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In the memory of my father, Ronald Hathorn
ABSTRACT

A major purpose with this thesis was to assess the incidence and mortality rates of uveal melanoma in Sweden during the period 1960 to 1998, using population-based registry data. In total, 2,995 patients (1,541 males and 1,454 females) were diagnosed with uveal melanoma. The age-standardized incidence rate of uveal melanoma declined significantly among men from 11.7 cases/million to 8.4 cases/million (p=0.002) and was stable in females, 10.3 cases/million to 8.7 cases/million (p=0.108). The annual decrease in incidence rate was estimated to 1% (95% CI: 0.8-1.2) in males and to 0.7% (95% CI: 0-1.3) in females. The 5-year observed and relative survival rates were 60% and 70% respectively, with better survival in younger age groups and later time periods.

The aetiology of uveal melanoma is unknown. By analyzing the coexistence of uveal melanoma and other malignancies, possible associations with shared risk factors might give indications of common etiologies. A 13% increased risk of subsequent cancers was found in uveal melanoma patients compared to population controls. No significantly elevated risk was found for any specific cancer site, including cutaneous melanoma. Only two familial cases of uveal melanoma were identified in the Multigeneration Registry, indicating that hereditary factors are of minor importance in the causation of uveal melanoma.

The impact on survival and functional outcome following brachytherapy with 106-ruthenium plaques was evaluated in 579 patients, treated during the period 1979-2003. The 5-year observed and relative survival rates were estimated at 83% and 95% in this selected patient group. 5-year cumulative incidence of enucleation was 16.8%. In patients with a 5-year follow-up visual acuity of ≥0.5 was retained in 31%, and visual acuity of >0.1 in 49%.

In conclusion, the incidence rate of uveal melanoma in the Swedish population decreased in males and was stable in females during the period 1960-98. In the same population the incidence rates of skin melanoma increased 2-5% yearly, which indicates that mechanisms other than UV-exposure are to be considered in the pathogenesis of uveal melanoma.

Keywords: Melanoma, uveal, choroidal, epidemiology, population-based registry, incidence, survival, familial, ruthenium brachytherapy

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LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their roman numerals.


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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>COMS</td>
<td>Collaborative Ocular Melanoma Study</td>
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<td>CT</td>
<td>Computerized Tomography</td>
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<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases, injuries and deaths</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<td>SIR</td>
<td>Standardized Incidence Ratio</td>
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ACKNOWLEDGEMENTS

Many people have in different ways contributed, inspired me and helped to accomplish this thesis. I am particularly indebted and thankful to the following persons:

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INTRODUCTION

The most common primary malignant tumour in the eye, uveal melanoma, carries the potential of both blinding the eye and causing the death of the patient. Although malignant melanoma of the eye is far less common than melanoma of the skin\textsuperscript{1}, the disease challenges ophthalmologists and researchers as the causes of the disease are unknown and the behaviour of the tumour is most unpredictable as metastases can appear several decades after removal of the eye\textsuperscript{2,3}.

The occurrence of uveal melanoma in human populations over time appears to follow a different course compared to skin melanoma\textsuperscript{4}, as no evidence so far has supported an increasing incidence rate\textsuperscript{5-9}, nor has any considerable improvements in survival\textsuperscript{10-12} been obtained for uveal melanomas during the last decades. In contrast to cutaneous melanoma, where ultraviolet (UV) light radiation is an established risk factor\textsuperscript{13,14}, the role of UV-light in the development of uveal melanoma remains controversial\textsuperscript{15,16}, with both supportive\textsuperscript{17-19} and inconclusive\textsuperscript{20,21} reports.

Malignant melanoma arises from malignant transformation of melanocytes. In the eye, melanocytes are located in the highly vascularized uvea, which comprises the iris, the ciliary body and the choroid (Figure 1). About 90\% of uveal melanomas originate in the choroid, whereas 5-10\% arise in the ciliary body and 2-3\% in the iris\textsuperscript{5,22,23}. Melanocytes are also found in the conjunctiva, the mucosal surface of the eye.

Uveal melanoma is an uncommon tumour in children; less than 1\% of the patients are 20 years or younger\textsuperscript{24}. The mean age at diagnosis for both men and women are in most series 55-60 years\textsuperscript{5-7}, with an incidence peak at 70 years. The highest incidence rates are reported from populations of northern European ancestry, especially Scandinavians, with 5-9 cases per million and year\textsuperscript{5,25-28}. Uveal melanoma is rare in nonwhite races; in the United States with a more genetically heterogeneous population the overall incidence rate during the period 1973-1997 was 4.3 cases per million and year\textsuperscript{6} but only 0.7 \% of the patients were of African or Asian origin.

The diagnosis of uveal melanoma is mainly based on clinical investigations, such as indirect ophthalmoscopy, slit-lamp biomicroscopy and ultrasound. Ancillary tests may include CT-scan, magnetic resonance imaging, and angiography with fluorescein/ indocyanine green. In rare instances biopsies through fine-needle aspiration might prove necessary in atypical cases. In spite of pre-treatment histological proof, the diagnostic accuracy among ocular oncologists
appears satisfactory, as correct classification rate of 99.7 % was found among enucleated patients within the multicentre Collaborative Ocular Melanoma Study (COMS)\textsuperscript{29}. Historically, the treatment of uveal melanoma has in the vast majority of cases consisted of removal of the eye, enucleation (Figure 2), until eye-sparing therapies such as brachytherapy with episcleral plaques loaded with radioactive isotopes\textsuperscript{30-33}, charged particle irradiation with proton\textsuperscript{34} or helium\textsuperscript{35} ions or local transscleral resection\textsuperscript{36,37} became more widely accepted in the 1970s. Iris melanomas have mainly been handled with local resection, due to their smaller size and accessibility. The patients’ survival appear to be unaffected by choice of treatment modalities\textsuperscript{31,38-40}, as survival rates have remained constant over decades\textsuperscript{11}. Also, this concept is further supported by findings of no significant difference in 5-year overall survival rates between enucleation or iodine plaque treatment of medium sized uveal melanomas in the randomized prospective Collaborative Ocular Melanoma Study\textsuperscript{41}. Pooled estimates from several large studies over survival following enucleation\textsuperscript{10} found a 5-year all-cause mortality rate of 16% for small tumours, 32% for medium-sized tumours and 53% for large tumours. Approximately 50% of the patients will eventually die of metastases from the uveal melanoma\textsuperscript{3}, but the prognosis is variable depending on factors such as size and location of the tumour, histology and cytogenetic alterations in the tumour cells. If the tumour is still confined within the eye wall the metastases spread haematogenously, due to the lack of intraocular lymphatic vessels. The liver is preferentially affected in 90-95\%\textsuperscript{42-46}, followed by the lung, bone, skin and lymph nodes\textsuperscript{5,45}. Although epidemiological studies have pointed out certain patient characteristics such as light coloured skin\textsuperscript{19} and lightly pigmented irides\textsuperscript{47,48} as associated with an increased risk of uveal melanoma and also an elevated risk of metastatic death\textsuperscript{49}, as long as the aetiology of uveal melanoma is unknown no preventive measures have so far been possible. The Swedish population carries high-risk phenotypic characteristics for both cutaneous and uveal melanoma. Since 1960, the incidence rate in Sweden for skin melanoma has increased between 2 to 5\% yearly\textsuperscript{4,50}. In the same population, the incidence and survival patterns regarding uveal melanoma has not been established, nor if uveal melanoma patients are at greater risk of developing other cancers, particularly skin melanomas.
Figure 1. The uvea comprises the iris, ciliary body and the choroid. Drawing by Pia Agervi.

Figure 2. Enucleated eye with a large choroidal melanoma. Prepared by Margareta Oskarsson.
BACKGROUND

The melanocyte and the eye

Melanocytes originate from melanoblasts in the neural crest of the human embryo, and emigration to their target organs, such as the skin and the eye, begins as early as at 2½ weeks of gestation. Melanocytes are further found in non-solar exposed extracutaneous sites such as the leptomeninges and mucosal surfaces of the genitalia, sinuses and palate. The melanocytes produce a dense pigment, melanin, derived from the amino acid tyrosine. Melanin is stored within melanocytes as cytoplasmatic granules in melanosomes. Two variants of melanin exist, the red/yellow pheomelanin and the brownish-black eumelanin.

The uveal melanocytes may still be melanogenically active at birth and during early childhood but will later become melanogenically dormant, although experimental data suggest that normal human choroidal melanocytes retain the capacity to produce pigment throughout adult life. The uveal melanocytes are relatively immobile in the stroma of the iris, choroid and ciliary body, with their cytoplasm packed with large melanosomes that are not transferred out of the cell.

In contrast, the skin melanocytes discharge their melanosomes to the surrounding keratinocytes through dendritic processes, and melanin production increases with ultraviolet light (UV) exposure, as melanin is believed to act as a protective cap around the genome of proliferating basal layer epithelial cells. Also, melanin has been suggested to act as a scavenger of oxidative free radicals, generated by UV-exposure, in order to prevent DNA-damage.

The function of the uveal melanocytes is less well characterized. The eye colour is not dependent on the number of melanocytes in the iris stroma, as it is found to be constant across the spectrum of eye colours. The amount of melanin granules in the superficial iris stoma is significantly lower in blue coloured eyes compared to brown, but differences in stromal pigmentation are due not only to the quantity, but also the nature of the melanin pigment. Prota found a pheomelanic-type pigmentation associated with green irides, while green-blue irides were mostly eumelanic; by contrast, green-brown and brown irides featured a mixed pigment content. The blue eye colour is, apart from a low content of melanin, also influenced by the density of the iris stroma by reflectance of light of shorter wavelengths from the posterior iris pigment epithelial layer back through the stroma.

The amount of melanin in the outer layers of the choroid parallel the skin pigmentation, and is less in fair-skinned individuals compared to those with darker skin.
Carcinogenesis

The transformation of normal human cells into malignant cells is considered a stepwise process involving multiple genetic alterations over time. Six major altered capabilities have been proposed to characterize malignant growth, namely self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis and tissue invasion and metastasis. The complex pattern of cell growth regulation, through interaction with extra-cellular matrix components, membrane receptors and signalling circuits within the cell have in recent decades become more understood through in-vitro studies of cell lines although less is known about interaction on tissue level and in vivo.

Disturbances in the key genes regulating the cell cycle, such as activation of a normal proto-oncogene to become an oncogene (“the cellular gas pedals”), inactivation of tumour suppressor genes (“the cellular brakes”) and defective DNA-repair genes are well-recognized events in the development of human cancers. In uveal melanoma over 50% of the tumours have deletions of chromosome 3, which has been demonstrated to correlate to increased risk of metastatic death, although it is not clear whether these gross chromosomal changes are markers of tumour progression or the expression of cancer-related genes. Other frequent chromosomal changes observed are extra copies or gain of material of chromosome 8, associated with worse prognosis and alterations of chromosome 6, which may carry a favourable survival prognosis. The pathways of the two important tumour suppressor genes, the p53 gene on chromosome 17 involved in detecting DNA-damage and in regulation of apoptosis, and the Rb (retinoblastoma) gene on chromosome 13, which regulates cell cycle progression, differentiation and senescence, are believed to be functionally inhibited and disrupted in uveal melanomas. The mechanisms postulated are through blocking of other tumour suppressor genes and/or over-expression of oncogenes in these pathways as, in the case of uveal melanoma, direct mutations of the p53 gene are rare and evidence of mutations in the Rb-gene is lacking. To date, no significant levels of mutated suppressor genes have convincingly been linked to uveal melanoma.
Epidemiology of uveal melanoma

Incidence rates

In a global perspective, uveal melanoma is a rare tumour. The incidence of eye cancer, which in several epidemiological studies has been used as a surrogate measure for uveal melanoma in the population above the age of 15, accounts for less than 1% of human cancers\(^8,70\). In spite of its rarity, uveal melanoma is the most common primary intraocular malignancy in white adult populations where it has been estimated to constitute 79-88% of primary intraocular cancers\(^28,71\). In the US National Cancer database\(^1\) uveal melanoma represented 5.3% of totally 84,836 melanoma cases, and in the Danish Cancer Registry during the period 1943-1989, 13.9% of melanomas were of uveal origin\(^72\).

