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Original research

Skin melanoma survival is improving in Europe but regional differences persist: Results of the EUROCARE-6 study

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ABSTRACT

Background: The aim of this study was to update previous EUROCARE survival estimates for skin melanoma (SM) monitoring trends and survival differences between European regions.
Methods: 1-year, 5-year, and 5-year/1-year conditional age-standardised relative survival (ASRS) and geographical comparisons were estimated on 280,498 patients participating in the EUROCARE-6 project (>=15 years old) with invasive SM (diagnosed 2008–2013; followed-up till 2014), applying a complete cohort approach. Survival time trends during 2003–2011 were analysed using the period approach for 306,715 patients. Survival analysis was estimated by age, gender, anatomical sub-sites and morphology subgroups.
Results: Among European patients 5-year ASRS estimate was 87.9 % (95 % confidence interval, CI 87.7–88.1 %). The highest values were measured in Central Europe (91.2 %; 90.9–91.6 %), Northern Europe (90.3 %; 89.7–90.9 %), Ireland and United Kingdom (89.2 %; 88.9–89.6 %), followed by Southern Europe (85.7 %; 85.2–86.2 %), while the lowest survival value was observed in Eastern Europe (75.0 %; 74.2–75.7 %). Within

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regions, the intercountry absolute difference in 5-year ASRS percentage points varied from 2.9 % (Northern Europe) to 24.7 % (Eastern Europe). Five-year RS was higher in women than men and decreased with patients' advancing age. Differences emerged in terms of SM morphology and skin sub-sites. Survival slightly increased from 2003 to 2011, with a small improvement in Northern and the most pronounced one in Eastern Europe.
Discussion: In Europe SM survival is high and still increasing. The gap between European average survival value and Eastern European countries is still present and has not diminished significantly yet. Improvements are needed in the whole SM clinical path, from diagnosis to therapy, to overcome differences across countries.

1. Introduction

According to the most up-to-date available estimates, incidence and mortality for skin melanoma (SM), for both women and men, vary widely across Europe. In 2022, age-adjusted incidence rates ranged from about 50 per 100,000 people in Denmark, Sweden and the Netherlands to about 10 per 100,000 in Spain, Portugal, Poland and Bulgaria [1]. A similar pattern was observed for mortality, but incidence to mortality ratio was between 5 and 10, due to the relatively good prognosis of this neoplasm [1].

During the last 50 years, population-based SM survival has increased steadily in Northern Europe [2], with improvements also recently found by several other European countries [3–7]. Such improvement has been driven by earlier diagnosis with associated earlier disease stage. In the more recent years, further contribution to advancements in SM survival has come from the introduction of targeted therapy with BRAF/MEK, BRAF inhibitors, and inhibitors of immune checkpoints [2,5,7–9].

Increases in survival due to earlier stage at diagnosis may to some extent be associated with over-diagnosis (i.e. the diagnosis of indolent lesions that would not have put in danger the life of patients) [10]. Nonetheless, persistent differences in SM mortality across Europe show the need for amelioration. Improvement in SM earlier diagnosis, treatment and survival outcomes has been variable between European countries. For SM cases diagnosed in 2000–2007, a previous EUROCARE study found that 5-year relative survival (RS) in Eastern European countries was about 11 percentage points lower than the European average [11]. More recently, SM prognosis has increased in some Eastern European countries (i.e. Estonia [12] and Hungary [13]), but not in others (i.e. Ukraine [14]). Indeed, SM population-based mortality is still increasing in Lithuania [15], Ukraine [14] and Poland [16]. The higher risk-fatality rates observed in Central and Eastern European countries have been considered the effect of disparities along the whole melanoma diagnostic and treatment path [17].

The aim of the present EUROCARE-6 study is to provide updated SM survival estimates by different subsites and morphological groups in adults, focusing on geographical, sex and age differences across Europe.

2. Material and methods

The methodology of the EUROCARE project was widely described elsewhere [18].

For the main analysis, 286,301 adult patients (>= 15 years) with first invasive SM (topography C440-C449 and morphology 8720–8790 ICDO-3 codes) [19] diagnosed in 2008–2013 were provided by 98 cancer registries (CRs) from 29 European countries participating in the EUROCARE-6 project. During quality checks, we excluded cases with major errors (348 cases, 0.1 %), those diagnosed from death certification only (DCO) (1047, 0.4 %), incidentally discovered at autopsy (38, 0.0 %) and cases with zero survival time (1031, 0.4 %) (globally 2464 patients) (Table 1). In addition, 3339 cases of multiple melanomas were removed. Therefore, the main analysis included 280,498 patients (complete cohort approach; analysis for topography). Besides, data from 61 of the 98 CRs with adequate morphology completeness (i.e., proportion of not otherwise specified (NOS) SM < 30 %) were included in the specific survival analyses (complete cohort approach; analysis for morphology; 182,956 patients included). Moreover, for survival trends we analysed 306,715 cases provided by 71 out of 98 CRs with data for the period 2003–2011 (period approach).

Data were analysed for single Europe countries and for 5 geographical regions: Northern Europe, including 4 CRs, Ireland and UK (5 CRs), Central Europe (29 CRs), Southern Europe (53 CRs) and Eastern Europe (7 CRs). Table 1 shows cases included in the survival analyses by registry, European country and region.

The following morphological groups (with corresponding ICD0–3 codes) were considered: superficial spreading melanoma (SSM, 8743), lentigo maligna (LM, 8742), nodular melanoma (NM, 8721), other specified types (8722–3, 8720, 8730, 8740–1, 8744–6, 8761, 8770–4, 8780) and SM NOS (8720).

Concerning topography, the following groups (with corresponding codes) were considered: head and neck (C44.0-C44.4), trunk (C44.5), limbs (C44.6-C44.7), overlapping (C44.8) and not specified sites (C44.9), the two latter included in NOS group.

2.1. Statistical analysis

We estimated RS for cases diagnosed with SM in 2008–2013 and followed-up for vital status to the end of 2014, applying the complete cohort approach [20] and 5-year survival trends in 2003–2011, using period approach for the three follow-up periods: 2003–2005, 2006–2008 and 2009–2011, based on cases diagnosed in 1999–2005, 2001–2008, and 2004–2011, respectively [18,20,21].

We computed age-specific, crude (i.e., unstandardised) and 1-year, 5-year age-standardised (using the Corazziari standard population) [22] relative survival (ASRS) and 5-year ASRS conditional to surviving 1 year (5-year/1-year ratio). We estimated expected survival using the Ederer II method.

3. Results

On average only 0.1 % of the cases were excluded due to major errors. Considering the European region, this value ranged from 0.0 % for Ireland and UK to 0.2 % in Central Europe. Also, for single CRs, the proportion of major errors was very small, ranging from 0 % to a maximum of 2.9 %. The European average proportion of cases known from DCO was 0.4 % (range 0.0 %-3.0 %) and from autopsy was 0.0 % (range 0.0 %-0.3 %). Furthermore, the proportion of alive cases with zero survival time was small on average (0.4 %) but showed slightly higher values in some French registries (Table 1). Quality checks showed a high proportion of microscopically verified (MV) cases, 97.4 % (with a single low value, 68.5 % in a German CR) (Table 1).

Data from 98 registries for topography and 61 out of 98 for morphology distribution were analysed among women and men (Table 2).

