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Occupation as risk factor for uveal melanoma in Germany;
a pooled analysis from two case-control studies

CONTENTS

1. INTRODUCTION

1.1 Uveal Melanoma

Uveal melanoma (UM) is a slow growing tumor with a high incidence of metastasis that occurs almost exclusively during adulthood. Although it is an infrequent malignant tumor, it is the most common primary intraocular disease in adults that threatens life.

Malignant melanomas account for approximately 85% of all primary cancers of the eye and orbit (Jensen 1963; Raivio 1977). Eye melanomas are mainly located in the choroid and ciliary body (posterior uvea) but up to 10% arise form the iris (anterior uvea)(Raivio 1977).

Despite several attempts carried out to find out the etiology of this cancer, no causative agent has been recognized as primary cause. Various associated risk factors have been explored ranging from demographic (age, sex, race, and socioeconomic status) and host factors (eye color, history of ocular nevi and melanocytosis, and hormonal and genetic factors), to environmental and occupational factors (sunlight exposure, exposition to chemicals, and ionizing radiation, viruses, and trauma). Researchers seem to agree in only few associated factors for the genesis of this tumor, but contradictory evidence for many other risk factors is quite common.

Although previous difficulties in diagnosing and classifying ocular melanomas have been reduced (Shields 1977; COMS 1990; Gamel & Lean 1977; McLean et al. 1983), the rates of metastasis and mortality remain basically unchanged, and survival has not improved substantially (Haukulinen et al. 1978; Strickland D & Lee 1981; Jensen 1982; Frisch & Olsen 1993). Accordingly, identification of risk factors for primary prevention has been a research priority.

1.2 Incidence

The annual age-standardized incidence ranges from 4 to 12 new cases per million within Europe, but incidence shows considerable international variation ranging from 1 to 23 incident cases per million worldwide according to the World Health Organization and the International Agency for Research on Cancer.

The incidence rate in the black race appears to be extremely low (Miller et al. 1981; Klauss & Chana 1983); in the United States of America, the rate is less than one-eighth that found in whites (Scotto et al.1976).

When excluding anterior uveal melanomas, the annual age-standardized incidence of posterior UM is in the range of 4.7 to 7.9 new cases per million (Seregard 1996).

In contrast to skin melanoma, except for one study (Swerdlow 1983), there appears to be no increase over time of the incidence rate of ocular melanoma (Hakulinen 1978; Strickland & Lee1981; Österlind 1987).

1.3 Etiology

Although no causative agent has been recognized as primary cause, a large number of related factors have been proposed for the genesis of this neoplasm. The most common studied factors linked to UM can be divided up into four major categories: demographic, host, environmental, and occupational risk factors.

1.3.1 Demographic risk factors

Age: Uveal melanoma is uncommonly diagnosed in children and adolescents (Apt 1962; Barr et al. 1981). For posterior UM, incidence is very low in the age group under 30, but increases with age with the highest incidence in sixth and seventh decades; the median age at diagnosis is around 50-60 years (Jensen 1982; Raivio 1977).

Sex: There is probably no major difference in the incidence rates between men and women; however, there is evidence that UM presents a slight predominance among males (Hakulinen 1978; Strickland & Lee 1981; Jensen 1982; Swerdlow 1983). This may be due to the fact that certain exposures related to the disease could be more common among men. However, an independent gender effect cannot be ruled out.

Racial influence: Surveys reveal an extremely low risk in black populations (Scotto et al. 1976; Miller et al. 1981; Klauss & Chana 1983). The risk is also low in races of intermediate pigmentation (Kuo et al. 1982; Hudson et al. 1994). Although detection bias might play a role if blacks are less likely to be diagnosed, the relative protection of increased pigmentation (assuming that UV radiation is associated to the etiology of UM) has been postulated as responsible of this difference as darker-skinned populations, normally exposed to intense solar radiation, develop protective DNA repair mechanisms (Crombie 1979).

Socioeconomic status: Higher risks have been found for cutaneous melanoma in the upper socioeconomic strata (Graham et al. 1985), but evidence is contradictory for UM.

Socioeconomic status, measured in terms of occupation, has been reported more frequently in non-manual occupations (Swerdlow 1983); however, other studies have found similar occupation distribution between patients with UM and the comparison groups (Jensen 1963; Ravio 1977).

1.3.2 Host risk factors

Iris color: Individuals with pale color of the iris have shown an increased risk for developing UM (Jensen 1982; Gallagher et al. 1985; Holly et al. 1990), a finding which implicates sunlight exposure as a possible risk factor. Since the iris is the only part of the uvea located before the lens, which acts as an efficient UV filter, the protective effect of the eye pigment seem to be more important in this area. In fact, a study showed a higher prevalence of melanoma of the iris compared to posterior melanoma in persons with light colored-eyes (Rottman & Gallagher 1984).

Uveal nevi: Even when it has been reported that choroidal nevi, present in 5-10% of the general population, may transform into melanomas (Augsburger et al. 1989; Butler et al. 1994), the absolute risk of individuals with choroidal nevi is very low (Ganley & Comstock 1973). Nevertheless, this risk is still much greater than the risk in individuals without choroidal nevi.

Heredity: Although familial UM, cases of bilateral UM, and even a case of congenital UM have been reported in the literature, hereditary factors seem to play a minor role in the development of the tumor. But even in cases among blood relatives, there is a possibility that shared environmental exposure caused the disease, as UM occurring in husbands and wives and among other non-blood relatives sharing the same household have been reported. Most researches agree that only very few cases may have a heritable component (Jensen 1963; Egan et al. 1988; Seregard 1996), for instance, some case reports suggest that individuals with dysplasic nevus syndrome phenotype may be at increased risk (McCarthy et al. 1993).

Genetics: The unbalanced racial risk with clear predominance among whites constitutes important evidence that a genetic component might be involved (Foss & Dolin 1996; Miller et al. 1981). On the other hand, some authors have postulated that genetic

factors (Singh et al. 1996), like the loss of alleles on chromosome 2 might be responsible for the development of some uveal melanomas (Mukai & Dryja 1986).

Melanocytosis and other diseases: Melanosis oculi (ocular melanocytosis) and Nevus of Ota (oculodermal melanocytosis) are congenital and unilateral hyperpigmentation of the episclera, uveal tract, or periorbital skin, and are likely to be etiologically associated to UM (Dutton et al. 1984). Other diseases such as neurofibromatosis or bilateral uveal melanocytic proliferation have also been associated to UM.

Hormonal influence: Several studies have looked at reproductive factors (Seddon et al. 1982; Egan et al. 1993; Holly et al. 1991) as it was postulated that estrogen receptors in ocular melanoma tissue could play a role in cancer development (Egan et al. 1988). Nevertheless, in a recent study to examine the relationship of exogenous and endogenous hormonal variables to the incidence of melanoma, the results indicate that these tumors are not influenced by sex hormones (Smith et al. 1998). This is consistent with the finding that this tumor lacks of progesterone and estrogen receptors (Foss et al. 1995).

1.3.3 Environmental risk factors

Sunlight exposure: Since uveal and cutaneous melanomas share a common cellular origin, ultraviolet exposure is the factor that has been most thoroughly studied due to the well-known hypothesis of a causal link between sunlight exposure and skin melanoma.

In contrast to cutaneous melanoma, where increased incidence has occurred (Stevens & Moolgavkar 1984), the incidence of UM remains fairly stable, or might even have decreased (Foss & Dolin 1996). The fact that temporal trends are not seen in UM could indicate that this tumor has reached its maximum incidence and leveled off, as it has occurred with melanomas of the face where incidence has remained basically unchanged (Stevens & Moolgavkar 1984), or alternatively, that sunlight is not related to this cancer. On the other hand, the isolated cases of UM reported in individuals with xeroderma pigmentosum, a disease with increased frequency in cutaneous melanoma, argue against sunlight exposure as a significant risk factor (Vivian et al. 1993).

Regarding geographic distribution, UM do not show the marked latitudinal gradient seen with cutaneous melanomas (Scotto et al. 1976; Stickland & Lee 1981; Gallagher et al. 1985). However, geographic patterns could be obscured by regional differences in the

ethnic mix of the population, or in the completeness of case finding. Moreover, the lack of latitudinal gradient can be also due to the fact that the higher intensity of overhead sunlight in the South may be offset by the greater reflectivity of ultraviolet rays from snow cover in the North (Sliney 1986).

Elevated odds ratios (OR; 95%CI) from a hospital-based case-control study have been reported for gardening (1.6; 1.01-2.4), not using eye protection while outside (1.6; 1.2-2.2), increased sun exposure during vacations (1.5; 0.97-2.3), and sun bathing (1.5; 0.9-2.3)(Tucker et al. 1985). Another case-control study showed increased risks for tendency to sunburn with no tanning (1.7; 1.2-2.4), and for eye burns from the sun, welding, or snow blindness (7.2; 2.5-20.5)(Holly et al. 1990). However, other studies have failed to show association between cumulative sun exposure (Graham et al. 1985), or average daily global solar radiation (Schwartz & Weiss 1988) and risk of eye melanoma.

A study by Tucker and associates showed that persons born in the Southern United States (where solar radiation is more intense) had almost a three-fold increase risk compared with those born in the North (Tucker et al. 1985). However, a posterior study showed nearly the same incidence of ocular melanoma between those born in the South and in the North (Schwartz & Weiss 1988).

The finding that ocular cancers tend to be more common among people living in the rural areas than in towns adds some support to the hypothesis that exposure to sunlight is linked to the etiology of UM (Doll 1991). Saftlas et al. found an excess in mortality from eye cancer among farmers in the State of Wisconsin, USA, and this was thought to be associated to the fact that farmers are more likely exposed to sunlight (Saftlas et al. 1987). Nevertheless, a previous case-control study among farmers and farm laborers in British Columbia, Canada, did not show significant associations (Gallagher et al. 1985).

Among adults, the cornea and lens absorb most of solar UV-A and UV-B wavelengths below 380 nm allowing less than 1% of radiation below 340 nm to reach the retina; however, juvenile lens may transmit greater amounts of ultraviolet radiation (Lerman 1987), especially shorter wavelengths of UV-B that are biologically of greater importance (Zigman 1983). Therefore, childhood exposure for UV-irradiation and intensive intermittent UV-exposure could be the most important risk factor for developing posterior UM (Dolin & Johnson 1994), and this might be responsible for the increased risks seen in those born in Southern United States. Nevertheless, no correlation between the location of choroidal melanoma and ultraviolet-radiation dose distribution has been found (Schwartz et al. 1997).

Regarding the biological mechanism of how UV-irradiation may cause malignant transformation, few hypotheses have been stated. Sunlight could have a systemic effect by impairing the immunologic capability of the host, or by triggering the production of the so-called “solar circulating factor” (Lee & Strickland 1980). However, if ultraviolet light has an effect on the risk of melanoma, this effect must to be direct, as no increased risk of melanoma in all sites at which melanocytes are present (i.e. visceral melanoma) have been noted (Neugut et al. 1994).

In a recent publication, melatonin, an endogenous neurohormone that has been found to inhibit the growth of a variety of carcinoma cell lines in vitro (Shellard et al. 1989; Sze et al. 1993) including UM cells (Hu & Roberts 1997), showed inhibition of cell growth on UM cells in vitro in a dose-dependent manner. The fact that light exposure disrupts the metabolic pathway, which produces melatonin from tryptophan, constitutes a plausible biological explanation of the link between light exposure and UM (Hu et al. 1998).

In summary, ultraviolet exposure as etiological factor for UM remains controversial and often contradictory.

Non-solar radiation: Diagnostic and therapeutic ionizing irradiation do not appear to be associated with increased risk of UM (Jensen1963). Sun lamps and tanning booths, which may cause over fivefold more DNA damage per unit of erythema than the sun (Nachtwey & Rundel 1981), have been found to be, although no significantly, more likely used among cases in one study (Tucker et al. 1985). The use of fluorescent lighting, which may emit in the ultraviolet rage (Jewess 1981), has not been yet studied for UM.

Viruses: Albert et al. published evidence that viruses may be etiologically related to UM; oncogenic DNA viruses induced in-vitro neoplastic transformation of uveal and retinal tissue, and further injection of these cells into animals caused tumors similar to uveal melanomas (Albert 1979). Thereafter, togavirus particles were identified in human uveal melanoma tissues, and virally induced uveal melanomas in animal models were reported. However, these findings must be taken carefully as virus particles can be normally found in human tissues and very few cancers have been positively related to a viral etiology.

Trauma: Some reports of malignant melanoma at the site of a previous penetrating ocular trauma have been documented, but no study has established yet if the proportion of previous injury in a group cases is higher to that of the controls.

1.3.4 Occupational and chemical risk factors

Animal studies: Eye melanocytic tumors and other ocular tumors have been produced in laboratory animals after administration of methylcholanthrene, n-2-fluorenylacetamide and ethionine, ^{226}radium, and nickel sulfide.

Occupational factors: Occupational exposure has been sought in the etiology of UM as various other rare cancers are caused by exposures occurring in the workplace (Althouse et al. 1979). Chemical risk factors have been associated with UM. In 1980, a cluster of ocular melanomas in workers exposed to a complex mixture of chemicals including ammonia, solvents, antifreeze, and nylon was documented (Albert et al. 1980).

Thereafter, a historical cohort of retired asbestos workers showed an elevated standardized mortality ratio for eye cancer, though only two observed cases (versus 0.13 expected) were seen (Enterline et al. 1987). In a case-control study from the United States increased risks for UM were seen among chemists, chemical engineers or chemical technicians (odds ratio 5.9; 95% confidence interval 1.6-22.7) and in those with asbestos exposure (1.8; 1.1-3.1)(Holly et al. 1996).

Farmers have also shown increased risks in some but not all studies. A study in farmers from Wisconsin showed an elevated proportional mortality ratio for eye cancer; however, the risk for UM was not significantly increased (Saftlas et al. 1987). Later, the Danish register linkage study showed elevated rates for UM among male farmers (Lynge & Thygesen 1990), and a cross-linkage system to explore occupational risks for UM in the United States showed elevated risks for agriculture (Ajani et al. 1992). Doll reported an excess of eye cancer in rural residents potentially reflecting exposure to farming activities (Doll 1991). Thereafter, a case-control study also found an increased odds ratio (OR) for eye cancer among farmers from Illinois (6.7; 1.7-23.7)(Keller & Howe 1994). However, Holly et al. found no augmented risk for agricultural occupations (1.2; 0.7-1.9)(Holly et al. 1996), and the Swedish (Wiklund & Dich 1995), Norwegian (Kristensen et al. 1996), and Finnish (Pukkala & Notkola 1997) cohorts failed to show increased standardized mortality ratios for eye cancer among agricultural workers.

Welding has also been linked to UM. In a case-control study, persons who had ever worked as welders showed an increased risk for intraocular melanoma (19.9; 2.1-56.5)(Tucker et al. 1985), and Holly et al. also showed an elevated OR in men ever exposed to welding (2.2; 1.3-3.5)(Holly et al. 1996). Also, in a very recent population-based case-control study, an elevated risk for ocular melanoma was seen among male

welders (7.3; 2.6-20.1), and a dose-response relationship with job duration was observed (Guenel et al. 2001). However, in other studies, having ever worked with welding arcs was not associated to UM (Ajani et al. 1992; Seddon et al. 1990).

Working in health-related occupations has been mentioned in two studies. Holly et al. found an elevated adjusted OR for intraocular melanoma (3.3; 1.3-8.2)(Holly et al. 1996), and Pukkala reported an increased standardized incidence ratio among auxiliary nurses (2.9; 1.1-6.4)(Pukkala 1995).

Various other occupations have also been reported sporadically. A population-based case-control study on eye cancer among women in the workplace showed augmented ORs for those working in bus-truck services (4.6; 1.2-17.9), and military services (4.4; 1.5-13.4)(Swanson & Burns 1995). A study to investigate the epidemiology of eye melanoma in England and Wales showed higher proportional registration ratios among men in the non-manual compared to the manual occupations; the analysis of twenty-six occupational orders revealed elevated ratios for electrical and electronic workers, administrators and managers, professionals, technical workers, and artists (Swerdlow 1983). In the English-Welsh-Swedish cooperative study, clerical workers (1.3; 1-1.8), and teachers (1.7; 1.2-2.4) showed increased proportional registration rates for ocular melanoma (Vågerö et al. 1990). Gallagher et al. also found an increased OR for ocular melanoma in government workers after controlling for hair and eye color (Gallagher et al. 1985). Recently, Stang et al. reported a positive link between radio frequency radiation exposures and UM in Germany, based on the pooling of two case-control studies (Stang et al. 2001).

Table 1 summarizes the findings reported in previous studies regarding occupational and chemical factors linked to UM.

1.4 Clinical Manifestations

Many melanomas cause no symptoms and are frequently discovered incidentally as a painless mass. If symptomatic, patients might present with visual symptoms such as diminished vision, contracted visual fields, vitreous floaters, or flashes. Medium and large tumors have been found to present more symptoms than small tumors (Servodidio & Abramson 1992).

The behavior of intraocular melanoma varies with site. Most posterior uveal melanomas are visible by ophthalmoscopy after dilation of the pupil. Large melanomas may rupture the Bruch's membrane, exhibiting the characteristically mushroom-shaped, but small melanomas might be difficult to differentiate from nevi (Char et al. 1980). Most choroidal

melanomas are presented initially as discrete, solid, and well-circumscribed masses localized in the choroid. The most common site of involvement is the region of the posterior pole (Grin-Jorgensen et al. 1992).