As uveal melanoma is uncommon in non-white races\(^1,6,73,74\) reported incidence rates from countries and regions vary considerably. Also, as published studies have been conducted with different methods of case selection from varying sources, such as national or regional cancer registries with shifting degrees of population coverage, with varying methods of case ascertainment, and with differences in statistical approach and stratum weights (if age-standardization has been used), the incidence rates are not entirely comparable. The highest rates have been reported from populations of Northern European ancestry\(^5,26,27\) and from Australia\(^75\) (Table 1).

Uveal melanoma is uncommon in children and young adults; in a case series of 8000 patients only 63 (0.8%) were 20 years or younger\(^24\). The mean age at diagnosis is 55-60 years\(^5,7,26\) for both males and females. The age-specific incidence rates increases from 1.7 cases per million during the third decade to reach a maximum of 24.5 respective 17.8 cases per million for males, respectively females, in their seventies\(^6\). A male predominance\(^5,6,70,73,75,76\), especially in the older age-groups\(^75\) has been reported in several large population-based investigations.

In contrast to cutaneous melanoma, where the incidence rates in most fair-skinned populations have risen 3-7% annually from the 1960s through the 1980s\(^77\), although the rates appear to have stabilized the last decade\(^78\), no such temporal trends have been reported for uveal melanoma. During the last decades the incidence rates have remained unchanged\(^6,73,79,80\), or even slightly decreasing\(^9\).

Due to the shift to eye-preserving treatments, the proportion of morphologically verified uveal melanomas in cancer registries have continuously decreased over the decades\(^9,73\). In the SEER registry in the United States, Inskip found a histopathological confirmation rate of 95% in 1974-79, which decreased to 71% in 1990-98\(^9\). When combining international registries,
Stang noted that morphological verification of uveal melanomas decreased from 82% to 75% during the period 1983-87 to 1993-97.

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Modified from Singh 2003.

Ocular melanoma = conjunctival, iris, ciliary body and choroidal melanoma

Uveal = iris, ciliary body and choroidal melanoma

Chor+Cb = Choroidal and ciliary body melanoma

* = Eye tumours in patients ≥15 years of age
Mortality rates
Long-term follow-up (>15 years) of uveal melanoma patients reveals that eventually more than 50% will die of disseminated disease\textsuperscript{2,3}. As survival rates in uveal melanoma patients are often presented from referral centres where selected patient groups (with respect to size and location of the tumour) have undergone treatment in accordance with the local therapeutic facilities available, the survival rates show a considerable variation between investigators. (Table 2).

Mortality rates can be expressed as either all-cause mortality or disease-specific mortality; in the latter the establishment of the underlying cause of death involves a degree of uncertainty due to, in many instances, lack of histological verification of suspected metastases. With longer follow-up and ageing patients, competing risks of death will have an increasing impact on mortality rates. The rates can be calculated through life-table methods such as Kaplan-Meier or actuarial methods, but in the case of disease-specific mortality rates these techniques requires knowledge of the underlying cause of death, which is achieved with varying degrees of reliability through autopsy, premortal biopsy, CT, MRI or ultrasound imaging, death certificates, hospital records, contacts with physicians or even relatives. An alternative method, often used at population levels in cancer epidemiology, is calculation of the relative survival rate as an estimate for disease-specific mortality. The relative survival is the ratio of the observed survival (in the patient group of interest) to the expected survival in a comparable group from the general population, taking age, gender and time-period into account\textsuperscript{84}.

At diagnosis, only 1-3 % of the patients have detectable metastases\textsuperscript{40,85} but evidence supports that micrometastases can be established several years before diagnosis of the uveal melanoma\textsuperscript{86-88}. Overt metastases are invariably fatal; if untreated the median survival time is 2-6 months\textsuperscript{42,43,89}, and only modest prolongation of survival up to 12-15 months has so far been achieved with chemotherapy, hepatic arterial embolisation or liver resection\textsuperscript{44,90-92}. The mortality pattern of uveal melanoma following treatment with enucleation\textsuperscript{93} or radiation\textsuperscript{94} demonstrates increasing mortality rates from a baseline level of 1-2% per year\textsuperscript{93,94} to around 4% the first year, reaching a peak during the second and third year with an annual excess mortality rate of approximately 6-8%. Mortality rates subsequently tapers off during the next three to five years. At 5 years, 62% of the deaths due to melanoma are reported to have occurred and 90 % at 15 years\textsuperscript{3}. Although most patients in long-time follow up series\textsuperscript{2,3} have undergone enucleation, metastatic disease is reported up to 42 years\textsuperscript{95} after treatment, underscoring the “dormant” capacity of metastatic uveal melanoma cells.
Table 2. Uveal (choroidal+ciliary body) melanoma mortality rates from published reports.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Author</th>
<th>Tumour size</th>
<th>5-year mortality</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>No/deferred treatment</td>
<td>COMS\textsuperscript{96}</td>
<td>Medium</td>
<td>30</td>
<td>All-cause, Kaplan-Meier</td>
</tr>
<tr>
<td>Enucleation</td>
<td>Jensen\textsuperscript{9}</td>
<td>All</td>
<td>34-37</td>
<td>Cause-specific, actuarial</td>
</tr>
<tr>
<td></td>
<td>COMS\textsuperscript{97}</td>
<td>Large</td>
<td>38-43</td>
<td>All-cause, Kaplan-Meier</td>
</tr>
<tr>
<td></td>
<td>Jensen\textsuperscript{10}</td>
<td>Small, Medium, Large</td>
<td>16, 32, 53</td>
<td>Meta-analysis, All-cause, Crude, Actuarial, Kaplan-Meier</td>
</tr>
<tr>
<td></td>
<td>Jensen\textsuperscript{9}</td>
<td>All</td>
<td>31</td>
<td>Cause specific, Cumulative incidence</td>
</tr>
<tr>
<td></td>
<td>Jensen\textsuperscript{97}</td>
<td>All</td>
<td>30</td>
<td>Cause-specific, Kaplan-Meier</td>
</tr>
<tr>
<td>COMS\textsuperscript{98}</td>
<td></td>
<td>Medium</td>
<td>18</td>
<td>All-cause, Kaplan-Meier</td>
</tr>
<tr>
<td></td>
<td>Puusaari\textsuperscript{100}</td>
<td>Large</td>
<td>38, 35</td>
<td>All-cause, Kaplan-Meier Cause-specific, Kaplan-Meier</td>
</tr>
<tr>
<td>Brachytherapy, Iodine</td>
<td>COMS\textsuperscript{98}</td>
<td>Medium</td>
<td>16</td>
<td>All-cause, Kaplan-Meier</td>
</tr>
<tr>
<td></td>
<td>Lommartsch\textsuperscript{101}</td>
<td>All (T1,T2,T3), All (T1,T2,T3)</td>
<td>11</td>
<td>All-cause, Actuarial Cause-specific, Actuarial</td>
</tr>
<tr>
<td></td>
<td>Seregard\textsuperscript{12}</td>
<td>Small-medium (T1-T2), Large (T3)</td>
<td>6, 26</td>
<td>Meta-analysis Cause-specific, Kaplan-Meier, Actuarial, Cumulative</td>
</tr>
<tr>
<td>Charged particles, Helium</td>
<td>Char\textsuperscript{13}</td>
<td>All</td>
<td>17</td>
<td>Cause-specific, Cumulative incidence</td>
</tr>
<tr>
<td>Charged particles, Protons</td>
<td>Gragoudas\textsuperscript{14}</td>
<td>All</td>
<td>19</td>
<td>Cause-specific, Kaplan-Meier</td>
</tr>
<tr>
<td>Several treatment modalities</td>
<td>Singh\textsuperscript{15}</td>
<td>All *</td>
<td>16-24</td>
<td>Cause-specific, Relative survival</td>
</tr>
<tr>
<td>Iris melanomas</td>
<td>Shields\textsuperscript{12}</td>
<td>Iris</td>
<td>3</td>
<td>Cause-specific, Kaplan-Meier</td>
</tr>
</tbody>
</table>

* Population-based registry series including iris melanomas
‡ % with metastasis at 5 years, death not specified
Risk factors for uveal melanoma

Host factors

Heredity:

Although a classical case series from London originating in the 19th century describes a family with four generations suffering from uveal melanoma and, in some individuals, also breast cancer\textsuperscript{101-103} (probably representing a Li-Fraumeni syndrome as p53 mutations were later found in archival specimens), uveal melanoma is rarely considered an inherited trait.

In a large case series of 4500 patients, Singh and coworkers\textsuperscript{104} found 56 patients (0.6%) in 27 families (first to third degree relatives) with a family history of uveal melanoma. Characteristics of cancer predisposition syndromes\textsuperscript{105} such as early onset, bilaterality in paired organs, multiple primary tumours, familial occurrence and phenotypic associations were analyzed. These patients were found to have a median age of onset (55 years) and a frequency of uveal nevi similar to the sporadic cases, one patient had a familial atypical mole and melanoma syndrome, none had bilateral uveal melanoma or cutaneous melanoma, but the incidence of second primary malignancies in the probands was four times higher than expected from population rates. Because of the low incidence of uveal melanoma, familial cases might occur more often than by chance alone\textsuperscript{106} but in the review by Kodjikan et al\textsuperscript{107} of the 154 patients in 71 families reported in the literature, no clear pattern of inheritance could be elucidated due to small pedigrees.

In cutaneous melanoma, where approximately 10% of cases are familial and 5% are estimated to be truly hereditary\textsuperscript{108}, mutations in the p16 tumour suppressor gene (CDKN2A) on chromosome 9p21 have been identified in 40% of the hereditary melanomas\textsuperscript{108}. In contrast, direct p16 mutations has rarely been found in familial uveal melanomas, nor in sporadic cases\textsuperscript{109-113} although the p16 gene (involved in the Rb pathway) may be silenced and inactivated through other mechanisms\textsuperscript{67}. Mutations in the DNA-repair gene BRCA2 on chromosome 13 predispose to hereditary breast and ovary cancer\textsuperscript{114} and an increased risk of uveal melanoma has been proposed in these patients\textsuperscript{115}. In uveal melanoma only a small minority of patients, 2-3%, appears to carry a BRCA2 mutation\textsuperscript{116,117}, where subsets of patients with onset before the age of 50 or a family history of breast cancer\textsuperscript{118,119} appears to be overrepresented.

Phenotype:

O.A. Jensen in his thorough monograph\textsuperscript{5} systematically related iris and hair colour to the risk of developing uveal melanoma and reported a significant preponderance of fair eyes (blue,
grey and grayish green) among the uveal melanoma patients compared to a population sample, but no difference regarding hair colour. Later epidemiological studies have verified the association between light iris colour and uveal melanoma\textsuperscript{20,21,47,48,120,121} with odds ratios suggesting a doubled risk of uveal melanoma in fair-eyed individuals compared to brown eyed. Some investigators found light skin colour\textsuperscript{19,21,120} or the tendency to sun-burn\textsuperscript{47,48} a risk factor for uveal melanoma, but other studies\textsuperscript{20,121} have not been able to confirm this finding, nor does hair colour in any consistent way appear to influence the risk of uveal melanoma\textsuperscript{19,20,47,48}.

Pigmented lesions:
Congenital hyperpigmentation of the episclera, the eyelids and surrounding skin due to an increased number of continent melanocytes in the sclera respectively deep dermal layers (oculodermal melanocytosis, nevus of Ota)\textsuperscript{122} is in Caucasians associated with an estimated life-time risk of 1 in 400\textsuperscript{123} of developing an uveal melanoma and occurs in approximately 1.4\% of uveal melanoma patients\textsuperscript{124}. In young patients (less than 20 years), the prevalence of oculo(dermal) melanocytosis appears even higher, 11\%\textsuperscript{24}.