Overall, in Europe analysis by anatomical site (280,498 cases) found 44.3 % of the SM cases located on the limbs, 34.6 % on the trunk, 15.4 % on head and neck and 5.7 % on NOS sites (Table 2). Higher-than-average European proportion of cases on the limbs were reported in Ireland and UK (48.3 %) and Central Europe (47.0 %), on the trunk in Northern (40.4 %), Southern (35.9 %) and Eastern Europe (39.4 %), on the head and neck in Ireland and UK (19.1 %) and overlapping and not specified sites in Southern Europe (13.9 %).

As regards to morphology, 182,956 cases were analysed (Table 2). In

Table 1
Quality indicators for skin melanoma cases (2008–2013) and number of cases included in the survival analyses, by registry, European country and region.

Cancer registry	Number of cases	Cases excluded from survival analysis								Multiple melanomas	Cases eligible for survival analysis	Quality indicators			
		Major errors		DCO		Autopsy		Alive with zero survival time				Microscopical verified		Unspecified morphology (NOS)	
	N	N	%	N	%	N	%	N	%	N	N	N	%	N	%
Northern Europe	**29,791**	**62**	**0.21**	**0**	**0.0**	**2**	**0.0**	**1**	**0.0**	**385**	**29,341**	**29,670**	**99.6**	**10,297**	**34.6**
Denmark	12,170	0	0.00	0	0.0	0	0.0	1	0.0	0	12,169	12,119	99.6	1769	14.5
Finland	7451	27	0.36	0	0.0	1	0.0	0	0.0	37	7386	7418	99.6	6289	84.7
Iceland	263	0	0.00	0	0.0	0	0.0	0	0.0	0	263	263	100.0	47	17.9
Norway	9907	35	0.35	0	0.0	1	0.0	0	0.0	348	9523	9870	99.6	2192	22.2
Ireland and UK	**79,828**	**3**	**0.00**	**113**	**0.1**	**0**	**0.0**	**0**	**0.0**	**1519**	**78,193**	**78,714**	**98.6**	**20,531**	**25.8**
Ireland	4140	0	0.00	1	0.0	0	0.0	0	0.0	47	4092	4135	99.9	1439	34.8
UK, England	63,266	3	0.00	104	0.2	0	0.0	0	0.0	1184	61,975	62,245	98.4	17,304	27.4
UK, Northern Ireland	1896	0	0.00	0	0.0	0	0.0	0	0.0	16	1880	1889	99.6	137	7.2
UK, Scotland	7086	0	0.00	1	0.0	0	0.0	0	0.0	214	6871	7075	99.8	804	11.3
UK, Wales	3440	0	0.00	7	0.2	0	0.0	0	0.0	58	3375	3370	98.0	847	24.7
Central Europe	**105,421**	**246**	**0.23**	**780**	**0.7**	**2**	**0.0**	**608**	**0.6**	**1079**	**102,706**	**100,169**	**95.0**	**24,013**	**23.1**
Austria	7150	0	0.00	207	2.9	0	0.0	0	0.0	0	6943	6624	92.6	4766	68.6
Belgium	13,024	0	0.00	0	0.0	0	0.0	31	0.2	190	12,803	12,984	99.7	4537	34.9
France	15,295	0	0.00	0	0.0	0	0.0	271	1.8	0	15,024	15,021	98.2	1333	8.9
Bas Rhin	1499	0	0.00	0	0.0	0	0.0	17	1.1	0	1482	1480	98.7	258	17.4
Calvados	667	0	0.00	0	0.0	0	0.0	2	0.3	0	665	665	99.7	86	12.9
Doubs	668	0	0.00	0	0.0	0	0.0	0	0.0	0	668	668	100.0	48	7.2
Gironde	1758	0	0.00	0	0.0	0	0.0	76	4.3	0	1682	1682	95.7	104	6.2
Haut-Rhin	1106	0	0.00	0	0.0	0	0.0	0	0.0	0	1106	1106	100.0	116	10.5
Herault	883	0	0.00	0	0.0	0	0.0	19	2.2	0	864	864	97.8	145	16.8
Isere	1600	0	0.00	0	0.0	0	0.0	19	1.2	0	1581	1581	98.8	126	8.0
Lille et sa region	710	0	0.00	0	0.0	0	0.0	6	0.8	0	704	703	99.0	37	5.3
Limousin	391	0	0.00	0	0.0	0	0.0	4	1.0	0	387	387	99.0	31	8.0
Loire Atlantique	2678	0	0.00	0	0.0	0	0.0	55	2.1	0	2623	2623	97.9	152	5.8
Manche	526	0	0.00	0	0.0	0	0.0	3	0.6	0	523	523	99.4	39	7.5
Poitou-Charentes	1998	0	0.00	0	0.0	0	0.0	66	3.3	0	1932	1932	96.7	111	5.7
Somme	433	0	0.00	0	0.0	0	0.0	3	0.7	0	430	430	99.3	36	8.4
Tarn	378	0	0.00	0	0.0	0	0.0	1	0.3	0	377	377	99.7	44	11.7
Germany	36,718	6	0.02	571	1.6	2	0.0	285	0.8	0	35,854	32,575	88.7	9599	26.8
Bremen	845	0	0.00	7	0.8	0	0.0	8	0.9	0	830	828	98.0	207	24.9
4 Federal States (BR,MW-P,SA, THU)§	12,660	0	0.00	158	1.2	0	0.0	0	0.0	0	12,502	12,482	98.6	3057	24.5
Hamburg	1751	6	0.34	36	2.1	0	0.0	0	0.0	0	1709	1707	97.5	830	48.6
Niedersachsen (Lower Saxony)	11,165	0	0.00	187	1.7	0	0.0	139	1.2	0	10,839	7643	68.5	2239	20.7
Rhineland-Palatinate	5857	0	0.00	137	2.3	2	0.0	83	1.4	0	5635	5609	95.8	2067	36.7
Saarland	1062	0	0.00	2	0.2	0	0.0	11	1.0	0	1049	1048	98.7	212	20.2
Schleswig-Holstein	3378	0	0.00	44	1.3	0	0.0	44	1.3	0	3290	3258	96.4	987	30.0
Switzerland	3232	14	0.43	2	0.1	0	0.0	21	0.6	67	3128	3192	98.8	625	19.6
Friburg	481	14	2.91	0	0.0	0	0.0	0	0.0	17	450	467	97.1	70	15.0
Geneva	963	0	0.00	0	0.0	0	0.0	0	0.0	43	920	962	99.9	124	12.9
Graubunden (Grison) and Glarus	405	0	0.00	0	0.0	0	0.0	7	1.7	0	398	398	98.3	78	19.6
St. Gallen	916	0	0.00	2	0.2	0	0.0	14	1.5	0	900	899	98.1	238	26.4
Ticino	467	0	0.00	0	0.0	0	0.0	0	0.0	7	460	466	99.8	115	24.6
The Netherlands*	30,002	226	0.75	0	0.0	0	0.0	0	0.0	822	28,954	29,773	99.2	3153	10.6
Southern Europe	**33,807**	**32**	**0.09**	**50**	**0.1**	**1**	**0.0**	**96**	**0.3**	**8**	**33,620**	**33,241**	**98.3**	**11,208**	**33.3**
Croatia	2901	0	0.00	0	0.0	0	0.0	42	1.4	3	2856	2859	98.6	2565	89.7
Cyprus	374	3	0.80	5	1.3	0	0.0	0	0.0	1	365	365	97.6	124	33.9
Italy	19,698	0	0.00	30	0.2	1	0.0	43	0.2	0	19,624	19,328	98.1	4542	23.1
Alto Adige	387	0	0.00	0	0.0	0	0.0	0	0.0	0	387	385	99.5	10	2.6
Bari-Trani	262	0	0.00	0	0.0	0	0.0	0	0.0	0	262	259	98.9	28	10.7
Basilicata	176	0	0.00	0	0.0	0	0.0	1	0.6	0	175	164	93.2	33	18.9
Bergamo	1018	0	0.00	1	0.1	0	0.0	0	0.0	0	1017	1016	99.8	170	16.7
Biella	210	0	0.00	1	0.5	0	0.0	3	1.4	0	206	206	98.1	12	5.8
Brescia	599	0	0.00	0	0.0	0	0.0	0	0.0	0	599	595	99.3	167	27.9
Catania-Messina-Enna	1052	0	0.00	2	0.2	0	0.0	0	0.0	0	1050	1041	99.0	139	13.2
Como	503	0	0.00	1	0.2	0	0.0	0	0.0	0	502	500	99.4	65	12.9
Cremona	131	0	0.00	0	0.0	0	0.0	1	0.8	0	130	127	96.9	38	29.2
Ferrara	228	0	0.00	0	0.0	0	0.0	0	0.0	0	228	228	100.0	40	17.5
Firenze-Prato	1051	0	0.00	0	0.0	0	0.0	12	1.1	0	1039	1010	96.1	197	19.0
Friuli Venezia Giulia	845	0	0.00	0	0.0	0	0.0	3	0.4	0	842	841	99.5	364	43.2

