomas. Less than 1.0% of cases diagnosed between 1995 and 1998 were censored before 5 years of follow-up.

3.2. *Incidence*

Crude overall, sex and age-specific incidence, together with the expected annual number of new cases diagnosed in the EU27 countries are shown in Table 2. The most common tumour was malignant melanomas of uvea with overall crude incidence rates of 5.1 per million pyr, followed by adnexal skin carcinomas (2.8) and malignant melanomas of mucosa (2.6). For mucosal melanomas, the most common sites were the head and neck (40.6%), the female genital tract (36.3%), and the anal canal/colo-rectal tract (18.5%). Incidence showed a positive association with age, with rates of 13.0 for adnexal skin carcinomas, 16.1 and 11.6 for malignant melanomas of uvea and mucosa, respectively, at age 65+. In Europe, about 5200 cases (10.5 per million per year) are expected to receive the diagnosis of one of these rare cancers per year, of which 48.7% are melanomas of uvea, 26.5% are adnexal carcinomas of the skin and 24.8% are melanomas of mucosa. Table 3 shows overall ASR by sex and European region, in 1995–2002. The age-standardised male-to-female ratio ranged between 0.5 (mucosa) and 1.6 (adnexal carcinoma of skin). Considering the geographical variation in ASR, malignant melanomas of uvea was the most common site (4.4 per million) ranging from 3.1 in Southern Europe to 5.8 in Northern Europe (Table 3). For mucosal melanomas, the ASR ranged from 0.9 per million in Eastern Europe to 2.7 in Northern Europe while adnexal skin carcinomas showed a rate which ranged from 1.4 in Central Europe to 4.0 in Northern Europe.

3.3. *Survival*

Table 4 shows the 1- and 5-year observed and relative survival rates overall and by sex, in 2000–2002. One- and five-year relative survival rates for mucosal melanomas were 74.5% and 40.6%, and for uveal melanoma survival rates 95.9% and 68.9%, respectively. Five-year relative survival rates were slightly lower for males than females for melanomas of uvea (66.5% *versus* 71.2%). Fig. 1 shows 5-year relative survival rates by cancer entity and European region. We found a better prognosis 5 years after the diagnosis for mucosal melanomas of female genital tract (43.9%) compared to the ones of head and neck (25.5%) and anal canal/colo-rectal tract (19.0%). The highest 5-year relative survival for mucosal melanomas was observed in Northern Europe (44.8%) and the lowest in Southern (36.2%) and Eastern Europe (37.1%). Survival rates for uveal melanomas ranged from 61.0% in Central Europe to 72.6% in Northern Europe. Adnexal skin carcinomas showed the best overall 5-year relative survival rates (87.7%) ranging from 82.0 in Central Europe to 89.6 in UK and Ireland.

Table 2 – Crude incidence rates (per 1,000,000) of malignant uveal, mucosal melanoma and adnexal carcinoma of the skin, overall and by age in 64 RARECARE cancer registries included in the analysis, in 1995–2002. Estimated incident cases arising in Europe (27 countries) per year.

Cancer entity	Overall			Age (years)								Estimated cancer cases per year in EU (27) at 2008
	Cancer cases	Rate	SE	0–14		15–24		25–64		65+		
				Rate	SE	Rate	SE	Rate	SE	Rate	SE	
Malignant melanomas												
Mucosa	2091	2.60	0.06	0.01	0.01	0.07	0.03	1.43	0.06	11.59	0.30	1293
Uvea	4097	5.09	0.08	0.02	0.01	0.33	0.06	4.72	0.10	16.06	0.36	2533
Adnexal skin carcinoma	2228	2.77	0.06	0.02	0.01	0.10	0.03	1.32	0.06	13.01	0.32	1378

SE = standard error.

3.4. *Prevalence*

Table 5 shows the observed prevalence within 2, 5 and 15 years of 1st January 2003, together with the complete prevalence and the estimated prevalent cancer cases in EU (27). The proportion of patients who were alive and diagnosed with these rare tumours within the 2 and 5 years before the prevalence index date was 18.7% and 40.7%, respectively. The remaining proportion (59.3%) includes patients who had survived at least 5 years after diagnosis of which less than 28% (15,854) had survived more than 15 years after diagnosis, being 70.4% (11,156) uveal melanoma cancer cases. More than 50,000 persons were estimated to be alive at the beginning of 2008 with a past diagnosis of one of these rare cancers, of these 58.8% were uveal melanomas. The most prevalent cancers were uveal melanomas (29,676 cases) followed by adnexal skin carcinomas (13,304 cases) and mucosal melanomas (7485).

