Drug effects on melanoma

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Chapter 2

Epidemiology of Extracutaneous Melanoma in The Netherlands

Extracutaneous melanoma

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Abstract

Background: Reliable population-based incidence and survival data on extracutaneous melanoma (ECM) are sparse.

Patients and Methods: Incidence data (1989-2006) from the Netherlands Cancer Registry were combined with vital status on January 1st 2008. Age-adjusted annual incidence rates were calculated by direct standardization and the Estimated Annual Percentage Change was estimated to detect changing trends in incidence. Additionally, we performed cohort-based relative survival analysis.

Results: Ocular melanomas were the most common ECM subsite with European Standardized incidence Rates (ESR) of 10.7 and 8.2 per 1,000,000 person-years for males and females, respectively. In comparison, for cutaneous melanoma (CM), the ESRs for men and women were 122 and 155 per million person-years, respectively.
No statistically significant trends in the incidence of ECM were detected whereas an annual increase of 4.4 percent for men and 3.6 percent for women was detected in the incidence of CM.
Relative survival for ECM was poor, but differed largely between anatomical subtypes ranging from a 5-year relative survival of 74% for ocular melanomas to 15% for certain subsites of mucosal melanomas.

Conclusion: Of all ECM subsites, ocular melanomas had the highest incidence and the best survival. Mucosal melanomas were the second most frequent subsite of ECM. Five-year relative survival for all ECM subtypes was worse if compared to CM. No statistically significant trends in the incidence of (subsites of) ECM were determined.

Impact: This study gives insight into the relative sizes of the different subgroups of ECM as well as an estimate of 5-year survival, which varies substantially by subsite.

Introduction

Although rare, melanomas can arise at noncutaneous sites. Such extracutaneous melanomas (ECM) include ocular, meningeal and mucosal melanomas or melanomas on exceedingly rare sites like the adrenal gland, kidney, lung or soft tissue. Ocular melanomas arise in the eye and adnexa, whereas meningeal melanomas occur in the dura mater or leptomeninges. Mucosal melanomas may occur at different anatomical sites, such as in the head & neck region, female or male genitals, esophagus, anorectally or very rarely in the urinary tract or biliary tract. [1]

Most of the available epidemiological data on ECM is restricted to anatomic sites and not based on well-described populations, e.g., from geographic regions or national databases. [2-5] Thus, population-based incidence and survival data on ECM are sparse. In 2005, McLaughlin *et al.* published incidence data on ECM from the US and showed that ocular melanoma was more common among men (men: 6.8 cases per million, women: 5.3 cases per million women, age-adjusted to U.S. population standard in 2000), whereas mucosal melanomas were more common among women (women: 2.8 cases per million, men: 1.5 cases per million men). [6] Unfortunately, trends in ECM incidence and survival were not reported. Comparable European data are not available.

In general, ECM are rare (incidence rates < 10 per million person years) [2-6] and have a poor prognosis with 5-year survival estimates ranging from 4 to 60 percent [1]. As opposed to cutaneous melanomas (CM), ECM's prognosis is poor due to late diagnosis as most ECM are not visible, early presenting signs and symptoms are often absent. Additionally, ECM seem to be biologically more aggressive than most CM. [1]

In The Netherlands, the age-adjusted incidence rate of CM has increased significantly with 3.3% in men and with 2.2% in women between 1989 and 1998. [7] This is likely due to increases in sun exposure, and partly due to increased awareness. [7] Since effects of sun exposure are considered to be small or absent for the development of ECM, no changes in incidence rates are expected to occur over time for ECM.

The objective of this study was to contribute to the very limited information on population level regarding this rare group of cancers by assessing incidence rates, relative survival and time trends in the incidence of ECM of different anatomical sites in the national general population-based Netherlands Cancer Registry between 1989 and 2006.

Patients and methods

Data

Incidence data from 1989 until 2006 according to sex, calendar year of diagnosis and anatomical site were obtained from the nationwide population-based Cancer Registry in The Netherlands. This registry receives lists of newly diagnosed cases on a regular basis from the PALGA network, the registry of histo- and cytopathology in the Netherlands. All pathology departments in the country participate in this nationwide network. Additional to these records, lists of hospitalized cancer patients are provided by the medical record departments and these are also checked. Sequentially, the medical records of patients with newly diagnosed primaries are collected. From these, trained tumor registrars summarize relevant information. Duplicate records are removed. [8]

From both hospital records and the death registry of the Central Bureau for Genealogy (which registers all deceased in The Netherlands via the municipal civil registries), vital status on January 1st 2008 was obtained. We recorded survival for the time periods between primary melanoma diagnosis and date of death or the latest date of follow-up. Patients who were alive at their last date of follow-up, were considered censored.