It has also been reported that patients with primary ocular tumors tend to have more systemic symptoms than those patients with cutaneous primary tumors (Albert et al. 1996).

Large size, elevation, serous detachment, sub-retinal fluid, and documented growth are all features suggestive of a malignancy. Accumulation of an orange pigment, lipofuscin, in the retinal pigment epithelium is also a common but nonspecific finding. Repeated photographic documentation is used to assess tumor growth.

1.5 Tumor Classification

For its location, melanomas of the uveal tract (i.e. iris, ciliary body and choroid) are divided into two main regions:

- Anterior uveal melanoma (located in the iris)
- Posterior uveal melanoma (located in the ciliary body/choroid)

For its size, melanomas are classified according to the basal diameter and elevation of the tumor expressed in millimeters (mm):

- Small: < 2-3 mm in elevation
- Medium: 2-3 to 10 mm in elevation and up to 16 mm of basal diameter
- Large: > 10 mm in elevation or >16 mm of basal diameter

For its cell type, UM are classified using the Callender´s modified classification. This classification, although broadly useful, is capable of great intra- and inter-observer variability (Gamel & McLean 1977); however, histopathologic misdiagnosis of melanoma is rare (COMS 1990):

- Spindle cell variety
  - Spindle A type
  - Spindle B type
- Non-spindle cell variety
  - Epithelioid type
  - Mixed type (usually spindle B and epithelioid)
  - Necrotic melanoma

1.6 Diagnosis

Patients themselves can discover melanomas of the iris. In eyes with clear media, visual inspection by ophthalmoscopy remains the most reliable method for diagnosis (Char et al. 1980). However, up to 20% of all eyes with opaque media harbor a melanoma (Nelson & Kincaid 1992).

Most posterior melanomas are initially diagnosed through a combination of clinical findings and auxiliary non-invasive procedures. These range from A and B-scan mode ultrasound, high-frequency echography, fluorescein angiography, and high-resolution magnetic resonance imaging being the most commonly used, to the less used techniques such as computerized tomography, and ^{32}P uptake test, which are thought to be inferior methods, or color Doppler imaging and immunoscintigraphy which or are not yet well investigated.

A more invasive method, the transocular fine-needle aspiration biopsy, offers a sensitivity of 88% and a specificity of 98%. Despite the risk of complications of this procedure, like vitreous hemorrhages in up to 30% of the cases, it is thought to be better than the incitional biopsy, as it reduces the risk of tumor spread.

When the diagnosis is established in experienced ophthalmologic oncology centers, clinical misdiagnosis occurs very rarely (Shields 1977). However, a study have shown that up to 9% of presumed uveal melanomas eligible for treatment were in fact non-melanomatous lesions (Char & Miller 1995). Final diagnosis is based on histopathological or cytological examination.

Over time, the numbers of eyes removed for the mistaken diagnosis of melanoma has diminished considerably. The rate of false-positive diagnoses has dropped form 12.5% in 1970 to even less than 0.5 % in 1990 in centers with considerable experience (COMS 1990).

A general physical examination and additional tests are done to diagnose metastatic disease. The most frequent site of metastasis is the liver, followed by the lung and the central nervous system.

Indirect ophtalmoscopy through a well-dilated pupil forms the backbone of clinical diagnosis and in conjunction with a detailed clinical history, ultrasonography, fluorescein angiography, transillumination and sequential diagnostic evaluation the accuracy of diagnosing melanomas greater than 4 mm in height is more than 99% percent.

A number of lesions can simulate melanoma, especially those that appear dark clinically. The eye diseases most commonly included in the differential diagnosis are:

Melanocytic nevi, melanocytomas, metastatic tumors, sub-retinal blood beneath the retinal pigment epithelium, retinal pigment epithelial proliferation, choroidal hemangioma, and choroidal osteoma.

1.7 Treatment

There is no single treatment modality that is ideal for all categories of uveal tract melanomas. The type of treatment depends on the site of origin; site and location of the lesion; whether secondary changes in the affected eye, extraocular invasion, recurrences, or metastases have occurred; the age, general condition and motivation of the patient; and the available equipment.

Since Zimmerman stated that enucleation may decrease the survival because of tumor seeding by manipulation of the globe during the surgical procedure (Zimmerman 1978) there have been an increasing interest in other –conservative and eye preserving– treatment modalities. Conservative therapy has resulted in more eyes retained and vision saved along with an increasing acceptance of therapy and patient satisfaction without a concomitant increase in mortality (Reader et al. 1997).

For iris melanomas local excision is in most cases effective and metastasis is seen rarely. In the management of patients with posterior uveal melanoma, treatment has included surgery (enucleation and orbital exenteration in very advanced cases) and also photocoagulation, local resection, and cryotherapy.

The primary goal of treatment is not only conservation of the eye with acceptable vision, but also to gain the same prognosis as with enucleation. All conservative treatment methods for uveal melanomas can only be justified if they prove to be as effective as enucleation regarding prognosis and the risk of metastatic disease. The conservative treatment includes:

- Periodic observation in patients with small melanocytic lesions of the posterior uvea (up to 1 mm in height) with periodic fundus photography and ultrasonography to document eventual growth.
- Photocoagulation is an option for selected small choroidal melanomas (<3mm thick an located more than 3 mm from the foveola, or on the nasal side of the optic disk) when diagnosis is certain.
- Radiotherapy it is by far the most widely used treatment option in posterior uveal melanoma. However, controversy exists regarding which method of radiotherapy may lead to the best therapeutic result, and the fewest side effects and complications. The

alternatives include: Radioactive plaques with ^{103}Palladium, ^{106}Ruthenium, ^{125}Iodine, ^{60}Co, charged particle radiotherapy (protons or helium ions), and thermoradiotherapy.

- Surgical resection of small melanomas of the iris and ciliary body have been performed successfully by the technique of iridocyclectomy, but attempts to resect choroidal melanomas have been rarely undertaken.

In 1986 a large clinical trial (Collaborative Ocular Melanoma Study -COMS-) started in the United States and Canada, including patients until 1994. This study has been design to provide important information regarding the choice of treatment, as well a natural history, quality of life and pathology findings (COMS 1998).

1.8 Prognosis

A number of factors influence prognosis. Tumor size at time of enucleation is a major prognostic factor for patients who have choroidal melanoma. The most important are size, location, cell type, and extraocular extension (tumor size being the most critical factor).

Iris melanomas usually have a low-grade histology with a good prognosis. In contrast to iris melanomas, melanoma of choroid or ciliary body pose a serious threat to life. Late metastasis after removal of the primary tumor is common, and one-year survival after liver metastasis is not higher than 10% with a median of only 2-4 months, and approximately half of the patients die form the disease within 10 years after diagnosis (Gragoudas et al. 1991).

Main risk factors for metastatic disease in order of significance include tumor extension into the ciliary body, extraocular tumor recurrence and largest tumor diameter; the most important risk factor for failure of eye salvaging therapy eventually resulting in secondary enucleation was tumor thickness before therapy. Patients with small melanomas not exceeding 4 mm in height have an excellent prognosis in terms of eye retention, preservation of useful visual function, and survival. In tumors exceeding 7 mm thickness but less than 15 mm, the best results could be achieved with transcleral local resection when the patient is eligible for surgery (Bornfeld et al. 1997). But, overall, once metastasis has occurred, survival is poor, and no treatment has been found to be effective (Albert 1997).

Maximum tumor dimension (MTD) has shown to be the most important factor-determining prognosis. Tumors less than 7 mm in any direction carries a much-reduced risk of death. Cytologic factors include nucleolar size, pleomorphism and access to

vascular beds, rupture of Bruch's membrane allows for seeding into the vitreous, orbital extension occurs in 10-23% of cases and is almost always associated with other poor prognostic features such as the presence of ephithelioid cells or a large tumor. Tumor cell morphology may influence survival, and in particular, the presence of epithelioid cells carries a worse prognosis (Seregard & Kock 1995).

2. OBJECTIVE

This doctoral thesis was aimed at presenting a pooled analysis of a population and hospital-based case-control study conducted in the Federal Republic of Germany between 1994 and 1998 to explore possible occupational risk factors linked to UM; it includes a description of the distribution of occupations between cases and controls and the testing of potential associations for different occupational groups and industrial branches.

3. Subjects and Methods

Designing and carrying out studies on occupational risk factors for UM is a complex task, in part because it is very difficult to gather enough incident cases of this infrequent cancer to perform an epidemiological study. The current work has taken advantage of the availability of data collected from two similarly designed case-control studies, to conduct a pooled analysis of these data.

3.1 Population-based case-control study

Between 1994 and 1997, Germany and other nine European countries participated in a multinational population-based case-control study on occupational risk factors for seven cancers including UM, mycosis fungoides, cancer of the small intestine and bones, cancer of the bile duct and breast in males, thymoma, UM, and testicular cancer, the later only in Germany. According to the published literature, all these rare malignant tumors have incidence rates below 15 cases per 100,000 inhabitants per year, and information regarding etiology is still unknown or very scarce (although there were some hints indicating that occupational factors could play a role).

3.1.1 Selection of cases

Potential eligible cases were those with primary incident UM (ICD-O-2, 1990: M8720 - M8774) located in the choroid and/or ciliary body (ICD-O-2, 1990: C69.3, C69.4, C69.9). Other eligibility criteria included: date at diagnosis (between July 1, 1995 to December 31, 1997), age of the patients at the time of diagnosis (between 35 and 69 years), language proficiency (being capable to complete the interview in German), and place of residency at diagnosis (Hamburg, Bremen, Essen, Saarbrücken, and Saarland).

An active reporting system from clinical and pathological departments regions within the studied regions was set up to retrieve cases; in addition, cancer registry reports were utilized in Hamburg. A close relationship with the involved institutions was established and kept throughout the study.

Potential participants were invited to join the study. If a patient agreed to participate, a personal interview (exceptionally a telephone interview) was conducted, and the treating physician was asked to fill in a clinical questionnaire. A single reference pathologist

reviewed the clinical and pathological reports (and specimens when available) to confirm the diagnosis.

Of the 47 observed cases, 44 were eligible for the study, and interviews were conducted with 37 patients or their closest relative (one surrogate interview), resulting in a response proportion of 84% calculated according to Slattery et al. (Stattery et al. 1995). The reasons for non-participation included refusals (11% of eligible cases), and inability to contact cases (5% of eligible cases).

3.1.2 Selection of controls

Controls were matched by *age* (5-year intervals), *region of residency* (Hamburg, Bremen, Essen, Saarbrücken, and the Federal State of Saarland without its capital Saarbrücken), and *gender*. A minimum of four controls per case in each stratum was attempted.

A two-stage sampling strategy to select potential controls was used. In the first stage, controls were selected randomly from mandatory lists of residence, which cover the total population of the local districts. The lists of residence are regarded as the most complete sampling frame for population-based studies in Germany (Stang et al. 1999).

In the first stage, to guarantee that the minimum number of controls per case needed would be fulfilled, the expected number of cases in the stratum of the rare cancer with the maximum frequency was multiplied by four to keep the 1:4 matching ratio; then, to assure that the minimum estimated ratio would be maintained, the cipher obtained was multiplied by either four, if the expected number of cases in the stratum of the rare cancer with the maximum frequency was ≥4, or by six if it was <4. In the second stage, a stratified random sample was taken from the list of potential controls selected in the fist stage. It was intended to match four controls for the rare cancer with the maximum frequency within the stratum.

Although a minimum of four controls per case in each stratum was foreseen, the matching resulted in ratios for the UM study of up to ten controls per case, as other cancers were more common than UM.

Of all eligible controls who were invited to participate, 699 controls (10 surrogate interviews) agreed to do so, resulting in a response proportion of 48%. The mayor reasons for nonparticipation among controls included refusal (31%), and inability to contact the patients (8% of the eligible controls)

Those interviewed controls that matched to the other rare cancer but not to UM were excluded from the analysis (372 controls).

3.2 Hospital-based case-control study

During the fieldwork of the population-based study, an additional hospital-based case-control study limited to the German Federal State of North-Rhine-Westphalia was carried out at the Eye Clinic, Division of Ophthalmology, University of Essen, using the same questionnaire and personnel. This hospital is a referral center for eye tumors that treats approximately 250 to 300 patients with UM per year.

3.2.1 Selection of cases

Eighty incident cases were expected during a 16-month recruitment period, based on the number of incident cases with primary UM diagnosed at the Eye Clinic between 1994 and 1995.

Those patients diagnosed with primary UM at this referral hospital between December 1, 1996 and March 31, 1998, aged 35-74 years at diagnosis, and who resided in the North-Rhine-Westphalia, Germany, were eligible to be included in the study. German language proficiency and provision of medical treatment were also included within the criteria for eligibility.

From the 99 incident cases diagnosed during the recruitment period, 92 patients were eligible to participate in the study, as the other seven did not fulfill the inclusion criteria. The reasons for being excluded from the study included: wrong diagnosis (n=1), age at diagnosis (n=1), date at diagnosis (n=2), lack of language proficiency (n=1), and no treatment was given (n=2).

From the remaining 92 eligible cases, 81 were actually interviewed. The reasons for why these eleven patients did not join the study were: too ill (n=2), refusal (n=7), no contact (n=1), and died before contact (n=1). Thus, response proportion was 88% of the eligible cases.

All interviewed patients were treated with episcleral plaque radiation therapy or enucleation, and diagnoses were confirmed histologically in all patients who underwent surgery.

3.2.2 Selection of controls

Similarly as in the population study, an active reporting system at the Division of ophthalmology, University of Essen, was established. Before March 01, 1998, ophthalmologists at the Eye Clinic were asked to report potential controls, and thereafter computer retrievals from patients visiting the clinic were used.

Eligible controls were patients with newly diagnosed benign disease of the posterior eye segment visiting the Eye Clinic during the same period as the cases were seen. The major diagnoses among controls included: retinal detachment and defects (32%), degeneration of the macula (18%), retinal vascular occlusion (14%), diabetic retinopathy (10%) and others (26%). No control suffered from an occupational accident involving the eye.

Matching criteria for controls at the time of diagnosis included: living in a similar industrial *region* within NRW (Ruhr Area, Non-Ruhr Area, South NRW, and North NRW); *size of the city of residence* in the Non-Ruhr Area (<100,000 or ≥100,000 persons); *age* (5-year intervals); and *gender*.

From the 248 potential controls reported, 61 did not fulfill the inclusion criteria and were excluded. The reasons for exclusion were: diagnosis not eligible (n=9), lack of language proficiency (n=3), matching stratum with no cases (n=13), matching stratum with case-control ratio already 1:4 (n=35), and place of residence outside NRW (n=1).

From the 187 eligible controls, 148 were interviewed. The reasons for not participation of the remaining patients were: too ill (n=4), refusal (n=25), no contact but eligible (n=2), no contact but eligibility unknown (n=7), and contact but eligibility unknown (n=1). Therefore, the response proportion was 79% of the eligible controls.

3.3 Pooling of the two studies

As mentioned previously, gathering a sample of UM incident cases big enough (i.e. with sufficient power) to detect significant associations can be rather complicated, especially when the prevalence of the potential occupational risk factors is low, and when the assessment of the exposition is unspecific.

Increasing the number of cases in the sample to improve the power of a study is one of the most efficient ways to increase the power of the study. Additionally, increasing the number of controls per case (i.e. the case-control ratio) also affects positively the efficiency of the study (Pike et al. 1980).

Pooling data from different studies has been seen also as a plausible alternative. The main goal is to enhance the precision of the overall estimate by calculating the weights for averaging the stratum-specific effects estimates. However, methodological differences between the studies (e.g. different study design, different exposition assessment, different definition of variables, etc.) often hamper the possibility to pool the data.

The fact that both case-control studies included in this thesis were conducted almost simultaneously, included very similar criteria for case definition, and utilized the same interview methods for exposure assessment, diminishes major conceptual and methodological constrains to pool the results. Notwithstanding, differences regarding the sources of controls, inherent to the design used, could result in bias, especially if, like in this analysis, two-thirds of the cases come from the hospital study, but two-thirds of the controls come from the population study. This, and other potential sources of bias, resulting by the pooling the two studies, was addressed in the discussion.

3.4 Study areas

The study area in the population-based study comprised five German geographic regions including Hamburg, Bremen, Essen, Saabrücken, and Saarland without Saarbrücken, covering a population of approximately four million inhabitants at risk.

The hospital-based study was limited to four defined geographic regions within North Rhine-Westphalia (NRW): Ruhr Area, South NRW (including Arnsberg, Düsseldorf, and Köln districts), and North NRW (including Münster and Detmold districts), with a population of nearly 18 million inhabitants.

Figure 1 presents a graphic overview of the study areas covered.

3.5 Sample size

For the hospital-based study, the sample size was determined based on the number of incident UM cases expected in a 16-month recruitment period, rather than on an expected odds ratio (OR), and a case-control matching ratio of 1:4 was initially set. Thus, the original number of cases and controls calculated was 50 and 200 respectively.