4. Discussion

4.1. *Data quality*

Most of the data quality indicators showed acceptably low values indicating a high quality dataset. For uveal melanomas, 22.8% of the cases were not microscopically verified, probably due to the fact that diagnosis is mainly based on ophthalmologic examination followed by skilled ultrasonography, rarely requiring cytologic or histologic confirmation.[12] The proportion of cases with clinical and unknown verification has increased with time in Northern Europe while was stable, but much higher, in the United Kingdom, negligible in Eastern Europe (data not shown).

4.2. *Mucosal melanomas*

Incidence increased with age with a peak in the 65+ as reported in previous studies.[13,14] In United States (US), the head and neck is the most common site of occurrence of mucosal melanoma (55.4% of cases) followed by female genital, anal/rectal, and urinary tract responsible for 18%, 23.8% and 2.8%, respectively.[13] In our dataset, mucosal melanoma has occurred most frequently in the female genital tract (33.7%) and in the head and neck (30.5%). The fact that no single definition has been used to date to identify mucosal melanomas does not allow strict comparison with previous results and the ASR of 2.5 per million among women and 1.3 among men we reported. In a US study done by McLaughlin et al.[14] it has been showed that mucosal melanomas (US population standard in 2000) were more common among women with 2.8 cases per million, than in men with 1.5 cases per million men. Melanomas were identified on the base of the International Classification of Diseases for Oncology, 2nd edition (ICD-O-2) as anorectal, genital, nasal cavity and accessory sinuses, and oral cavity (morphology codes 8720 through 8790). In the Netherlands a recent study reported European ASR of 1.8 cases per million among men and 2.8 cases per million in women, in the period 1989–2006.[15] The authors identified cases of mucosal melanomas of the ear–nose–throat region, genitals, vulva, gastrointestinal tract, lung or urinary tract, on the base of the International Classification of Disease 9th and 10th revision (ICD-9, ICD-10). We observed a very low incidence rate of mucosal melanomas in Eastern Europe. It has been shown that also incidence rates for cutaneous melanomas are low in Eastern Europe but are increasing with time[16] due to either increasing exposure to the sun or increasing ambient solar UV irradiance. To date, light hair and eyes, sunburns, sun exposure, latitude and familial history of melanoma have not been implicated as aetiologic or risk factors for mucosal melanomas. More than 2/3 of head and neck mucosal melanoma are pigmented. In particular, primary oral melanomas may arise from nevi and pigmented areas such as amalgam tattoos, or post inflammatory pigmentations due to tobacco usage or drugs aberrant reactions.[17,18] As neuroectodermal derivates, melanocytes are known to migrate to the skin but much less frequently to ectodermally and endodermally derived mucosa. This may explain the lower frequency of melanoma in these locations. Exposure to formaldehyde and chronic irritants[19] or human papillomavirus[20] has been considered as risk factors which may be associated with mucosal melanoma. However none of these has been further substantiated. Thus, the observed geographical differences in incidence may be more likely due to difficulties in pathological classification which could be reduced by pathology panels. Caution is needed in interpreting the geographical differences we found in survival due to the large variability of the estimated survival rates. Diagnostic delay may be one of the reasons for the lower survival of mucosal melanomas in Eastern and Southern Europe.

Table 3 – Age-standardised incidence rates (per 1,000,000) of malignant uveal, mucosal melanoma and adnexal carcinoma of the skin overall, by sex and European region in 64 RARECARE cancer registries included in the analysis, in 1995–2002. Rates are standardised to the European standard population.

