Incidence of Uveal Melanoma in Sweden from 1960 to 1998

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PURPOSE. To investigate the incidence of uveal melanoma in Sweden during the period from 1960 to 1998, with respect to age distribution, gender, and changes in incidence over time.

METHODS. The Swedish Cancer Registry was searched for patients with uveal melanoma and cross-checked against hospital files over patients where an eye-sparing treatment had been applied, to ensure inclusion in the Registry even when no histologic specimen was available. The crude and age-standardized incidence was estimated separately for each gender. The Swedish population of 1970 to 1974 was used as a standard, and the annual change in incidence was calculated by using a regression model with logarithmic incidence numbers.

RESULTS. In total, 2997 patients met the criteria, of whom 1542 were males and 1455 females. During the 39-year period, the age-standardized incidence of uveal melanoma declined significantly in the male population, from 11.7 cases/million to 8.4 cases/million (P = 0.002). The trend toward reduced incidence in females, from 10.3 to 8.7 cases/million did not reach statistical significance (P = 0.108). The annual relative change in incidence was 1% (95% CI, 0.8%–1.2%) in males and 0.7% (95% CI, 0%–1.3%) in females. The age-specific incidence revealed a significantly higher incidence among men older than 45 years (23.5 cases/million) compared with the incidence in women of the same age group (19.2 cases/million; P < 0.001).


The eye is the second most common site of malignant melanoma, (5.2%), as documented in a summary of more than 84,000 cases of melanoma from the U.S. National Cancer Data Base.1 Uveal melanoma accounts for 85% of ocular melanomas and is by far the most common primary intraocular malignancy in the population older than 15 years.2 The annual incidence in Scandinavia has previously been reported stable at approximately 5.0 to 7.5 cases/million inhabitants.3–5 The incidence in populations with fair complexion and light iris color is likely to be high, because these features are considered strong risk factors for uveal melanoma.10,11

In Israel, where the phenotypes of Jewish immigrants from many countries are exceptionally heterogeneous, significant differences mark the incidence of uveal melanoma among the individual subpopulations. The highest incidence, 7.5 cases/million occurs in Jews of European-American origin, whereas the lowest incidence, 1.6 to 2.8 cases/million has been estimated in Jews born in Africa or Asia.12 The incidence rate in Israel is later reported to be stable and was no higher in descendants of high-risk subpopulations, despite their having been reared in an environment with more exposure to ultraviolet (UV) light.13

Because the incidence of cutaneous melanoma in the Swedish population has increased considerably during the past several decades, we wanted to investigate and clarify the incidence pattern of uveal melanoma in Sweden, based on data from a nationwide and population-based registry.

MATERIALS AND METHODS

The Swedish National Cancer Registry, founded in 1958, receives reports when a malignant disease is diagnosed. Compulsory dual registration from the clinician and pathologist-cytologist ensures inclusion. Each patient is identified through a unique national registration number, and the registry is estimated to include more than 95% of all cases of cancer in the country.14

The research protocol for the present study was approved by the Human Ethics Committee at the Karolinska Institute, in accordance with the statutes of the World Medical Association’s Declaration of Helsinki. Files from the Swedish Cancer Registry during the period from 1960 to 199815 were searched for patients with intraocular melanoma, using both the International Classification of Diseases, Seventh Revision (ICD-7) code and the Systematized Nomenclature of Medicine (SNOMED) code. In the instances in which an eye-sparing treatment had been applied, the data files were double-checked against hospital files covering all patients treated with radioactive plaques, along with the records from a small group of patients who received proton beam irradiation. These treatment modalities were the only alternatives to local resection or enucleation during the investigation period. The eye-sparing treatments were centralized in two university clinics in Sweden.

The search of hospital files revealed 140 patients treated for uveal melanoma who were not included in the original files from the Cancer Registry. Therefore, the noninclusion rate was 4.7%. The missing cases were included in the database of the present study and reported to the Cancer Registry. The database thus revealed 2997 cases of uveal melanoma, including melanomas of the iris, ciliary body, and choroid.