Nevertheless, the study analysis ended with a larger number of cases (n=81), and a smaller number of controls (n=148), so that the final matching ratio was reduced by half from 1:4 to almost 1:2. **Table 2** presents the relationship between the prevalence of the

risk factor and the OR required to obtain significant estimates with a matching ratio of 1:2, setting a 95% confidence level and a 80% relative precision.

In the population-based study, a total of 254 incident cases for the seven rare cancers together were expected to be collected during the study period in the five geographic German areas, including 41 cases of eye melanoma. And to improve the precision of the estimates, a minimum of four controls per case was also established.

For the analysis, a total of 37 cases and 327 controls were available. Although the number of cases and controls obtained was relatively adequate, the fact that the sample size calculations in the population-based study were made only to obtain estimates at European level hindered the possibility to obtain reasonable national estimates.

Hence, the final sample size used in the pooled analysis consisted in 118 cases (81 + 37) and 475 controls (148 + 327).

3.6 Exposure assessment and coding

Individuals' interviews covered several topics ranging form medical history and phenotypic characteristics, to life style factors and lifetime occupational history. The evaluation of the exposure was based on the lifetime occupational history. A work biography was constructed for each participant of the study. All jobs with duration of at least six months were chronologically recorded. Within each job period, the duty of the individual consuming most of the person's working time was defined as "main task", and all others as "secondary tasks".

All recorded jobs were classified into 34 "job groups" according to the International Standard Classification of Occupations (ISCO)(International Labour Office 1968), and 36 "industrial branches" according to the General Industrial Classification of Economic Activities within the European Communities (NACE)(Statistical Office of the European Communities 1985). Additionally, at the end of the standard interview, a checklist containing 30 different occupational groups (ever/never) was administered to the participants. If the respondent worked in one or more of these groups, a Job-Specific Questionnaire (JSQ), which has proven to be useful in classifying occupations in previous epidemiological studies (Jöckel et al. 1992; Jöckel et al. 1995), was applied. All occupational categories utilized by these classification systems consisted of pre-determined and fixed categories that were not modified or adjusted for the purpose of this study.

The ISCO classification included 34 job groups, the NACE classification included 36 industrial branches, and the JSQ classification included 30 job groups. The complete list of categories within each classification is presented in **Table 3**.

Interviewers were unaware of the study hypotheses as they administered structured questionnaires. Each interview took approximately 70 minutes (median). The status of case and control was unknown during the coding process. A different person conducted a second coding to assure the quality of the data. Comparisons between the first and second coding were made, and if inconsistencies were found, a definitive coding was assigned based on consensus.

3.7 Methodological considerations

Epidemiological studies of potential work-related diseases are predominantly non-experimental and subject to inherent difficulties, especially in providing evidence for or against the causality of an observed association between two phenomena. The demonstration of a slight increase in the occurrence of a disorder among those exposed to a work-related factor often requires a large study and a sharp design. The later means that random errors, such as sampling errors, non-differential misclassifications, and other measurement errors must be avoided as much as possible (Hernberg 1980; Hernberg 1986). Although biases cannot be completely eliminated, keeping them to a minimum and taking them into account when interpreting the results constitute a major responsibility of the researcher.

Since direct measurement of an exposure in occupational epidemiology may be not always feasible, many case-control studies must rely on indirect sources to infer exposure levels for individuals. Occupation title may then serve as a surrogate for exposure, particularly when no specific agent is known to cause a disease. However, information regarding cumulative exposure, intensity, and dose might no be available, leaving the evaluation of exposition to a dichotomous analysis. In spite the fact that questionnaires frequently lack of objective external information to validate the self-reported exposures, questionnaires, conducted through interviews, are commonly used instruments to determine the individual's occupational history.

The coding process of job title, which can be seen as the interface between the questionnaire information and the analysis, can pose serious threats to the accuracy of the exposure status. Coding difficulties arise when jobs do not fit exactly into the coding scheme (too heterogeneous jobs), or when ambiguous job descriptions are given. An

imprecise coding could lead to a misclassification of occupations slanting the estimates towards the null value. Therefore, training interviewers to obtain precise descriptions of the occupation, instructing coders to assign codes as specific as possible, and using standardized rules for coding are needed to improve the accuracy of coding.

Using occupational codes to determine the exposition can bear important restrictions if sufficient numbers of cases in the exposure categories are not available. Therefore, clustering occupational titles into smaller numbers of occupational categories according to shared exposures is an alternative method to define the exposure status. However, the homogeneity of the different occupations grouped will depend on the concerned exposition. Although aggregating jobs into broader categories may dilute the exposition across different occupations hampering hypothesis testing of possible occupational hazards, this strategy can be useful in producing stable risk estimates when the sample size of the study is small.

Defining what is, or is not, a work-related disease has itself proved contentious. This is partly because present recording systems have been design for the purpose of justifying compensation for injured workers, rather than for elucidating future preventive strategies. Classifying occupations has also received a great deal of attention, due to the necessity of considering economic factors related to labor-market statistics.

International and national classification of occupations are usually based on parameters such as qualifications, skills, and training required, rather than on a system that can usefully define risk encountered in particular occupations (e.g. according to potential substance exposure). Some occupational classifications relate to specific tasks from which exposure to certain hazards can be deduced; however, many do not, and rubrics often cover persons carrying out tasks that involve dissimilar hazards and safety risks. Another drawback of these classifications is that they do not allow coding workers performing a great variety of job tasks simultaneously.

Despite these limitations, the major advantage of using international codes and classifications at the national level is that international comparisons can be made. Current occupational classifications such as the ISCO and NACE have been regarded as major references on which comparative data could be based. These classifications allow a more or less precise identification of the work done by workers, and by inference, of the risks involved.

3.8 Analyses and statistical procedures

A total of 118 cases and 475 controls were included in the pooled analyses. The population study provided 37 cases and 327 controls, and the hospital study added 81 cases and 148 controls to the analyses.

The following analyses are included in this thesis:

- Description of cases and controls in the hospital-based study
- Description of the socio-demographic characteristics between cases and controls including type of interview, gender, age, schooling and smoking history, stratifying by study design
- Analysis of the medical history (ever had) as risk factor for UM including parotiditis, measles, chickenpox, herpes, hepatitis, liver cirrhosis, asthma, dermatitis, urticaria, diabetes, psoriasis, typhus, paratyphus, bone disease, thyroid disease, and inf. bowel disease.
- Analysis of eye color as risk factors for UM
- Complete conditional logistic regression analyses between occupational categories (ISCO and NACE: main, main + secondary tasks; JSQ: main task) and UM stratifying by gender
- Main positive associations between occupational categories (ISCO and NACE: main, main + secondary tasks; JSQ: main task) and UM stratifying by gender
- Main negative associations between occupational categories (ISCO and NACE: main, main + secondary tasks; JSQ: main task) and UM stratifying by gender
- Comparison between the principal associations found in previous studies regarding potential occupational risks for UM and the associations found in the pooled analysis
- Consistency of findings between the hospital and population-based studies
- Consistency of findings across the classification systems (ISCO, NACE, and JSQ)

Pearson Chi^2 tests were used to detect differences between categorical variables in the descriptive analyses. The probability level at which differences were considered statistically significant was 0.05.

Conditional logistic regression analyses were utilized to estimate the adjusted odds ratios, and the 95% confidence intervals (CI) were computed according to standard methods. Cases and controls were matched (m:n matching) by age, gender, and region. Dichotomous categorization using “never” versus “ever” being exposed to the occupational category in question was used to determine the exposure status. Conditional logistic

regression is used to investigate the relationship between an outcome and the explanatory factors in matched case-control studies. The outcome is whether the subject is a case or a control.

Regression analyses included the unadjusted and adjusted OR with 95% CI, and the number (n) and frequency (%) of cases and controls by occupational category was always presented. The analyses presented were always stratified by gender (men + women, men, and women).

Both, descriptive and conditional logistic regression analyses were performed in the SAS® computer software (Breslow 1980; SAS Institute 1996).

3.9 Ethical considerations

The ethical, legal and medical confidentiality aspects of epidemiological studies need to be considered carefully. Such matters are important when designing, conducting, analyzing, interpreting, and reporting epidemiological studies. There are also ethical considerations to be taken into account concerning the use of the findings of epidemiological studies. As these case-control studies involved human subjects, it was mandatory to comply with the social and legal requirements applicable, giving due consideration to ethical codes developed internationally.

Additionally, a few key provisions for epidemiological studies needed to be addressed: informed consent by participants; justification of the study in terms of the benefits to the participants and to society; protection of participants from potential harmful effects attributable to the study; information to participants regarding the study results and their interpretation; and confidentiality regarding the participants' personal health information.

All these issues were systematically taken care of when applicable, namely, potential participants were explained the aims and potential benefits of the study, participants involved provided informed consents, and the information collected (including data stored electronically) was held strictly in confidence.

4. PRESENTATION OF RESULTS

4.1 Cases and controls in the hospital-based study

Table 4 summarizes the clinical information of the 81 interviewed patients from the hospital-based study. Most UM were located in the choroid (85.2%), 13.6% in overlapping tissues, and only 1.2% in the iris. The left eye was affected slightly more often than the right eye. Two-thirds of the patients were treated initially with episclearal plaque radiation, and 22.2% with enucleation.

Table 5 compares some of the basic demographic and socioeconomic characteristics between cases and controls in the hospital-based study. No significant differences in the proportions observed for *city of residence*, *type of health insurance*, and *socioeconomic status* between cases and controls were seen. Nonetheless, for *region of residence*, controls were more likely to come from the Ruhr area than cases (p= 0.03).

Table 6 presents a comparison of selected characteristics between non-participating and participating controls. There were statistically significant differences in several of the demographic characteristics analyzed between the participating and non-participating controls. These included *gender*, *city of residence*, and *region of residence*: the proportion of women who did not participate as controls was higher than the proportion of those who participated; there were also more persons who lived in cities with <100,000 inhabitants who did not join the study than those who did; and there were more participants controls coming from the Ruhr area than non-participants. Regarding *age at diagnosis* and *type of health insurance*, no significant differences were observed.

The number of cases and controls in each age group category, stratifying by gender, and region and size of the city of residence is presented in **Table 7**. There were fewer numbers of cases and controls reported in the younger age groups than in the older age groups; in fact, only one case was included in the age group 35-39 years. On the other hand, there were also very few cases and controls reported in the area *Non-Ruhr North*, especially for cities with *≥100,000* inhabitants where no cases were reported at all, compared to the area *Non-Ruhr South*.

The case-control ratio ranged from 1:0.4 for men aged 65-69 years in the *Non-Ruhr South ≥100,000* (5 cases and 2 controls) to 1:9 for women aged 65-69 years in the *Ruhr area* (one case and nine controls). No controls were available for an “exact” matching for three cases (highlighted in the table with an asterisk), thus a control from the closest neighboring strata was assigned.

4.2 Description of cases and controls

Table 8 presents a description of cases and controls stratifying by study design. The number of cases and controls interviewed was 37 and 327 for the population-based study, and 81 and 148 respectively for the hospital-based study. Thus, the pooled analysis included 118 cases and 474 controls. *Face-to-face interviews* accounted for most interviews conducted among cases and controls in the population-based study. However, in the hospital-based study, *telephone interviews* accounted for 25% and 44% of the cases and controls respectively. Similar *educational background* (schooling years), and *smoking status* were seen between cases and controls in either study and in the pooled analysis.

4.3 Past medical history as risk factor for UM

There were no significant associations found with any of the explored diseases. The OR (95% CI) observed were as follows: Parotiditis 0.98 (0.92-1.05); Measles 1.00 (0.94-1.08); Chickenpox 1.00 (0.94-1.07); Herpes 0.74 (0.49-1.13); Hepatitis 0.77 (0.51-1.15); Liver cirrhosis 0.98 (0.71-1.45); Asthma 0.64 (0.35-1.17); Dermatitis 0.85 (0.64-1.12); Urticaria 0.87 (0.66-1.16); Diabetes Mellitus 0.82 (0.55-1.24); Psoriasis 0.68 (0.38-1.22); Typhus and Para-typhus 0.87 (0.60-1.27); Bone disease 0.82 (0.49-1.37); Thyroid disease 0.67 (0.43-1.06); Inflammatory bowel disease 0.58 (0.21-1.55).

4.4 Host risk factors for UM

Having light color eyes was positively associated to UM when compared to dark eyes, especially in the hospital-based study where significant associations were found for men. The pooled analysis showed that the risk for UM was almost three times bigger in light color eyes than in dark eyes.

4.5 Complete analyses

The following tables present the distribution of subjects and odds ratios (OR) with 95% confidence intervals (CI) for UM according to the ISCO, NACE and JSQ occupational classifications stratifying by gender, for main and main + secondary task.

4.5.1 ISCO: International Standard Classification of Occupations

Table 9 shows the pooled analysis by ISCO occupational categories (main task) in both sexes. *Service workers* and *general farmers* presented significant unadjusted ORs with 1.7 (1.07-2.65) and 2.1 (1.03-4.38) respectively. However, the statistical significance was lost when the ORs were adjusted for age, gender and region of residence. The OR for s*ervice workers* decreased to 1.6 (0.93-2.87), and for *general farmers* to 1.6 (0.71-3.51).

On the other hand, *electric and electronic workers, broadcasting-cinema operators* showed a significant unadjusted OR (0.2; 0.07-0.74) but a non-significant adjusted OR (0.3; 0.1-1.19), but only three cases were included in the analysis.

In **Table 10** "secondary task" was added to the analyses. The number of cases and controls increased, especially for the controls, but no significant adjusted ORs were seen for either *service workers* or *general farmers*. In fact, both, the unadjusted and adjusted ORs decreased compared to when only "main task" was included in the analysis.

On the other hand, *blacksmiths, toolmakers, machine-tool operators* (0.4; 0.15-0.99); *electric-electronic workers, broadcasting-cinema operators* (0.2; 0.06-0.65); and *plumbers, welders, sheet-structural metal workers* (0.4; 0.19-0.98) showed protective associations in the unadjusted ORs, but the magnitude of the association decreased and the significance was lost in the adjusted analyses.

Table 11 presents the pooled analysis by ISCO occupational categories (main task) for men. *General farmers* (2.7; 1.04-6.84); *miners* (2.8; 1.26-6.35); and *food, beverage and tobacco processors* (4.5; 1.16-17.05) presented significant unadjusted ORs, but no one remained significant when the ORs were adjusted for age and region of residence. However, for *miners* (2.3; 0.92-5.99) and *food, beverage and tobacco processors* (4.7; 0.99-22.05) the adjusted ORs remained elevated and the lower CI was close to the significance level. Nevertheless, the number of cases and controls was ≤5 for *food, beverage and tobacco processors.*

The pooled analyses for men based on the ISCO classification including "secondary task" are presented in **Table 12**. The inclusion of "secondary task" added only few cases. The association for *general workers* was no longer significant in the unadjusted OR, and even lowers in the adjusted OR. For *miners* the number of cases and controls remained unchanged. For *food, beverage and tobacco processors* only one case and two controls were added, having a negative impact in the ORs.

In addition, *fur and leather workers, show and leather good makers,* and *electric and electronic workers, broadcasting-cinema operator* showed significantly positive and negative unadjusted ORs respectively, but both adjusted ORs were non-significant. Moreover, the number of cases in both occupational groups was very small (n=3)

Table 13 presents the pooled analysis by ISCO occupational categories (main task) for women. No unadjusted or adjusted OR appeared statistically significant. Although *service workers*; *medical, dental, pharmaceutical and veterinary workers*; *station-engine-heavy equipment operators and freight handlers*; and *jewelers, musical instrument and other production workers* had all more than five cases and showed positive associations, none of the adjusted ORs reached statistical significance.

The inclusion of "secondary task" in the pooled analyses by ISCO occupational groups for women (**Table 14**) allowed the inclusion of few cases and some more controls for the occupations of interest, except for *medical, dental, pharmaceutical and veterinary workers* where no cases neither controls were added. However, the unadjusted and adjusted ORs decreased compared to when only "main task" was included, and the lower CI appeared far away from the null value in all analyzed occupations.

4.5.2 NACE: European Community Industrial Classification

Table 15 presents the pooled analyses by NACE occupational branches for the "main task" among men and women. Although several occupational branches were significantly associated to UM in the unadjusted analyses, none reached statistical significance when the analyses were adjusted by age, gender and region of residence. *Coal mining, petroleum and gas production and manufacturing* (3.4; 1.04-11.48); *chemical and pharmaceutical industry* (2.2; 1.07-4.6); and *health and veterinary sector* (2.1; 1.02-4.11) presented statistically positive unadjusted ORs. The adjusted ORs decreased slightly and the statistical significance was lost for the last two occupational branches. However, for *coal mining, petroleum and gas production and manufacturing* the adjusted OR increased and the lower CI remained very close to the null value (3.8; 0.98-14.87). Some other branches also showed non-significant, but elevated adjusted ORs such as *mining*; *wholesale traders and intermediates*; and *catering trade*.

Metal manufacturing was the only branch that was negatively and significantly associated to UV in both the unadjusted (0.3; 0.13-0.86) and adjusted (0.4, 0.14-0.99) OR.

The inclusion of "secondary task" added one case and one control for the analysis of *coal mining, petroleum and gas production and manufacturing* elevating the ORs, and

reaching statistical significance in the adjusted OR (3.8; 1.11-12.99). The number of cases and controls remained basically unchanged for *chemical and pharmaceutical industry*; and *health and veterinary sector*, and so did the ORs (**Table 16**).