Cancer entity	Incidence																			
	Overall			Sex				European region												
				Male		Female		Northern Europe		Central Europe		Eastern Europe		Southern Europe		UK and Ireland				
	No. of cases	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE			
Malignant melanomas	2091	2.00	0.05	1.33	0.06	2.52	0.07	2.70	0.14	1.96	0.09	0.88	0.11	1.80	0.10	2.09	0.08			
Mucosa	4097	4.39	0.07	4.94	0.11	3.97	0.09	5.81	0.22	3.79	0.14	3.31	0.22	3.13	0.13	5.16	0.13			
Uvea	2228	2.06	0.05	2.63	0.08	1.67	0.06	4.04	0.17	1.41	0.08	1.57	0.14	2.49	0.11	1.55	0.07			
Adnexal skin carcinomas																				

SE = standard error.

4.3. *Uveal melanomas*

For uveal melanomas also, incidence increased noticeably up to age 65. The ASR of 4.4 cases per million for uveal melanomas is in agreement with the results reported by Virgili et al.[21]: from less than 2 cases per million in countries like southern Italy and Spain, to more than 8 cases per million in Norway and Denmark, between 1983 and 1994. The above mentioned study of Mclaughin et al.[14] based on data collected by the North American Association of Central Cancer Registries, showed ASR to the 2000 US population standard of uveal melanomas (ICD-O-2; codes: C69.3, C69.4) of 4.9 per million, between 1996 and 2000. Northern Europe and United Kingdom/Ireland showed the highest ASR for melanomas of uvea, as previously reported.[21,22] The geographical variations in uveal melanomas incidence usually observed have a controversial explanation. Some studies have reported a positive association between sun exposure (or latitude considered as a proxy of solar exposure) and ocular melanoma.[23–25] A US case-control study on uveal melanoma showed an adjusted relative risk of 6.5 for Northern European ancestry as compared with Southern European or other Mediterranean heritage,[26] in accordance with the hypothesis that uveal melanoma is associated with the sun-susceptibility of people with light eye and skin rather than to sunlight exposure. A protective effect of eye/skin colour, darker in Southern Europe and lighter in the North against the direct harmful effect of sunlight, was also found in the study of uveal melanoma incidence in Europe of Virgili et al.[21] and our results of higher incidence in Northern Europe are consistent with this hypothesis. However, some authors[27–29] suggested that the geographical differences observed in uveal melanoma incidence in the US are due to dual effects of ultraviolet exposure rather than eye/skin colour: a mutagenic effect of direct solar radiation on external ocular melanomas and a protective effect for internal uveal melanoma. The survival rates for uveal melanomas confirmed, as previously reported, a peak excess mortality between 2 and 4 years after diagnosis.[30,31] Eskelin et al.[32] suggested that most uveal melanoma metastases are present at time of diagnosis but become clinically detectable within years after uveal melanoma diagnosis. Long term studies have shown that about 70% of patients with monosomy 3 in the primary tumour died from metastases within 4 years after the initial diagnosis, whereas tumours with normal chromosome 3 status rarely gave rise to metastatic disease.[33] The 5-year survival rate of 68.8% is not changed compared to the rate of 68.9% obtained by Virgili et al.[30] for uveal melanoma (ICD9 codes: 1900–1909, ICDO codes: 8720–8780), in the period 1983–1994. In the Netherlands primary ocular melanoma (ICD9-10 codes: 1900–1909, C69), diagnosed in 1989–2006, had the best survival, with a relative 5-year survival of 74%.[15] The Collaborative Ocular Melanoma Study showed a slightly lower estimate of 60%,[34] while the 5-year survival reported by Chang et al.[13] is quite similar (75%). Five-year survival rates for uveal melanomas were better for women than for men and tended to worsen with age. The EUROCARE-4 study found that women have an

Table 4 – One- and five-year observed and relative survival rates by cancer entities, overall and by sex. Period survival analysis 2000–2002 on 46 RARECARE cancer registries.

Cancer entity	Survival								No. of cases analysed
	1-year				5-year				
	Observed (%)	Relative			Observed (%)	Relative			
		(%)	95% CI			(%)	95(%) CI		
			Lower	Upper			Lower	Upper	
Malignant melanomas									
Mucosa									
Male	66.9	70.4	62.4	76.9	32.5	40.9	25.9	39.2	207
Female	72.6	76.1	71.5	80.0	31.8	40.5	27.7	36.1	503
Overall	71.0	74.5	70.6	77.9	32.1	40.6	28.5	35.6	710
Uvea									
Male	92.3	95.4	92.5	97.2	56.3	66.5	61.8	70.8	659
Female	94.1	96.5	93.8	98.0	62.5	71.2	66.7	75.3	666
Overall	93.1	95.9	94.1	97.2	59.4	68.9	65.7	71.9	1319
Adnexal skin carcinomas									
Male	88.4	93.9	89.4	96.5	64.1	86.9	59.2	68.7	423
Female	92.1	98.5	87.8	99.8	64.0	88.9	58.9	68.7	399
Overall	90.1	96.0	92.8	97.8	64.0	87.7	60.5	67.3	820

SE = standard error.
95% CI = 95% confidence intervals.