Anatomical sites of ECM were identified based on the International Classification of Disease for Oncology, 9th and 10th revision (ICD-9, ICD-10) and regrouped in the melanoma of the CNS (brain, benign brain tumors, meninges and other CNS; ICD codes: 1921-1922, C70-C71), ocular melanoma (eye, eye lids, orbita, choroid, corpus ciliare and the eye muscles; ICD codes: 1900-1909, C69), or mucosal melanoma of the ear, nose & throat region (nasal cavity, middle ear, sinuses, larynx, lip, pharynx and oral cavity; ICD codes: 1404, 1430, 1439, 1452, 1453, 1600-1609, C00-C09, C11-C14, C30-C33), genitals (males: penis and other not otherwise specified male genitals, females: cervix uteri, ovary, vagina and other female genitals, but excluding the vulva; ICD codes: 1840-1848, 1871-1877, C52, C53, C56, C57, C60, C63), vulva (ICD code: C51), gastrointestinal tract (esophagus and anus/anal canal; ICD codes: 1504, 1505, 1541-1548, C15, C20-C21), lung (ICD codes: 1625, C34, C38) or urinary tract (including urinary bladder; ICD codes: 1881, C68), and ECM of other sites (such as adrenal gland, kidney, soft tissue; ICD codes: 1890, C49, C74, C77). ECM of the stomach, small intestine and colorectal are exceedingly rare and can be metastases of an occult primary melanoma. Therefore, ECM registered as the subsites stomach, small intestine and colorectal (ICD codes 1521, 1570, C16, C17 and C18) were excluded from analyses (n=10).

The Netherlands Cancer Registry records are assumed to be complete from 1989 onwards. [9] However, data collection before 2003 on ocular melanomas was incomplete because, at the time, non-pathologically confirmed ocular melanomas were not systematically included in the Netherlands Cancer Registry. Likewise, vulvar melanomas were not systematically reported prior to 1993 because a unique ICD code was lacking. Consequently, we included only data from 2003 and 1993 onwards for ocular and vulvar melanomas, respectively.

Analysis

For each site, incidence rates were calculated stratified by sex and calendar year. Annual incidence rates were age adjusted by direct standardization according to the European Standard Population, resulting in European standardized incidence rates (ESR) per million person-years. Subsequently, 3-year moving averages of the ESR were calculated. To detect changing trends in ECM incidence over time, the Estimated Annual Percentage Change (EAPC) was calculated. The EAPC was estimated by fitting a regression line with the following equation: $y = mx + b$, where $y = \ln ESR$ and $x =$ calendar year. The EAPC is then equal to $100*(e^m - 1)$. This method assumes that the incidence rates increase or decrease at a constant rate in the study period (1989-2006). For each EAPC, 95% confidence intervals were calculated using the standard error of m obtained with the regression line. [7] EAPCs were calculated separately for men and women, for CM, all mucosal melanomas, and mucosal melanomas of the vulva and Ear-Nose-Throat region.

Additionally, joinpoint analyses were carried out to determine if significant changes in the time trends were present and, if so, when they occurred. [10] In joinpoint analyses, linear line segments are connected on a log scale to identify changes in the EAPC values over time. [10]

Relative survival was estimated in a cohort-based analysis by dividing the crude survival among cancer patients by the expected survival from the general population-based upon the same age- and sex-distributions as has been described earlier. [11] Relative rather than crude survival was estimated because these reflect the excess mortality among the cancer patients rather than the overall survival experience of the patients, including the non-cancer related deaths. Standard errors were calculated according to Greenwood's method. [12]

All calculated *p*-values were two-sided and considered significant if $p<0.05$. All analyses were performed using SPSS 16.0 (SPSS Inc. Chicago, IL), except relative survival which was calculated using the SAS computer package, version 9.1 (SAS Institute Inc., Cary, NC).