(*continued on next page*)

Europe the most frequent proportion of MV cases was SSM (58.4 %), followed by NM (12.6 %), LM (6.4 %) and other specified types (2.6 %). These proportions were generally similar across European regions, apart from a high proportion of NM (24.1 %) in Eastern countries. The proportion of SM MV but histologically NOS was 19.9 %, ranging from 15.0 % in Central Europe to 25.7 % in Ireland and UK.

Five-year ASRS for women and men diagnosed during 2008–2013 was reported by country and region (Fig. 1; Supplementary Material Table 1).

Five-year ASRS for Europe overall was 87.9 % (95 % CI 87.7–88.1 %), with values over 90 % observed in Central (91.2 %; 90.9–91.6 %) and Northern Europe (90.3 %; 89.7–90.9 %), 89.2 % (88.9–89.6 %) in Ireland and UK, 85.7 % (85.2–86.2 %) in Southern Europe and 75.0 % (74.2–75.7 %) in Eastern European countries with the lowest ASRS found in Bulgaria (60.4 %; 57.8–63.0 %). Five-year ASRS for SM in Eastern countries was 12.9 percentage points lower that the European average. The range of 5-year ASRS between countries within European regions was lowest in the Northern European region (absolute difference between highest and lowest survival rates among countries in the region equal to 2.9 percentage points) with heterogeneity within regions increasing from Ireland and UK (5.7 %), Central (6.4 %), Southern (8.2 %) and Eastern (24.7 %) Europe.

One-year ASRS for Europe overall was very high at 96.9 % (95 % CI 96.8–96.9 %) with only a few countries in Eastern Europe with 1-year ASRS below 90 % (Bulgaria 86.5 %, Latvia 89.1 %, Poland 89.5 %) (Supplementary Material Table 1). Five-year ASRS improved on average of 3 % points for patients who survived the first year after diagnosis (5-year/1-year conditional ASRS). The improvement was around 2.0–2.5 % for Northern, Ireland and UK and Central European countries, 3.7 % in Southern European countries but 6.6 % in Eastern Europe ones.

One-, 3- and 5-year crude observed, and RS were reported by age-groups and sex (Table 3). Women had higher overall 1-year RS (97.4

Table 1 (*continued*)

Cancer registry	Number of cases	Cases excluded from survival analysis								Multiple melanomas	Cases eligible for survival analysis	Quality indicators			
		Major errors		DCO		Autopsy		Alive with zero survival time				Microscopical verified		Unspecified morphology (NOS)	
Genova	586	0	0.00	0	0.0	0	0.0	0	0.0	0	586	579	98.8	93	15.9
Latina	499	0	0.00	2	0.4	0	0.0	4	0.8	0	493	455	91.2	89	18.1
Lodi	211	0	0.00	0	0.0	0	0.0	0	0.0	0	211	209	99.1	60	28.4
Mantova	186	0	0.00	0	0.0	0	0.0	0	0.0	0	186	186	100.0	96	51.6
Modena	728	0	0.00	0	0.0	0	0.0	0	0.0	0	728	722	99.2	78	10.7
Monza e Brianza	742	0	0.00	0	0.0	0	0.0	0	0.0	0	742	689	92.9	162	21.8
Napoli	784	0	0.00	1	0.1	0	0.0	0	0.0	0	783	780	99.5	87	11.1
Nuoro	65	0	0.00	0	0.0	0	0.0	0	0.0	0	65	64	98.5	10	15.4
Palermo	656	0	0.00	7	1.1	0	0.0	1	0.2	0	648	622	94.8	197	30.4
Parma	618	0	0.00	1	0.2	0	0.0	0	0.0	0	617	617	99.8	17	2.8
Piacenza	317	0	0.00	0	0.0	0	0.0	2	0.6	0	315	299	94.3	64	20.3
Ragusa	273	0	0.00	1	0.4	0	0.0	0	0.0	0	272	271	99.3	51	18.8
Reggio Emilia	615	0	0.00	1	0.2	0	0.0	0	0.0	0	614	612	99.5	62	10.1
Romagna	1688	0	0.00	3	0.2	0	0.0	0	0.0	0	1685	1667	98.8	120	7.1
Salerno	334	0	0.00	0	0.0	0	0.0	13	3.9	0	321	315	94.3	95	29.6
Sassari	174	0	0.00	0	0.0	0	0.0	0	0.0	0	174	168	96.6	60	34.5
Siracusa	175	0	0.00	1	0.6	0	0.0	0	0.0	0	174	174	99.4	23	13.2
Sondrio	173	0	0.00	0	0.0	0	0.0	0	0.0	0	173	173	100.0	39	22.5
Taranto	361	0	0.00	1	0.3	0	0.0	0	0.0	0	360	359	99.4	112	31.1
Trapani	153	0	0.00	0	0.0	0	0.0	3	2.0	0	150	150	98.0	20	13.3
Trento	215	0	0.00	0	0.0	0	0.0	0	0.0	0	215	215	100.0	45	20.9
Umbria	958	0	0.00	0	0.0	0	0.0	0	0.0	0	958	937	97.8	294	30.7
Varese	799	0	0.00	1	0.1	1	0.1	0	0.0	0	797	788	98.6	132	16.6
Veneto	1711	0	0.00	5	0.3	0	0.0	0	0.0	0	1706	1695	99.1	1253	73.4
Viterbo	215	0	0.00	1	0.5	0	0.0	0	0.0	0	214	210	97.7	20	9.3
Malta	292	0	0.00	0	0.0	0	0.0	0	0.0	1	291	292	100.0	104	10400.0
Portugal	3618	10	0.28	0	0.0	0	0.0	11	0.3	0	3597	3518	97.2	1832	50.9
Central Portugal	443	2	0.45	0	0.0	0	0.0	0	0.0	0	441	401	90.5	300	68.0
Northern Portugal	739	8	1.08	0	0.0	0	0.0	0	0.0	0	731	704	95.3	344	47.1
Southern Portugal	2436	0	0.00	0	0.0	0	0.0	11	0.5	0	2425	2413	99.1	1188	49.0
Slovenia	2399	1	0.04	0	0.0	0	0.0	0	0.0	0	2398	2398	100.0	923	38.5
Spain	4525	18	0.40	15	0.3	0	0.0	0	0.0	3	4489	4481	99.0	1118	24.9
Balearic Islands	375	8	2.13	1	0.3	0	0.0	0	0.0	0	366	366	97.6	105	28.7
Basque Country	1254	6	0.48	4	0.3	0	0.0	0	0.0	0	1244	1243	99.1	453	36.4
Canarie	623	4	0.64	0	0.0	0	0.0	0	0.0	2	617	618	99.2	128	20.7
Castellon	256	0	0.00	1	0.4	0	0.0	0	0.0	0	255	254	99.2	81	31.8
Girona	437	0	0.00	3	0.7	0	0.0	0	0.0	0	434	431	98.6	47	10.8
Granada	524	0	0.00	0	0.0	0	0.0	0	0.0	0	524	522	99.6	75	14.3
Murcia	457	0	0.00	1	0.2	0	0.0	0	0.0	0	456	455	99.6	88	19.3
Navarra	250	0	0.00	0	0.0	0	0.0	0	0.0	1	249	249	99.6	97	38.8
Tarragona	349	0	0.00	5	1.4	0	0.0	0	0.0	0	344	343	98.3	44	12.8
Eastern Europe	**37,454**	**5**	**0.01**	**104**	**0.3**	**33**	**0.1**	**326**	**0.9**	**348**	**36,638**	**36,959**	**98.7**	**19,975**	**54.0**
Bulgaria	2793	0	0.00	84	3.0	0	0.0	0	0.0	3	2706	2709	97.0	1955	72.2
Czech Republic	12,651	2	0.02	0	0.0	32	0.3	127	1.0	286	12,204	12,490	98.7	3910	31.3
Estonia	956	0	0.00	10	1.0	1	0.1	0	0.0	0	945	918	96.0	400	42.3
Latvia	1128	0	0.00	0	0.0	0	0.0	0	0.0	5	1123	1128	100.0	489	43.4
Lithuania	1485	1	0.07	0	0.0	0	0.0	5	0.3	0	1479	1479	99.6	525	35.5
Poland	16,323	2	0.01	0	0.0	0	0.0	194	1.2	37	16,090	16,127	98.8	12,342	76.5
Slovakia	2118	0	0.00	10	0.5	0	0.0	0	0.0	17	2091	2108	99.5	354	16.8
Europe	**286,301**	**348**	**0.12**	**1047**	**0.4**	**38**	**0.0**	**1031**	**0.36**	**3339**	**280,498**	**278,753**	**97.4**	**86,024**	**30.3**