Each gender was analyzed separately, and the patients were divided into eight age groups, each spanning 10 years, except the youngest (0–24 years) and the oldest (>85 years) age groups. The analysis over time was performed for 5-year periods from 1960, except the period from 1995 to 1998.

Files from the National Central Bureau of Statistics16 including records from the Swedish population censuses of 1960 through 1998 and immigration statistics were used. Before 1970, the statistics were incomplete according to the age distribution and gender of immigrants and so did not permit analysis for the period 1960 to 1969. The country of birth was not specified until 1980. Previously, only the original citizenship was noted in the files. For this study we accepted patients’
original citizenship as an estimate of birthplace when calculating the proportion of immigrants in the Swedish population before 1980.

An overall crude and age-standardized incidence rate in the total Swedish population was calculated, and the genders were further analyzed separately. Age-standardization on incidence numbers over the study period was performed by a direct method, with the Swedish population during the period 1970 to 1974 taken as a standard, according to the stratum weights shown in Table 1. The relative change in incidence over the 39-year period was calculated by linear regression after logarithmic transformation of incidence data. The annual change was expressed as a percentage with 95% confidence intervals. The level for statistical significance was set at a $P \leq 0.05$. The probabilities were corrected with the Bonferroni adjustment when subgroup comparisons were made.

The number of immigrants to Sweden born outside Europe was estimated for the years 1970, 1980, 1990, and 1998. In the calculations the extreme value of null incidence of uveal melanoma was set for this subpopulation. The influence of immigrants on the incidence of uveal melanoma for each gender was estimated by using the crude incidence numbers in the Swedish population of 1970, 1980, 1990, and 1998. These incidence numbers were then compared with the estimated incidence in the population when the immigrants were excluded. The crude incidence numbers in the Swedish population were expressed with 95% confidence intervals. Data were processed with statistical-analysis software (SPSS, ver. 10.0; SPSS Inc., Chicago, IL).

To compare the average density of uveal melanoma per ocular area unit in relationship with that of cutaneous melanoma the total uveal area of both eyes was estimated. According to the 0.5 mm shorter average axial length in females, the uveal area was estimated to be 34 cm$^2$ in males and 33 cm$^2$ in females.\textsuperscript{17,18} The mean body surface area has previously been found to be 1.9 m$^2$ in men and 1.7 m$^2$ in women.\textsuperscript{19} During the investigation period specified (1960-1998) 17,090 and 18,334 cases of cutaneous melanoma were diagnosed in the male and female Swedish population, respectively,\textsuperscript{15} and the ratios of uveal versus cutaneous melanomas per surface unit consequently could therefore be calculated.

**RESULTS**

During the period 1960 to 1998 a total of 2997 patients with uveal melanoma was reported to the Swedish National Cancer Registry. Of these patients, 1542 were males and 1455 females (male-female ratio, 1.06). The males' ages ranged from 11 to 94 years, and the females' from 8 to 95 years. In the group younger than 25 years, there were 10 females and 8 males, but only three were younger than 15 years (two girls, aged 8 and 10 years, and a boy aged 11 years). Judging from the crude incidence shown in Figure 1, it appears that uveal melanoma was an extremely uncommon disease in the young population, with an age-specific incidence (Fig. 2) of 0.1 and 0.2 male and female cases/million, respectively, in the age group of less than 25 years. In the 25- to 34-year age group the incidence was low (1.7 cases/million for both genders), but in the population of 35- to 44-year-olds, the incidence increased to 4.0 and 5.6 cases/million, respectively. The age distribution revealed that the peak incidence appeared in a slightly earlier age group in females (65-74 years; 26.5 cases/million) compared with males, in which the maximum incidence (36.6 cases/million) occurred in the 75- to 84-year age group. The difference in crude incidence between genders in the age groups older than 45 years was statistically significant, with the male incidence

<table>
<thead>
<tr>
<th>Age Groups (y)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24</td>
<td>0.36</td>
<td>0.34</td>
</tr>
<tr>
<td>25-34</td>
<td>0.15</td>
<td>0.14</td>
</tr>
<tr>
<td>35-44</td>
<td>0.11</td>
<td>0.11</td>
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<tr>
<td>45-54</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>55-64</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>65-74</td>
<td>0.08</td>
<td>0.10</td>
</tr>
<tr>
<td>75-84</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt;85</td>
<td>0.01</td>
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</tr>
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</table>

**FIGURE 1.** The age distribution of incidence of uveal melanoma in the male and female Swedish population during the period from 1960 to 1998, based on reports in the Swedish Cancer Registry.