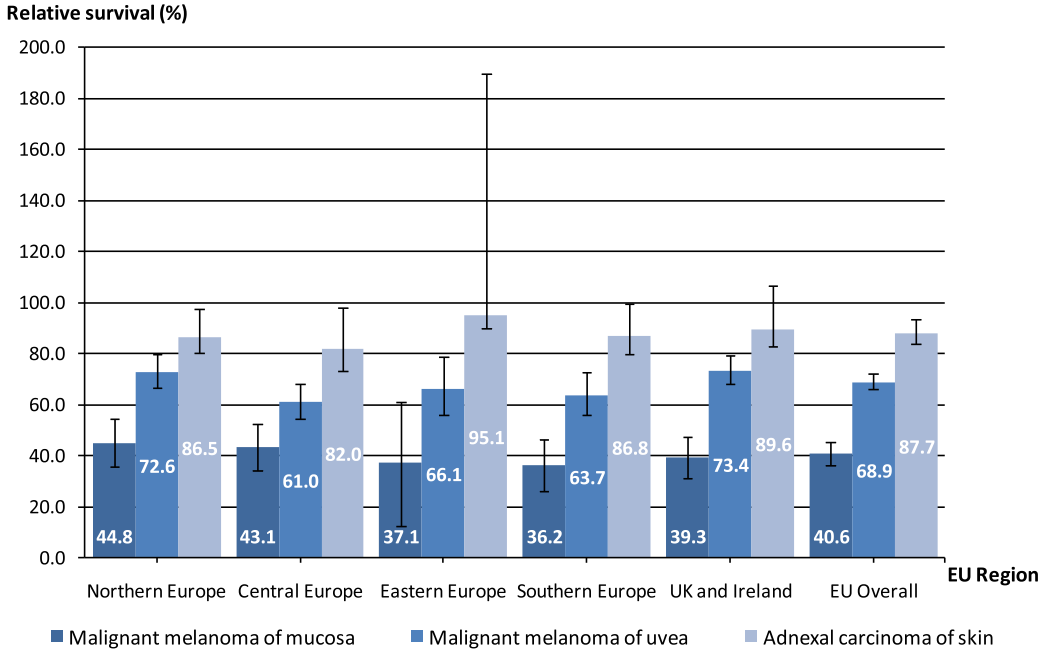

Fig. 1 – Five-year relative survival rates (%) and confidence intervals (95%) of malignant uveal and mucosal melanomas and skin adnexal carcinomas by European region. Period survival analysis 2000–2002 on 46 RARECARE cancer registries.

advantage over men in coping with cancer in general, probably due to lower prevalence of comorbidity, earlier stage at diagnosis than men and biological factors such as hormonal status[35] rather than cultural factors. For cutaneous melanomas in particular, Joosse et al.[36] proposed that gender differences in oxidative stress caused by radical oxygen species (ROS) underlie the observed survival differences. For uveal melanomas, we reported higher 5-year survival rates in Northern Europe and UK and Ireland, in agreement with the results reported by Virgili et al.[30] Clinical factors (i.e. late diagnosis) or different treatment patterns might have affected the estimates of relative survival.

4.4. *Adnexal skin carcinomas*

Our finding of ASR for adnexal carcinomas of the skin of 2.1 per million differs from previously available results. Riou-Gotta et al.[37] reported an ASR of 0.16 (world population) per

Table 5 – Observed prevalence by duration, and complete prevalence (per 1,000,000) of malignant uveal, mucosal melanoma and adnexal carcinoma of the skin in 22 RARECARE cancer registries included in the analysis. Index date at 1st January 2003. Estimated prevalent cases in Europe (27 countries).