Choroidal naevi have an estimated prevalence of 5-10\% in adults\textsuperscript{125,126}. Although regarded as precursor lesions to uveal melanoma naevi probably seldom (1 in 4000-5000) undergo malignant transformation\textsuperscript{125}. In the population-based Blue Mountains Eye Study in which the prevalence of choroidal naevi was 6.5\%, only 1 naevus of 160 showed clinical growth over a 5-year period\textsuperscript{127}. Factors indicating risk of growth and transition of a choroidal naevi into a small malignant melanoma include thickness >2 mm, subretinal fluid, visual symptoms, orange pigment and margins touching the optic disc\textsuperscript{128}. None of these features indicate a 5-year risk of growth of 3\%, one factor 38\% and two factors or more a 50-56\% risk of growth\textsuperscript{128}. In practice, most unsuspicious melanocytic lesions less than 3 mm in diameter and 1 mm in thickness are managed by observation and serial fundus photography for documented growth.

The relationship between pigmented cutaneous lesions and uveal melanoma remains obscure. The total number of benign naevi are recognized as the most important risk factor for cutaneous melanoma in Northern European populations\textsuperscript{78}. The dysplastic naevus syndrome, DNS (also named atypical mole syndrome, familial atypical mole and melanoma syndrome or B-K mole syndrome) with a large number of clinically atypical naevi (>5 mm, varying degrees of cytologic atypia, irregular borders and uneven pigmentation) and a family history of cutaneous melanoma is also a risk factor for cutaneous melanoma\textsuperscript{129}. The prevalence of dysplastic naevi in the general population is estimated to 1-8\% in Europe and Australia\textsuperscript{130-133}.
A previous Swedish case-control study was unable to detect a higher frequency of uveal naevi in patients with dysplastic naevus syndrome\textsuperscript{134}.

Reports of co-existing atypical naevi\textsuperscript{135}, cutaneous melanoma and ocular melanoma in probands and their families exist in the literature, often as case reports or case series\textsuperscript{130,136-142} or in small case-control studies\textsuperscript{143,144} with varying definitions of atypical naevi. Bataille\textsuperscript{138} examined 207 eye melanoma patients, of which 5 had cutaneous melanoma, in three cases combined with DNS (expected cases of cutaneous melanoma = 0.4). Three of the eye melanomas were choroidal and two were of conjunctival origin. In a study by Richtig\textsuperscript{130} of 136 eye melanoma patients (129 uveal, 2 bilateral uveal, 4 conjunctival and 1 lacrimal sac melanoma), 35\% had more than 5 dysplastic naevi compared to 1.2\% in the general population, and 3.7\% of the patients were diagnosed with concurrent cutaneous melanoma.

An article reviewing the relationship between ocular melanoma and cutaneous melanoma\textsuperscript{145} pointed out that 18-23\% of the ocular melanomas associated with cutaneous melanoma or DNS in published reports were conjunctival, which indicates an overrepresentation as the incidence rate of conjunctival melanoma is 0.2 - 0.5 cases /10\textsuperscript{6} in white populations\textsuperscript{146}. The authors concluded that evidence exists for comorbid cutaneous melanoma and ocular melanoma in individuals with DNS and conjunctival melanoma.

The co-occurrence of uveal and cutaneous melanoma has further been investigated through a few studies utilizing population-based cancer registries\textsuperscript{72,147-149} where a non-significantly elevated relative risk of 1.75 (95\% CI: 0.48-4.47)\textsuperscript{72} for cutaneous melanoma following eye melanoma, no association\textsuperscript{147}, respectively an increased relative risk (4.0\textsuperscript{148} to 4.6 times\textsuperscript{149}) have been reported. Other registry-based studies exploring subsequent cancers after eye cancers\textsuperscript{150-152} are less interpretable, as they also include retinoblastomas with a well acknowledged risk of multiple primary cancers as a component of an inherited cancer syndrome.

**External risk factors**

Solar ultraviolet (UV) radiation:

Ultraviolet radiation affecting humans are UV-A (315-400 nm) and UV-B (280-315 nm) as UV-C (100-295 nm) is absorbed by the atmosphere. UV-B radiation more effectively produces sunburns and DNA-damage than UV-A\textsuperscript{15} and is a cause of both cutaneous melanomas\textsuperscript{14} and non-melanocytic skin cancer (i.e. basal cell and squamous cell carcinoma)\textsuperscript{13,15,153}. The pattern of UV-exposure and risk of cancer is complex and differs between these entities, as for cutaneous melanoma a significant positive association exists.
between intermittent exposure and sunburns, but no relationship or even a reduced risk for heavy occupational exposure. Evidence further supports that UV-exposure causing sunburns during childhood and adolescence may be particularly harmful. Also, both intermittent and cumulative UV-exposure are found to be causal factors in basal cell carcinoma in contrast to squamous cell carcinoma where total sun exposure is a risk factor.

Evidence supporting UV-light as a risk factor for uveal melanoma is inconclusive. During early childhood 75% of UV-light is transmitted through the lens, but after the age of 10 the lens progressively becomes an effective filter due to increasing nuclear accumulation of chromatophores. The vulnerability of the ocular structures to UV-light might therefore change during life. Case-control studies carried out to evaluate the association between uveal melanoma and temporal, latitudinal and quantitative measures of UV-radiation have produced conflicting results. A positive correlation to UV-exposure, expressed in terms of sunbathing, outdoor activities, use of sun lamps was found in some studies, where in other studies no support for this association could be assessed. Birthplace south of latitude 40º N in the United States was in one study found protective, although living more than 5 years in the same area was associated with increased risk. No latitude gradient in the incidence of ocular melanoma has been demonstrated in white populations. In countries with high ambient UV-light exposure and populations of European ancestry, such as Australia, the incidence rates of uveal melanoma equals the rates reported from Europe and the United States. No increase in incidence rates paralleling cutaneous melanoma has so far been observed. In Israel, Iscovitch concluded that second generation Jewish immigrants, despite being reared in an environment with more intense UV-light, had the same incidence rates of uveal melanoma as their parents.

The fact that lightly pigmented eyes have an increased risk of uveal melanoma could support the concept of UV-light as an aetiologic factor, as transmittance of light might be enhanced through a lightly pigmented iris and uveal melanocytes with less amount of melanin around the nuclei possibly have reduced photo-protective properties and may be more prone to the carcinogenic effects of UV-light. One study, which investigated the relationship between tumour location and retinal topography, found an uneven distribution of melanomas with predilection for the macular region, which positively correlated with the dose distribution of solar light. Others have reported lack of correlation between location of uveal melanomas and UV-radiation distribution in the eye.
In cutaneous melanoma, mutations in the N-ras oncogene are common, preferentially in melanomas located on sun-exposed areas\textsuperscript{158} which indicate an association with UV-light. In uveal melanomas on the other hand, no mutations so far have been found in the N-ras pathway\textsuperscript{159,160,161} which further questions the role and possible mechanisms of UV-radiation in the pathogenesis of uveal melanoma.

Occupational risk factors:
Epidemiological studies evaluating occupational risk factors for uveal melanoma have not been able to establish consistent evidence of specific occupations, chemicals or environmental factors associated with uveal melanoma\textsuperscript{76,120,121}. Both farming\textsuperscript{162} and indoor work\textsuperscript{76,121,163} has been related to excess risk of uveal melanoma. In a study by Guénel\textsuperscript{120}, exposure to artificial sources of UV-radiation (welding) was strongly correlated to an elevated risk for uveal melanoma (OR 7.3; 95% CI 2.6-20.1). The positive association has previously been reported by Tucker\textsuperscript{20} and Holly\textsuperscript{164}, but other studies have not found such an association\textsuperscript{19,163}. The authors\textsuperscript{120} commented that the ultraviolet spectrum from artificial sources may contain different proportions of the UV-spectra compared to solar light, is delivered in intermittent peaks, and that gas welding also entails exposure to infrared light. In the same study\textsuperscript{120} no association was found to exposure to solar UV-radiation occurring in outdoor occupations.

To date, no evidence exists for an association between radiofrequency waves (microwaves) from mobile telephones and uveal melanoma\textsuperscript{9,165}, which has been suggested\textsuperscript{166} but the issue is presently under investigation\textsuperscript{167}.

**Tumour related prognostic factors**

*Clinical prognostic factors*

Tumour location:
Ciliary body melanomas are considered carrying a more unfavorable prognosis\textsuperscript{168-172}, compared to melanomas posterior to the equator, whereas iris melanomas are reported to metastasize in 3% after 5 years, and with a 20-year risk of 10% of metastatic disease\textsuperscript{23,170}. Ciliary body melanomas are often larger, consists of a greater proportion of epitelioid cells\textsuperscript{173} and have recently been found to have more frequent cytogenetic alterations (monosomy 3)\textsuperscript{63,64} which correlates to adverse outcome\textsuperscript{65,66,174}. 
Tumour size:

Increasing tumour size has proved a robust indicator of worse prognosis in numerous studies\textsuperscript{10,99,169,170,175,176}. Meta-analysis has estimated a 5-year all-cause mortality rate of 16\% for small tumours, 32\% for medium-sized tumours and 53\% for large tumours following enucleation\textsuperscript{10} (Table 2).

The classification system largely relies on measurements of largest basal diameter (LBD), or largest tumour diameter (LTD), through ophthalmoscopy or ultrasonography. Uveal melanomas have become classified into small (LBD $\leq$10 mm), medium (LBD 10-15 mm) and large (LBD>15 mm) tumours. More formal classifications systems have also included tumour height, such as the TNM where small (T1) tumours are $\leq$3 mm, medium (T2) are $>$3-$\leq$5 mm and large (T3) $>$5 mm high. In the COMS, uveal melanomas were classified as small (LTD 5-16 mm, height 1-2.5 mm), medium (LTD $>$16 mm, height 2.5-$\leq$10 mm) and large tumours (LTD $>$16 mm, height $>$10 mm), with the exception of a peripapillary location, in which instance the tumour was classified as large when 8 mm high\textsuperscript{97,98}.

Extraocular extension is associated with an adverse prognosis\textsuperscript{169,171,177,178}. The fibrous scleral wall is a resistant barrier to penetrate but extraocular growth is reported to occur in 4\% to 17\%\textsuperscript{29,99,171,178}, either via anterior invasion of a ciliary body melanoma to the anterior chamber and aqueous outflow channels or more posteriorly through the scleral wall, following the emissaries of the vortex veins, ciliary nerves and the optic nerve\textsuperscript{177}.

Histopathological prognostic factors

Cell type:

The original classification system described by Callender\textsuperscript{179} in 1931 was modified and simplified in 1983 by pathologists at the Armed Forces Institute of Pathology\textsuperscript{180} into spindle, epithelioid and mixed cell types. The spindle cell tumours with cohesive growth and slender nuclei has a more favourable prognosis compared to the epithelioid cell tumours with larger, polygonal cells with nuclear polymorphisms\textsuperscript{99,170}. As transitional cell morphology may pose classification difficulties, classifications tend to exhibit intra- and interobserver variability, nor does any exact definition exist of the proportion of epithelioid cells that constitutes a mixed cell type tumour\textsuperscript{181}.

Cell proliferation:

Elevated levels of cell proliferation markers such as mitotic counts\textsuperscript{182}, the mean of the ten largest nucleoli\textsuperscript{183} and immuno-expression of proteins from cells undergoing active phases in the cell cycle, such as proliferating cellular antigen (PCNA)\textsuperscript{184} or Ki67\textsuperscript{185}, have in some
studies been correlated to increased mortality. Also, the microvascular architecture (now recognized as extracellular matrix patterns of possible tumour cell origin or so-called vasculogenic mimicry) in uveal melanomas with nine different patterns, described by Folberg\textsuperscript{186}, has been associated with increased risk of metastatic death in the presence of networks and closed vascular loops\textsuperscript{187-189}.