§Four Federal States: Brandenburg, Mecklenburg-Western Pomerania and the Free States of Saxony and Thuringia.
*Most of major errors are incomplete information for immigrant citizens.

women vs 95.5 % men), 3-year RS (92.6 vs 87.7 %), and 5-year RS (89.8 vs 83.6 %) compared to men and across age-groups. The proportion of women in the study cohort was 51.8 %, with higher values in younger patients (15–44 years: females 63.1 %) but lower values in older patients (65–74 years: females 43.8 %). Five-year age-specific RS decreased with advancing age varying from 93.7 % (95 % CI 93.4–94.0 %) for patients aged 15–44 years to 77.2 % (95 % CI 76.4–78.0 %) for those 75 + years old.

Regarding topography, 5-year ASRS was generally slightly higher for SM of the limbs (Europe average 92.2 %; 95 % CI 91.9–92.5 %) than for trunk (89.8 %; 95 % CI 89.4–90.2 %), head and neck (87.1 %; 95 % CI 86.4–87.8 %) and especially for not specified sites (66.6 %; 95 % CI 65.1–68.1 %) (Fig. 2). This pattern was found in all the European regions. Notably, for all anatomical locations the 5-year ASRS was lowest in Eastern European countries (data not shown). Women had a better 5-year ASRS than men in all European regions for all SM anatomical sites: limbs (94.0 %; 95 % CI 93.6–94.4 % vs 88.5 %; 95 % CI 87.9–89.1 %), trunk (90.4 %; 95 % CI 89.7–91.1 % vs 89.1 %; 95 % CI 88.6–89.6 %), head and neck (91.1 %; 95 % CI 90.2–92.0 % vs 84.0 %; 95 % CI 83.0–85.0 %) and NOS (70.7 %; 95 % CI 68.7–72.7 % vs 62.3 %; 95 % CI 60.2–64.4 %) (Fig. 2).

Regarding morphology, the highest 5-year ASRS (men and women) for LM was in Southern (ASRS>100.0 %) and Central Europe (98.6 %; 95 % CI 97.2–100.0 %), while for SSM in Central Europe (96.4 %; 95 % CI 96.0–96.8 %), Ireland and UK (95.5 %; 95 % CI 95.0–96.0 %) and Northern Europe (96.1 %; 95 % CI 95.3–96.9 %), while in Eastern SSM survival was 89.3 % (95 % CI 86.4–92.2 %) (Fig. 3). For all morphologies, globally considered, women had better survival than men. This result was confirmed across all European regions.

Five-year ASRS trends for the periods 2003–2005, 2006–2008 and 2009–2011 (Fig. 4) were evaluated. The average European SM survival improved from 83.0 % (95 % CI 82.7–83.3 %) in 2003–2005 to 87.3 % (95 % CI 87.1–87.5 %) in the 2009–2011. This improvement was found in all the European regions, with an absolute improvement between 2009–2011 and 2003–2005 of 2.9 % for Central Europe, 2.5 % for Northern Europe, 3.1 % for Southern Europe, 4.7 % for Ireland and UK and 4.7 % for Eastern Europe (average improvement 4.3 %).

4. Discussion

The present study provides European SM updated survival estimates by topography and morphology based on almost 300,000 SM patients of the EUROCARE-6 database.

The results, supported by data from 98 CR in 29 countries, found that for patients diagnosed in 2008–2013, the European average 5-year ASRS was 87.9 % (95 % CI 87.7–88.1 %). These overall European survival rates were lower than those reported by US SEER (93.6 %; 95 % CI 93.0–94.1 %; cases diagnosed in 2015), although the current study covers an earlier period [23]. Data from three Australian CRs (cases diagnosed in 2007–2011) also showed slightly higher survival rates for both men (84.9 %; 85 %-91 %) and women (90.4 %;93 %-95 %) [24]. When evaluating these data, the effect of using different standard populations should be keep in mind.

However, several individual European countries from Central and Northern Europe and UK and Ireland show some of the highest SM RS rates in the world [25]. In fact, observed 5-year ASRS was above or around 90 % in Central (with the highest RS in Switzerland, at 92.9 %) and Northern Europe (91.7 % in Denmark) and Ireland and UK (92.5 % in Northern Ireland and 92.3 % in Scotland), with rates of 85.7 % in Southern (87.2 % in Italy and 87.1 % Spain) but only 75.0 % in Eastern Europe.

The 5-year European ASRS reported here (cases diagnosed in 2008–2013) was 4.7 % higher than in the previous SM EUROCARE-5 analysis (cases diagnosed in 2000–2007) [11], but with substantial variation in improvement across European regions. Although SM 5-year survival has still improved in Europe over the study period, this improvement was ineffective in Eastern European countries in narrowing the gap between other European regions. On the contrary, the gap has widened over time, with 5-year RS in Eastern Europe 14.0 % below the European average, having previously been 11.1 % below [11].