Cancer entity	Observed prevalence by duration before 1st January 2003						Complete prevalence at 1st January 2003		Estimated prevalent cancer cases in EU (27) at 2008
	2-year		5-year		15-year				
	Prop.	SE	Prop.	SE	Prop.	SE	Prop.	SE	
Malignant melanomas									
Mucosa	3.95	0.25	7.44	0.40	11.46	0.42	15.05	0.56	7485
Uvea	9.25	0.38	21.18	0.58	41.28	0.80	59.66	1.32	29,676
Adnexal skin carcinomas	5.76	0.30	12.69	0.45	20.49	0.57	26.74	0.77	13,304

SE = standard error.

100,000 for patients recorded in 1980–2003 by the Doubs Cancer Registry. In England an ASR of 0.9 per 100,000 in 2008 was reported for rare malignant skin cancers (ICD10; code C44) with an increase over the past decade. For dermatofibrosarcoma NOS (8832/3), Merkel cell carcinoma (8247/3) and sebaceous adenocarcinoma (8410/3) the ASRs were 0.28, 0.23, 0.11 per 100,000, respectively.[38] In the Netherlands, an ASR of 0.43 per 100,000 was observed during 2001–2005 for the appendageal tumours.[39] For adnexal skin carcinomas, the highest incidence rate of 4.0 per million was observed in Northern Europe. Again ultraviolet exposure, but also previous radiation therapy and genetic predispositions have been postulated as risk factors[40–43] for this cancer. A good prognosis was observed for adnexal skin carcinomas (5-year rate 87.7%). This result is lower than the 5-year relative survival rates of 96.4% reported by Blake et al.[44] for appendageal carcinomas cancer cases diagnosed in US between 1992–1999 and between 2000–2004. The authors suggested that the overall high survival may be in part explained by the fact that most of the cases were diagnosed at a localised stage so with a better prognosis.

5. Conclusions

To our knowledge, prevalence data regarding uveal and mucosal malignant melanomas, and adnexal skin carcinomas are provided for the first time in this work. Although the study is based on historical data, it also provides more up-to-date survival estimates on the base of period survival analysis. In 2008 more than 50,000 persons had one of these rare cancers across Europe. Of these, 58.8% were melanomas of uvea due to its good prognosis and high incidence. The poor prognosis for mucosal melanomas, despite its incidence rate of 4.2 per million, impacts on complete prevalence estimate which was the lowest one. For adnexal carcinoma of skin the quota of prevalent cases at 2008 (26.4%) is similar to the quota of new cases per year (26.5%). This is mainly explained by the good survival rate of 87.7%. Rare cancers described in this study are a heterogeneous group of malignant cancers, with appreciable differences in burden by sex, age and European regions. These differences could be further investigated if CRs collect more information such as the centre of treatment, the stage at diagnosis and the treatment. Due to the good prognosis and high incidence of uveal melanomas, these malignancies are highly represented among the long-term survivors of the studied rare cancer types. Therefore, maximising quality of life is particularly important in treatment of uveal melanoma. As regards mucosal melanomas, the centralisation of treatment to a select number of specialist centres as well as the establishment of expert pathology panels should be promoted.

Funding

This research was supported by the European Commission through the Executive Agency for Health and Consumers (Grant No. 2006113), and the Programma Italia-USA Malattie Rare (Grant No. 526D/42).

Conflict of interest statement

The authors declare no conflicts of interest. The founding sources had no role in study design, data collection, data analysis, data interpretation, in writing this report, or in the decision to submit for publication.