Cytogenetic prognostic factors
Non-random chromosomal alterations have been detected in uveal melanomas, including loss of chromosome 3 (monosomy 3), amplifications or extra copies of chromosome 8 and abnormalities in the long and short arms of chromosome 6\textsuperscript{190,191}. Abundant evidence has confirmed prognostic significance of monosomy 3\textsuperscript{63-66,174,192}, associated with a reduced 5-year survival rate to less than 50\%\textsuperscript{63,174}. Monosomy 3 has further been positively associated with epithelioid cytology, ciliary body involvement and intratumoural vascular loops\textsuperscript{174}. Gains on chromosome 8 also implicate reduced survival\textsuperscript{64} and are often co-current with alterations on chromosome 3. On the other hand, abnormalities on chromosome 6 (gain on the short arm) appears to have a protective effect associated with a more favourable prognosis\textsuperscript{192}.

Growing knowledge of gene expression profiling using microarray chip-based techniques have indicated that uveal melanomas can be dichotomized into two molecular classes (correlating to increased copies on chromosome 6 respectively monosomy 3) associated with survival\textsuperscript{66}.

As fine-needle aspiration biopsies are not routinely used in the diagnosis of uveal melanomas it should be noted that chromosomal rearrangements mainly have been studied in large tumours undergoing enucleation and local resection, as medium and smaller sized tumours preferentially are handled with radiotherapy and therefore lacks histological specimens\textsuperscript{66,174}.

Treatment of uveal melanoma

Removal of the eye, enucleation, was the dominating therapy for uveal melanoma until the late 1970s, when Zimmerman and McLean\textsuperscript{93} in 1978 suggested that enucleation might instead promote seeding of tumour cells and/or lower the host’s immunological defense, thus accelerating the metastatic process, as increased mortality rates two to three years following enucleation had been observed by many investigators. The issue resulted in popularization and further development of eye-sparing treatments, although pioneer work was performed as early as in 1929 by R.B. Moore\textsuperscript{193} implanting radon seeds in an uveal melanoma. Stallard
further modified radiotherapy, by placing radioactive cobalt-60 seeds on a plaque, which could be sutured onto the surface of eye and later removed, and a case series of 100 patients\textsuperscript{194} was published in 1966. Due to the high activity in cobalt plaques, isotopes with presumably lower radiobiological side effects, such as 125-iodine and 106-ruthenium later came to replace cobalt. In Europe, Lommatzsch\textsuperscript{30,195,196} introduced the use of the β-emitter 106-ruthenium, which has become widely used for mainly small to medium sized uveal melanomas\textsuperscript{197-201} whereas the γ-emitter 125-iodine preferentially has been used for larger tumours\textsuperscript{39,100,202} as an alternative to enucleation or local resection. In North America, brachytherapy with 125-iodine episcleral plaques\textsuperscript{32,203,204} has gained wide acceptance even for small to medium melanomas and was therefore chosen for the brachytherapy arm of the COMS study when randomizing patients with medium melanomas to plaque treatment or enucleation\textsuperscript{98}.

Alternative eye-sparing treatments include external beam radiotherapy with charged protons\textsuperscript{34,38} or helium ions\textsuperscript{35} which is offered at a few centres in the world, and transscleral resection\textsuperscript{36,37,205,206} can also provide an option in selected cases, although the technique is surgically demanding and requires anaesthesia under hypotony. The role of more recent therapeutic developments, such as radiosurgery with gamma-knifes\textsuperscript{207,208} in the treatment of uveal melanoma is not yet established.

Transpupillary thermotherapy (TTT)\textsuperscript{209-211}, delivered with a 810 nm diode laser through a dilated pupil was introduced by Oosterhuis in 1995. Initially, TTT was suggested as an adjunct to brachytherapy, and has as such become well established in the therapeutic arsenal\textsuperscript{212,213}. TTT has also been used as the sole treatment for small melanomas up to 3.9 mm height\textsuperscript{214,215} but with growing concern about the inability of TTT to eradicate intrascleral melanoma cells\textsuperscript{216,217} and with a reported treatment failure rate up to 29%\textsuperscript{217}, the initial promising role of TTT as sole therapy has become reevaluated.

Enucleation is still a primary choice of treatment in cases of large uveal melanomas, especially in eyes lacking visual potential, with secondary complications such as glaucoma or pain, or a peripapillary growth preventing a proper placement of a plaque. The role of ancillary external radiotherapy became investigated in the COMS large melanoma study, where 1003 patients were randomized to enucleation only or enucleation preceded by 2000 cGy external radiation. No significant difference in 5-year all-cause survival or local orbital complications was detected between the groups\textsuperscript{97}. Although accumulating evidence indicated that probably no relevant difference in survival rates existed due to choice of treatment\textsuperscript{31,38,218,219}, the issue was finally settled when the randomized COMS study presented the results of the medium sized melanoma trial in which 1317 patients participated, receiving
either brachytherapy with 125-iodine or enucleation. The 5-year all-cause survival rate was 82% in the brachytherapy arm and 81% in the enucleated group respectively.\textsuperscript{98}

Outcome measures have now become more focused on local tumour control, relapse rates and occurrence of secondary enucleation, visual function and quality of life assessments.\textsuperscript{220,221} Local recurrence following radiotherapy is observed in 3-22\%\textsuperscript{30,200,219,222-224}, where treatment with ruthenium appears to carry a slightly higher relapse rate\textsuperscript{30,197,200,222} compared to iodine\textsuperscript{222,225} and charged particles\textsuperscript{34,35,219,226}. Relapses are most likely to occur at the tumour margins and have been associated with an increased risk of metastatic death.\textsuperscript{227,228} The side effects are mainly due to radiation delivered to adjacent structures. Damage to the anterior part of the eye and adnexal structures may include epiphora, lash loss, cataract and neovascular glaucoma, in the posterior segment complications such as maculopathy, vascular occlusions, radiation retinopathy and optic neuropathy account for substantial morbidity. The pattern of complications differs slightly between methods of treatment. Charged particle therapy carries a higher rate of anterior segment complications, particularly neovascular glaucoma\textsuperscript{35,39,229} which has been reported to occur in 7-35\%\textsuperscript{35}. For all treatment modalities, adverse effects of radiation commonly occur in the posterior segment. Signs of radiation retinopathy have been identified in up to 43\% of plaque treated patients.\textsuperscript{230} The incidence of maculopathy and optic neuropathy is dependant on the distance from the tumour border to these structures and accordingly vary between case series due to patient selection. Following proton beam therapy, the 5-year cumulative incidence of maculopathy was 75\% for tumours within one disc diameter (1.5 mm) from the macula, and 40\% otherwise.\textsuperscript{229} In a ruthenium series\textsuperscript{231} the overall 5-year risk of maculopathy was 30\% and risk of optic neuropathy 12\%, with increasing risks with closer proximity to the macula and optic disc, respectively. Visual acuity following treatment is, apart from pretreatment values, subsequently a function of the amount of damage to the posterior pole caused by the location of the tumour and the consequences of applied treatment.
AIMS OF THE STUDY

To investigate the incidence rates of uveal melanoma in the Swedish population during the period 1960 through 1998 using the Swedish Cancer Registry

To study the all-cause and disease-specific survival rates in Swedish uveal melanoma patients during the same period

To investigate the relationship between uveal melanoma and other primary malignancies, especially the risk of co-existing cutaneous melanoma using the Swedish Cancer Registry

To study familiar relationships between uveal melanoma patients and estimate the incidence of familial cases on a population level with the aid of the Multigeneration Registry

To analyze the impact of treatment with 106-ruthenium episcleral plaques on survival, functional outcome and rate of secondary enucleation in Swedish uveal melanoma patients receiving brachytherapy during the period 1979 up to and including April 2003
MATERIAL AND METHODS

Population-based registries

Population-based registries have a long tradition in Sweden, since the nation began to collect population statistics as early as in 1749. The registries’ usefulness in epidemiological research is facilitated by the ten-digit personal identification number, introduced in 1947, which is unique for every inhabitant and permits linkage of each individual into different registries. In the present studies, information from the Cancer Registry, the Cause of Death Registry, the Multigeneration Registry and official demographic population statistics from Statistics Sweden is used, along with a control group drawn from the Registry of the Total Population for a matched case-control study. To protect personal integrity, the use of registries and personal identification numbers in research is strictly regulated according to legislations and regulations from the National Data Inspection Authority, in addition to requiring permission from ethical research committees at the universities.

The Swedish Cancer Registry

The registry was founded in 1958 and covers the whole population, as it is compulsory for every health care provider to report newly detected cancer cases. Since 1982, the reports are primarily sent to six regional oncology centres where they undergo control, registration and coding. The incident cancer cases are annually reported to the Swedish Cancer Registry, administrated by the National Board of Health and Welfare (Socialstyrelsen). Multiplicative registrations from clinicians, pathologists/ cytologists along with cases diagnosed at autopsy ensure a high inclusion rate, with elimination of duplicates through the personal identification number. The overall inclusion rates is estimated to 96\%\textsuperscript{232,233}. The Cancer Registry does not accept notifications from death certificates. The information available in the Swedish Cancer Registry is the personal identification number, sex, age, place of residence, date of death, cause of death and date of emigration, apart from medical data. The registry records solid malignant tumours (since 2003 including basal cell carcinomas), malignant diseases in the haematopoetic system, epithelial and melanocytic carcinomas in situ along with certain benign tumours affecting the central nervous system, endocrine system and reproductive organs. For the whole period 1958 and onwards, the site of tumour is available as the WHO
ICD-7 code, for the years 1987-1992 also as ICD-9 and from 1993 ICD-O/2, in 2005 changed to ICD-O/3. The histological type has throughout the period 1958- been available as the old histology code (WHO/HS/CANC/24.1) and from 1993 according to ICD-O/2, changed to ICD-O/3 in 2005. Tumour stage has been collected since 2004 according to TNM (6th edition). Information is also provided concerning the date of diagnosis, the method of assessment of diagnosis, reporting hospital and pathology department and identification number of the tissue specimen.

The Cause of Death Registry

Statistics on causes of death were published annually between 1911-1993 by Statistics Sweden (SCB). The National Swedish Board of Health and Welfare has been responsible for publication since 1994. The Cause of Death Registry is linked to the Cancer Registry. The registrations in the Cause of Death Registry are taken from death certificates, issued by a physician, according to instructions from the WHO. The underlying cause of death is defined as the disease or injury that initiated the chain of diseases that finally resulted in death. The main source of the statistical unreliability is the varying level of certainty in defining the underlying causes of death. A decrease in the number of autopsies performed might lead to inaccurate statistics. In Sweden, the proportion of autopsies has decreased from about 50% at the beginning of the seventies to about 14% in 2002. The ICD-coding of the cause of death has changed during the investigation period 1960-2003; during the period 1960-68 the coding was according to ICD-7, 1969-86 to ICD-8, 1987-1996 to ICD-9 and from 1997 according to ICD-10. The main variables in the registry are personal identification number, sex, place of residence, date of death, underlying cause of death, nature of injury and the method of establishing the cause of death (autopsy or clinical investigation).

The Multigeneration Registry

The Multigeneration Registry, founded in year 2000 and administered by Statistics Sweden, is a database in which the index persons, born after 1931 and living in Sweden after 1961, can be linked to their parents, siblings and children and, to a lesser extent, grandparents and cousins. The source of information is the general Population Registry, administered through the Swedish taxation authorities.
The Multigeneration Registry is population-based but not complete regarding parents who have died before 1947, when the personal identification number was introduced, but approximately 85% of the index persons have their parents in the registry. The registry presently contains 8.5 million index persons and 11 million unique individuals (index persons + parents).

The Registry of the Total Population

Since 1968, Statistics Sweden keeps the Registry of the Total Population containing extracted information from the general Population Registry. The variables found are personal identification number, name, address, marital status, citizenship and country of birth, family members, income, date of immigration and emigration, and parents’ country of birth. The information can be used for pure demographic purposes, such as analysis of the population size and distribution, marital status, death and migration rates in different parts of the country. The information in the Registry of the Total Population is often used as background information in medical and behavioural research and can also provide researchers with samples, cohorts and controls from the general population.