A possible reason for geographical differences may be later diagnosis, which may be associated with higher Breslow's thickness at diagnosis, the main prognostic factor for SM. Unfortunately, this information is not available for all CRs in this EUROCARE-6 project. Differences in ASRS between European regions were also found in 1-year ASRS, with the European average of 96.9 %, ranging from 97 %–98 % in Central Europe (98.1 %), Northern Europe (97.8 %) and Ireland and UK

Table 2
Skin melanoma. Distribution of topography and morphology subgroups for cases diagnosed in 2008–2013, overall and by European region.

		Codes		European Regions					
				Northern Europe	Ireland and UK	Central Europe	Southern Europe	Eastern Europe	Europe
Topography (a)	Head and neck	C44.0-C44.4	N	3875	14,905	15,098	4252	5133	43,263
			%	13.2	19.1	14.7	12.6	14.0	15.4
	Trunk	C44.5	N	11,860	23,313	35,296	12,055	14,424	96,948
			%	40.4	29.8	34.4	35.9	39.4	34.6
	Limbs	C44.6-C44.7	N	11,515	37,762	48,249	12,630	14,031	124,187
			%	39.2	48.3	47.0	37.6	38.3	44.3
	Not specified	C44.8-C44.9	N	2091	2213	4063	4683	3050	16,100
			%	7.1	2.8	4.0	13.9	8.3	5.7
	All cases		N	29,341	78,193	102,706	33,620	36,638	280,498
Morphology (b)	Nodular melanoma	8721	N	3045	9472	8560	1562	502	23,141
			%	13.8	12.8	11.9	12.5	24.1	12.6
	Lentigo melanoma	8742	N	672	5327	5074	493	62	11,628
			%	3.0	7.2	7.0	4.0	3.0	6.4
	Superficial spreading	8743	N	14,198	39,044	45,296	7221	1115	106,874
			%	64.3	52.6	62.9	57.9	53.6	58.4
	Other specified types (c)		N	165	1354	2279	1002	46	4846
			%	0.7	1.8	3.2	8.0	2.2	2.6
	NOS	8720	N	4008	19,092	10,826	2187	354	36,467
			%	18.1	25.7	15.0	17.5	17.0	19.9
	All cases		N	22,088	74,289	72,035	12,465	2079	182,956

Nota:

(a) Data from 98 European Cancer Registries (CRs)
(b) Data from 61/98 CRs with adequate information on morphology (arbitrary defined as <30 % NOS morphology code 8720)
(c) Comprising the following morphology codes: 8722–3, 8730, 8740–1, 8744–6, 8761, 8770–4, 8780

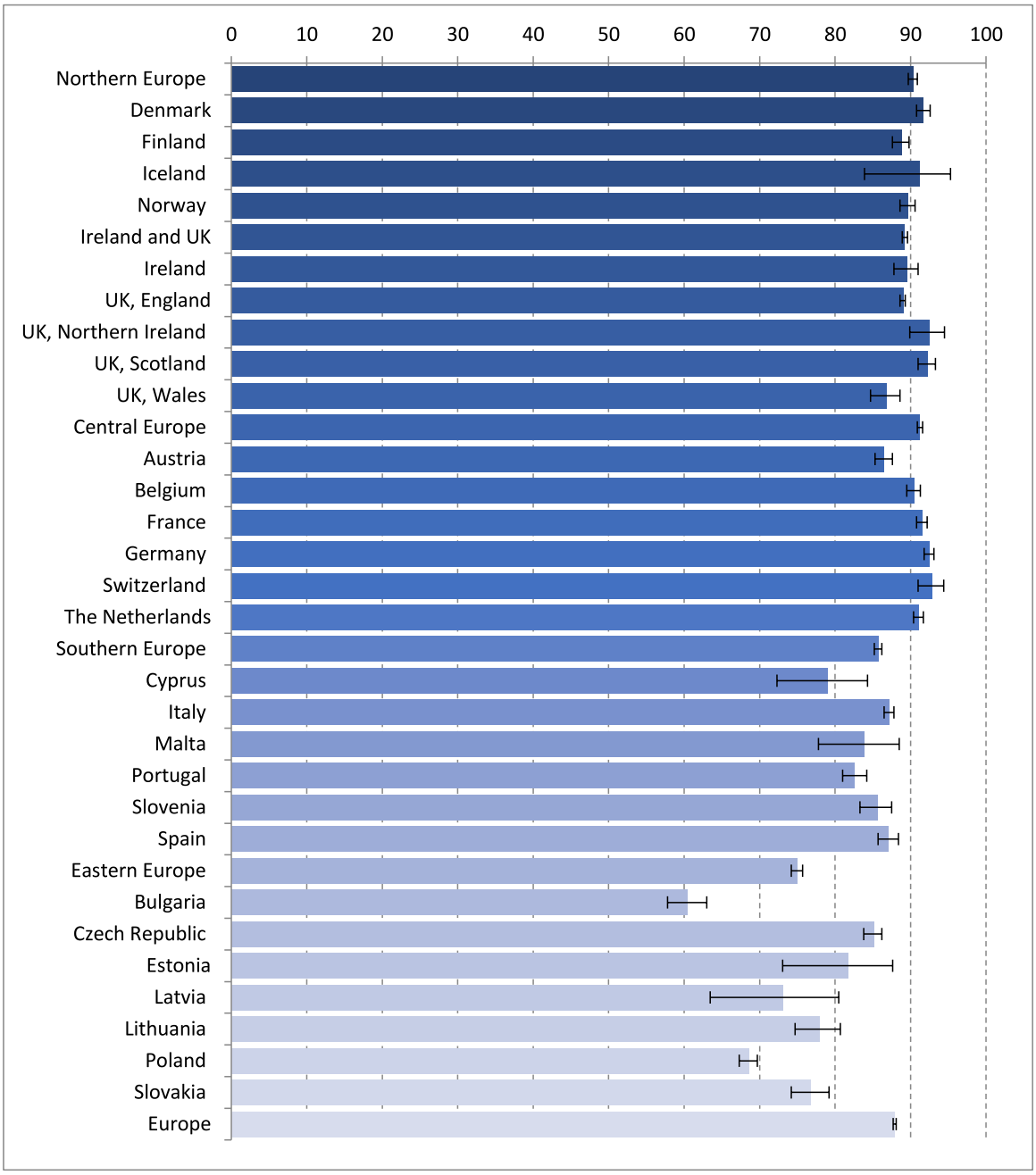


Fig. 1. Skin melanoma: 5-year ASRS, for women and men, by country and region, during 2008–2013. * Croatia has not been included because 5-year survival was unavailable.
Legend: age-standardised relative survival, ASRS.

(97.4 %), to 95.9 % in Southern Europe and 91.9 % in Eastern Europe. The highest risk of early death was observed in Eastern Europe, possible due to deeper invasion at diagnosis in this region.

Furthermore, the gap between regions was less pronounced for conditional 5-year ASRS, suggesting that after early SM deaths in Eastern Europe, the surviving SM cases have a prognosis much closer to the rest of Europe. A previous study focused on short term 1-year and 3-year mortality for SM patients found remarkable variability among European countries (e.g., 1-year lethality rate per 1000, from around 33 in Iceland to 63 in Slovenia), with a general decreasing trend in early deaths, albeit with opposite pattern in some countries (the Netherlands, Slovenia and Ragusa in Italy) [26].