Metal manufacturing with 7 cases and 60 controls, remained negatively associated to UM, though the adjusted OR lost its significance (0.3; 0.09-1.1).

Table 17 presents the pooled analysis by NACE occupational branches (main task) for men. *Food industry* (3.4; 1.08-10.57), and *chemical and pharmaceutical industry* (2.8; 1.01-7.78) presented statistically significant adjusted ORs. *Coal mining, petroleum and gas production and manufacturing*, with three cases and three controls, showed a significant unadjusted OR, but a non-significant OR after adjusting for age and region. *Mining* was also positively associated but did not reach statistically significance in either OR.

Table 18 presents the analyses for women with the inclusion of "secondary task". The ORs for *food industry* did not changed, as neither cases nor controls were added. For *mining*; *coal mining, petroleum and gas production and manufacturing*; and *chemical and pharmaceutical industry* only very few more cases and/or controls were included. Although all presented significant unadjusted ORs, none of the three adjusted ORs reached statistical significance.

A few controls, but no cases, were added for *metal manufacturing* remaining negatively associated to UM. The statistical significance reached in the unadjusted OR was lost after the adjustment for age and region of residence.

The pooled analysis for the "main task" by NACE occupational branches among women is presented in **Table 19**. *Health and veterinary sector* showed a significantly positive unadjusted OR (2.3; 1.03-5.24) remaining very close to the null value after adjustment for age and region of residence (2.4; 0.97-5.71). For *machine production*; *catering trade*; and *landed property services, business services* the adjusted ratios, were higher than the non-adjusted ORs, though they did not reached statistical significance. No statistically significant protective associations were seen in either ORs.

The introduction of "secondary task" did not improve the number of cases in the occupational branches mentioned previously (**Table 20**). Only a few controls were added, except for *health and veterinary sector* that remained unchanged. However, the inclusion of these controls had a negative impact in both, the unadjusted and adjusted ORs.

4.4.3 JSQ: Job-Specific Questionnaire Classification

Tables 21 and 22 present the pooled analyses for the "main task" based on the JSQ occupational classification, among men-women and stratifying by gender respectively. Very few cases were included in the occupational categories, especially when the analyses were stratified by gender.

The unadjusted (2; 1.08-3.67) and adjusted (2.1; 1.04-4.29) odds ratios for *cooking* were statistically significant. *Shoe and leather* showed a significant unadjusted OR (4.1; 1.16-14.54) that lost its significance after adjustment. *Farmers*; *health care*; *working with animals*; and *pulp-paper production* also presented positive but non-significant associations (**Table 21**).

Conversely, *electricians*; *welding, brazing, soldering*; and *metal working* showed significantly protective unadjusted associations, though the significance was lost after adjustment.

The stratified analysis by gender presented in **Table 22** showed a significantly positive association for *cooking* in both the unadjusted and adjusted OR. Other positive associations were seen for *farmers*; *working with animals*; *chemical industry*; and *builder, stonemason, plasterer* though no significant associations in either the unadjusted or adjusted OR were observed.

Male *metal workers* had a significantly protective unadjusted OR, but the statistical significance of the estimate was lost after the adjustment.

For women, no significant associations were seen in the unadjusted or the adjusted ORs, and very small number of cases was seen in most occupational groups. Although did not reach statistical significance in either OR, *health care*, with nine cases, was positively associated to UM.

4.6 Main positive associations

4.6.1 ISCO: International Standard Classification of occupations

Table 23 summarizes the most important findings positively associated to UM among men and women for both, main task, and main and secondary task, according to the International Standard Classification of occupations (ISCO).

The following job groups were positively associated to UM among **men**:

- ***Clerical workers*** showed an adjusted of 1.8 (0.86-3.78). The inclusion of secondary task (one case and 18 controls more) lowered the OR to 1.4 (0.70-2.94).
- ***General farmers*** showed a non-significant adjusted OR at 1.7 (0.60-4.95). The inclusion of secondary task increased only the number of controls from 15 to 18, lowering the adjusted OR to 1.5 (0.53-4.13).
- ***Miners*** presented a strong adjusted OR at 2.3 in the analysis of main task, with a lower CI near the null value (0.92-5.99). No cases or controls were added when secondary task was taken into account.
- ***Food, beverage, and tobacco processors*** had an almost significant adjusted OR of 4.7 (0.99-22.05) for main task. However, only 4 cases and 5 controls were included in the analysis. When secondary task was added (one case and two controls more) the adjusted OR was 3.7 (0.94-14.11).

The following groups were positively associated to UM among **women**.

- ***Service workers*** presented an adjusted OR of 1.8 (0.86-3.80). Including secondary task (2 cases and 12 controls more) lowered the adjusted OR to 1.5 (0.73-2.95)
- ***Medical, dental, pharmaceutical and veterinary workers*** showed an adjusted OR at 2.1 (0.71-6.02). Secondary task did not add cases or controls
- ***Station, engine, heavy equipment operators, and freight handlers*** had an adjusted OR of 2.5 (0.94-6.58). Secondary job added 1 case and 10 controls to the analysis, lowering the OR to 1.5 (0.63-3.70).

4.6.2 NACE: European Community Industrial Classification

Table 24 summarizes the most important findings positively associated to UM among men and women for both, main task, and main and secondary task, according to the European Community Industrial Classification (NACE).

The following branches were positively associated to UM among **men**:

- ***Mining*** presented an adjusted OR of 1.9 (0.81-4.66) for the main task. Although secondary occupation added only one case and one control, this had a positive effect raising the adjusted OR at 2.0 (0.87-4.78).
- ***Coal-mining, petroleum and gas production and manufacturing*** with only three cases and three controls, showed an adjusted OR 4.8 (0.67-33.62). With the inclusion of secondary task (one case and one control more) the OR was 4.4 (0.87-22.0).

- ***Food industry*** was positively and significantly associated to UM for the main task. The adjusted OR was 3.4 (1.08-10.57). However, for secondary task, the OR remained unchanged as no cases or controls were added.
- ***Chemical and pharmaceutical industry*** was also positively and significantly associated to UM, with an adjusted OR of 2.8 (1.01-7.78). Secondary task added only one control, which had negative effect in the adjusted OR at 2.6 (0.97-7.24).

The following branches were positively associated to UM among **women**:

- ***Machine production*** with six cases and eight controls, presented an almost significant adjusted OR of 3.2 (0.96-10.77). The inclusion of secondary task added two more controls having a negative impact in the adjusted OR at 2.4 (0.72-8.12).
- ***Catering trade*** presented an adjusted OR of 2.3 (0.85-6.19) for the main task. The inclusion of secondary task to the analysis (three controls more) had a negative impact in the estimates, with an adjusted OR of 1.7 (0.68-4.46).
- ***Landed property services and business services*** showed an adjusted OR of 2.1 (0.83-5.40) for the main task. The addition of secondary task to the analysis (one control more) had a marginal impact in the adjusted OR 2.1 (0.81-5.25).
- ***Health and veterinary sector*** presented an almost significant adjusted OR of 2.4 (0.97-5.71) for the main task. However, no change was seen in the adjusted OR for secondary task, as no cases or controls were added.

4.6.3 JSQ: Job Specific Questionnaire Classification

Table 25 summarizes the most important findings positively associated to UM among men and women for both, main task, and main and secondary task, according to the JSQ classification system.

The following job groups were positively associated to UM among **men**:

- ***Cooking***, with six cases and eight controls, showed a strong and significant association with an adjusted OR of 5.6 (1.66-19.19).
- ***Farmers*** showed a positive but non-significant association with an adjusted OR of 1.4 (0.50-3.77).
- ***Builder, stonemason and plasterers*** presented a non-significant adjusted OR of 1.4 (0.64-2.99).
- ***Chemical industry*** had a positive but non-significant adjusted OR of 1.9 (0.57-6.34).

The following job groups were positively associated to UM among **women**:

- *Health care* (9 cases; 16 controls) had a non-significant adjusted OR of 1.5 (0.60-3.76).

- *Cooking* showed a non-significant association with an adjusted OR of 1.4 (0.58-3.19).

4.7 Main negative associations

The most important findings negatively associated to UM among men and women for main task, and main and secondary task, according to the ISCO, NACE and JSQ classification systems, is summarized as follows:

ISCO: *Electric-electronic workers, broadcast-cinema operators* (3 cases; 47 controls) showed a non-significant protective association among men with an adjusted OR of 0.4 (0.10-1.25). The inclusion of secondary task (5 more controls) further lowered the adjusted OR at 0.3 (0.09-1.10), but still remained statistically non-significant.

NACE: *Metal manufacturing* (5 cases; 55 controls) had a significantly protective effect in men and women together with an adjusted OR of 0.4 (0.14-0.99). The statistical significance was lost after the inclusion of secondary task (2 cases and 5 controls more) with an adjusted OR 0.5 (0.20-1.10). Men were mostly responsible for this finding as they contributed with the majority of cases and controls.

JSQ: *Metal workers* (11 cases; 101 controls) showed a protective but non-significant association among men with an adjusted OR of 0.6 (0.30-1.29).

4.8 Comparison between previous and current findings

Table 26 compares the principal associations found in previous studies regarding potential occupational risks for uveal melanoma and the associations found in the pooled analysis.

Albert et al (1980) reported an increased incidence of UM among workers in a chemical plant, and Enterline et al (1987) documented an increased SMR for eye cancer in an historical cohort of asbestos workers. Holly et al (1996) also showed increased adjusted OR for asbestos exposure (1.8; 1.1-3.1) and among chemists-chemical engineers-chemical technicians (5.8; 1.6-22.7). Yet, the pooled analysis for main occupation showed

that men working the chemical and pharmaceutical industry according to NACE had a significantly elevated OR of 2.8 (1.01-7.78) after matching for age and region. Similarly, although non-significant, the JSQ showed a positive association for men in the pooled analysis with an adjusted OR of 1.9 (0.57-6.34).

In a proportion mortality study, Saftlas et al (1987) found an increased PMR and PCMR for eye cancer in white male farmers. Lynge and Thygsen (1990) also found high rates for male farmers in the Danish register linkage study. Ajani et al (1992) also reported increased risks for agriculture, and the Illinois farmers' case-control study (1993) found a significantly elevated OR for eye cancer. Conversely, Wiklund and Dich (1995) did not found an increased SIR for eye cancer in the Swedish cohort for male agricultural workers. In the present study, although not statistically significant, farmers had consistently elevated adjusted ORs for main task, among men across to the categorization systems: ISCO-General farmers 1.7 (0.60-4.96); NACE-Agriculture, forestry, hunting and fishing 1.4 (0.51-3.60); and JSQ-farmers 1.4 (0.50-3.77)

Tucker et al (1985) found a significantly high OR for welders. Later on, Holly et al (1996) also found an increased OR for welding exposure (2.2; 1.3-3.5). In the pooled analysis, none of the categorization systems used detected any increased risk for welders.

Other occupations, including managerial employees, clerical workers, wood workers, livestock workers, and health workers, have also been sporadically mentioned in the literature as possibly associated to UM. Despite the fact that most of these occupations, especially among men, showed increased risks in the pooled analyses, none of the ORs drawn reached statistical significance.

4.9 Consistency between the hospital and population studies

Consistency between the hospital and population-based studies was assessed through comparing the adjusted odds ratios (point estimate) in those occupational groups with more than three cases and controls in each study. It was not possible to stratify the results by gender, as important sample size limitations existed, especially for the population-based study.

Table 27 presents the evaluation of the consistency between studies according to the ISCO classification system. Around half of the job groups presented consistent associations, that is, the odds ratios pointed to the same direction in both studies, either positive (OR >1) or negative (OR<1). The other half of the job groups presented inconsistent associations, namely, one of the odds ratios was positive and the other was

negative. Major inconsistencies were seen for *medical, dental, pharmaceutical and veterinary workers* (0.8 vs. 2.7); *Managers, managerial employees* (0.7 vs. 1.4); and *service workers* (2.8 vs. 0.8).

Table 28 presents the assessment of the consistency according to the NACE classification system. Except for *machine production* (0.9 vs. 1.1); *transport* (0.8 vs. 1.9); and *public administration, social security, defense, and police* (1.4 vs. 0.7) where inconsistencies were seen, most analyzed branches presented consistent adjusted OR between both studies.

Consistency was assessed on very few job groups for the JSQ, due to sample size constrains. *Health care* (0.9 vs. 1.8) and *welding, brazing, soldering* (0.8 vs. 1.1) had inconsistent ORs, while *cooking*; *builder, stonemason, plasterer*; and *metal working* showed consistent ORs (**Table 29**).

Table 30 evaluates the consistency of the adjusted OR between the hospital and population studies for five selected occupational categories. It can be seen that, except for health, basically all estimates in both studies point towards the same positive direction for the chemical, farming, food, and mining occupations, though it is worth noting the scanty number of cases for some categories.

4.10 Consistency across classification systems: ISCO-NACE- JSQ

Assessing the consistency of results across the three classification systems used through comparison of the adjusted ORs (point estimates) is troublesome, as they do not classify individuals according to equivalent criteria. While the International Standard Classification of Occupations (ISCO) categorizes the individual's occupation within a determined job-group category, the European Community Industrial Classification (NACE) classifies the person's job within the industrial branch where it belongs. The Job-Specific Questionnaires (JSQ) can be even more specific than ISCO, as the tasks performed must correspond more or less directly to one of the jobs listed. It is therefore important to make several observations before interpreting the results presented here.

Consistency between ISCO and JSQ could be expected as both methods classify individuals according to the job or task performed. However, NACE must not necessarily be consistent with the ISCO or JSQ categorisation methods, as not all jobs within a determined branch are similar; for instance, a chemical worker and a secretary working in a chemical factory would be classified within the branch "chemical and pharmaceutical industry" in spite the enormous difference in the task performed.

On the other hand, not all categories of a determined classification system match an equivalent category of the other classification systems. For example, the NACE branch *church and trade unions* cannot be compared to any category within ISCO or JSQ, as these classification methods do no include a similar category.

Moreover, some jobs groups/industrial branches included two or more sub-categories within the principal headline; for instance, the ISCO job group *medical, dental, pharmaceutical, and veterinary workers* includes four sub-categories and therefore matches partially the JSQ categories *health care* and *dentistry*.

All these limitations must be kept in mind when interpreting the following comparisons. The assessment presented here includes the most relevant occupations positively associated to UM. It includes job groups and industrial branches in which equivalencies can be more or less established for at least two categorization methods.

Table 31 presents the consistency across the categorization methods used for the main task in the pooled analyses, stratifying by gender. Overall, consistent odds ratios (point estimates) were seen throughout the compared occupational groups (ISCO–JSQ–NACE).

Among men, although non-statistically significant, *general farmers – farming – agriculture, forestry, hunting, fishing* showed all positive associations, that is to say, consistent ORs across the classification methods. For women, weaker associations, but still pointing at the same direction were observed.

For men, *food, beverage, and tobacco processors – cooking – food industry* presented consistently positive and strong associations. In fact, the ORs were statistically significant in the JSQ and NACE classifications, and almost reached significance in the ISCO classification (0.99-22.05). Consistency was partially evaluated among women because no cases were available according to ISCO. Inconsistent ORs were observed; *cooking* (JSQ) was positively associated, and *food industry* (NACE) negatively.

Chemical, rubber, and plastic workers and *chemical and pharmaceutical industry* showed also positively consistent ORs across the classifications among males. Statistical significance was reached among *chemical and pharmaceutical industry* (NACE). Only two cases were available for *chemical, rubber, and plastic wo*rkers (ISCO).

Medical, dental, pharmaceutical, veterinary workers – health care – health and veterinary sector were consistent among women. Non-significant but positive associations were seen across the three classification methods.

5. DISCUSSION

Uveal melanoma belongs to those malignancies in which very little etiological information exists. Various risk factors have been linked to the genesis of this tumor, but these have not yet proven to be causative. Methodological constrains have frequently hampered the clear interpretation of the results. Problems arising from the impossibility to conduct prospective studies in this extremely rare cancer have been a major limitation in understanding the potential factors associated to this tumor. Moreover, as no specific hypotheses regarding causative agents have been postulated, the question of carrying out expensive cohort studies has been ruled out.

Assessing the exposition status has been also a major concern referred by several authors. Very often, the results drawn from studies in which the exposition was not accurately assessed have been judged to be of explorative nature. This issue has been particularly relevant when looking at occupational risk factors.

The potential role of occupational factors in the etiology of UM has been explored in very few studies, and the available evidence has not yet enlightened this issue. The published results have been inconsistent, and frequently surrounded by methodological drawbacks Therefore, controversies among authors of whether occupational factors exist or not are still ongoing.

The present thesis took advantage of the availability of data collected from two case-control studies that were similarly design to conduct a pooled analysis aimed at exploring the possible links between occupation and UM. It could not anyway escape form many of the methodological problems previously mentioned, especially those related to the assessment of the exposition. Notwithstanding these limitations, the results presented here added important evidence regarding the role of occupation in the etiology of this cancer.