Appendix A. The RARECARE Working Group

Austria: N Zielonk (Austrian National Cancer Registry); *Belgium:* E. Van Eycken (Belgian Cancer Registry); H. Sundseth (European Cancer Patient Coalition); *France:* G. Hedelin (Bas-Rhin Cancer Registry); A.S. Woronoff (Doubs Cancer Registry); A. Buemi (Haut-Rhin Cancer Registry); B. Tretarre (Hérault Cancer Registry); M. Colonna (Isère Cancer Registry); S. Bara (Manche Cancer Registry); O. Ganry (Somme Cancer Registry); P. Grosclaude (Tarn Cancer Registry); *Germany:* B. Holleczek (Saarland Cancer Registry); J. Geissler (CML Advocates Network); *Iceland:* L. Tryggvadottir (Icelandic Cancer Registry); *Ireland:* S. Deady (National Cancer Registry of Ireland); *Italy:* F. Bellù (Alto Adige Cancer Registry); S. Ferretti (Ferrara Cancer Registry); D. Serraino (Friuli Venezia Giulia Cancer Registry); M. Vercelli (Liguria Cancer Registry c/o IST/UNIGE, Genoa); S. Vitarelli (Macerata Province Cancer Registry); M. Federico (Modena Cancer Registry); M. Fusco (Napoli Cancer Registry); M. Michiara (Parma Cancer Registry); A. Giacomin (Piedmont Cancer Registry, Province of Biella); R. Tumino (Cancer Registry and Histopathology Unit, 'M.P. Arezzo' Civic Hospital, Ragusa); L. Mangone (Department of Research Azienda Ospedaliera Arcispedale Santa Maria Nuova – IRCCS, Reggio Emilia); F. Falcini (Romagna Cancer Registry); G. Senatore (Salerno Cancer Registry), M. Budroni (Sassari Cancer Registry); S. Piffer (Trento Cancer Registry); E. Crocetti (Tuscan Cancer Registry); F. La Rosa (Umbria Cancer Registry); P. Contiero (Varese Cancer Registry); P. Zambon (Veneto Cancer Registry); P.G. Casali, G. Gatta, A. Gronchi, L. Licitra, M. Ruzza, S. Sowe, A. Trama (Fondazione IRCCS Istituto Nazionale dei Tumori); R. Capocaccia, R. De Angelis, A. Tavilla (Centro Nazionale di Epidemiologia, Istituto Superiore di Sanità); A.P. Dei Tos (Local Health Unit No. 9, Region of Veneto); *Malta:* K. England (Malta National Cancer Registry); *Norway:* G. Ursin (Cancer Registry of Norway); *Poland:* J. Rachtan (Cracow Cancer Registry); S. Gozdz, (Kielce Cancer Registry); M. Zwierko (Warsaw Cancer Registry); M. Bielska-Lasota (National Institute of Public Health – National Institute of Hygiene, Warsaw); J. Slowinski (Department of Neurosurgery in Sosnowiec, Medical University of Silesia); *Portugal:* A. Miranda (Southern Portugal Cancer Registry); *Slovakia:* Ch. Safaei Diba (National Cancer Registry of Slovakia); *Slovenia:* M. Primic-Zakelj (Cancer Registry of Slovenia); *Spain:* A. Mateos (Albacete Cancer Registry); I. Izarzugaza (Basque Country Cancer Registry); A. Torrella-Ramos (Castillon Cancer Registry); J. Galceran (Tarragona Cancer Registry); C. Martinez-Garcia, M.J. Sanchez Perez, J.M. Melchor (Escuela Andaluza de Salud Pública), A. Cervantes (University of Valencia); *Sweden:* Jan Adolfsson (Stockholm-Gotland Cancer Registry); M. Lambe (Uppsala Regional Cancer Registry); T.R. Möller (Lund University Hospital); Ulrik Ringborg (Karolinska Institute); *Switzerland:* G. Jundt (Basel Cancer Registry); M. Usel, (Geneva Cancer Registry); S.M. Ess (St. Gallen Cancer Registry); A. Spitale (Ticino Cancer Registry); I. Konzelmann (Valais Cancer Registry); J.M. Lutz (National Institute for Cancer Epidemiology and Registration); *The Netherlands:* O. Visser (Amsterdam Cancer Registry); R. Otter, S. Siesling, J.M. van der Zwan (Comprehensive Cancer Centre the Netherlands), H. Schouten (University of Maastricht); *UK England:* D.C. Greenberg (Eastern Cancer Registration and Information Centre); J. Wilkinson (Northern and Yorkshire Cancer Registry); M. Roche (Oxford Cancer Intelligence Unit); D. Meechan (Trent Cancer Registry); G. Lawrence (West-Midlands Cancer Intelligence Unit); M.P. Coleman (London School of Hygiene and Tropical Medicine); J. Mackay (University College of London); *UK-Northern Ireland:* A. Gavin (Northern Ireland Cancer Registry); *UK-Scotland:* D.H. Brewster, R.J. Black (Scottish Cancer Registry); I. Kunkler (University of Edinburgh); *UK-Wales:* C. White (Welsh Cancer Intelligence & Surveillance Unit).