**FIGURE 2.** Age-specific incidence rates of uveal melanoma in the male and female populations of Sweden during the period from 1960 to 1998. In the age groups older than 45 years, a statistically significant male predominance was observed (23.5 cases/million) compared with the incidence among the females (19.2 cases/million; $P < 0.001$).
During the period from 1960 to 1998 the age-standardized incidence of uveal melanoma in the total Swedish population was reduced from 11.0 cases/million to 8.5 cases/million ($P = 0.006$). In the male population, a significant reduction in incidence was found. The calculated age-standardized incidence decreased from 11.7 to 8.4 cases/million by the end of study period ($P = 0.002$). The female population also manifested a declining trend in incidence, from 10.3 to 8.7 cases/million during the investigation period, although the difference was not statistically significant ($P = 0.108$), as Figure 3 depicts. By applying a log regression model, we determined the annual change in incidence rate. The male incidence declined 1% yearly (95% CI, 0.8%–1.2%) whereas the female incidence decreased 0.7% (95% CI, 0%–1.3%) annually from 1960 to 1998.

The influence of non-European immigrants (with a presumably lower incidence of uveal melanoma) was analyzed for the years 1970, 1980, 1990, and 1998. For both genders, the estimated crude incidence for the population excluding the immigrants did not differ statistically significantly from the true crude incidence, which included them (Table 2).

To evaluate whether the diagnostic criteria for uveal melanoma changed over the investigative period, one of the authors (Seregard S, unpublished data, 2001) reexamined a random sample of 916 paraffin-embedded specimens originally reported to be uveal melanoma during the period from 1960 to 1998. The specimens originated from several laboratories across Sweden. In only three cases (0.33%) did the original diagnosis require alteration, which confirms the high level of accuracy in the Cancer Registry.

The average tumor density (i.e., skin compared with uveal melanomas per unit of body area) of uveal melanomas was found to be 50 times higher in males and 41 times higher in females than that of cutaneous melanomas.

### DISCUSSION

Throughout the 39-year investigation period, the incidence of uveal melanoma in Sweden was remarkably high from a global perspective. In the first period (1960–1964) the age-standardized incidence was 11.7 and 10.3 cases/million in males and females, respectively. The incidence declined to 8.1 and 8.6 cases/million during the period 1995 to 1998, a level similar to the incidence recently reported for Jews of Polish and Romanian ancestry.13

The incidence of uveal melanoma in Scandinavia was once recognized as among the highest worldwide. In Denmark, Jensen3 reviewed the period from 1943 to 1952 and found a crude, but not age-standardized incidence of uveal melanoma of 7.4 cases/million. Østerlind7 later analyzed the Danish population of 1943 to 1982 with age standardization and found a stable incidence of ocular melanoma (conjunctival melanomas.

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence</th>
<th>Excluding Immigration</th>
<th>95% CI†</th>
</tr>
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<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>1970</td>
<td>10.1</td>
<td>9.4</td>
<td>10.1</td>
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<tr>
<td>1980</td>
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<tr>
<td>1990</td>
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<tr>
<td>1998</td>
<td>9.3</td>
<td>9.7</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Incidence in the non-European immigrants was set at 0.

* The incidence in cases/million.