Concerning the study design used, there were two main reasons for having chosen case-control studies to explore the potential risk factors linked to this neoplasm. First, a case-control study is an efficient design for evaluating the etiology of very infrequent diseases such as UM. The sample size required to be able to use a design with more powerful etiological capabilities like a cohort study would have been almost prohibited; and second, the use of an alternative observational design such as a cross-sectional study would have been of a limited etiological value since it does not guarantee that the cause (risk factor) preceded the effect (disease). Therefore, a case-referent design was an appropriated choice to approach the occupational risks for UM, as it is relatively cheap and

easy to implement compared to a cohort study, and it does provide stronger evidence of causal associations than a cross-sectional study.

Spurious estimates often result from errors in the classification of the subjects either in the exposition status, or in the disease status, or in both, and may falsely amplify or diminish the true association between exposure and disease. The use of a validated measurement instrument often helps avoiding misclassification of the exposure status

Probably the major concern of this pooled analysis was that related to the exposure assessment. In both case-control studies included in the pooled analyses, the assessment of the exposition relied on an indirect source to infer the exposure status for individuals. Occupation title was used a surrogate for exposure, as no specific occupation was known to cause the disease, and direct measurements of the exposition (e.g. chemical agent) were not feasible.

The exposition to occupations was evaluated utilizing three different systems to classify jobs or tasks, namely the ISCO, NACE and JSQ classifications. These systems use a clustering procedure to group occupational titles into smaller numbers of occupational categories according to shared characteristics. Although aggregation of jobs into broader categories can result in a dilution of the exposition across different occupations, hampering hypothesis testing of possible occupational hazards, this strategy helps producing stable risk estimates when the sample size of the study is small, such in the presented here. Besides, the use of the ISCO and NACE classifications provide the major advantage of being able to establish international comparisons of the results. These two reasons provide the rationale for having use these classifications for assessing the exposure status.

Training interviewers and masking for study hypothesis also prevents bias in ascertaining the exposure status. Consequently, in both case-control studies included in the pooled analyses, the interviewers were carefully trained to obtain precise descriptions of the occupations. Furthermore, the interviewers conducted structured questionnaires, and were unaware of the occupations potentially associated to UM, or of any specific hypotheses.

In addition to this, the persons responsible to assign codes to the individuals' occupations were instructed to be as specific as possible, and standardized rules were use to improving the accuracy of coding. Thereafter, another person performed a second coding, and comparisons between the first and second coding were made. Where inconsistencies were found, a definitive coding based on consensus was given.

To avoid misclassification of the disease status, eligible incident cases with a standard confirmation of the diagnosis are frequently preferred. This prevents the fact that a long pre-morbid exposure to risk factors would have been harder to ascertain, especially because the exposition depended on people's memories. Also the presence and severity of the disease (prevalent cases) can influence the person's ability to recall potential risk factors.

In this regard, the identification of cases was based on confirmed histological diagnoses of primary incident UM (according to the International Classification of Diseases) through experienced pathologists in both case-control studies.

Recall bias is another drawback in any case-control study, and occurs when anamnestic responses (i.e. retrospective assessment of the exposure) differ between cases and controls. Inaccuracy in reporting past exposures arise from faculty memory, bias on the cases or interviewers about likely causes of the disease, or other psychosocial or interpersonal factors that may lead to an exaggerated or understated exposure.

The degree of misclassification of recalled job periods or occupations that could have occurred in these case-control studies was to a great extent due to the complexity of the individuals' occupational histories. Although it is difficult to avoid recall bias, some factors such as the interviewer skills, the interview quality, and the type of respondent are known to have a strong influence in the accuracy of the recall. Therefore, training interviewers, using appropriated questionnaires, showing examples of job tasks entailing exposures, and conducting personal interviews may be helpful to prevent recall bias. Regarding the first two issues, the interviewers' skills were carefully tailored to obtain information as detailed as possible by using an extensive structured questionnaire. With respect to the last issue, it was intended to conduct preferably personal interviews. The overall proportion of face-to-face interviews in the pooled analyses was 76.3 and 80.9% for cases and controls respectively.

A distortion of the effect resulting from differences between cases and controls in past exposition and other confounding factors can occur. To avoid this, cases and controls must be very similar to each other except for the presence of the disease. For example, cases and controls must be unbiased with respect to age, which is obviously linked with the duration of occupation. One way to ensure similarity between cases and control groups is matching for factors believed to be important (i.e. age, gender, socioeconomic status, place of residence, etc.), thought this precludes the analysis of these characteristics.

The matching variables included in the case-control studies of the pooled analyses were gender, age, and region of residence. Nevertheless, matching cases and controls resulted

much more difficult than expected for the hospital-based study. The main reason for this was the problems faced to gather enough appropriated controls. While cases in some age groups ended up with basically no paired controls, some others accounted for a huge number of controls. In spite of these problems, the matching procedures performed prevented indeed risks of selection bias or confounding by the matched variables.

On the other hand, no statistically significant differences in the number of schooling years (i.e. educational level), or in the smoking status were seen between cases and controls, ruling out distorted estimates because of the possible effect of these two known potential confounders.

The pooling of the data from the hospital and population-based studies was made to improve the size of the sample aimed at enhancing the precision of the estimates. Although this procedure could be methodologically questioned, especially because the controls might represent different populations “at risk”, the fact that both studies used the same interview methods for exposure assessment, used similar criteria for case definition, and were conducted almost simultaneously, diminishes other major conceptual and methodological constrains to pool the results.

Only minor differences existed in the case definition between both studies, for instance, differences in the criteria for age at diagnosis; whereas in the population-based study this was limited to 69 years, in the hospital-based study, the period was extended up to 74 years.

In addition, some differences regarding the selection of cases was seen between both studies; while in the hospital study cases were taken exclusively from a reference ophthalmologic center, in the population study cases came from various relevant institutions in the studied regions. Though probably minimal, this could be reflected in a slightly better exposure assessment in those cases from the hospital study.

When looking at the response proportions among cases, very similar proportions were observed in the population study (85%) compared to the hospital-based (88%) study. Furthermore, the reasons for not having participated in the studies were also very similar.

Obtaining suitable controls proved to be much more problematic. The selection of controls followed very different strategies between the studies, and so did the response proportions: 48% and 79% for the population and hospital-based studies respectively. Refusals to participate in the study reached 34% in the population-based study, and 13% in the hospital-based study. This might have had an impact on the estimates if the participating and non-participating controls differed importantly, especially in the population-based study, where only half of the eligible controls participated.

When comparing the characteristics between the participating and non-participating controls in the hospital-based study, no major differences were seen for age at diagnosis and type of health insurance, but statistically significant differences in the proportions for gender, size of the city of residence, and region of residence were observed.

Differences regarding the sources of controls used were inherent to the study design used. Those controls selected from the general population had the advantage that their exposures were likely to be representative of those at risk of becoming cases. However, the exposure assessment might not be that comparable with that of cases, especially because the evaluation was achieved by personal recall. Unlike controls, cases are often motivated to remember details of their past as they are keen to find out what caused their disease. This might have cause an overestimation of the risk due to differential recall.

Conversely, hospital controls certainly do not represent the general population. However, measurement of the exposition between cases and controls could have been more comparable in the hospital-based study, as the controls also suffered from a disease. The fact that subjects were not told the exact focus of the investigation, and that diagnoses for controls included a range of benign posterior eye segment diseases was fundamental to assuming that the exposition was similarly assessed in both cases and controls. Even if one of the control diseases happened to be related to the risk factors under study, the resultant bias (underestimation of the risk) would not have been too large.

As the number of cases was limited due to the rarity of the disease under investigation, the inclusion of several controls per case was foreseen to increase the statistical confidence in both studies. One case per four controls was the ratio originally set in both, the population and hospital-based studies.

In contrast to the population study where the anticipated case-control ratio was easily attained, gathering controls in the hospital study was an arduous task as previously mentioned. However, the lack of controls in the hospital study was slightly counterbalanced by an increased participation of cases in comparison to the original number expected.

After having assessed most of the methodological issues concerning the precision and validity of the results, the discussion moves on into the major findings obtained.

The analyses were able to replicate findings linked to UM in previous investigations. For instance, the risk of UM was significantly higher among those individuals with light-color eyes compared to dark-color eyes (OR 2.8; 95%CI 1.5-5.3) as previously reported (Jensen 1982; Gallagher et al. 1985; Holly et al. 1990). This supports trustworthiness of the results presented here.

The current absence of clear answers from previous studies indicated that there was unlikely to be a strong association with any occupational exposure. However, several occupational categories appeared positively associated to UM according to the three classification systems for the main task, but only a few were statistically significant.

Among men (OR; 95% CI), miners (2.3; 0.92-5.99), general farmers (1.7, 0.60-4.95), and clerical workers (1.8, 0.86-3.78) were among the occupational categories showing the largest positive associations for the ISCO classification, although none was statistical significant. With a very small number of cases (n=4), food, beverage, and tobacco processors presented the highest adjusted OR, almost reaching the statistical level (4.7; 0.99-22.1). Among women, service workers (1.8; 0.86-3.80), medical, dental, pharmaceutical and veterinary workers (2.1; 0.71-6.02), and station, engine, heavy equipment operators, and freight handlers (2.5; 0.94-6.58) showed the largest adjusted associations for the ISCO classification.

Somewhat similar to that found by ISCO, the most important branches positively associated to UM among men according to the NACE classification were mining (1.9; 0.81-4.66), food industry (3.4; 1.08-10.5), and chemical and pharmaceutical industry (2.8; 1.01-7.78), with the last two odds ratios showing statistical significance. For women, health and veterinary sector had the strongest association, with a lower confidence interval near the significance level (2.4; 0.97-5.71). Other branches positively associated included machine production (2.3; 0.85-6.19), catering trade (1.7; 0.68-4.46), and landed property services and business services (2.1; 0.83-5.40).

The inclusion of secondary task added several controls but very few cases into the analyses for ISCO and NACE classifications impacting the point estimates negatively for most of the principal occupational categories calculated.

In the JSQ, men showed a significantly increased risk for cooking (5.6; 1.66-19.1). Although the ORs for farmers (1.4; 0.50-3.77), and chemical industry (1.9; 0.57-6.34) did not reach statistical significance, they were also among the most relevant associations. For women, those working in health care category presented the highest adjusted OR (1.5; 0.60-3.76).

Very few protective associations were observed for the main task in the pooled analyses. According to the ISCO classification, electric-electronic workers and broadcast-cinema operators had a non-significant negative association among men (0.4; 0.10-1.25), but only three cases were included in the analysis. Metal manufacturing presented a significantly protective association for men and women together according to the NACE

classification (0.4; 0.14-0.99). At last, metal workers showed a non-significant protective association among men (0.6; 0.30-1.29).

The results form these analyses can be compared with the some relevant occupational associations previously suggested. It is noteworthy that food-related workers among men showed the highest adjusted OR in ISCO, NACE, and JSQ classifications, some reaching statistical significance. The study by Vågerö et al. reported a significantly increased proportional registration ratio for ocular melanoma in "kitchen hands" among women (319;117-695) (Vågerö et al. 1990), and Guenel et al. also showed an elevated risk of ocular melanoma among male cooks (Guenel et al. 2001). However, no other reference was found in the literature. Cooking fumes might be responsible for the higher risks.

Various studies have found increased risks among chemical workers (Albert 1980 ; Enterline et al. 1987 ; Holly et al. 1996), and farmers (Saftlas et al. 1987; Lynge & Thygesen 1990; Ajani et al. 1992; Keller & Howe 1994). Yet, although not statistically significant, the pooled analyses also showed increased risks for workers in the chemical industry and farmers consistently across the occupational classifications used.

Miners or mining also had increased risks, however, only one study made reference to "miners, quarrymen" and found no elevated risks whatsoever (Vågerö et al. 1990).

The occupational categories that included welders did not showed positive associations as found before (Tucker et al. 1985; Holly et al. 1996). Unfortunately, the number of welders was too small to perform an independent analysis.

Health-related workers among women presented consistently elevated risks across the classification methods. This has also been reported previously (Pukkala 1995; Holly et al. 1996), and has been though to be the result from referral bias (Holly et al. 1996).

However, as mentioned before, very rarely the estimates reached statistical significance. The relatively small number of observations, particularly for the cases, and the dilution of the effect by pooling several jobs within an occupational category could have been responsible for the lack of statistical significance of some adjusted ORs.

Contrarily to that published by some studies, welders, or rather, the occupational categories that included welders, did not showed positive associations. Unfortunately, the number of welders was too small as to perform an independent analysis.

Consistent results between the population and hospital-based studies were thought to enhance the trustworthiness of the findings of the pooled analysis, namely, those occupations showing elevated risks in one study, were expected to present augmented risks in the other and vice versa. However, the small number of cases, especially for the population-based study, was the principal limitation to evaluate the consistency between

studies. The inclusion of secondary task increased very little the number controls and even less the number of cases in each of the selected occupational categories. For this reason, the consistency of results between studies was assessed only for the main task, in those occupational groups with more than three cases and controls in each study. The consistency of the results was assessed through comparing the direction of the point estimate (i.e. adjusted OR) in the two studies.

For the three classification, the estimates showed mixed results, namely consistent and inconsistent results were observed. The inconsistencies could be due to several reasons. One possibility could be that the assessment of the exposition differed in cases and controls between the studies as it was mentioned at the beginning of the discussion. The small number of cases seen in several occupational groups could also explain these differences, as many estimates presented very wide and overlapping confidence intervals. Another possibility could be that, if fact, no association between the occupational categories and UM existed, and that the inconsistencies resulted from differences in the distribution of non-occupational risk factors between cases and controls in the two studies.

Nevertheless, when the consistency was evaluated for the five most relevant occupational groups outlined here (chemical, farming, food, health, and mining occupations), except for health, most estimates pointed to the same direction in both studies. Although it was not possible to stratify the results by gender due to sample size constraints, these findings enhance the validity of the results.

On the other hand it is very important to underline that no specific exposition was measured, but tasks performed grouped into occupational categories. Even when a specific occupation would have been related to UM, the fact that it was pooled together with other occupations probably not linked to UM, could be the reason why the association was not observed. Therefore, if the proportion of such occupation from the occupational group was big in one study but small in the other, the likelihood of observing inconsistent associations increases.

Despite the fact that the classification systems used did not classify individuals based on the same criteria, the consistency across them was evaluated following the same methodology as in the consistency between studies. It was done basically to explore whether the findings encountered by these classification systems correlate and at what extent, especially between the ISCO and the JSQ systems. As stated before, sample size problems were faced, and therefore only the most relevant occupations positively associated to UM were compared.

The fact that the direction of the association measures correlated between the ISCO and JSQ categorization methods for all the occupational categories evaluated (and with most of the estimates form the NACE classification) pointed to an adequate coding and categorization of jobs.

Summarizing, this pooled analysis provides some evidence to support the potential role of occupation as risk factor for UM. The results presented here must be interpreted with caution especially because an indirect assessment of the exposure status (i.e. through occupational categories) was utilized.

6. ABSTRACT

Background: Uveal melanoma (UM) is an uncommon tumor occurring almost exclusively during adulthood, and accounts for 85% of all primary eye cancers. Although various potential risk factors have been explored, no primary causative agent has been yet recognized and contradictory evidence is commonly found. Despite important advances in diagnosing this neoplasm, the rate of metastasis has not been reduced, and survival and mortality rates remain unchanged. Currently, prevention seems to be an effective way to reducing morbidity and mortality. Thus, identification of risk factors for the development of this malignancy has been a major goal in this field. **Objective:** This thesis was aim at conducting a pooled analysis from two case-control studies conducted in Germany between 1995 and 1998, to explore potential occupational risk factors linked to the etiology of UM. **Methodology:** The analysis included a population-based study conducted between 1994 and 1997 in five geographic regions (Hamburg, Bremen, Essen, Saarbrücken, and Saarland), and a hospital-based study carried out in North-Rhine Westphalia between 1994 and 1995 at the Eye Clinic, University of Essen. Both studies included incident UM cases. Several controls per case were matched by age, gender, and region of residence. Individuals were contacted through face-to-face and telephone interviews. Exposure status was based on the individuals' occupational history. All jobs performed for at least six months were recorded. The person's principal activity was defined as "main" task, an all others as "secondary" tasks. Activities were coded and categorized into occupational groups according to the International Standard Classification of Occupations (ISCO), and the Job-Specific Questionnaire Classification (JSQ). They were also grouped into industrial branches based on the General Industrial classification of Economic Activities within the European Communities (NACE). Exposition was defined dichotomously as ever versus never worked in the occupational group or branch in question. A total of 118 cases and 475 controls were included in the pooled analysis. Adjusted odds ratios (adj. OR) and 95% confidence intervals (CI) were calculated by conditional logistic regression. Comparisons of the findings across classification systems and between the two case-control studies were performed to look for consistency of the results. **Results:** For the main task; the most relevant occupational groups positively associated to UM according to ISCO were (adj. OR;95%CI): miners (2.3;0.92-5.9), general farmers (1.7;0.60-4.9), clerical workers (1.8;0.86-3.7), and food-beverage-tobacco processors (4.7;0.99-22) in men; and medical-dental-pharmaceutical-veterinary workers (2.1;0.71-6), service workers (1.8;0.86-3.8), and station-engine-heavy equipment operators and freight handlers (2.5;0.94-6.5) in women. For NACE, the industrial branches of importance included: food industry (3.4;1.08-10), chemical-pharmaceutical industry (2.8;1.01-7.7), and mining (1.9;0.81-4.6) in men; and health-veterinary sector (2.4;0.97-5.7), machine production (2.3;0.85-6.1), catering trade (1.7;0.68-4.4), and landed property services and business services (2.1;0.83-5.4) in women. In the JSQ classification, cooking (5.6; 1.66-19), farmers (1.4;0.50-3.7), and chemical industry (1.9;0.57-6.3) were the most relevant occupational job groups in men; and health care (1.5;0.60-3.7) in women. The inclusion of secondary task into the analyses added very few cases and impacted negatively most of the estimates. Consistency of results across classification systems was observed, but mixed results were seen between studies. **Conclusion:** This pooled analysis provided some evidence to support the potential role of occupation as risk factor for UM. Increased risks in men were seen for miners, farmers, chemical workers, and those working in the food sector, though statistical significance was rarely reached. Some of these occupations have also showed increased risks in previous studies. Consistent results across classifications were observed and consistency of major results between the hospital and population studies was also seen. Nevertheless, the results presented here must be interpreted with caution especially because an indirect assessment of the exposure was utilized. Other major methodological limitations faced included the small number of cases in the analyzed occupational categories, and difficulties to obtain and match controls.