REFERENCES

1. RARECARE. Available from: <http://www.rarecare.eu> [accessed 25.09.11].
2. EUROCARE. Available from: <http://www.eurocare.it/> [accessed 25.09.11].
3. Percy C, Fritz A, Jack A, et al. *International Classification of Diseases for the Oncology (ICD-O)*. 3rd ed. World Health Organisation; 2000.
4. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer* 1996;**78**:2004–10.
5. Capocaccia R, Colonna M, Corazziari I, et al. Measuring cancer prevalence in Europe: the EUROPREVAL Project. *Ann Oncol* 2002;**13**:831–9.
6. Capocaccia R, De Angelis R. Estimating the completeness of prevalence based on cancer registry data. *Stat Med* 1997;**16**:425–40.
7. De Angelis R, Capocaccia R, Hakulinen T, Soderman B, Verdecchia A. Mixture models for cancer survival analysis: application to population-based data with covariates. *Stat Med* 1999;**18**:441–54.
8. EUROSTAT. Available from: <http://epp.eurostat.ec.europa.eu/tgm/refreshTableAction.do;jsessionid=9ea7974b30e8913a6291f74c4afca4aa83e45e410058.e34 SbxiOchiKc40LbNmLahiKb3uQe0?tab= table&plugin=1&pcode=tps00001&language=en> [accessed 02.04.09].
9. NCI. Seer*Stat – surveillance, epidemiology, and end results software. Version 6.6.2. Program of the National Cancer Institute; 2010. Available from: <http://seer.cancer.gov/seerstat/> [released 13.04.10].
10. SAS software. Version 9.1.3. Cary, NC, USA: Statistical Analysis System Institute Inc.; 2003.
11. NCI. ComPrev – complete prevalence software. Version 1.0. Program of the National Cancer Institute; 2005. Available from: <http://surveillance.cancer.gov/comprev/> [released August 2005].
12. COMS, The Collaborative Ocular Melanoma Study Group. Accuracy of diagnosis of choroidal melanoma in the Collaborative Ocular Melanoma Study. COMS report No. 1. *Arch Ophthalmol* 1990;**108**:1268–73.
13. Chang AE, Karnell LH, Menck HR. The national cancer data base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer* 1998;**83**:1664–78.