Recruitment of patients into the present studies

The study base is the Swedish population, in which individuals diagnosed with uveal melanoma during the period 1st January 1960 to 31st December 1998 were searched through the files of the Cancer Registry. As the Cancer Registry has consistently coded cancers according to ICD-7 throughout the investigation period, the patients selected were registered with ICD-7 code 192 (malignant intraocular tumour) combined with the WHO/HS/CANC/24.1 histology code 176 (malignant melanoma). The staging of uveal melanoma was not possible to assess as the variable stage became introduced only in 2004. Until 1979, uveal melanoma patients underwent enucleation (or, in the case of iris melanomas, local resection) and histopathologically classified specimens were available. Following the introduction of brachytherapy for uveal melanoma in Sweden in 1979, a steadily increasing number of patients lacked histopathologic verification and became registered with ICD-7 code 192 combined with histology code 996 (unspecified malignant tumour) in the Cancer Registry. Treatment with brachytherapy in Sweden has always been centralized to one ophthalmic oncology centre at the Department of Ophthalmology at the...
Karolinska Hospital (in 1990 relocated to St. Erik’s Eye Hospital) in collaboration with the Hospital Physics Unit at the Department of Oncology at the Karolinska Hospital. Patients who had received ocular radiotherapy could be traced through a dedicated database set up at the Department of Oncology at the Karolinska Hospital, containing information extracted from hospital files along with radiophysical data. Through comparing patients in the Cancer Registry registered with intraocular cancer (ICD-7 code 192) and unspecified malignant tumour (histology code 996) with the patients in the radiotherapy database receiving brachytherapy for a uveal melanoma, patients not having uveal melanoma could be removed and patients missing in the Cancer Registry could be added to the final file over uveal melanoma patients. During the period 1989-1991 did, in addition, a small group of patients receive external beam radiation with protons at the Gustaf Werner Institute in Uppsala, Sweden. The records of these 20 patients were retrieved, checked against the Cancer Registry and missing cases put into the file of uveal melanoma patients (used in papers I, II and IV). Through these measures, an almost complete inclusion rate is assumed, with the exception of the rare patient who might have chosen treatment abroad.

Diagnostic accuracy was confirmed by re-examination by an experienced pathologist (SS) of a random sample of 916 paraffin-embedded specimens of eyes, presumably enucleated for a uveal melanoma during the period 1960 to 1998. The specimens originated from several pathology laboratories across Sweden. In three cases (0.33%) did the original diagnosis require revision.

Through the personal identification number, several malignant tumours in the Cancer Registry can be linked to the same patient. The files of the uveal melanoma patients could contain up to five separate registrations of other primary malignancies, which were further investigated when evaluating the notations in the Cause of Death Registry (in paper II) and when studying the association of uveal melanomas with other cancers (paper IV).

Treatment with ruthenium brachytherapy during the period 1\textsuperscript{st} January 1979 to 30\textsuperscript{th} April 2003 was separately investigated in one study (paper III). The patients were recruited from the database with patients treated with radiotherapy at the Department of Oncology at the Karolinska Hospital. The clinical data were in some instances checked against archival hospital files from the Ocular Oncology Service at St. Eriks’s Eye Hospital/ Karolinska Hospital.

In the study concerning familial cases of uveal melanoma (paper IV), information was sought in the Multigeneration Registry. The uveal melanoma patients (index persons) in our database were crosschecked with each other in the Multigeneration Registry to find related cases. The
number of relatives of the index person and their mode of relationship to the index person were also identified, along with the relatives’ gender, date of birth and, when applicable, date of death or emigration. The latter search was performed in order to estimate the number of expected uveal melanoma cases among the relatives.

When performing the case-control study (paper IV) in order to evaluate the risk of acquiring a primary cancer prior to the diagnosis of uveal melanoma, five gender and age-matched (± 1 day) population controls per uveal melanoma patient were drawn from the Registry of the Total Population by Statistics Sweden. The controls had further to be alive on the day the corresponding case became diagnosed with uveal melanoma to assure an equivalent time at risk. The file with the control population was sent directly from Statistics Sweden to the Cancer Registry to search for records of cancers amongst the controls occurring prior to the date of diagnosis of uveal melanoma for the corresponding case. Each control received a file number, which made it possible to link them and their registered cancers to the corresponding uveal melanoma patient, as detailed information, such as name and personal identification number of the controls, was kept within the Registries and not disclosed to the investigators.

**Follow-up of patients**

Patients in studies I, II and IV were followed until 31\textsuperscript{st} December 1998 if death or emigration did not occur before. In paper III, the recruitment of patients continued until 30\textsuperscript{th} April 2003 and follow-up of vital status extended to 30\textsuperscript{th} April 2004.

For paper II, information from the Cause of Death Registry was sought concerning date of death, underlying cause of death and how the cause of death was established. Both the ICD-coding (as mentioned above) and the coding of the manner of establishing the cause of death shift between time periods, but throughout the study period data was available of whether an autopsy or forensic investigation has been undertaken, otherwise it was assumed that no such investigation was performed. The underlying cause of death was in many instances registered as due to cutaneous melanoma or other cancers, a finding that necessitated further controls against the Cancer Registry to ascertain validity. Previously, an inter-registry concordance of 87\% between cancer registry diagnoses and certified underlying causes of death has been shown\textsuperscript{233}. In the case of a registered skin melanoma, tissue specimens were requested from pathology laboratories and, if available, re-evaluated (by SS) in order to confirm the diagnosis of a primary cutaneous melanoma. In study IV, available specimens from primary liver
cancers became evaluated in the same manner to rule out miscoded metastases from the uveal melanoma.

**Epidemiological and statistical analyses**

**Incidence rates**

The incidence rate is a ratio, with the number of subjects developing disease in the numerator and total time experienced for the population followed in the denominator. Incidence rate is often expressed as new cases per million occurring during a specified time-period, usually a year. As cancer usually affects elderly people, an absolute increase in the number of cases over time can therefore be expected with increasing crude incidence rates, due to altered demographic patterns with a higher proportion of elderly people in many populations. Through age-standardization, a comparison of incidence rates over time is possible. Standardization is a method of combining the rates in two or more categories (for example age groups) by taking a weighted average of them. The weights are derived from an arbitrary standard population and reflect the age distribution at a specific point in time in that population. In paper I, age-standardization for each gender was undertaken with the direct method, using the age distribution in the Swedish population during the period 1970-74 as weights (Table 3), along with an estimation of the age-specific incidence for the eight age-groups specified in Table 4.

Table 3. Stratum weights of the Swedish population during the period 1970-74

<table>
<thead>
<tr>
<th>Age group (years)</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>
</tr>
<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>85-</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The relative change in age-standardized incidence rates over time was calculated with a linear regression model, \( Y = e^{a+bx} \) in which the incidence numbers are transformed into logarithms.
and related to a linear trend, assuming a constant annual change. The annual change was
given as a percentage with 95% confidence intervals (CI). The level for statistical significance
was set at a p-value of 0.05 or less.

The influence of immigration of individuals from countries outside Europe, where the
incidence of uveal melanoma is presumable lower, was estimated for the years 1970, 1980,
1990 and 1998 (paper I). At each point in time, the number of immigrants and their age-
distribution was collected gender-wise through official statistics. The crude incidence number
of uveal melanoma in the total Swedish population for the years specified above was
calculated, with 95% CI, along with an estimation of these rates when the immigrant
population was excluded. For the purpose of calculation, the incidence rate in immigrants was
set at nil.

When comparing incidence rates of subsequent cancers in uveal melanoma patients to the
expected rates in the general population, the standardized incidence ratio (SIR), was used
(paper IV). The expected number of invasive cancer cases, calculated as person-years at risk
was estimated according to the incidence rates in the general Swedish population with
consideration to gender, age and calendar period, using the software PYRS\textsuperscript{235}. The population
was divided into four age groups (0-44, 45-59, 60-74, and 75+ years), four calendar periods
(1960-69, 1970-79, 1980-89, 1990-98) and gender. The SIRs with 95% confidence intervals
were calculated by dividing the observed number of cancer cases with the expected, assuming
a Poisson distribution of the observed cases.

As the number of cancers experienced prior to diagnosis of uveal melanoma excludes the
most aggressive forms with fatal outcome, the uveal melanoma patients are until the date of
diagnosis of uveal melanoma thus selected from the general population with respect to
incidence of lethal tumours. To evaluate prior cancer experience (paper IV), a matched case-
control study was set up with five controls from the general population per case, as described
previously. The study was estimated to have a 90% power to detect a 20% difference with a
two-sided $\alpha$ of 0.05. Statistical analysis was performed with conditional logistic regression for
matched data.
Mortality rates

Minimal loss to follow-up provides reliable estimates of all-cause mortality rates, but accurate estimates of disease-specific mortality rates also require correct information regarding the underlying cause of death, which is a well-acknowledged dilemma. The validity of death certificates is questionable and has been analyzed in many papers\textsuperscript{236-238}. When estimating mortality rates in paper II and III, the relative survival rates were used to express the melanoma-related mortality, as the information derived from death certificates was associated with uncertainty. The survival rates were calculated according to the method described by Hakulinen and Abeywickrama\textsuperscript{84} where the relative survival rate is the ratio of the observed (crude) survival in the patient group of interest to the survival rate expected in a group from the general population similar to the patient group at the beginning of the follow-up, with respect to age, sex and calendar time. The 5- and 10-year observed and relative survival rates were estimated. Swedish population life tables for the period 1960 to 1998, covering the ages 0 to 99 years by gender, were used in the calculations. The mortality rates put into the matrix were the mid-values for every 5-year period (1960-64, 65-69..).

Univariate analyses of survival classified by age group (0–44, 45–59, 60–74, and 75+ years), calendar periods (1960–1969, 1970–1979, 1980–1989, and 1990–1998), and gender were undertaken for the first five years after diagnosis. Multivariate regression analysis of the simultaneous influence of gender, age and time period on 5-year relative survival rates was performed according to the life-table proportional hazards model suggested by Hakulinen and Tenkanen\textsuperscript{239}. This is a fixed-interval grouped version of the Cox model, and the Generalized Linear Interactive Modelling (GLIM) software package\textsuperscript{240} was used to fit the model. The best fitting model, based on the likelihood ratio test, included a constant and the categorical variables of the four age groups; four time periods; follow-up years 1 to 5 and gender. Relative risk ratio with 95% confidence intervals was estimated for each factor, taking the first level as baseline.

Analysis of outcomes following brachytherapy

In paper III, tumour size was defined according to the COMS classification, and threshold levels of visual acuity (0.5 equivalent to 20/40, and 0.1 equivalent to 20/200 respectively) following ruthenium brachytherapy were chosen to facilitate comparison with the COMS study\textsuperscript{241}. Loss of visual acuity was estimated by actuarial life table methods and enucleation
by the Kaplan-Meier product limit method. Visual acuity was analyzed with two end points, deterioration of visual acuity to less than 0.5 or to 0.1 or less. The visual levels were recorded at annual visits.

Cox’s proportional hazards regression was used for univariate and multivariate analyses on prognostic factors for overall survival, visual outcome, and enucleation. Time to death from treatment was analyzed with enucleation as a time-dependent covariate in the Cox regression, because enucleation took place after treatment start, when the follow-up with respect to death had already started\textsuperscript{242}. The variables from the univariate model were entered with a stepwise forward procedure into the multivariate analysis if $p<0.05$ to fit the final model. The relative hazards ratios with 95\% confidence intervals and $p$-values were estimated. The variables were analyzed as categories except for age, tumour height, largest tumour diameter, and distance from posterior tumour border to the optic disc, distance from posterior tumour border to the foveola, radiation dose rates, and radiation doses.

The statistical analyses were performed with SPSS computer software, versions 10.0 to 12.5 (SPSS Inc., Chicago, IL) For analysis of relative survival, a computer program from the Finnish Cancer Registry\textsuperscript{84} was used and, for the multivariate analysis in paper II, the GLIM software\textsuperscript{240}. When estimating the expected number of cancers according to population rates in paper IV we used the software PYRS\textsuperscript{235}. 