Some Eastern European countries showed a relevant survival improvement, particularly the Czech Republic (5-year ASRS, 85.1 %) and to a lesser extent Estonia (81.7 %), while the lowest ASRS was reported in Bulgaria (60.4 %). Variation in levels of public awareness of skin cancer and melanoma across these countries may be associated with differing levels of early diagnosis of SM. For example, the high RS observed in the Czech Republic [27] paralleled the increase of *in situ* melanoma that was associated with the improved earlier diagnosis. Also, in Estonia the number of T1 SM cases increased over time, but their proportion was still far below that reported in Sweden [12].

Women were found to have better SM survival compared to men. Differences in RS by sex were found at 1-year (97.4 % women vs 95.5 % men), 3-years (92.6 % vs 87.7 %), and at 5-years after diagnosis (89.8 % vs 83.6 %). Furthermore, women had better survival rates than men across all age-groups, anatomical locations, morphologies, and European regions. Better SM survival outcomes in females have been well

Table 3
Skin melanoma 1-year, 3-year, 5-year OBS and age-specific RS (95 % CI) in Europe by age group and sex. Period of diagnosis 2008–2013.

			1-year			3-year			5-year		
Age group	N		Survival	Lower CI	Upper CI	Survival	Lower CI	Upper CI	Survival	Lower CI	Upper CI
15–44	55,147	OBS	98.3	98.2	98.4	95.3	95.1	95.5	93.2	93.0	93.5
		RS	98.4	98.3	98.5	95.6	95.4	95.8	93.7	93.4	94.0
45–54	45,577	OBS	97.1	96.9	97.2	92.1	91.8	92.4	88.6	88.2	88.9
		RS	97.4	97.2	97.5	93.0	92.7	93.3	90.2	89.8	90.5
55–64	56,487	OBS	96.0	95.8	96.1	88.5	88.2	88.8	83.4	83.0	83.8
		RS	96.8	96.6	96.9	90.8	90.5	91.1	87.3	86.9	87.7
65–74	61,341	OBS	94.5	94.3	94.7	83.8	83.5	84.2	76.5	76.1	77.0
		RS	96.3	96.1	96.5	89.1	88.8	89.5	85.5	85.1	86.0
75 +	61,871	OBS	86.9	86.6	87.2	65.2	64.8	65.6	50.4	49.9	50.9
		RS	93.8	93.5	94.1	82.9	82.4	83.4	77.2	76.4	78.0
All cases	280,423	OBS	94.3	94.2	94.4	84.3	84.2	84.5	77.7	77.5	77.9
		RS	96.5	96.4	96.5	90.2	90.1	90.4	86.8	86.6	87.1
Men											
15–44	20,326	OBS	97.2	97.0	97.5	92.6	92.2	93.0	89.8	89.3	90.2
		RS	97.4	97.1	97.6	93.0	92.6	93.4	90.4	89.9	90.9
45–54	20,146	OBS	95.8	95.5	96.1	89.3	88.9	89.8	84.5	83.9	85.2
		RS	96.2	95.9	96.5	90.5	90.0	91.0	86.6	85.9	87.2
55–64	29,202	OBS	94.8	94.6	95.1	85.3	84.9	85.7	79.1	78.5	79.7
		RS	95.8	95.6	96.1	88.2	87.7	88.7	84.0	83.4	84.6
65–74	34,473	OBS	93.4	93.1	93.6	80.8	80.4	81.3	72.5	71.9	73.1
		RS	95.6	95.3	95.9	87.2	86.7	87.7	83.3	82.6	84.0
75 +	31,102	OBS	85.7	85.3	86.1	62.4	61.8	62.9	47.0	46.3	47.8
		RS	93.2	92.7	93.6	81.3	80.5	82.1	75.4	74.2	76.6
All cases	135,249	OBS	92.9	92.7	93.0	80.7	80.5	80.9	72.8	72.5	73.1
		RS	95.5	95.3	95.6	87.7	87.4	87.9	83.6	83.2	83.9
Women											
15–44	34,821	OBS	98.9	98.8	99.0	96.9	96.7	97.1	95.3	95.0	95.5
		RS	99.0	98.9	99.1	97.1	96.9	97.3	95.6	95.3	95.9
45–54	25,431	OBS	98.0	97.9	98.2	94.3	94.0	94.6	91.8	91.4	92.2
		RS	98.3	98.1	98.4	95.0	94.7	95.3	93.0	92.5	93.4
55–64	27,285	OBS	97.2	97.0	97.4	91.9	91.5	92.2	88.0	87.5	88.5
		RS	97.7	97.5	97.9	93.5	93.2	93.9	90.9	90.4	91.4
65–74	26,868	OBS	96.0	95.7	96.2	87.7	87.3	88.1	81.6	81.0	82.2
		RS	97.2	97.0	97.5	91.6	91.1	92.0	88.4	87.7	89.0
75 +	30,769	OBS	88.1	87.7	88.5	68.0	67.4	68.6	53.7	53.0	54.4
		RS	94.4	94.0	94.7	84.5	83.8	85.2	79.0	77.8	80.0
All cases	145,174	OBS	95.6	95.5	95.7	87.7	87.5	87.9	82.1	81.9	82.4
		RS	97.4	97.2	97.5	92.6	92.4	92.7	89.8	89.5	90.1

Legend:
Confidence interval, CI
Relative survival, RS
Observed crude survival, OBS

documented [3,6,11,28,29] and are not only due to better thickness profile at diagnosis, but also to a complex combination of phenotypic and genotypic factors, of which the latter is largely still unknown [30].

As for anatomical location, 5-year not adjusted RS was higher for limbs than for trunk and head and neck, especially for women, while the lowest survival rates were observed for the not specified sites. For all anatomical locations and for both sexes, the lowest regional survival rates were again found in Eastern European countries. We should take into account the limitation of the anatomical site definition, that is based on the ICDO-3 sub-codes of skin (C44): it does not include genital skin in both men and women (e.g., labia majora of the vagina is coded C51 and skin of the penis as C60.9) and comprise a large proportion of NOS skin (C44.9).

The prognostic role of morphology is well known, the good survival of LM and SSM reported worldwide and the poorest for NM [25]. The distribution of morphologies across Europe showed twice the proportion of nodular SM observed in Eastern countries (24.1 %) than the European average (12.6 %). As regards, 5-year ASRS European values showed good prognosis for LM (98.7 %) and SSM (97.0 %) and the low value for NM (79.0 %) confirming the international pattern [25]. On average, the Eastern European countries ranked the last survival value for any morphology. Therefore, the overall results cannot be related to the high proportion of NM only, but more probably to the global timely diagnostic and effective therapeutic approach to SM. Although early diagnosis causes a certain amount of overdiagnosis by definition [10] thus artificially boosting survival, it is essentially concentrated among *in situ* and SM with best prognosis. On the contrary, NM due to its quite common atypical presentation and the rapid vertical growth challenges early detection [31].

For many years the increase in SM incidence was paralleled by mortality [32]. Then, in several countries, mortality flattened, as in France where SM mortality increase halted in the second half of 2010, especially among younger people (<70 years old) [33], or in Italy where mortality was stable during 2003–2014, with decrease in sub-populations (by sex and age class) [34]. In Zurich (Switzerland) mortality was stable during 1981 to 2017 among men but decreased in women [35]. In the Netherlands around 2009 started a clear change in SM mortality trend towards reduction [36], and in 2010 the same happened among Nordic countries [37]. Although heterogeneity is present among the regions in Eastern European countries, in Poland [16], Ukraine [14] and Lithuania [15] SM mortality is still increasing.