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8. INDEX OF TABLES

Table 1. Summary list of studies on occupational risk factors and uveal melanoma (UM) previously published in chronological order

First author	Study description and principal association(s) reported	Year
1. Albert DM	Increased incidence of choroidal melanoma was found in workers of a chemical plant. The possible human carcinogens identified included dimethylsulfate, hydrazine, and 4,4´-methylene dianiline	1980
2. Swerdlow A	In a proportional registration ratios study for eye cancer in England and Wales, higher ratios for non-manual versus manual social classes were found. Notably high for electrical-electronic and professionals-technical workers, administrators-managers, and artists	1983
3. Tucker MA	A case-control study showed an increased OR for welders (10.9; 2.1-56.5) for intraocular melanoma	1985
4. Gallagher RP	In a population-based case-control study, government workers (indoor managerial group) showed a significant OR of 3.5 ($p<0.01$) after controlling for hair and eye color	1985
5. Saftlas AF	In a proportional mortality study, white male farmers showed an elevated proportional mortality ratio 3.75 ($p<0.05$) for eye cancer, but not for UM	1987
6. Enterline PE	A historical cohort of retired asbestos workers showed a significant standardized mortality ratio for eye cancer of 15.4, but only two cases were seen	1987
7. Lynge E	In the Danish register linkage study, men working in financial institutions, farmers and bricklayers, and women working in shops showed high rates	1990
8. Vågerö D	A cancer registration study for ocular melanoma (England-Wales-Sweden) showed increased proportional registration rates for clerical workers (1.3; 1-1.8) and teachers (1.7; 1.2-2.4)	1990
9. Seddon JM	In a case-control study, having ever worked with welding arcs showed no significantly elevated OR (1.3; 0.5-3.1)	1990
10. Doll R	Excess of eye cancer in rural residents potentially reflecting exposure to farming activities	1991
11. Ajani A	An occupation-exposure linkage system to explore occupational risks for UM showed increased OR for agriculture-forestry-fishing (2; 0.6-6.7); operators-fabricators-laborers (1.7; 1-3.1); exposed to ink (2.4; 1.1-5.2); and exposed to other chemicals (2; 1.1-3.5)	1992
12. Keller JE	The Illinois Farmers case-control study showed an increased OR for eye cancer (6.4; 1.7-23.7)	1994
13. Pukkala E	Finish retrospective cohort, increased standardized incidence rates were found for goldsmiths repairing watches (13.5; 1.6-48.6), plumbers (3.8; 1.4-8.2); and auxiliary nurses (2.9; 1.08-6.40)	1995
14. Wiklund K	In a cohort among Swedish male agricultural workers, the standardized incidence rate for eye cancer was 1.09 (0.81-1.43)	1995
15. Swanson M	A population-based case-control study on eye cancer among women in the workplace showed increased OR for fabricated metal products manufacturing (2.9; 1-8.6); bus and truck services (4.6; 1.2-17.9); postal service (5.1; 1-25); laundry and dry cleaning services (3.2; 1-10.5); and military service (4.4; 1.5-13.4)	1995
16. Bulbulia A	A study on conjunctival melanosis showed a relative risk of 1.5 (1.1-2.2) for chemical industrial workers compared to the non-exposed group	1995
17. Holly EA	Increased adjusted OR in a population-based case-control study in the USA: asbestos exposure (1.8; 1.1-3.1); welding exposure (2.2; 1.3-3.5); chemists-chemical engineers-chemical technicians (5.8; 1.6-22.7); health-related occupations (3.3; 1.3-8.2)	1996
18. Kristensen P	In a Norwegian cohort among agricultural workers, no increased standardized incidence rates for eye cancer were found in either men (0.9; 0.5-1.4) or women (1.6; 0.7-3)	1996
19. Pukkala E	A cohort among Finnish farmers showed no increased standardized incidence rates for eye cancer in either men (0.8; 0.5-1.1) or women (0.6; 0.3-1)(personal communication)	1997
20. Stang A	Pooled analysis of 2 case-control studies (hospital and population-based) form Germany showed increased adjusted OR for exposition to radio sets (3; 1.4-6.3) and mobile phones (4.2; 1.2-14.5)	2001
21. Guenel P	Elevated risk for ocular melanoma among male welders (7.3;2.6-20.1). Dose-response relationship with job duration was seen	2001

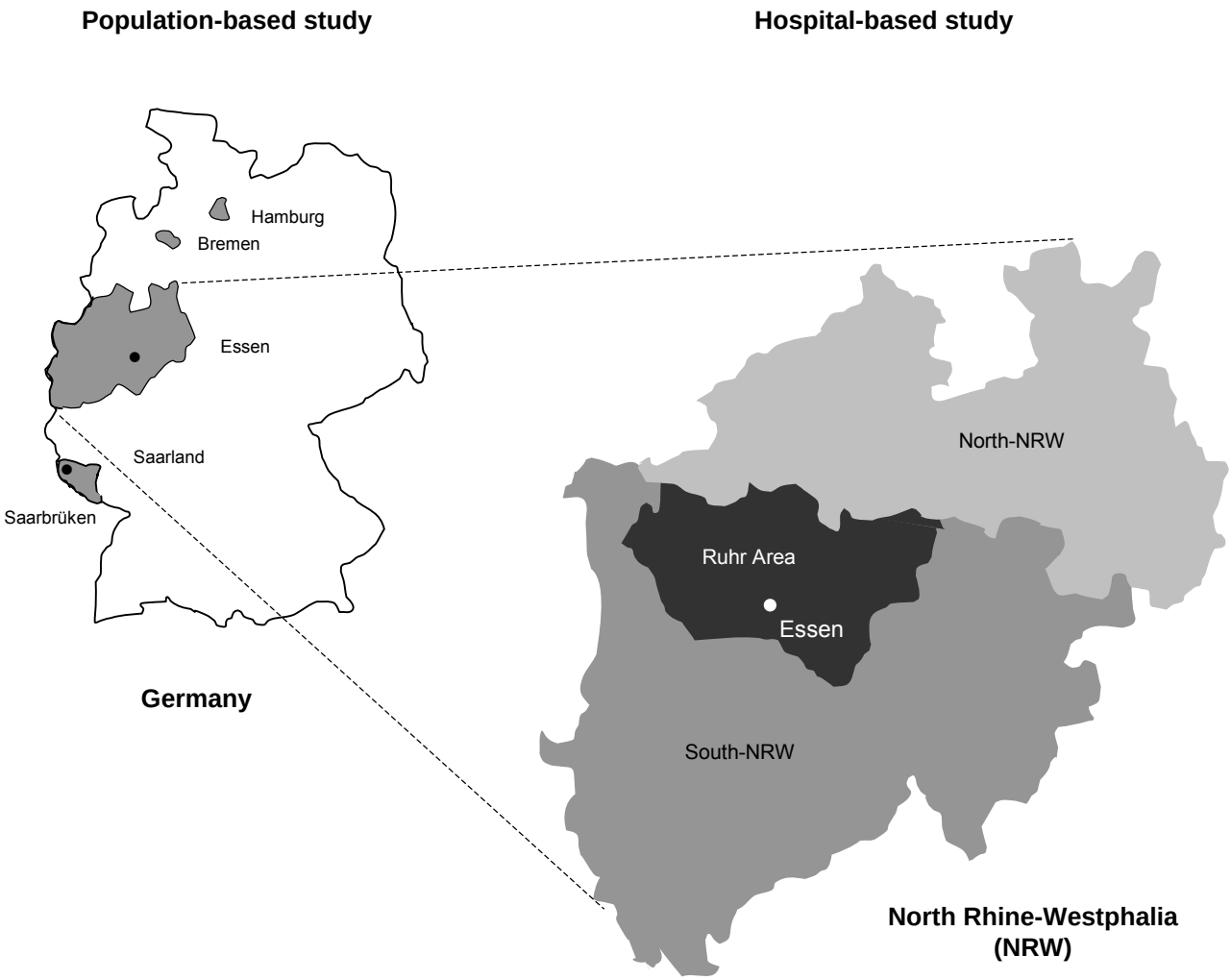

Figure 1. Geographic areas covered by the population and hospital-based case-control studies in the Federal Republic of Germany

Table 2: Relationship between the minimum prevalence of the risk factor and the minimum detectable odds ratio (OR) needed to obtain significant estimates with a case-control matching ratio of 1:2*

Minimum prevalence of the risk factor	Minimum detectable OR needed
20%	2.4
10%	2.9
5%	3.9
1%	10.4

*α=0.05; β=0.20

Table 3. Occupational classifications (ISCO, NACE, and JSQ) used to assess the exposure status in the pooled analysis

International Standard Classification of Occupations (ISCO)

1. Physical and life scientist, and technicians **2.** Architects, engineers, airship craft workers, and office and production supervisor **3.** Medical, dental, pharmaceutical, and veterinary workers **4.** Statisticians, economists, and accountants **5.** Jurists, teachers, and religious, social, scientific and other professional specialists **6.** Journalists, artists, and sport men **7.** Managers, and managerial employees **8.** Clerical workers **9.** Sales workers **10.** Service workers **11.** General farmers **12.** Specialized farmers (orchard, livestock, and machinery) **13.** Forestry workers, fishermen, and hunters **14.** Miners **15.** Metal producers **16.** Chemical, rubber and plastic workers **17.** Food, beverage and tobacco processors **18.** Spinners, weavers, textile workers, and upholsterers **19.** Fur and leather workers, and leather good makers **20.** Wood workers **21.** Stone and cut-cravers, non-metal mineral production makers **22.** Blacksmiths, toolmakers, and machine-tool operators **23.** Machinery fitters and assemblers, and precision-instrument makers **24.** Electric and electronic workers, and broadcasting and cinema operator **25.** Plumbers, welders, and sheet and structural metal workers **26.** Glass formers, potters and related **27.** Pulp, paper and printing workers **28.** Painters **29.** Jewelers, and musical instrument and other production workers **30.** Bricklayers, roofers, and other construction workers **31.** Station, engine and heavy equipment operators, and freight handlers **32.** Transport equipment operators **33.** Workers non-else classified **34.** Special codes 1-7

European Community Industrial Classification (NACE)

1. Agriculture, forestry; hunting; and fishing **2.** Mining **3.** Coal mining, petroleum and gas production and manufacturing **4.** Food industry **5.** Textile production and manufacturing **6.** Leather and shoe production and manufacturing **7.** Wood working (furniture and music instrument manufacturing) **8.** Paper, editorial and printing industry **9.** Chemical and pharmaceutical industry **10.** Rubber and plastic production **11.** Glass, ceramic and natural stone working **12.** Metal production and metal recycling **13.** Metal manufacturing **14.** Machine production **15.** Office goods manufacturing, electro-technicians, precision workers, jewelers, and optic and toys manufacturers **16.** Vehicle production **17.** Non-metal recycling and cleaning, drainage, and trash workers **18.** Provision of water and electricity **19.** Construction industry **20.** Reconstruction **21.** Vehicle trade and repairment **22.** Wholesale traders and intermediates **23.** Retail traders **24.** Catering trade **25.** Transport **26.** Media industry **27.** Credit and insurance business **28.** Landed property services and business services **29.**Public administration, social security, defense and police **30.** Education and social affaires **31.** Health and veterinary sector **32.** Church and representations of interests **33.** Culture, sports, and entertainment sector **34.** Other services **35.** House makers **36.** Other categories

Job-Specific Questionnaire Classification (JSQ)

1. Health care **2.** Dentistry **3.** Cooking **4.** Textile dry cleaning **5.** Farming **6.** Working with farm animals **7.** Forestry **8.** Metal smelting **9.** Foundries **10.** Electro plating **11.** Wood working **12.** Pulp and paper production **13.** Textile working **14.** Tanneries **15.** Slaughtering **16.** Shoe and leather production **17.** Electricians **18.** Welding, brazing and soldering **19.** Glass industry **20.** Pottery and ceramic industry **21.** Rubber industry **22.** Plastic production **23.** Painting **24.** Painting manufacturing **25.** Builder, stonemason and plasterer **26.** Railway working **27.** Chemical industry **28.** Air and spaceship construction **29.** Automobile repair and construction **30.** Metal working

Table 4. Clinical information of the interviewed cases in the hospital-based study

Clinical information	Number	Percent
Location of the uveal melanoma		
Choroid	69	85.2
Iris	1	1.2
Overlapping tissues	11	13.6
Choroid-Iris	*4*	*4.9*
Choroid-Ciliary body	*5*	*6.2*
Ciliary body-Iris	*2*	*2.5*
Affected eye		
Left eye	37	45.7
Right eye	44	54.3
Initial therapy used		
Enucleation	18	22.2
Episclearal plaque radiation (EPR)	62	76.5
Local excision and EPR	1	1.2

Table 5. Comparison of selected demographic and socioeconomic information between cases and controls in the hospital-based study

	Cases		Controls	
	n	%	n	%
City of residence	32	39.5	63	42.6
<100,000 persons	49	60.5	85	57.4
≥100,000 persons				
Region of residence				
Ruhr area	40	49.4 *	94	63.5 *
Non-Ruhr area	41	50.6	54	36.5
Type of health insurance				
Public	62	76.5	105	70.9
Private	19	23.5	43	29.1
Socioeconomic status				
Index 1-3	52	64.0	91	61.0
Index 4-6	14	17.0	32	22.0
Index 7-8	15	19.0	25	17.0

** Pearson Chi-square p<0.05*

Table 6. Comparisons of various selected socio-demographic characteristics between non-participating and participating controls

	Controls			
	Participating		Non-participating	
	n	%	n	%
Gender				
Male	75	51.4 *	12	30.8 *
Female	72	48.6	27	69.2
Age at diagnosis				
35-54 years	38	25.7	12	30.8
55-64 years	63	42.6	11	28.2
65-74 years	47	31.8	16	41.0
City of residence				
<100,000 persons	63	42.6 *	25	64.1 *
≥100,000 persons	85	57.4	14	35.9
Region of residence				
Ruhr area	94	63.5 *	17	43.6 *
Non-Ruhr area	54	36.5	22	56.4
Type of health insurance				
Public	107	70.9	27	69.2
Private	42	29.1	12	30.8

** Pearson Chi-square p<0.05*

Table 7. Number of cases and controls by age group and region of residence, stratifying by gender

	Age groups							
	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74
Total								
Ruhr area	1/2	9/9	2/6	3/10	8/21	10/21	4/19	3/6
Non-Ruhr North <100,000	-	-	-	-	1/1	2/2	2/4	-
Non-Ruhr North ≥100,000	-	-	-	-	-	-	-	-
Non-Ruhr South <100,000	-	1/1	2/3	2/1	4/6	4/10	3/6	5/5
Non-Ruhr South ≥100,000	-	1/1	2/4	2/1	1/1	2/1	7/4	1/3
Men								
Ruhr area	-	2/5	1/5	2/6	3/7	5/11	3/10	1/2
Non-Ruhr North <100,000	-	-	-	-	1/1	-	1/2	-
Non-Ruhr North ≥100,000	-	-	-	-	-	-	-	-
Non-Ruhr South <100,000	-	-	-	-	2/3	3/6	2/4	3/3
Non-Ruhr South ≥100,000	-	-	2/4	-	1/1	2/1	5/2	1/3
Women								
Ruhr area	1/2	7/4	1/1	1/4	5/14	5/10	1/9	2/4
Non-Ruhr North <100,000	-	-	-	-	-	2/2	1/2	-
Non-Ruhr North ≥100,000	-	-	-	-	-	-	-	-
Non-Ruhr South <100,000	-	1/1	2/3	2/1	2/3	1/4	1/2	1/2
Non-Ruhr South ≥100,000	-	1/1	-	1/1	1/0*	-	1/2	2/0*

** Cases with no controls were assigned to the closest neighboring strata*

Table 8. Description of selected characteristics among cases and controls for the population and hospital-based studies, and the pooled analysis