Results

Between 1989 and 2006, a total number of 3134 primary invasive ECM were registered among Dutch citizens aged 18 years or older. In comparison, the Netherlands Cancer Registry recorded 42,124 primary invasive CM in the same period. The number of melanomas with an unknown primary was <0.2% and these were considered to have a cutaneous origin in this study.

Incidence

Table 1 summarizes the number of incident melanoma cases diagnosed between 1989 and 2006 by anatomical location and sex. During this period, a total of 42,124 CM were diagnosed. The age-standardized incidence rates (ESR) of CM were 122 and 155 per million person-years for males and females, respectively (Table 1). The male-to-female rate ratio was 0.79.

Between 2003 and 2006, ECM compromised 6.4% of all invasive melanomas. The proportion of ECM was slightly higher among men (7.0% versus 6.0%).

During this period, ocular melanomas were the most commonly occurring subsite of ECM and represented 87% and 68% of all ECM among men and women, respectively. The ESRs of ocular melanoma were 10.7 and 8.2 per 1,000,000 person-years for males and females, respectively. Thus, the male-to-female rate ratio of ocular melanomas was 1.3.

After excluding ocular melanomas reported before 2003 and vulvar melanomas reported before 1993 (see method section for explanation), 1502 incident primary ECM among 1493 patients were eligible for further analyses.

Patients with ECM had a median age at diagnosis of 68 years whereas CM patients had a median age of 53 years. Median ages at diagnosis and the 25th and 75th percentile of patients with different melanoma subtypes are presented in Table 1. Overall, ECM patients are generally older at diagnosis than CM patients and male ECM patients are younger at diagnosis (median age: 65 years) than female ECM patients (median age: 71 years).

Mucosal melanomas, such as vulvar (ESR 1.06) and ECM of the ear, nose and throat (ESR 0.88 for males and 0.71 for females) also contributed substantially to the total ECM incidence. The male-to-female rate ratio of mucosal melanomas was 0.48.

Only 13 incident primary ECM within the central nervous system were reported in the total study period (1989-2006) resulting in extreme low ESRs for men and women (0.038 and 0.052 per million person-years, respectively).

Table 1 Invasive Cutaneous and Extracutaneous Melanomas in the Netherlands National Cancer Registry

Anatomical location	Men		Women		Both Sexes	
	Incident cases (n)	ESR 1989 - 2006 (rate [1])	Incident cases (n)	ESR 1989 - 2006 (rate [1])	5y-Relative Survival [2] (%)	Median age (years) [3]
Skin	17,723	121.9	24,401	155.2	86 (86-87)	53 (40-66)
Non Skin, Non-Mucosal						
CNS [4]	6	0.038	7	0.052	-	51 (32-60)
Ocular [4,5]	373	10.67	322	8.19	74 (67-81)	62 (54-72)
Others [4]	1	0.01	4	0.03	-	61 (51-74)
Non Skin, Mucosal						
Ear-Nose-Throat [4]	122	0.880	139	0.708	27 (20-34)	71 (60-80)
Genitals [4]	48	0.338	121	0.653	26 (18-34)	72 (58-81)
Vulva	n.a.	n.a.	214	1.06	40 (31-49)	75 (65-83)
Gastrointestinal tract [4]	53	0.382	78	0.400	15 (8-22)	72 (59-80)
Lung [4]	6	0.045	1	0.009	-	66 (59-79)
Urinary tract [4]	1	0.007	6	0.031	-	71 (67-82)

[1] ESR = European Standarized Incidence Rate, expressed in 1 per 1.000.000 person years.
[2] Calculated 5-year cumulative overall survival relative to the general Dutch population standarized for age and gender.
[3] Median age at diagnosis In years and 25 and 75 percentile.
[4] The extracutaneous localizations were defined as:
- Central Nervous System (CNS) includes brain, benign brain tunours, meninges and other CNS.
- Ocular includes melanoma of the eye and its adnexa, such as the eye lids, orbita, choroidia, corpus ciliare and the eye muscles.
- Others includes adrenal gland, kidney and soft tissue.
- Mucosal melanomas were subdivided in several categories, such as:
- Ear-Nose-Throat which included sinonasal and oropharyngeal mucosal melanomas (larynx, lip, pharynx, oral cavity, nasal cavity, middle ear and sinuses).
- Genitals which included for males: penis and other NOS (not otherwise specified) male genitals and for women: female genitals including cervix uteri, ovary, vagina and other female genitals, but excluding the vulva.
- Gastrointestinal tract which included oesophagus and anus/anal canal.
- Urinary tract which included urinary bladder and other urinary tract structures.
[5] Only data from 2003 intil 2006 were included for ocular melanomas since the Dutch Cancer Registry was incomplete for ocular melanomas before 2003.