This study grounded on robust high-quality population-based data and on a consolidated procedure for quality check and analysis [38]. We must highlight that, unfortunately, some quality data require caution as some CRs declared zero DCO cases because they have no access to mortality records.

Moreover, a few other limitations ought to be pointed out.

First, we referred to Europe and European macro-areas (regions) based on the available data. However, not all the European countries joined the EUROCARE project. Therefore, this point must be taken in

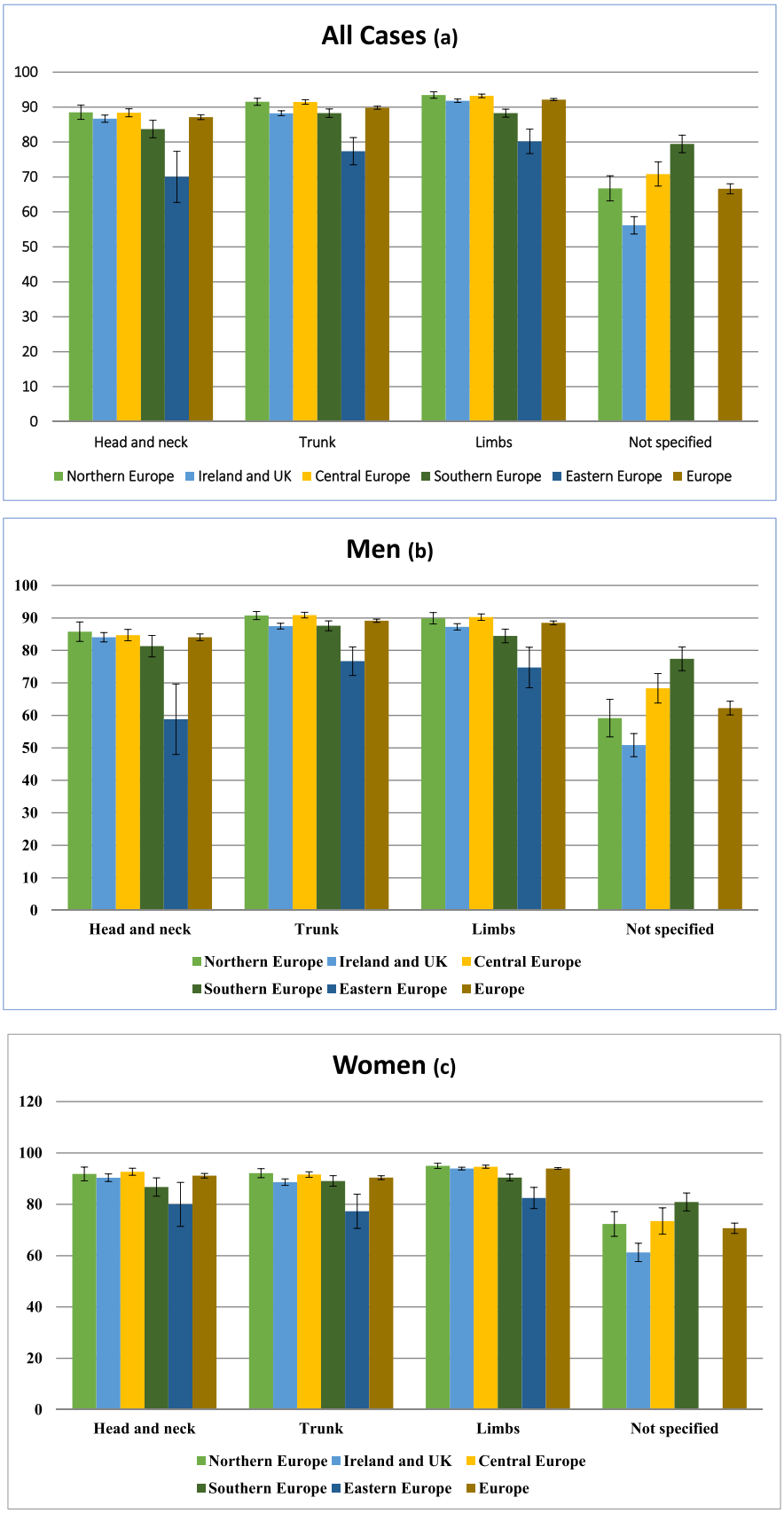
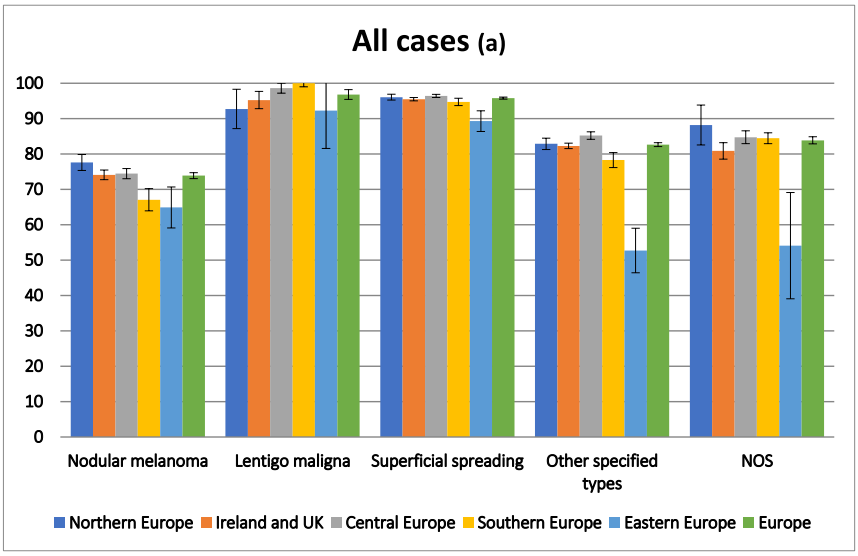
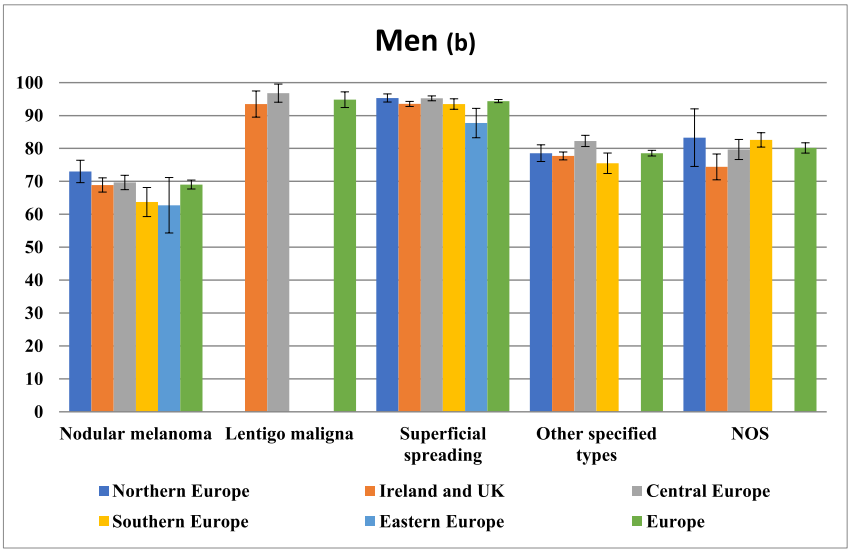


Fig. 2. Skin melanoma: 5-years ASRS by topography, sex and region [all cases (a), men (b) and women (c)].
Legend: relative survival, RS. (The missing data is due to the inability to standardise by age).