	Population-based				Hospital-based				Pooled analysis			
	Cases		Controls		Cases		Controls		Cases		Controls	
	n	%	n	%	n	%	n	%	n	%	n	%
Interviewed subjects	37		327		81		148		118		475	
Type of interview												
Face-to-face	33	89.2	302	92.4	57	70.4	82	5.4	90	76.3	384	80.9
Telephonic	4	10.8	21	6.4	21	25.9	66	4.6	25	21.2	87	18.3
Other	0	o	4	1.2	3	3.7	0	0	3	2.5	4	0.8
Gender												
Males	20	54.1	237	72.5	39	48.1	76	51.4	59	50.0	313	69.9
Females	17	5.9	90	27.5	42	51.9	72	48.6	59	50.0	162	34.1
Age distribution												
35-44	4	10.8	85	26.0	12	14.8	13	8.8	16	13.6	98	20.6
45-54	7	18.9	57	17.4	13	16.1	25	16.9	20	16.9	82	17.2
55-64	15	40.5	113	34.6	32	39.5	63	42.6	47	39.8	176	37.1
65-74*	11	29.8	72	22.0	24	29.7	47	31.8	35	29.6	119	25.0
Schooling years												
<10	23	62.2	186	56.9	51	63.0	90	60.8	74	62.7	276	58.1
10-11	7	18.9	72	22.0	9	11.1	27	18.2	16	13.6	99	20.8
12-13	7	18.9	60	18.3	18	22.2	28	18.9	25	21.2	88	18.5
Other	-	-	9	2.8	3	3.7	3	2.0	3	2.5	12	2.5
Smoking												
No smoking	15	40.6	129	39.5	32	39.6	77	52.0	47	39.8	206	43.4
Mild	7	18.9	57	17.4	17	21.0	32	21.6	24	20.4	89	18.8
Moderate	5	13.5	73	22.3	16	19.7	17	11.5	21	17.8	90	18.9
Heavy	10	27.0	68	20.8	16	19.7	22	14.9	26	22.0	90	18.9

** For the population-based study only 65-69 years*

Table 9. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma in the pooled analysis by ISCO occupational categories –main task–[1] including men and women

	Cases (N=118)		Controls (N=475)		Unadjusted		Adjusted[4]	
Occupational groups[2]	**n**	**%**	**n**	**%**	**OR**[3]	**95%-CI**	**OR**[3]	**95%-CI**
Physical and life scientist, technicians	2	1.7	13	2.7	0.6	0.14-2.75	0.6	0.12-2.55
Architect, engineers, air-ship craft, office-production supervisor	13	11.0	66	13.9	0.8	0.41-1.44	1.0	0.49-1.97
Medical, dental, pharmaceutical and veterinary workers	9	7.6	23	4.8	1.6	0.73-3.60	1.4	0.58-3.57
Statisticians, economists, accountants	4	3.4	16	3.4	1.0	0.33-3.07	1.3	0.37-4.45
Jurists, teachers, religious/social/scientific/professional specialists	12	10.2	41	8.6	1.2	0.61-2.36	1.1	0.54-2.40
Journalists, artists, sport men	1	0.8	15	3.2	0.3	0.03-2.01	0.2	0.03-1.83
Managers, managerial employees	27	22.9	118	24.8	0.9	0.56-1.45	1.0	0.57-1.64
Clerical workers	36	30.5	110	23.2	1.5	0.93-2.27	1.2	0.73-2.07
Sales workers	24	20.3	93	19.6	1.0	0.63-1.73	0.8	0.45-1.40
Service workers	35	29.7	95	20.0	*1.7	1.07-2.65	1.6	0.93-2.87
General farmers	12	10.2	24	5.1	*2.1	1.03-4.38	1.6	0.71-3.51
Specialized farmers (orchard, livestock, machinery)	2	1.7	8	1.7	1.0	0.21-4.80	1.1	0.21-5.88
Miners	10	8.5	23	4.8	1.8	0.84-3.93	2.0	0.81-4.90
Chemical, rubber and plastic workers	3	2.5	11	2.3	1.1	0.30-4.00	1.3	0.32-5.45
Food, beverage and tobacco processors	4	3.4	8	1.7	2.0	0.61-6.90	2.7	0.71-10.2
Spinners, weavers, textile workers and upholsterers	10	8.5	28	5.9	1.5	0.70-3.13	1.1	0.48-2.57
Fur and leather workers, show and leather good makers	2	1.7	6	1.3	1.3	0.27-6.75	0.5	0.08-3.67
Wood workers	7	5.9	26	5.5	1.1	0.46-2.57	1.1	0.43-2.97
Blacksmiths, toolmakers, machine-tool operators	5	4.2	46	9.7	0.4	0.16-1.06	0.5	0.18-1.39
Machinery fitters/assemblers and precision-instrument makers	8	6.8	52	10.9	0.6	0.27-1.28	0.9	0.38-2.03
Electric and electronic workers, broadcasting-cinema operator	3	2.5	49	10.3	*0.2	0.07-0.74	0.3	0.10-1.19
Plumbers, welders, sheet/structural metal workers	6	5.1	47	9.9	0.5	0.20-1.17	0.6	0.25-1.66
Pulp, paper and printing workers	3	2.5	11	2.3	1.1	0.30-4.00	1.5	0.36-5.81
Jewelers, musical instrument and other production workers	6	5.1	15	3.2	1.6	0.62-4.32	1.6	0.53-4.68
Bricklayers, roofers and other construction workers	12	10.2	42	8.8	1.2	0.59-2.29	1.3	0.57-2.98
Station/engine/heavy equipment operators, freight handlers	14	11.9	50	10.5	1.1	0.61-2.15	1.2	0.61-2.31
Transport equipment operators	11	9.3	44	9.3	1.0	0.50-2.01	1.4	0.64-3.07
Workers non-else classified	8	6.8	30	6.3	1.1	0.48-2.42	1.3	0.55-3.24
Special codes 1-7	97	82.2	348	73.3	*1.7	1.01-2.81	0.9	0.50-1.63

[1] According to the International Standard Classification of Occupations (ISCO) for the main task performed
[2] No ORs were calculated for the following occupational groups, as no cases or controls were reported: Forestry workers, fishermen, hunters; Metal producers; Stone and cut-cravers, non-metal mineral production makers; Glass formers, potters and related; and Painters
[3] The reference group for all occupational groups was non-exposed individuals (men/women) to the occupational group of interest
[4] Odds ratios were estimated from a conditional logistic-regression model including age, gender and region of residence
[*] Statistically significant at P<0.05

Table 10. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma in the pooled analysis by ISCO occupational categories –main and secondary task–[1] including men and women

	Cases (N=118)		Controls (N=475)		Unadjusted		Adjusted[4]	
Occupational groups[2]	**n**	**%**	**n**	**%**	**OR**[3]	**95%-CI**	**OR**[3]	**95%-CI**
Physical and life scientist, technicians	3	2.5	17	3.6	0.7	0.20-2.44	0.7	0.21-2.67
Architect, engineers, air-ship craft, office-production supervisor	14	11.9	72	15.2	0.8	0.41-1.39	1.0	0.49-1.89
Medical, dental, pharmaceutical and veterinary workers	9	7.6	24	5.1	1.6	0.70-3.43	1.4	0.56-3.40
Statisticians, economists, accountants	4	3.4	16	3.4	1.0	0.33-3.07	1.3	0.37-4.45
Jurists, teachers, religious/social/scientific/professional specialists	14	11.9	49	10.3	1.2	0.62-2.20	1.2	0.59-2.39
Journalists, artists, sport men	2	1.7	19	4.0	0.4	0.10-1.80	0.4	0.08-1.70
Managers, managerial employees	30	25.4	136	28.6	0.8	0.54-1.35	0.9	0.56-1.54
Clerical workers	42	35.6	130	27.4	1.5	0.96-2.25	1.3	0.82-2.23
Sales workers	31	26.3	103	21.7	1.3	0.81-2.05	1.1	0.66-1.88
Service workers	39	33.1	117	24.6	1.5	0.98-2.33	1.4	0.84-2.43
General farmers	13	11.0	33	6.9	1.7	0.84-3.26	1.3	0.60-2.69
Specialized farmers (orchard, livestock, machinery)	2	1.7	11	2.3	0.7	0.16-3.32	1.0	0.19-4.79
Forestry workers, fishermen, hunters	2	1.7	5	1.1	1.6	0.31-8.44	1.3	0.20-7.74
Miners	10	8.5	23	4.8	1.8	0.84-3.93	2.0	0.81-4.90
Chemical, rubber and plastic workers	3	2.5	13	2.7	0.9	0.26-3.30	1.0	0.26-4.10
Food, beverage and tobacco processors	6	5.1	15	3.2	1.6	0.62-4.32	1.4	0.50-4.08
Spinners, weavers, textile workers and upholsterers	12	10.2	28	5.9	1.8	0.89-3.66	1.4	0.62-3.09
Fur and leather workers, show and leather good makers	4	3.4	6	1.3	2.7	0.76-9.84	1.3	0.30-5.37
Wood workers	7	5.9	28	5.9	1.0	0.43-2.36	1.1	0.40-2.75
Blacksmiths, toolmakers, machine-tool operators	5	4.2	49	10.3	*0.4	0.15-0.99	0.5	0.17-1.30
Machinery fitters/assemblers and precision-instrument makers	9	7.6	60	12.6	0.6	0.28-1.19	0.9	0.40-1.96
Electric and electronic workers, broadcasting-cinema operator	3	2.5	55	11.6	*0.2	0.06-0.65	0.3	0.08-1.03
Plumbers, welders, sheet/structural metal workers	7	5.9	60	12.6	*0.4	0.19-0.98	0.6	0.24-1.39
Pulp, paper and printing workers	4	3.4	15	3.2	1.1	0.35-3.30	1.4	0.40-5.16
Painters	2	1.7	25	5.3	0.3	0.07-1.33	0.2	0.03-1.87
Jewelers, musical instrument and other production workers	7	5.9	17	3.6	1.7	0.69-4.19	1.7	0.61-4.57
Bricklayers, roofers and other construction workers	15	12.7	48	10.1	1.3	0.70-2.40	1.5	0.68-3.22
Station/engine/heavy equipment operators, freight handlers	18	15.3	79	16.6	0.9	0.52-1.57	1.0	0.53-1.83
Transport equipment operators	15	12.7	60	12.6	1.0	0.55-1.84	1.3	0.66-2.71
Workers non-else classified	9	7.6	49	10.3	0.7	0.34-1.51	0.9	0.39-1.92
Special codes 1-7	97	82.2	350	73.7	1.6	0.99-2.76	0.9	0.48-1.56

[1] According to the International Standard Classification of Occupations (ISCO) for the main and secondary task performed
[2] No ORs were calculated for the following occupational groups, as no cases or controls were reported: Metal producers; Stone and cut-cravers, non-metal mineral production makers; and Glass formers, potters and related
[3] The reference group for all occupational groups was non-exposed individuals (men/women) to the occupational group of interest
[4] Odds ratios were estimated from a conditional logistic-regression model including age, gender and region of residence
[*] Statistically significant at P<0.05

Table 11. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma in the pooled analysis by ISCO occupational categories –main task–[1] among men

	Cases (N=59)		Controls (N=313)		Unadjusted		Adjusted[4]	
Occupational groups[2]	**n**	**%**	**n**	**%**	**OR**[3]	**95%-CI**	**OR**[3]	**95%-CI**
Physical and life scientist, technicians	1	1.7	8	2.6	0.7	0.08-5.35	0.4	0.05-3.43
Architect, engineers, air-ship craft, office-production supervisor	10	16.9	61	19.5	0.8	0.40-1.76	0.8	0.36-1.73
Medical, dental, pharmaceutical and veterinary workers	1	1.7	13	4.2	0.4	0.05-3.10	0.5	0.06-4.29
Statisticians, economists, accountants	3	5.1	16	5.1	1.0	0.28-3.52	0.9	0.21-3.41
Jurists, teachers, religious/social/scientific/professional specialists	6	10.2	26	8.3	1.2	0.49-3.18	1.1	0.39-3.23
Managers, managerial employees	16	27.1	86	27.5	1.0	0.53-1.83	1.1	0.56-2.23
Clerical workers	17	28.8	57	18.2	1.8	0.97-3.41	1.8	0.86-3.78
Sales workers	8	13.6	40	12.8	1.1	0.47-2.42	1.0	0.40-2.43
Service workers	8	13.6	34	10.9	1.3	0.56-2.93	1.4	0.57-3.45
General farmers	7	11.9	15	4.8	*2.7	1.04-6.84	1.7	0.60-4.95
Specialized farmers (orchard, livestock, machinery)	2	3.4	7	2.2	1.5	0.31-7.54	1.4	0.25-7.85
Miners	10	16.9	21	6.7	*2.8	1.26-6.35	2.3	0.92-5.99
Chemical, rubber and plastic workers	2	3.4	10	3.2	1.1	0.23-4.97	1.2	0.24-6.33
Food, beverage and tobacco processors	4	6.8	5	1.6	*4.5	1.16-17.0	4.7	0.99-22.0
Spinners, weavers, textile workers and upholsterers	1	1.7	4	1.3	1.3	0.15-12.0	1.1	0.06-22.1
Fur and leather workers, show and leather good makers	2	3.4	3	1.0	3.6	0.59-21.9	1.0	0.10-8.71
Wood workers	5	8.5	26	8.3	1.0	0.38-2.78	0.9	0.29-2.55
Blacksmiths, toolmakers, machine-tool operators	4	6.8	41	13.1	0.5	0.17-1.40	0.5	0.15-1.45
Machinery fitters/assemblers and precision-instrument makers	7	11.9	49	15.7	0.7	0.31-1.69	0.8	0.34-2.07
Electric and electronic workers, broadcasting-cinema operator	3	5.1	47	15.0	0.3	0.09-1.01	0.4	0.10-1.25
Plumbers, welders, sheet/structural metal workers	6	10.2	45	14.4	0.7	0.27-1.66	0.7	0.27-1.85
Bricklayers, roofers and other construction workers	12	20.3	42	13.4	1.6	0.81-3.35	1.3	0.57-2.98
Station/engine/heavy equipment operators, freight handlers	5	8.5	38	12.1	0.7	0.25-1.78	0.6	0.22-1.69
Transport equipment operators	11	18.6	42	13.4	1.5	0.71-3.07	1.5	0.66-3.23
Workers non-else classified	6	10.2	25	8.0	1.3	0.51-3.32	1.3	0.47-3.66
Special codes 1-7	1	1.7	8	2.6	0.7	0.08-5.35	0.4	0.05-3.43

[1] According to the International Standard Classification of Occupations (ISCO) for the main task performed
[2] No ORs were calculated for the following occupational groups, as no cases or controls were reported: Journalists, artists, sport men; Forestry workers, fishermen, hunters; Metal producers; Stone and cut-cravers, non-metal mineral production makers; Glass formers, potters and related; Pulp, paper and printing workers; Painters; and Jewelers, musical instrument and other production workers
[3] The reference group for all occupational groups was non-exposed individuals (men/women) to the occupational group of interest
[4] Odds ratios were estimated from a conditional logistic-regression model including age, gender and region of residence
[*] Statistically significant at P<0.05

Table 12. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma in the pooled analysis by ISCO occupational categories –main and secondary task–[1] among men

	Cases (N=59)		Controls (N=313)		Unadjusted		Adjusted[4]	
Occupational groups[2]	**n**	**%**	**n**	**%**	**OR**[3]	**95%-CI**	**OR**[3]	**95%-CI**
Physical and life scientist, technicians	2	3.4	10	3.2	1.1	0.23-4.97	0.8	0.16-3.83
Architect, engineers, air-ship craft, office-production supervisor	11	18.6	67	21.4	0.8	0.41-1.71	0.8	0.37-1.66
Medical, dental, pharmaceutical and veterinary workers	1	1.7	14	4.5	0.4	0.05-2.86	0.4	0.05-3.85
Statisticians, economists, accountants	3	5.1	16	5.1	1.0	0.28-3.52	0.9	0.21-3.41
Jurists, teachers, religious/social/scientific/professional specialists	7	11.9	33	10.5	1.1	0.48-2.72	1.1	0.41-2.96
Journalists, artists, sport men	1	1.7	14	4.5	0.4	0.05-2.86	0.2	0.03-1.95
Managers, managerial employees	17	28.8	101	32.3	0.8	0.46-1.56	1.0	0.49-1.93
Clerical workers	18	30.5	75	24.0	1.4	0.76-2.56	1.4	0.70-2.94
Sales workers	11	18.6	46	14.7	1.3	0.64-2.74	1.4	0.62-3.22
Service workers	10	16.9	44	14.1	1.2	0.59-2.64	1.4	0.60-3.15
General farmers	7	11.9	18	5.8	2.2	0.88-5.52	1.5	0.53-4.13
Specialized farmers (orchard, livestock, machinery)	2	3.4	10	3.2	1.1	0.23-4.97	1.2	0.22-5.99
Forestry workers, fishermen, hunters	2	3.4	5	1.6	2.2	0.41-11.3	1.3	0.20-7.74
Miners	10	16.9	21	6.7	*2.8	1.26-6.35	2.3	0.92-5.99
Chemical, rubber and plastic workers	2	3.4	12	3.8	0.9	0.19-4.03	0.9	0.17-4.47
Food, beverage and tobacco processors	5	8.5	7	2.2	*4.0	1.24-13.1	3.7	0.94-14.1
Spinners, weavers, textile workers and upholsterers	2	3.4	4	1.3	2.7	0.49-15.0	3.5	0.44-27.4
Fur and leather workers, show and leather good makers	3	5.1	3	1.0	*5.5	1.09-27.8	1.5	0.23-10.1
Wood workers	5	8.5	28	8.9	0.9	0.35-2.55	0.8	0.27-2.34
Blacksmiths, toolmakers, machine-tool operators	4	6.8	44	14.1	0.4	0.15-1.29	0.4	0.14-1.33
Machinery fitters/assemblers and precision-instrument makers	8	13.6	57	18.2	0.7	0.32-1.57	0.9	0.37-1.99
Electric and electronic workers, broadcasting-cinema operator	3	5.1	52	16.6	*0.3	0.08-0.89	0.3	0.09-1.10
Plumbers, welders, sheet/structural metal workers	7	11.9	58	18.5	0.6	0.26-1.37	0.6	0.25-1.51
Painters	2	3.4	24	7.7	0.4	0.10-1.84	0.3	0.03-2.06
Jewelers, musical instrument and other production workers	1	1.7	10	3.2	0.5	0.07-4.16	0.8	0.09-7.39
Bricklayers, roofers and other construction workers	15	25.4	48	15.3	1.9	0.97-3.64	1.5	0.68-3.22
Station/engine/heavy equipment operators, freight handlers	8	13.6	57	18.2	0.7	0.32-1.57	0.7	0.28-1.63
Transport equipment operators	15	25.4	56	17.9	1.6	0.81-3.00	1.5	0.73-3.13
Workers non-else classified	7	11.9	40	12.8	0.9	0.39-2.16	1.0	0.40-2.55
Special codes 1-7	44	74.6	211	67.4	1.4	0.75-2.66	0.7	0.35-1.53