Relative survival

Five-year relative survival for CM unstratified for gender was 86% overall between 1989 and 2006. Relative survival of all ECM subtypes was poor compared to those of CM. However, there are large differences in 5-year-relative survival estimates between ECM subtypes. Of all ECM, ocular melanomas had the best 5-year relative survival of 74% whereas vulvar melanomas had a 5-year relative survival of 40%. The 5-year relative survival of different subsites of mucosal melanomas varied between 15% and 40% (Table 1).

Trends in incidence

For both sexes, the ESR for CM increased significantly between 1989 and 2006 (Table 2). For males, the ESR for CM increased with 4.4% (95%CI: 3.9, 4.9%) per year. Increases among females were 3.6% (95%CI: 2.9, 4.2%).

The age-adjusted incidence rates of all mucosal melanomas and of the selected mucosal region of ear-nose-throat (Fig. 1) showed an increasing, but nonsignificant trend among women (EAPC: 1.8%, 95%CI: –0.5, 4.2%, and EAPC: 2.8%, 95%CI: –0.1, 6.8%, respectively). For men, lower increases were observed in the annual incidence of all mucosal melanomas and these of the ear, nose and throat region (EAPC: 1.0%, 95%CI: –1.8, 3.8, and EAPC: 1.1%, 95%CI: –4.4, 7.1, respectively). The estimated increase in incidence of vulvar melanoma between 1993 and 2006 was only 0.3% (95% CI: –2.6, 3.4).

Despite apparent changes in trend, no statistically significant joinpoints were demonstrated in the joinpoint analyses that were carried out (results not shown).

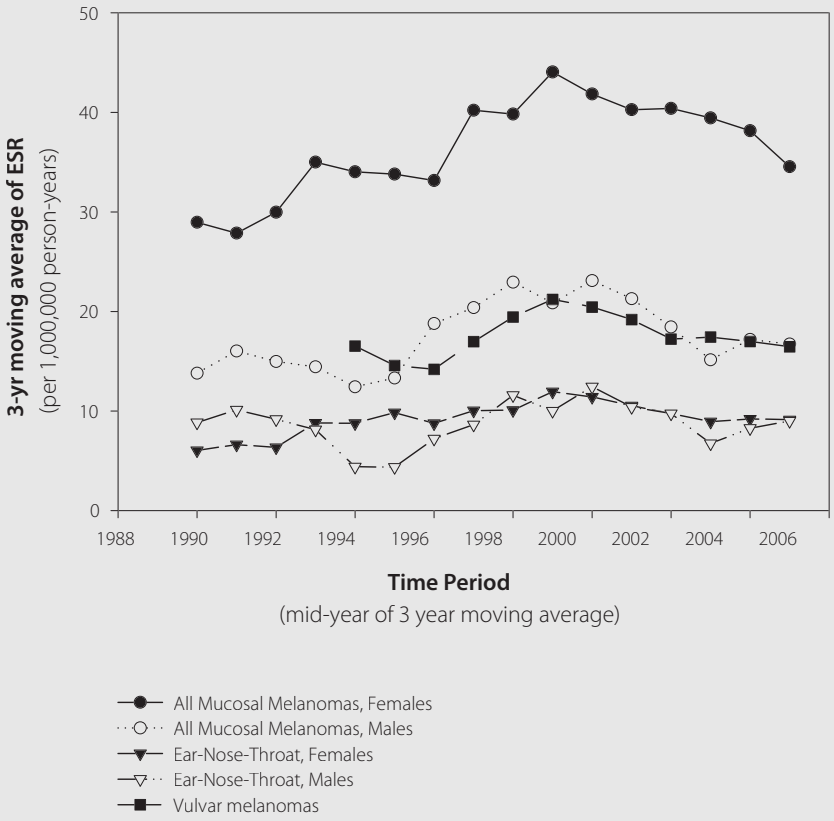
Table 2 European Standardized Incidence Rates for melanomas of different locations in 3-year periods between 1989 and 2006