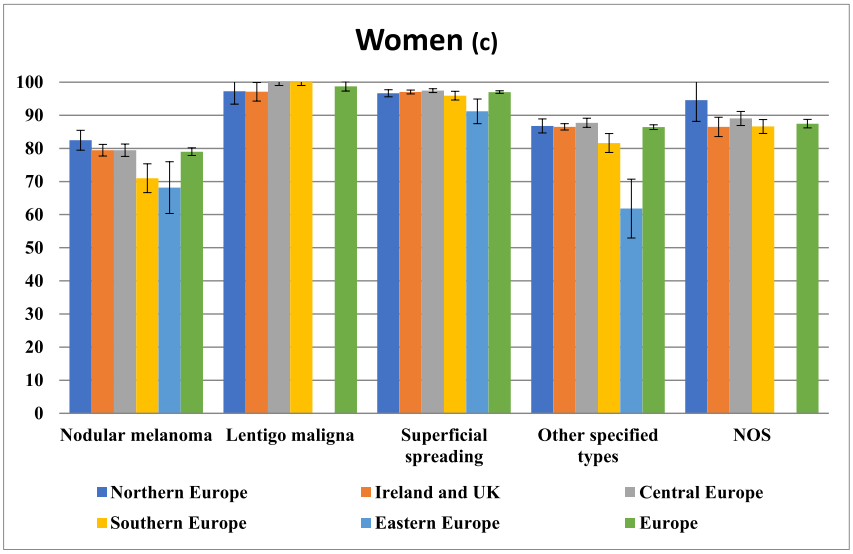


Fig. 3. Skin melanoma: 5-years ASRS by morphology, sex and region [all cases (a), men (b) and women (c)]. Legend: relative survival, RS. (The missing data is due to the inability to standardise by age).

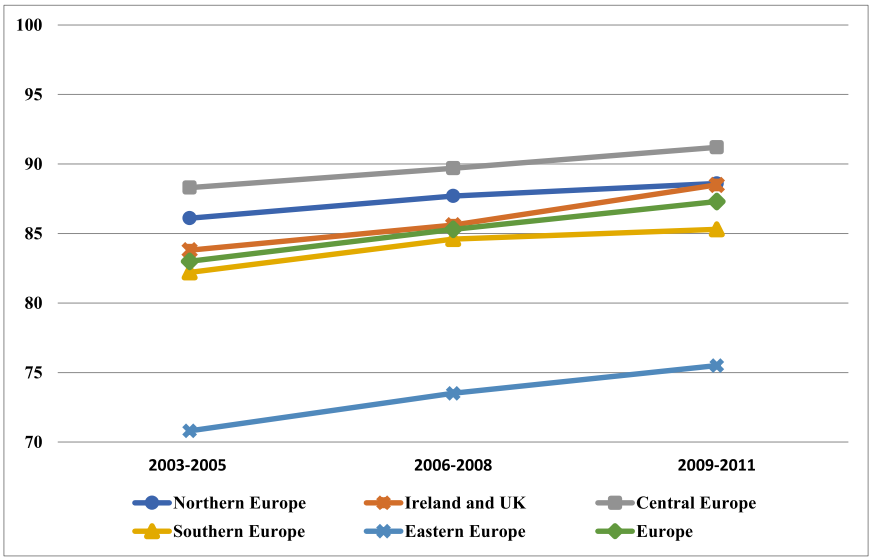


Fig. 4. Skin melanoma: 5-year ASRS trends for the periods 2003–2005, 2006–2008 and 2009–2011, by European region. Legend: age-standardised relative survival, ASRS.

mind when evaluating the estimates. Moreover, Sweden, whose data were included in the previous round of the European study, [11] did not contribute to this new analysis. This may have partially influenced the estimates of Northern Europe and, to a minor extent, the European average [28].

Furthermore, we have already mentioned that data on stage or Breslow' thickness were not available for several of the CRs in the EUROCARE-6 project. Therefore, higher survival rates let presume a better stage distribution at diagnosis. Thus, we were not able to take account of potential overdiagnosis [10] Moreover, prevalence of overdiagnosis is associated with the intensity of dermatological aggressiveness and is unlikely to be the same in different European countries and over time. Improvement may have occurred also due to new immunotherapy drugs (e.g., BRAF/MEK inhibitors and inhibitors of immune checkpoints) that have increased survival in advanced and metastatic patients [39]. However, only a few patients of the present population-based study may have benefitted of them, considering the time of authorization by the European Medicine Agency of such drugs (e.g., for Ipilimumab June 2011, for Vemurafenib February 2012).

With the abovementioned limitations, the observed heterogeneity in SM RS underlined at least two areas of improvement which will allow to bridge the evidenced gap, for Eastern countries, but not only considering the survival variability present within European regions. First, it is important to remember that a relevant proportion of SM are caused by the exposure to ultraviolet radiation (UV) and therefore, preventable avoiding UV exposure and/or with physical protection and the use of sunscreens [40]. Hence, public health campaign for increasing fair-skinned population's awareness on primary prevention of SM should be implemented. Secondly, another point of action is the timeliness of diagnosis, which acts on stage (thickness) at diagnosis, and finally, the availability of innovative therapies capable to change the clinical course of advanced SM [41].

For the joint effect of increasing incidence and improving survival, the number of European citizens with a previous history of SM (prevalent), who were estimated 1000,000 in 2010, [42] has grown to 1400, 000 in 2020 [38]. In addition, the International Agency for Research on Cancer predicted an increase in the number of newly diagnosed SM in Europe in both sexes until 2045, considering incidence but also the concurring ageing of the population [43].

New SM cases must be timely diagnosed and appropriately treated but also prevalent SM patients need an appropriate follow-up. As regards prevalent patients and their growing number, we must consider that SM has an average good prognosis as it has been evidenced also in this study. Therefore, many of these patients will not die for SM but from other causes. In other words, most SM patients will be cured, and almost all those with Breslow thickness<=1 mm [5]. The cure fraction for European SM cases diagnosed in 2000 was 76 % in men and 86 % in women [44]. This information is relevant for both patients and national health systems for a correct and cost-effective allocation of the limited resources.

In conclusion, the results of this EUROCARE-6 study will help all the stakeholders to cope with SM in Europe, underlining the needs for primary prevention and early diagnosis. This involves both citizens, general practitioners and dermatologists, but also those for a proper and up-to-date treatment for localized and advanced SM, making possible for any European SM patients the free availability and access to best personalized therapies [41] and the most appropriate clinical follow-up for the increasing number of prevalent SM patients. Moreover, these data will be also useful for the Comprehensive Cancer Centres whose implementation in all the member states has been promoted by the European Commission for improving the quality of cancer care (https://crane4health.eu).

CRediT authorship contribution statement

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Ethical approval and data sharing

We analysed pseudonymised data collected from 98 population-based CRs, after approval by the Ethics Committee of the National Cancer Institute of Milan (INT73/16; April 21, 2016). We hold these data in trust from each participating registry for the statistical analyses agreed in the EUROCARE-6 protocol, available at http://www.eurocare.it. We are not permitted to share individual data. Aggregated level data, in the form of counts, rates, or survival proportions, can be only shared after express permission from the participating registries. These data should be requested by contacting the corresponding author or the Eurocare Secretariat (eurocare.secretariat@istitutotumori.mi.it).

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Emanuele Crocetti** declares consultancy for AstraZeneca. **All other authors** declare no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.116061.

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