28
RESULTS

Paper I

During the period 1960 to 1998, a total of 2,997 uveal melanoma cases in 2,995 patients were diagnosed in Sweden, of whom 1,541 were males and 1,454 were females. Two bilateral melanomas were detected.

The search in the files of patients treated with brachytherapy or protons revealed 140 cases not notified in the Cancer Registry, the non-inclusion rate thus being 4.7%. The proportion of cases without morphological verification increased from nil during the years 1960-1978 to 12.3% in 1979 to 1988, and to 30.6% during the period 1989 to 1998.

Uveal melanoma was uncommon in young individuals. The mean age at diagnosis was 62.8 and 62.7 years for males and females respectively, and the median was 64.0 years in both sexes. The age-specific incidence rate was significantly higher (23.5 cases/10^6) among males compared to females (19.2 cases/10^6) in the age groups older than 45 years, as presented in Table 4 (not shown in paper I) and Figure 3.

Table 4. Age-specific incidence rates in uveal melanoma patients in the Swedish population.

<table>
<thead>
<tr>
<th>Age-group</th>
<th>Incidence rate per million</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>0-24</td>
<td>0.14</td>
</tr>
<tr>
<td>25-34</td>
<td>1.75</td>
</tr>
<tr>
<td>35-44</td>
<td>4.07</td>
</tr>
<tr>
<td>45-54</td>
<td>12.2</td>
</tr>
<tr>
<td>55-64</td>
<td>23.3</td>
</tr>
<tr>
<td>65-74</td>
<td>33.5</td>
</tr>
<tr>
<td>75-84</td>
<td>36.6</td>
</tr>
<tr>
<td>85-</td>
<td>28.6</td>
</tr>
</tbody>
</table>
The average annual number of newly detected uveal melanomas has fluctuated between 70 to 84 cases throughout the period 1960 to 1998. The age-standardized rates, on the other hand, decreased significantly (p=0.006) in the population, from 11.0 cases/million to 8.5 cases/million during the investigation period. The reduction was most prominent in the male population (11.7 cases/million to 8.4 cases/million; p=0.002), as in the female population no significant decrease in incidence rates was found (10.3 cases/million to 8.7 cases/million; p=0.108). See Figure 4. During the investigation period, the male incidence rate declined by 1% (95% CI: 0.8-1.2) and the female incidence rate decreased by 0.7% (95% CI: 0-1.3) yearly.

Figure 4. Age-standardized and crude incidence rates in the male and female Swedish population during the period 1960 to 1998.
In 1960, only 0.2% of the Swedish population was of non-European origin, but due to increasing immigration the proportion in 1998 was 4%. The crude incidence rates of uveal melanoma appeared not to be significantly affected by the influx of individuals with supposedly lower incidence of the disease, Table 5.

Table 5. Crude incidence rates (cases/million) of uveal melanoma in the Swedish population compared with estimated incidence excluding non-European immigrants (incidence rate set at 0)

<table>
<thead>
<tr>
<th>Year</th>
<th>Males</th>
<th>Females</th>
<th>Males</th>
<th>Females</th>
<th>Males</th>
<th>Females</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>10.1</td>
<td>9.4</td>
<td>10.1</td>
<td>9.5</td>
<td>6.7– 13.0</td>
<td>13.6</td>
<td>7.1–13.0</td>
</tr>
<tr>
<td>1980</td>
<td>9.5</td>
<td>8.2</td>
<td>9.7</td>
<td>8.3</td>
<td>6.7–13.0</td>
<td>5.6–11.4</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>8.8</td>
<td>8.6</td>
<td>9.0</td>
<td>8.9</td>
<td>6.2–12.1</td>
<td>6.0–11.8</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>9.3</td>
<td>9.7</td>
<td>9.7</td>
<td>10.1</td>
<td>6.7–12.7</td>
<td>7.0–13.0</td>
<td></td>
</tr>
</tbody>
</table>

**Paper II**

At the end of follow-up on 31\textsuperscript{st} December 1998, 2,003 patients had died. Nine patients were lost to follow-up due to emigration. According to the information in the Cause of Death Registry, 474 patients had uveal melanoma registered as underlying cause of death, 574 cutaneous melanoma, 291 other malignancies, 662 non-cancer causes and 2 persons lacked a specified cause. Of the 574 patients with death certificates mentioning cutaneous melanoma as underlying cause of death, only 25 patients had a registration of a cutaneous melanoma in the Cancer Registry. Only 150 of these 574 patients underwent autopsy. In general, the autopsy rate declined throughout the investigation period, from 44% to 15% (Table 6). Twelve patients surviving 20 up to 35 years or more following diagnosis of uveal melanoma were registered with a melanoma (uveal or cutaneous) as underlying cause of death.
Table 6. Autopsy rate in uveal melanoma patients 1960 to 1998.

<table>
<thead>
<tr>
<th>Period</th>
<th>Autopsy</th>
<th>Forensic investigation</th>
<th>No deaths</th>
<th>Proportion autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960-69</td>
<td>123</td>
<td>3</td>
<td>286</td>
<td>0.44</td>
</tr>
<tr>
<td>1970-79</td>
<td>224</td>
<td>1</td>
<td>560</td>
<td>0.40</td>
</tr>
<tr>
<td>1980-89</td>
<td>166</td>
<td>6</td>
<td>624</td>
<td>0.27</td>
</tr>
<tr>
<td>1990-98</td>
<td>71</td>
<td>8</td>
<td>533</td>
<td>0.15</td>
</tr>
</tbody>
</table>

As a considerable uncertainty about the true underlying cause of death was found in uveal melanoma patients, the relative survival rate was used as an estimate for the disease-specific mortality as the method does not require knowledge of the cause of death. The cumulative observed and cumulative relative survival rates for the first ten years after diagnosis are presented in Table 7 and in Figure 5.

Table 7. Cumulative observed and relative survival rates in Swedish uveal melanoma patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Males</th>
<th>At risk</th>
<th>Deaths</th>
<th>Observed</th>
<th>Relative</th>
<th>Females</th>
<th>At risk</th>
<th>Deaths</th>
<th>Observed</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td></td>
<td>1541</td>
<td>132</td>
<td>0.913</td>
<td>0.944</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td></td>
<td>1377</td>
<td>159</td>
<td>0.807</td>
<td>0.863</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td></td>
<td>1188</td>
<td>135</td>
<td>0.713</td>
<td>0.791</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td></td>
<td>1010</td>
<td>106</td>
<td>0.637</td>
<td>0.733</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-5</td>
<td></td>
<td>869</td>
<td>88</td>
<td>0.572</td>
<td>0.683</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-6</td>
<td></td>
<td>755</td>
<td>64</td>
<td>0.523</td>
<td>0.650</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-7</td>
<td></td>
<td>670</td>
<td>35</td>
<td>0.494</td>
<td>0.642</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-8</td>
<td></td>
<td>613</td>
<td>49</td>
<td>0.454</td>
<td>0.615</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-9</td>
<td></td>
<td>537</td>
<td>37</td>
<td>0.423</td>
<td>0.599</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-10</td>
<td></td>
<td>487</td>
<td>37</td>
<td>0.389</td>
<td>0.578</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 5. Observed and relative survival rates following in Swedish uveal melanoma patients (males and females combined) during the period 1960 to 1998.

Excess mortality rates seemed to be elevated up to year 5-6 following diagnosis. The peak excess mortality rate of 8% was observed during year 3-4 as shown in Figure 6.

Figure 6. Excess mortality rates (with 95% CI) following diagnosis of uveal melanoma

In the univariate analysis of relative 5-year survival, younger age groups (p<0.001) and later calendar periods (p=0.002) but not gender (p=0.123) proved significant. In the multivariate regression model, again the factors age (p<0.001), calendar period (p=0.002) but not gender (p=0.117) had simultaneous influence on the 5-year relative survival rate (Table 8).
Table 8. Multivariate regression on 5-year relative survival rate

<table>
<thead>
<tr>
<th>Factor</th>
<th>df</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vs 2</td>
<td>1</td>
<td>1.34</td>
<td>1.02-1.75</td>
<td>0.33</td>
</tr>
<tr>
<td>1 vs 3</td>
<td>1</td>
<td>1.44</td>
<td>1.10-1.89</td>
<td>0.008</td>
</tr>
<tr>
<td>1 vs 4</td>
<td>1</td>
<td>1.54</td>
<td>1.17-2.04</td>
<td>0.001</td>
</tr>
<tr>
<td>1 vs 5</td>
<td>1</td>
<td>1.26</td>
<td>0.93-1.72</td>
<td>0.142</td>
</tr>
<tr>
<td>Period</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1 vs 2</td>
<td>1</td>
<td>0.99</td>
<td>0.80-1.24</td>
<td>0.952</td>
</tr>
<tr>
<td>1 vs 3</td>
<td>1</td>
<td>0.82</td>
<td>0.65-1.03</td>
<td>0.09</td>
</tr>
<tr>
<td>1 vs 4</td>
<td>1</td>
<td>0.58</td>
<td>0.43-0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vs 2</td>
<td>1</td>
<td>2.05</td>
<td>1.41-2.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 vs 3</td>
<td>1</td>
<td>2.77</td>
<td>1.93-3.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 vs 4</td>
<td>1</td>
<td>3.89</td>
<td>2.59-5.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs female</td>
<td>1</td>
<td>0.88</td>
<td>0.73-1.05</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**Paper III**

During the period 1\textsuperscript{st} January 1979 to 30\textsuperscript{th} April 2003, 579 uveal melanoma patients (278 males, 301 females) underwent brachytherapy with a 106-ruthenium episcleral plaque. The tumour size was small in 11\%, medium in 78\% and large in 9\%; in 2\% of the tumours were not classifiable according to the COMS criteria. The study included 55 tumours of > 7 mm height, which currently is considered a contraindication for ruthenium brachytherapy, due to the radiophysical properties of the isotope.

The posterior tumour border was located posterior to the equator in 92\%, anterior in 3\% and 2\% were ciliary body melanomas, whereas 3\% lacked information as to be accurately classified. The target dose at the prescription point was 100 Gy (calculated with an additional 1 mm at tumour apex, apart from 1 mm for the thickness of sclera) and was achieved in 75\% of the patients. In order not to exceed the limit set for the scleral dose (1000 Gy, in 1986 increased to 1500 Gy), 49 patients (8\%) received a dose less than 80 Gy.

During the investigation period, 130 patients died, and two patients were lost to follow-up due to emigration. The 5- and 10 year observed overall survival rates were 83.3\% (95\% CI: 80.5-87.1), and 71.5\% (95\% CI: 67.0-76.0), the corresponding relative rates were 95.5 (95\% CI: 34
91.1-98.6) % and 94% (95% CI: 87.7-99.6). In the multivariate model, the factors predicting observed survival were patient age, tumour diameter and enucleation (Table 9).

Table 9. Multivariate Cox proportional hazards regression analysis with respect to observed survival rates.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Wald</th>
<th>RH</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.5</td>
<td>1.65</td>
<td>1.42-1.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumour diameter</td>
<td>21.9</td>
<td>1.12</td>
<td>1.07-1.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enucleation</td>
<td>8.7</td>
<td>1.87</td>
<td>1.23-2.83</td>
<td>0.003</td>
</tr>
</tbody>
</table>

RH= Relative hazard ratio

1Age in 10 years increment
2Tumour diameter in mm-s increment
3Time dependent factor

Enucleation was performed in 106 patients, with a 5-years cumulative incidence of 16.8%. 75% of the enucleations were undertaken during the first three years following treatment, but relapses were found to occur up to 14 years after treatment (Figure 7). The main reason for enucleation was lack of tumour regression or progression of tumour. Insufficient tumour control was handled with a second ruthenium plaque in 44 patients, of which 13 later underwent enucleation. Since 1998, TTT has frequently become applied as an adjunct, especially at edge recurrences. In 19.8%, did ocular side effects such as pain or neovascular glaucoma necessitate enucleation.
Figure 7. Cumulative incidence of enucleation following ruthenium brachytherapy for uveal melanoma.