	Time period												EAPC [2]	
Gender & location	1989-1991		1992-1994		1995-1997		1998-2000		2001-2003		2004-2006			
	n	ESR[1]	n	ESR[1]	n	ESR[1]	n	ESR[1]	n	ESR[1]	n	ESR[1]	mean	95% CI
Men														
Skin	1,900	88.5	2,154	96.0	2,600	111.6	3,007	124.1	3,605	142.6	4,457	168.9	**+4.4%**	**+3.9 to +4.9%**
Mucosal [3]	28	1.95	29	2.54	38	1.97	47	3.21	41	1.67	43	3.14	+0.9%	-2.0 to +3.9%
Ear-Nose-Throat [3]	18	0.88	17	0.81	16	0.72	23	1.00	24	0.97	24	0.90	+1.1%	-4.4 to +7.1%
Ocular [3]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	289	10.92	n.a.	n.a.
Women														
Skin	2,909	124.7	3,149	130.8	3,699	150.8	4,063	161.2	4,892	189.5	5,689	213.6	**+3.6%**	**+2.9 to +4.2%**
Mucosal [3]	71	2.89	87	3.65	83	2.58	111	3.21	104	2.41	104	2.78	+1.8%	-0.5 to +4.2%
Ear-Nose-Throat [3]	15	0.60	22	0.88	22	0.87	30	1.19	25	0.97	25	0.91	+2.8%	-0.1 to +6.8%
Vulva [4]	n.a.	n.a.	n.a.	n.a.	35	1.42	55	2.12	45	1.72	47	1.64	+0.3%	-2.6 to +3.4%
Ocular [3]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	234	7.94	n.a.	n.a.

[1] European Standarized Incidence Rate, expressed in 1 per 1.000.000 person years.
[2] EAPC = Estimated Annual Percentage Change, data printed in bold if statistically significant ($p<0.05$).
[3] Subcategories of the extracutaneous melanomas that were tested for an incidence trend were:
- Mucosal melanomas includes all mucosal melanomas (Ear-Nose-Throat, Genitals, Vulva, Gastrointestinal tract, Lungs and Urinary tract).
- Ear-Nose-Throat which included only the sinonasal and oropharyngeal mucosal melanomas (larynx, lip, pharynx, oral cavity, nasal cavity, middle ear and sinuses).
- Vulvar mucosal melanomas.

[4] Before 1993 there were no separate ICD codes registered for vulvar melanomas. Both in 1993 and 1994, 16 vulvar melanomas were registered.

Figure 1 Trends in the incidence of muscosal melanomas in The Netherlands: 1989 - 2006



Discussion

Incidence

Our results show that, between 2003 and 2006, about 6.4% of all primary melanomas in The Netherlands were ECM. This proportion is similar to previous reports (4-6.8%). [6,13] In general, ECM patients, especially those with mucosal melanomas, are older at diagnosis than CM patients. Similarly, Chang *et al.* observed a median age of ~ 70 years for mucosal melanomas. [15]

No statistically significant time trend in the ECM incidence was observed, whereas an annual increase in age-adjusted standardized CM incidence among both sexes was observed.

Ocular melanoma was the most common ECM subsite and its' incidence was somewhat higher than reported by McLaughlin *et al.* (ESR females: 10.7 versus 6.8 per million person-years; males: 8.2 versus 5.3 per million person-years) [6]. The male-to-female rate ratio of 1.3, however, was similar [6].

Mucosal melanomas were the second most frequent subsite of ECM and the incidence we report is in agreement with the US data reported in McLaughlin's paper (ESR men: 1.8 versus 1.5 per million person-years; women: 2.8 versus 2.8 per million person-years) [6]. The male-to-female rate ratio for mucosal melanomas was 0.48 which seems to be rather consistent throughout the literature [6,14,15], and the female predominance is most likely a reflection of the lack of a male counterpart for vulvovaginal lesions. [14]

The incidence of vulvar melanoma in our study (ESR: 1.1 per million person-years) is similar to a previously published study from Sweden (1960-1984) [3]. In their study, however, the annual age-standardized incidence of vulvar melanoma decreased with 3.2% annually (mainly due to a decrease among younger age groups) [3], whereas our results showed no definite trend in incidence (EAPC 0.3%, 95% CI: –2.6 to +3.4%). These Swedish data are, however, outdated (data up to 1984) and were based on a consecutive series of cases rather than a population-based sample. [3]

Relative survival

Five-year relative survival proportions of ECM subtypes, except ocular melanoma, were poor compared to CM (86%) and differed substantially between subsites. Preferably, we would have stratified for the clinical stage of disease at diagnosis in the survival analysis which was not possible due to low numbers of incident ECM.