14. McLaughlin CC, Wu XC, Jemal A, et al. Incidence of noncutaneous melanomas in the US. *Cancer* 2005;**103**:1000–7.
15. Koomen ER, de Vries E, van Kempen LC, et al. Epidemiology of extracutaneous melanoma in the Netherlands. *Cancer Epidemiol Biomarkers Prev* 2010;**19**(6):1453–9.
16. De Vries E, Bray FI, Coebergh JWW, Parkin DM. Changing epidemiology of malignant cutaneous melanoma in Europe 1953–1997: rising trends in incidence and mortality but recent stabilizations in Western Europe and decreases in Scandinavia. *Int J Cancer* 2003;**107**:119–26.
17. Hicks MJ, Flaitz CM. Oral mucosal melanoma: epidemiology and pathobiology. *Oral Oncol* 2000;**36**(2):152–69.
18. Shah JP. *Cancer of head and neck*. Hamilton: BC Decker Inc.; 2001. p. 40–42, 79–80.
19. Holmstrom M, Lund VJ. Malignant melanoma of the nasal cavity after occupational exposure to formaldehyde. *Br J Ind Med* 1991;**48**:9–11.
20. Dahlgren L, Schedvins K, Kanter-Lewensohn L, et al. Human papilloma virus (HPV) is rarely detected in malignant melanomas of sun sheltered mucosal membranes. *Acta Oncol* 2005;**44**:694–9.
21. Virgili G, Gatta G, Ciccolallo L, et al. Incidence of uveal melanoma in Europe. *Opthalmology* 2007;**114**(12):2309–15.
22. Stang A, Parkin DM, Ferlay J, Jockel KH. International uveal melanoma incidence trends in view of a decreasing proportion of morphological verification. *Int J Cancer* 2005;**114**(1):114–23.
23. Vajdic CM, Kricker A, Giblin M, et al. Sun exposure predicts risk of ocular melanoma in Australia. *Int J Cancer* 2002;**101**:175–82.
24. Lutz JM, Cree I, Sabroe S, et al. Occupational risks for uveal melanoma results from a case-control study in nine European countries. *Cancer Causes Control* 2005;**16**:437–47.
25. Guenel P, Laforest L, Cyr D, et al. Occupational risk factors, ultraviolet radiation, and ocular melanoma: a case-control study in France. *Cancer Causes Control* 2001;**12**:451–9.
26. Seddon JM, Gragoudas ES, Glynn RJ, et al. Host factors, UV radiation, and risk of uveal melanoma. A case-control study. *Arch Ophthalmol* 1990;**108**:1274–80.
27. Hu D, Yu G, McCormick SA, et al. Population-based incidence of uveal melanoma in various races and ethnic groups. *Am J Ophthalmol* 2005;**140**:612–7.
28. Hu DN, McCormick SA, Yu GP. Letter to the editor – latitude and uveal melanoma. *Ophthalmology* 2008;**115**(4):757.
29. Yu GP, Hu DN, McCormick SA. Latitude and incidence of ocular melanoma. *Photochem Photobiol* 2006;**82**:1621–6.
30. Virgili G, Gatta G, Ciccolallo L, et al. Survival in patients with uveal melanoma in Europe. *Arch Ophthalmol* 2008;**126**(10):1413–8.
31. Bergman L, Seregard S, Nilsson B, et al. Uveal melanoma survival in Sweden from 1960 to 1998. *Invest Ophthalmol Vis Sci* 2003;**44**(8):3282–7.
32. Eskelin S, Pyrhönen S, Summanen P, et al. Tumor doubling times in metastatic malignant melanoma of the uvea: tumor progression before and after treatment. *Ophthalmology* 2000;**107**:1443–9.
33. Midena E, Bonaldi L, Parrozzani R, et al. In vivo monosomy 3 detection of posterior uveal melanoma: 3-year follow-up. *Graefes Arch Clin Exp Ophthalmol* 2008;**246**:609–14.
34. Thoelke A, Willrodt S, Hauschild A, Schadendorf D. Primary extracutaneous malignant melanoma: a comprehensive review with emphasis on treatment. *Onkologie* 2004;**27**:492–9.
35. Micheli A, Ciampichini R, Oberaigner W, et althe EUROCARE Working Group. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. *Eur J Cancer* 2009;**45**:1017–22.
36. Joosse A, De Vries E, van Eijck CH, et al. Reactive oxygen species and melanoma: an explanation for gender differences in survival? *Pigment Cell Melanoma Res* 2010;**23**(3):352–64.
37. Riou-Gotta MO, Fournier E, Danzon A, et al. Rare skin cancer: a population-based cancer registry descriptive study of 151 consecutive cases diagnosed between 1980 and 2004. *Acta Oncol* 2009;**48**(4):605–9.
38. South West Public Health Observatory. Rare skin cancer in England. NCIN. Available from: <http://www.swpho.nhs.uk/skincancerhub>.
39. Holterhues C, De Vries E, Louwman MW, Koljenović S, Nijsten T. Incidence and trends of cutaneous malignancies in the Netherlands, 1989–2005. *J Invest Dermatol* 2010;**130**:1807–12.
40. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B* 2001;**63**(1–3):8–18.
41. Chiller K, Passaro D, Scheuller M, et al. Microcystic adnexal carcinoma: forty-eight cases, their treatment, and their outcome. *Arch Dermatol* 2000;**136**(11):1355–9.
42. Abbate M, Zeitouni NC, Seyler M, et al. Clinical course, risk factors, and treatment of microcystic adnexal carcinoma: a short series report. *Dermatol Surg* 2003;**29**(10):1035–8.
43. Amis Jr ES, Butler PF, Applegate KE, et al. American College of Radiology. American College of Radiology white paper on radiation dose in medicine. *J Am Coll Radiol* 2007;**4**(5):272–84.
44. Blake PW, Bradford PT, Devesa SS, Toro JR. Cutaneous appendageal carcinoma incidence and survival patterns in the United States: a population-based study. *Arch Dermatol* 2010;**146**(6):625.