The factors predictive for enucleation were in the univariate analysis tumour size, dose rate at scleral surface and apex dose, but in the multivariate analysis only tumours size predicted later enucleation (p=0.011). The observed 5-year mortality rate following enucleation was 68.6%, which justified treating enucleation as a time-dependent variable in the multivariate regression model on predictive factors for overall survival.

Median baseline visual acuity was 0.65, and only 13% of the patients had a visual acuity of 0.1 or less at presentation. The group of patients with an initial visual acuity of 0.5 or better had five years following plaque treatment retained this level in 31% and in 21% after 10 years. Predictive factors for decline of visual acuity to less than 0.5 were in the Cox multivariate regression model increasing tumour height, decreasing initial visual acuity and decreasing distance from the posterior tumour border to the foveola, as shown in Table 10.
Table 10. Cox proportional hazards regression analysis with respect to loss of visual acuity to below 0.5 level

<table>
<thead>
<tr>
<th>Factor</th>
<th>Wald</th>
<th>RH</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour height</td>
<td>10.80</td>
<td>1.15</td>
<td>1.06-1.24</td>
<td>0.001</td>
</tr>
<tr>
<td>Dist fovea&lt;sup&gt;1&lt;/sup&gt;</td>
<td>7.70</td>
<td></td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td>Grp 2 vs 1</td>
<td>4.00</td>
<td>0.69</td>
<td>0.49-0.99</td>
<td>0.046</td>
</tr>
<tr>
<td>Grp 3 vs 1</td>
<td>6.07</td>
<td>0.58</td>
<td>0.38-0.89</td>
<td>0.014</td>
</tr>
<tr>
<td>Initial VA&lt;sup&gt;2&lt;/sup&gt;</td>
<td>14.8</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Grp 2 vs 1</td>
<td>8.06</td>
<td>0.59</td>
<td>0.41-0.85</td>
<td>0.005</td>
</tr>
<tr>
<td>Grp 3 vs 1</td>
<td>12.7</td>
<td>0.51</td>
<td>0.35-0.74</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>1</sup> Distance posterior tumour border to foveola
<sup>2</sup> Initial visual acuity

At baseline, 404 patients had a visual acuity above 0.1. After 5 years of follow-up 49% of remaining patients retained this level and at 10 years 39%. Predictive factors for visual loss to 0.1 or worse were in the univariate analysis distance from the posterior tumour border to the optic disc respectively to the foveola and initial visual acuity, whereas only the two latter factors proved statistically significant in the multivariate analysis, Table 11.
Table 11. Cox proportional hazards regression analysis with respect to loss of visual acuity to 0.1 or less

<table>
<thead>
<tr>
<th>Factor</th>
<th>Wald</th>
<th>RH</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dist fovea(^1)</td>
<td>8.4</td>
<td>0.61</td>
<td>0.41-0.91</td>
<td>0.015</td>
</tr>
<tr>
<td>Grp 2 vs 1</td>
<td>5.8</td>
<td>0.61</td>
<td>0.41-0.91</td>
<td>0.016</td>
</tr>
<tr>
<td>Grp 3 vs 1</td>
<td>4.7</td>
<td>0.57</td>
<td>0.34-0.94</td>
<td>0.029</td>
</tr>
<tr>
<td>Initial VA(^2)</td>
<td>14.8</td>
<td>0.61</td>
<td>0.43-0.99</td>
<td>0.001</td>
</tr>
<tr>
<td>Grp 2 vs 1</td>
<td>4.0</td>
<td>0.65</td>
<td>0.43-0.99</td>
<td>0.046</td>
</tr>
<tr>
<td>Grp 3 vs 1</td>
<td>7.0</td>
<td>0.54</td>
<td>0.34-0.85</td>
<td>0.008</td>
</tr>
<tr>
<td>Grp 4 vs 1</td>
<td>15.2</td>
<td>0.38</td>
<td>0.23-0.61</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^{1}\)Distance posterior tumour border to foveola

\(^{2}\)Initial visual acuity

| Group 1 (0 - 2 mm); reference level          | Group 1 Initial VA (0.13-0.4); reference level |
| Group 2 (3 - 5 mm)                           | Group 2 Initial VA (0.5-0.65)                  |
| Group 3 (6-24 mm)                            | Group 3 Initial VA (0.7-0.9)                   |
| Group 4 Initial VA (\(\geq\)1.0)             |                                               |

**Paper IV**

Primary malignancies occurring prior to diagnosis of uveal melanoma were evaluated in 2,916 uveal melanoma patients and 14,577 age-and sex matched controls from the general population. The risk of a prior malignancy in uveal melanoma patients had an OR of 1.25 (95% CI: 0.98-1.59). Compared to population controls the risk of prior cutaneous melanoma was 1.74 (95% CI: 0.78-3.89). No subtype of malignancy was significantly overrepresented among the cases compared to the controls.

The risk of acquiring a second primary after diagnosis of uveal melanoma was increased with a SIR of 1.13 (95% CI: 1.02-1.26). If cases notified as secondary liver cancer (most likely metastases from the uveal melanoma) were included in the estimation, the SIR was 1.26 (95% CI: 1.14-1.40). Reevaluation of available archival specimens from cases registered as cutaneous melanoma and primary liver cancer revealed that of the original 29 registrations of cutaneous melanoma, 10 specimens were melanoma metastases to the skin, liver or muscle...
tissue and 9 were skin melanomas. Two patients without available archival specimens survived 8 respectively 10 years after diagnosis of cutaneous melanoma, which in light of the short survival time of metastatic uveal melanoma almost certainly excludes the possibility of a miscoded metastasis. When applying stringent criteria to the registrations of subsequent cutaneous melanomas, the SIR was adjusted to 1.75 (95% CI: 0.87-3.12). The registrations of primary liver cancers were also found to harbour miscoded melanoma metastasis. Originally, 19 cases were notified, of which ten had available archival specimens. Reevaluation confirmed in four cases a primary hepatic or bile duct cancer, in four cases a metastatic melanoma and in two cases undifferentiated cancer. The SIR of a primary liver cancer, after adjustment, was 0.86 (95% CI: 0.50-1.28). In the Multigeneration Registry 6,055 relatives of 2,061 uveal melanoma patients were identified, as 934 patients had no registrations about relatives in the registry. The expected number of uveal melanomas among the relatives was 0.44, and among the uveal melanoma patients only one mother and son were found to be related.
DISCUSSION

The use of population-based registries, compared to hospital case series carries advantages as bias (systematic errors) due to selection and classification can be reduced. Also, uveal melanoma is a rare disease and more statistical power can be achieved through the large number of patients accumulated in a national cancer registry. As uveal melanomas, in contrast to most other malignancies, are diagnosed clinically and as an increasing proportion is treated without obtaining a morphological specimen, the risk of misdiagnosis and underreporting to cancer registries should be considered when analyzing incidence rates over time. Theoretically, the various reported stable incidence rates of uveal melanoma could partly be due to an increasing proportion of cases lacking histopathological verification, which therefore might have escaped notification in cancer registries. When comparing data from Australian cancer registries during the years 1996-1998 with hospital records over treated uveal melanomas, Vajdic and coworkers found that 51% of the uveal melanomas lacked morphological verification and further observed a 20% non-notification rate in the cancer registries, where the majority of the un-registered cases consisted of tumours treated with eye-preserving modalities.

In the present investigation we found that among the 407 patients receiving eye-sparing treatment, 140 patients (34%) were un-notified in the Cancer Registry, although the total percentage of non-notification was only 4.7%. Ocular oncology has been centralized in Sweden since the 1970s with hospital-based registries kept over patients receiving radiotherapy, which made it possible to doublecheck these files against the Cancer Registry and identify missing patients. We believe that in the current investigation, the stable rates of uveal melanoma in Swedish females, and even the decreasing rates in males, are not artifacts but represent a true temporal trend as the unregistered patients could be captured and added to the Cancer Registry files.

With increasing immigration from populations of non-European descent that has occurred since the 1960s, a possible explanation for the decreased incidence rates of uveal melanoma over time could be the low incidence rates of uveal melanoma in these individuals. Nevertheless, the crude incidence rates were not significantly affected by excluding the immigrant population in the calculations.

The issue whether uveal melanomas are diagnosed earlier in latter decades could not be addressed in our study, as information about stage was not available in the Cancer Registry. Factors that might influence earlier detection could be increased accessibility to ophthalmic
examinations through the expansion of cataract surgery and the screening programs for diabetic retinopathy that has been introduced in the last twenty years. Also, the decision of when to treat a suspicious large nevus undergoing transition into a small uveal melanoma (and consequently reported to the Cancer Registry) might have been facilitated in recent years by the possibility to offer eye-sparing treatments as an alternative to enucleation. However, the stable incidence rates of uveal melanoma contradicts the concept that earlier recognition has taken place over time or that a large number of benign naevi have mistakenly been treated and registered as small uveal melanomas. Evidence refuting uveal melanomas having been detected earlier in latter time periods was recently published in study from Denmark by Isager and coworkers\textsuperscript{172}, in which tumour size at diagnosis was found to be unchanged during the investigation period 1955 to 2000. The mode of presentation in the Danish cohort was in 96% of cases due to tumour related symptoms, and only 4% of uveal melanomas were detected en passant. In contrast, when evaluating tumour size over time in 6,705 patients examined at centres participating in the COMS, a significant decrease (p=0.002) was observed. During the period 1987-89, 30% of the patients presented with a longest tumour basal diameter of >15 mm, which declined to 25% of the patients during the period 1996-97\textsuperscript{243}.

Using the relative survival rate as an estimate of melanoma-specific deaths implies adjusting for competing causes of death. As population life-tables covering the investigation period 1960 to 1998 were used in the calculations, the method accounts for the prolongation of life expectancy, which has occurred in Sweden during the study period. However, the disease-specific survival in Swedish uveal melanoma patients did not improve in any substantial way. Although the effect of age is embedded in the expected survival rates, still younger age was found to be a predictor for improved survival rates in uveal melanoma.

The introduction of eye-sparing therapies in 1979 appears not to have adversely affected mortality rates on a population level. The 5-year melanoma specific survival rate of 70.1% is compatible with the range 65-84% previously reported from population-based studies of unselected uveal melanoma cases\textsuperscript{5,11}. The improved 5-year relative survival rate observed during the period 1990-1998 is not convincingly explained by earlier recognition and lead-time bias, as no previous parallel increase in incidence rates could be established. Finding this improved survival might be a matter of chance and has to be further investigated with prolonged follow-up and by other investigators in different populations.

Following ruthenium brachytherapy, a 5-year relative survival rate of 95.5\% was expectedly better, due to patient selection. Secondary enucleation was associated with increased risk of all-cause death in the multivariate analysis. This could indicate that the tumour initially had,
or developed, more aggressive properties and was less respondent to radiotherapy treatment, or alternatively that enucleation itself theoretically could induce an altered tumour-host relationship.

When analyzing the underlying causes of death as notified in the Cause of Death Registry we found numerous uveal melanoma patients (574) being erroneously registered as having died from cutaneous melanoma, whereas only a minority (25 of 574; 4%) had a registration of both uveal and cutaneous melanoma in the Cancer Registry. Most probably, a majority of these patients had a (uveal) melanoma-related cause of death with liver metastases, but clinicians issuing death certificates might have overlooked the fact that uveal and cutaneous melanoma are differently classified in the ICD. The infrequency of uveal melanoma compared to skin melanoma could be a source of misclassification in the ICD-coding and might possibly also explain why some uveal melanoma patients became registered with cutaneous melanoma in close conjunction (≤10 months) to their deaths, whereas available re-evaluated archival specimens only confirmed a melanoma metastasis with no evidence of primary cutaneous melanoma.

Our findings are in accordance with other studies evaluating the accuracy of death certificates\textsuperscript{236,238,244}. Specifically, in cancer deaths coding errors appear to derive from an over-representation of sites common for metastasis (bone, liver) and an under-representation of more specific sites such as rectal cancer (coded as colon cancer) and eye cancer\textsuperscript{236}.