Of all ECM subsites, patients with primary ocular melanoma had the best survival with a relative 5-year survival of 74% (95% CI: 67-81%). Estimates from the Collaborative Ocular Melanoma Study (COMS) [1] were slightly lower (60%), but the 5-year disease specific survival of 75 percent published by Chang *et al.* [15] is comparable. Our estimate may be somewhat underestimated due to the fact that we could only use data from 2003 until 2006 and vital status on the 1st of January 2008 resulting in relatively short follow-up for part of the patients with ocular melanoma in our dataset and hence relatively many patients being censored alive.

Vulvar melanomas in our dataset resulted in a 5-year survival proportion of 40% (95% CI: 31-49%), comparable with the 50% reported by Weinstock on US data [17] .

The survival proportion for gastrointestinal melanoma was calculated to be 15%

(95%CI: 8-22%), slightly better than the overall crude 5-year survival of 6% presented in a Dutch case series of anorectal melanoma (63 cases, 1960-1995) [16]. Although we included anorectal as well as esophageal melanomas in this subsite, survival estimates for patients with anorectal and esophageal melanomas did not substantially differ in our dataset (data not shown).

Reflection

The poor survival proportions estimated for ECM could obviously reflect the often advanced stages in which ECM are diagnosed. However, ECM and CM also differ substantially in their clinicopathologic and molecular aspects. Even between subgroups of CM, such as acral melanoma and chronic versus non-chronic sun exposed melanomas, the genetic makeup and morphological features differ. [18] The clinical heterogeneity of melanoma can, in part, be explained by distinct sets of genetic alterations. Approximately 80% of melanomas in skin without chronic sun-induced damage contain a mutation in either BRAF or NRAS, whereas cutaneous melanoma arising in non-damaged skin, as well as acral and mucosal melanomas do not. [19] Instead, these tumors frequently display increased gene copy number of cyclin-dependent kinase 4 and cyclin D1. Oncogenic BRAF mutations in ocular melanoma are rare, if not absent, or restricted to only a subset of cells in posterior uveal melanomas. [20-23] However, somatic mutations in the heterotrimeric G protein alpha-subunit, GNAQ, are frequently observed in uveal melanoma, but rarely in other melanomas. [24] Mutations and/or copy number increases of receptor tyrosine kinase KIT have been detected in 39% of mucosal, 36% of acral, and 28% of melanomas on chronically sun-damaged skin. [25] These genetic changes commonly result in various alternative routes to MAP kinase activation and hence proliferation. However, upstream oncogenic mutations in BRAF, NRAS, KIT, and GNAQ will activate additional signaling cascades specific for that tumor type and therefore contribute to the diversity in melanoma biology, prognosis, and response to therapy.

Future research

Future epidemiological research on ECM should include large (international) datasets. This would enable researchers to stratify for clinical stage at diagnosis in survival analysis and therefore to study how much of the poor prognosis of ECM is due to delayed diagnosis. It would also allow for studying the male-to-female ratios reported and time trends in incidence and survival, investigate possible geographical gradients in comparison with CM. Ideally, these datasets would be population-based to avoid biases occurring from selected patient groups. Whenever possible such international

databases should include aspects that may explain the clinical heterogeneity, such as the morphological features and mutational status of an ECM. If treatment were to be adequately collected, the effects of targeted therapies such as imatinib for c-kit mutated mucosal melanomas could be studied.

Conclusion

With incidence rates for different subsites of extracutaneous melanoma ranging from less than 0.1 per million person-years for ECM of the lung or urinary tract until about 10-11 per million person-years for ocular melanomas among men, ECM is a rare type of melanoma. Of all ECM subsites, ocular melanomas had the highest incidence (10.7 and 8.2 per million person-years for men and women, respectively) and the best survival with a 5-year relative survival of 74%. Mucosal melanomas, such as vulvar melanomas, were the second most frequent subsite of ECM. Five-year relative survival for mucosal melanomas ranged between 15 and 40% and survival for all ECM subtypes was worse if compared to the 86% five-year relative survival for CM. Also in contrast with CM, no statistically significant trends in the incidence of (subsites of) ECM were determined.

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