† The estimated 95% confidence interval for the crude incidence in the total male compared with the female population is given.
included) of 7.5 and 6 cases/million in males and females, respectively, during that period. In the United States with its heterogeneous population, the age-standardized incidence of uveal melanoma was estimated at 6 cases/million, based on the Third National Cancer Survey during the period from 1969 to 1971.20 Because different standard populations, and, hence, stratum weights, were used in these studies, the figures are not fully comparable. Other investigations, mainly in white populations have resulted in similar data.21–25 However, in many earlier studies, the incidence of ocular malignancies in the population older than 15 years has been used as an approximation for the incidence of uveal melanoma, suggesting inaccuracies stemming from inclusion of too broad a group. The temporal trends in incidence have often been regarded as stable, although with small fluctuations in many populations.5,13,24,25 A recent investigation in the United States (Singh A, personal communication, 2001) supports the impression of a stable incidence of uveal melanoma during the period 1973 to 1997, with an overall rate of 4.3 cases/million inhabitants. However, in our data, we detected a statistically significant reduction in the incidence of uveal melanoma of 1% yearly for the male population in Sweden during the period from 1960 to 1998. In the female population, the incidence rates declined by 0.7% annually, but the reduction did not quite reach a statistically significant level (P = 0.108). A slight predominance of males has been found in several epidemiologic studies on uveal melanoma. To our knowledge no statistically significant age-dependent gender difference has previously been demonstrated for this tumor. However, we discovered a significantly higher incidence in males than in females in the group more than 45 years of age, although the reasons are unknown.

Until brachytherapy became a preferred treatment for smaller melanomas, almost every eye with uveal melanoma was enucleated and a specimen submitted for pathologic analysis. Ocular pathology in the earlier decades of the study period was not centralized, and therefore various pathologists at different laboratories examined the specimens. In an evaluation to determine whether the diagnostic criteria for uveal melanoma changed over the investigative period, reexamination of specimens identified misdiagnoses in only 0.33%. The diagnostic accuracy appears to be in the same low range as reported in the Collaborative Ocular Melanoma Study (COMS) in which the rate of misdiagnoses was 0.3%.26 The risk of not reporting uveal melanoma cases could have increased in later years, because more eyes are treated without obtaining a pathology specimen, and therefore the cases were not reported dually by both clinician and pathologist. To reduce this risk, hospital files from the only two centers treating patients with eye-sparing procedures (brachytherapy and proton beam irradiation) were checked and missing patients included in the study.

Although the Swedish population was once considered ethnically homogeneous, a small but growing immigration from both European and non-European countries has occurred in the past few decades. However, the net immigration rate remains comparatively low: the Swedish rate is estimated at 0.86/1000 population compared with 3.5/1000 population for the United States during 2000.27 Data from the Swedish National Bureau of Statistics16 indicate that the proportion of the population of non-European origin in 1960 was 0.2% and in 1998 had increased to 4.0%.

Furthermore, the age distribution of the immigrant population differed, because it was proportionally younger than the total Swedish population for every period investigated. The influence on the crude incidence of uveal melanoma for each gender over time when taking into account a presumably lower incidence in the immigrant population was estimated and found to be insignificant. Therefore, immigration alone probably does not account for the decreasing incidence of uveal melanoma documented in this study.

The stable incidence rates of uveal melanoma published since the 1950s contrasts sharply with the well acknowledged increase in incidence of skin melanoma in populations with fair complexions.28 Our results concur with those found in a recently published population-based Swedish survey of incidence rates for vulvar melanoma.29 At this extracutaneous UV-light protected site, the incidence declined 3% annually during the investigation period of 1960 to 1984.

The average density of cutaneous melanoma is lower than that of uveal melanoma when the relationship between the skin area and the uveal area is considered. Specifically, uveal melanomas are 50 times more common in men and 41 times more common in women than cutaneous melanomas. Also, vulvar melanomas were found to be overrepresented by a factor of 2.5, compared with cutaneous melanomas.30

The potential role of UV light in the development of uveal melanoma is a matter of controversy. Some studies indicate that sunlight exposure may be a risk factor,10,31–32 but others found no clear latitudinal gradient.20 Nearly all UV light in the adult eye is absorbed before reaching the uvea, although greater transmission is possible in childhood,33 and a blue or light-colored iris is also suggested to transmit more UV-light.

Our results in a national survey in Sweden during a 39-year period point out a stable, and, in males, even decreasing, incidence of uveal melanoma during the same period that the incidence of cutaneous melanoma increased four to five times. The results therefore suggest that the initiation of uveal melanoma is less dependent on UV light exposure than that of cutaneous melanoma.

References