As the aetiology of uveal melanoma is a conundrum, the occurrence of other primary cancers in uveal melanoma patients might give indications of shared risk factors. When evaluating the risk of a second cancer, the impact of factors such as environmental exposures, host susceptibility, treatment with radiotherapy or chemotherapy, increased surveillance, age of the patient at first cancer diagnosis and length of follow-up are of importance. In a population-based investigation from the Connecticut Cancer Registry\textsuperscript{151} cancer patients in general had a 31% increased risk of developing a second cancer. In Denmark\textsuperscript{245} no over-all increased risk for second primaries was found, although age <60 at first diagnosis and smoking related sites were associated with elevated risks. A similar pattern was observed in Finland by Teppo\textsuperscript{246} where only cancer patients less than 50 years had an increased relative risk of a subsequent new primaries. In uveal melanoma patients, very few population-based investigations on additional primary malignancies have been undertaken\textsuperscript{72,148,149}. Swerdlow\textsuperscript{72} found among 2,018 ocular melanomas a SIR of 1.23 (1.03-1.45) for males to contract a second primary but no elevated risk for females, although the risk for primary liver cancer was increased (SIR 5.10) for both genders.
Recently (2005), the COMS study group\textsuperscript{247} published data concerning second primary cancers after enrollment. Prior cancer was an exclusion criterion for participation in the COMS, and occurred in approximately 10% of patients evaluated. With a median follow-up of 10 years following treatment, 9.6% of patients were diagnosed with a new second primary cancer, non-melanoma skin cancer excluded, which was similar to rates expected from the general US population.

Previous case-control-studies\textsuperscript{248,249} and other investigations of additional cancers in uveal melanoma patients\textsuperscript{141,142,250} have been undertaken on relatively small (n= 129 to 627) selected patient groups from referral centres. No statistically significant elevated risk for prior cancer or skin-cancers was found in either case-control study. Subsequent cancers was reported with a SIR of 1.14 in a Canadian cohort\textsuperscript{250} but, due to small sample size, with wide confidence intervals (0.52-2.17).

Our population-based cohort of Swedish uveal melanoma patients was found to carry a 13% higher risk of a subsequent second primary cancer compared to the general population. The elevated odds ratio of a prior cancer (1.25) was not statistically significant although cancers diagnosed before 1958, when the Cancer Registry was founded, could not be explored, which introduces bias and diminishes the power to find such an association. Except from secondary liver cancer, no significantly elevated risks of specific tumour sites were found in uveal melanoma patients, indicative of a common risk factor. Almost half of the cases of primary liver cancer became reclassified as a melanoma metastasis when archival specimens were evaluated.

The finding of an OR of 1.74 (0.71-3.89) for cutaneous melanoma prior to uveal melanoma and a SIR of 1.75 (0.87-3.12) for a subsequent cutaneous melanoma suggests that an elevated risk for skin melanoma might exist in uveal melanoma patients, which calls for further explorations. Equivalent figures have been published from the Danish Cancer Registry, with SIR 1.75 (0.48-4.47) for subsequent skin melanomas, although based on only 4 cases\textsuperscript{72}. The previously published SIRs from the SEER database (4.6)\textsuperscript{149} and the Swedish Family-Cancer database (4.0)\textsuperscript{148} of the risk of a cutaneous melanoma following a uveal melanoma, and our unadjusted SIR of 4.6 (calculated directly from notified cases of cutaneous melanoma in the Cancer Registry, with no re-evaluation of archival specimens) are compatible. This could indicate that previously published SIRs in uveal melanoma patients\textsuperscript{148,149} might have included cases where a uveal melanoma metastasis became miscoded as emanating from a (unknown) primary cutaneous melanoma. When estimating the adjusted SIR, as audited data indicated misclassifications and coding errors, we omitted the registered cases of cutaneous melanoma.
which lacked confirmative archival specimens and which were diagnosed only at autopsy or within two years of the patients´ death.

The coexistence of two melanocytic malignancies in the same individual is not, however, a proof of a similar aetiology such as UV-light. Although phenotypic characteristics such as a fair complexion are overrepresented in both skin and uveal melanoma patients, the mechanisms and pathways inducing melanomas might differ. Supporting this view is the finding of stable incidence rates of uveal melanoma in females and decreasing rates in males in Sweden during the 39-year investigation period, whereas in the same population the incidence rate of cutaneous melanoma increased by 2-5% yearly\textsuperscript{129,251} mainly due to changed life-style patterns with high intermittent UV-exposure and, probably in latter years, earlier recognition. Interestingly, in a UV-protected site such as the vulva the incidence rate of melanoma in Swedish females declined by 3% annually during the years 1960 to 1984\textsuperscript{252}. Cumulative UV-exposure is considered to be a strong risk factor for non-melanoma skin cancer, but no excess (SIR 0.68) was found among uveal melanoma patients, which is in accordance with the SIR of 0.85 of non-melanoma skin cancer after ocular melanoma reported from Denmark\textsuperscript{72}.

Therapy with 106-ruthenium episcleral plaques for uveal melanoma was introduced in Sweden 1979. Since then a growing proportion of patients have undergone treatment with brachytherapy, at present (2005) >75 % of newly detected patients are offered brachytherapy as primary treatment. The indication for ruthenium plaques is tumour height ≤ 7 mm and a location suitable for placement of a plaque, which excludes peripapillary growth. 125-iodine plaques came into use in Sweden in 1999, which extended the indications for brachytherapy to include tumours of <7 to 11 mm height.

The current follow-up study of 579 ruthenium-treated patients during the period 1979 to 2003 revealed that a small number of patients (n=55) became treated with ruthenium plaques in spite of tumour height exceeding 7 mm. The classification of tumour size was made according to COMS criteria, in which 53 (9.2%) tumours were classified as large and 454 (78.4%) as medium sized. A formal comparison with the COMS medium sized tumour trial\textsuperscript{41} is not feasible, as the patients emanate from different populations, are not randomized with each other and both treatment periods and treatment criteria differ. However, our observed 5-year survival rate of 84% (95% CI: 80-87%) and relative 5-year survival rate of 95% (95% CI: 98-91%) for ruthenium-treated patients are suggestive of only minor, and probably insignificant differences to the survival rates experienced in the COMS medium trial with a observed 5-year survival rate of 82% (95% CI: 79-85) and a 5-year melanoma-specific mortality rate of
9% (95% CI: 7-11%). Equivalently, in a meta-analysis over survival rates following ruthenium brachytherapy\textsuperscript{12} a 5-year cause-specific mortality rate of 6% were found for small-medium melanomas and 26% for large melanomas.

In spite of finding that 47% of the tumours were located within 2 mm off the foveola and 37% were within 2 mm off the optic nerve, some patients retained useful visual function following ruthenium brachytherapy. Nevertheless, in multivariate analysis visual outcome was predicted by initial visual acuity and distance of the posterior tumour border to the foveola. At 5-year follow-up, of the remaining patients with an initial visual acuity of >0.1 (n=113) and ≥0.5 (n=65) respectively, 49% and 31% respectively of the patients retained these levels.

An increasing proportion (106/ 579) of patients underwent enucleation during follow-up, with a 5-year cumulative incidence of 16.8%. The majority (80 enucleations) was performed during the first three years following the primary plaque, mainly due to insufficient local tumour control, either recurrence or lack of regression. Ocular side effects, such as neovacular glaucoma accounted only for 20% of the enucleations. The only predictive factor for enucleation was tumour size, which indicates that patient selection is mandatory and our series contains patients that, with current knowledge, would not be considered for ruthenium brachytherapy today.

The survival rates following brachytherapy with 106-ruthenium in the present case series are comparable to previously published rates\textsuperscript{30,35,30,200,201} and the results from the COMS-trial\textsuperscript{41} which adds to the accumulating evidence in favour of the concept that mode of treatment is of minor, or no, importance for the survival of the patient. Apart from restrictions inflicted by lack of local resources to perform the entire range of eye-sparing therapies, the choice of an appropriate treatment for uveal melanoma includes a balance between the risk of secondary enucleation due to inefficient local tumour control by radiotherapy, ocular side effects of treatment, visual acuity in the fellow eye and the chance of retaining vision in the treated eye, and of outmost importance, the patients’ preference for enucleation contra retaining the eye.
CONCLUSIONS

During the period 1st January 1960 to 31st December 1998, 2995 patients in Sweden were diagnosed with uveal melanoma.

The age-standardized incidence rate of uveal melanoma in the Swedish population during the period 1960 to 1998 declined significantly among men from 11.7 cases/million to 8.4 cases/million; p=0.002. In the female population, no significant decrease in incidence rate was found during the investigation period, 10.3 cases/million to 8.7 cases/million; p=0.108.

The annual decrease in incidence rate was estimated to 1% (95% CI: 0.8-1.2) in males and to 0.7% (95% CI: 0-1.3) in females.

The stable incidence rates could not be explained by non-notification of patients treated without obtaining a morphological specimen, as these patients could be identified and added to the Cancer Registry, nor by any alterations in diagnostic accuracy during the investigation period. Reassessment of enucleated specimens revealed a total misclassification rate of 0.3%.

The influence of immigrants with a presumably lower incidence rate of uveal melanoma was not found to significantly affect the crude incidence rates.

The observed and relative 5-year survival rates of 60.3% and 70.1%, and significant excess mortality prevailing up to year 5-6 are in concordance with previously reported estimates. The finding of improved 5-year relative survival rates during the period 1990 to 1998 remains to be scrutinized, as no indication of earlier recognition and lead time bias could be anticipated by previously increasing incidence rates.

The 579 patients selected for ruthenium brachytherapy for mainly small to medium sized uveal melanomas experienced a 5-year observed and relative survival rate of 83.3% and 95.5% respectively, the corresponding rates at 10 years were 71.5% and 94%. In spite of a comparatively high enucleation rate the survival rates appear comparable to other series of radiotherapy treated patients. An overall decline in visual acuity was noted in the patient group from initial a median value of 0.65 to 0.2 at 5 years. However, in some individuals retention of the 0.5 visual acuity level or better was possible.

Two cases of familial uveal melanoma were identified through the Swedish Multigeneration Registry. Due to the rarity of the disease and the demographic distribution of relatives 0.44 cases were expected. However, the 0.1% incidence of familial uveal melanoma could be an underestimation, as 31% of the patients in the uveal melanoma cohort had no information about relatives, and pedigrees are still under compilation in the Multigeneration Registry.
Uveal melanoma patients had a significantly increased risk of 13% for subsequent primary malignancies compared to expected rates in the general population, even when cases of secondary liver cancer were withdrawn in the calculations as they most likely reflected metastasis from the uveal melanoma. No significantly elevated risk for any specific cancer site was found. Coexistence of uveal and cutaneous melanoma may be more common than previously believed; prior to uveal melanoma the OR for contracting a cutaneous melanoma was 1.74 (0.71-3.89). Subsequent skin melanomas had a SIR of 1.75 (0.87-3.12) when using strict inclusion criteria following re-evaluation of archival specimens. Current epidemiological data from the present investigation, confirming the stability of incidence rates of uveal melanoma found by other investigators, does however question the importance of UV-light in the pathogenesis of uveal melanoma.

In our investigations using population-based registries of acknowledged high quality, certain pit-falls were nevertheless inevitable, mainly due to the increasing lack of morphological verification of uveal melanomas. In the future, under-ascertainment of uveal melanoma in cancer registries appears to be a growing matter of concern. Also, in instances of disseminated uveal melanoma misclassification as a cutaneous melanoma were common. In the Cause of Death Registry, deaths due to uveal melanoma became miscoded as due to cutaneous melanoma in approximately 50%. In the Cancer Registry, metastatic uveal melanoma was in some instances registered as primary cutaneous melanoma or primary liver cancer. The above-mentioned issues underscore the importance of evaluating registry data in light of the changing therapeutic regimens and the clinical behaviour of the studied disease.
REFERENCES