[1] According to the International Standard Classification of Occupations (ISCO) for the main and secondary task performed
[2] No ORs were calculated for the following occupational groups, as no cases or controls were reported: Metal producers; Stone and cut-cravers, non-metal mineral production makers; Glass formers, potters and related; and Pulp, paper and printing workers
[3] The reference group for all occupational groups was non-exposed individuals (men/women) to the occupational group of interest
[4] Odds ratios were estimated from a conditional logistic-regression model including age, gender and region of residence
[*] Statistically significant at P<0.05

Table 13. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma in the pooled analysis by ISCO occupational categories –main task–[1] among women

	Cases (N=59)		Controls (N=162)		Unadjusted		Adjusted[4]	
Occupational groups[2]	**n**	**%**	**n**	**%**	**OR**[3]	**95%-CI**	**OR**[3]	**95%-CI**
Physical and life scientist, technicians	1	1.7	5	3.1	0.5	0.06-4.73	0.8	0.09-7.49
Architect, engineers, air-ship craft, office-production supervisor	3	5.1	5	3.1	1.7	0.39-7.22	2.5	0.58-11.0
Medical, dental, pharmaceutical and veterinary workers	8	13.6	10	6.2	2.4	0.89-6.32	2.1	0.71-6.02
Jurists, teachers, religious/social/scientific/professional specialists	6	10.2	15	9.3	1.1	0.41-3.00	1.1	0.40-3.30
Journalists, artists, sport men	1	1.7	3	1.9	0.9	0.09-8.92	1.2	0.11-12.6
Managers, managerial employees	11	18.6	32	19.8	0.9	0.44-1.99	0.8	0.36-1.81
Clerical workers	19	32.2	53	32.7	1.0	0.52-1.84	0.9	0.42-1.80
Sales workers	16	27.1	53	32.7	0.8	0.40-1.48	0.7	0.34-1.44
Service workers	27	45.8	61	37.7	1.4	0.76-2.55	1.8	0.86-3.80
General farmers	5	8.5	9	5.6	1.6	0.51-4.88	1.4	0.41-4.78
Chemical, rubber and plastic workers	1	1.7	1	0.6	2.8	0.17-44.5	1.7	0.10-30.7
Spinners, weavers, textile workers and upholsterers	9	15.3	24	14.8	1.0	0.45-2.37	1.1	0.46-2.66
Blacksmiths, toolmakers, machine-tool operators	1	1.7	5	3.1	0.5	0.06-4.73	0.7	0.08-6.54
Machinery fitters/assemblers and precision-instrument makers	1	1.7	3	1.9	0.9	0.09-8.92	1.1	0.10-12.9
Glass formers, potters and related	3	5.1	6	3.7	1.4	0.34-5.73	2.0	0.44-8.83
Pulp, paper and printing workers	1	1.7	5	3.1	0.5	0.06-4.73	0.7	0.08-6.54
Jewelers, musical instrument and other production workers	6	10.2	6	3.7	2.9	0.91-9.43	2.3	0.68-7.99
Station/engine/heavy equipment operators, freight handlers	9	15.3	12	7.4	2.2	0.89-5.62	2.5	0.94-6.58
Workers non-else classified	2	3.4	5	3.1	1.1	0.21-5.81	1.4	0.26-7.90
Special codes 1-7	53	89.8	138	85.2	1.5	0.59-3.95	1.3	0.47-3.49

[1] According to the International Standard Classification of Occupations (ISCO) for the main task performed
[2] No ORs were calculated for the following occupational groups, as no cases or controls were reported: Statisticians, economists, accountants; Specialized farmers (orchard, livestock, machinery); Forestry workers, fishermen, hunters; Miners; Metal producers; Food, beverage and tobacco processors; Fur and leather workers, show and leather good makers; Wood workers; Stone and cut-cravers, non-metal mineral production makers; Electric and electronic workers, broadcasting-cinema operator; Plumbers, welders, sheet/structural metal workers ; Painters; Bricklayers, roofers and other construction workers; and Transport equipment operators
[3] The reference group for all occupational groups was non-exposed individuals (men/women) to the occupational group of interest
[4] Odds ratios were estimated from a conditional logistic-regression model including age, gender and region of residence
[*] Statistically significant at P<0.05

Table 15. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma in the pooled analysis by NACE occupational branches –main task–[1] including men and women

	Cases (N=118)		Controls (N=475)		Unadjusted		Adjusted[4]	
Occupational groups[2]	**n**	**%**	**n**	**%**	**OR**[3]	**95%-CI**	**OR**[3]	**95%-CI**
Agriculture, forestry; hunting; fishing	13	11.0	37	7.8	1.5	0.75-2.85	1.2	0.61-2.55
Mining	12	10.2	34	7.2	1.5	0.74-2.93	1.8	0.81-4.10
Coal-mining, petroleum and gas production and manufacturing	5	4.2	6	1.3	*3.4	1.04-11.4	3.8	0.98-14.8
Food industry	11	9.3	35	7.4	1.3	0.64-2.62	1.3	0.59-2.89
Textile production and manufacturing	12	10.2	26	5.5	2.0	0.95-3.99	1.6	0.71-3.56
Leather and shoe production and manufacturing	3	2.5	6	1.3	2.0	0.50-8.25	1.3	0.29-5.82
Wood working (furniture, music instrument manufacturing)	6	5.1	19	4.0	1.3	0.50-3.29	1.2	0.41-3.27
Paper, editorial and printing industry	7	5.9	23	4.8	1.2	0.52-2.96	1.4	0.53-3.44
Chemical and pharmaceutical industry	12	10.2	23	4.8	*2.2	1.07-4.60	2.0	0.88-4.53
Rubber and plastic production	2	1.7	9	1.9	0.9	0.19-4.18	1.0	0.17-5.65
Glass, ceramic, and natural-stone working	2	1.7	21	4.4	0.4	0.09-1.61	0.5	0.11-2.19
Metal production, waste-metal-recycling	4	3.4	41	8.6	0.4	0.13-1.06	0.5	0.15-1.48
Metal manufacturing	5	4.2	55	11.6	*0.3	0.13-0.86	0.4	*0.14-0.99
Machine production	10	8.5	50	10.5	0.8	0.39-1.60	1.0	0.48-2.23
Office-goods manuf, electrotech, precision-optic-jewel-toy work	11	9.3	37	7.8	1.2	0.60-2.46	1.5	0.69-3.44
Vehicle production	5	4.2	40	8.4	0.5	0.19-1.25	0.6	0.23-1.80
Provision of water and electricity	2	1.7	12	2.5	0.7	0.15-3.01	1.0	0.21-4.89
Construction industry	15	12.7	64	13.5	0.9	0.51-1.71	0.9	0.44-1.92
Reconstruction	9	7.6	51	10.7	0.7	0.33-1.44	0.9	0.40-2.01
Vehicle trade and repair	1	0.8	23	4.8	0.2	0.02-1.26	0.2	0.03-1.80
Wholesale traders and intermediates	16	13.6	49	10.3	1.4	0.75-2.49	1.5	0.77-2.95
Retail traders	24	20.3	88	18.5	1.1	0.68-1.86	0.8	0.45-1.44
Catering trade	12	10.2	28	5.9	1.8	0.89-3.66	1.9	0.90-4.12
Transport	10	8.5	50	10.5	0.8	0.39-1.60	1.3	0.57-2.79
Media industry	1	0.8	14	2.9	0.3	0.04-2.16	0.5	0.06-3.79
Credit and insurance business	4	3.4	33	6.9	0.5	0.16-1.35	0.4	0.13-1.30
Landed property services, business services	19	16.1	56	11.8	1.4	0.82-2.52	1.3	0.68-2.44
Public administration, social security, defense, police	26	22.0	126	26.5	0.8	0.48-1.27	1.1	0.58-1.90
Education and social affaires	12	10.2	45	9.5	1.1	0.55-2.12	1.1	0.51-2.30
Health and veterinary sector	13	11.0	27	5.7	*2.1	1.02-4.11	1.7	0.76-3.61
Church, trade unions	2	1.7	9	1.9	0.9	0.19-4.18	0.7	0.12-3.68
Other services	3	2.5	19	4.0	0.6	0.18-2.15	0.3	0.06-1.35
House makers	12	10.2	27	5.7	1.9	0.92-3.82	1.5	0.63-3.41
Other categories	97	82.2	341	71.8	*1.8	1.09-3.03	1.0	0.53-1.71

[1] According to the European Community Industrial Classification (NACE) for the main task performed
[2] No ORs were calculated for the following occupational branches, as no cases or controls were reported: Non-metal recycling, cleaning, drainage, trash; and Culture, sport, entertainment
[3] The reference group for all occupational branches was non-exposed individuals (men/women) to the occupational group of interest
[4] Odds ratios were estimated from a conditional logistic-regression model including age, gender and region of residence
[*] Statistically significant at P<0.05

Table 16. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma the in pooled analysis by NACE occupational branches –main and secondary task–[1] including men and women

	Cases (N=118)		Controls (N=475)		Unadjusted		Adjusted[4]	
Occupational groups[2]	**n**	**%**	**n**	**%**	**OR**[3]	**95%-CI**	**OR**[3]	**95%-CI**
Agriculture, forestry; hunting; fishing	14	11.9	39	8.2	1.5	0.79-2.87	1.3	0.62-2.54
Mining	13	11.0	36	7.6	1.5	0.77-2.94	1.8	0.82-3.91
Coal-mining, petroleum and gas production and manufacturing	6	5.1	7	1.5	*3.6	1.18-10.8	*3.8	1.11-12.9
Food industry	13	11.0	37	7.8	1.5	0.75-2.85	1.6	0.73-3.33
Textile production and manufacturing	12	10.2	28	5.9	1.8	0.89-3.66	1.4	0.64-3.07
Leather and shoe production and manufacturing	4	3.4	7	1.5	2.3	0.68-8.12	1.5	0.38-5.58
Wood working (furniture, music instrument manufacturing)	6	5.1	23	4.8	1.1	0.42-2.64	1.0	0.37-2.83
Paper, editorial and printing industry	7	5.9	23	4.8	1.2	0.52-2.96	1.4	0.53-3.44
Chemical and pharmaceutical industry	12	10.2	24	5.1	*2.1	1.03-4.38	1.9	0.86-4.36
Rubber and plastic production	2	1.7	10	2.1	0.8	0.17-3.71	0.8	0.15-4.66
Glass, ceramic, and natural-stone working	2	1.7	22	4.6	0.4	0.08-1.53	0.5	0.10-2.13
Metal production, waste-metal-recycling	4	3.4	41	8.6	0.4	0.13-1.06	0.5	0.15-1.48
Metal manufacturing	7	5.9	60	12.6	*0.4	0.19-0.98	0.5	0.20-1.10
Machine production	10	8.5	56	11.8	0.7	0.34-1.40	0.8	0.38-1.83
Office-goods manuf, electrotech, precision-optic-jewel-toy work	11	9.3	41	8.6	1.1	0.54-2.19	1.4	0.63-3.06
Vehicle production	5	4.2	43	9.1	0.4	0.17-1.15	0.6	0.21-1.59
Provision of water and electricity	2	1.7	12	2.5	0.7	0.15-3.01	1.0	0.21-4.89
Construction industry	15	12.7	68	14.3	0.9	0.48-1.59	0.9	0.41-1.80
Reconstruction	9	7.6	53	11.2	0.7	0.31-1.37	0.9	0.38-1.93
Vehicle trade and repair	1	0.8	26	5.5	0.1	0.02-1.10	0.2	0.03-1.65
Wholesale traders and intermediates	18	15.3	51	10.7	1.5	0.84-2.67	1.7	0.91-3.33
Retail traders	28	23.7	91	19.2	1.3	0.81-2.12	1.0	0.59-1.79
Catering trade	12	10.2	32	6.7	1.6	0.78-3.14	1.6	0.78-3.43
Transport	10	8.5	52	10.9	0.8	0.37-1.53	1.2	0.55-2.66
Media industry	1	0.8	14	2.9	0.3	0.04-2.16	0.5	0.06-3.79
Credit and insurance business	4	3.4	33	6.9	0.5	0.16-1.35	0.4	0.13-1.30
Landed property services, business services	21	17.8	59	12.4	1.5	0.89-2.63	1.4	0.76-2.66
Public administration, social security, defense, police	26	22.0	126	26.5	0.8	0.48-1.27	1.1	0.58-1.90
Education and social affaires	14	11.9	49	10.3	1.2	0.62-2.20	1.2	0.60-2.52
Health and veterinary sector	13	11.0	27	5.7	*2.1	1.02-4.11	1.7	0.76-3.61
Church, trade unions	2	1.7	11	2.3	0.7	0.16-3.32	0.5	0.09-2.27
Culture, sport, entertainment	1	0.8	19	4.0	0.2	0.03-1.55	0.2	0.02-1.54
Other services	3	2.5	21	4.4	0.6	0.17-1.92	0.1	0.01-1.04
House makers	13	11.0	29	6.1	1.9	0.96-3.78	1.6	0.68-3.55
Other categories	97	82.2	342	72.0	*1.8	1.08-3.00	0.9	0.52-1.65

[1] According to the European Community Industrial Classification (NACE) for the main and secondary task performed
[2] No ORs were calculated for the following occupational branches, as no cases or controls were reported: Non-metal recycling, cleaning, drainage, trash
[3] The reference group for all occupational branches was non-exposed individuals (men/women) to the occupational group of interest
[4] Odds ratios were estimated from a conditional logistic-regression model including age, gender and region of residence
** Statistically significant at P<0.05*

Table 17. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma in the pooled analysis by NACE occupational branches –main task–[1] among men

	Cases (N=59)		Controls (N=313)		Unadjusted		Adjusted[4]	
Occupational groups[2]	**n**	**%**	**n**	**%**	**OR**[3]	**95%-CI**	**OR**[3]	**95%-CI**
Agriculture, forestry; hunting; fishing	7	11.9	23	7.3	1.7	0.69-4.14	1.4	0.51-3.60
Mining	11	18.6	31	9.9	2.1	0.98-4.41	1.9	0.81-4.66
Coal-mining, petroleum and gas production and manufacturing	3	5.1	3	1.0	*5.5	1.09-27.8	4.8	0.67-33.6
Food industry	7	11.9	12	3.8	*3.4	1.27-8.91	*3.4	1.08-10.5
Textile production and manufacturing	2	3.4	5	1.6	2.2	0.41-11.3	1.5	0.22-10.1
Leather and shoe production and manufacturing	1	1.7	2	0.6	2.7	0.24-29.7	0.8	0.05-11.2
Wood working (furniture, music instrument manufacturing)	4	6.8	17	5.4	1.3	0.41-3.90	1.0	0.29-3.41
Paper, editorial and printing industry	2	3.4	12	3.8	0.9	0.19-4.03	0.9	0.17-4.37
Chemical and pharmaceutical industry	9	15.3	15	4.8	*3.6	1.48-8.55	*2.8	1.01-7.78
Glass, ceramic, and natural-stone working	1	1.7	18	5.8	0.3	0.04-2.16	0.4	0.05-2.95
Metal production, waste-metal-recycling	4	6.8	37	11.8	0.5	0.19-1.58	0.6	0.18-1.92
Metal manufacturing	3	5.1	44	14.1	0.3	0.10-1.09	0.4	0.11-1.38
Machine production	4	6.8	42	13.4	0.5	0.16-1.36	0.5	0.16-1.50
Office-goods manuf, electrotech, precision-optic-jewel-toy work	6	10.2	24	7.7	1.4	0.53-3.49	1.9	0.62-5.96
Vehicle production	3	5.1	35	11.2	0.4	0.13-1.43	0.4	0.12-1.61
Provision of water and electricity	1	1.7	10	3.2	0.5	0.07-4.16	0.7	0.08-5.94
Vehicle trade and repair	1	1.7	16	5.1	0.3	0.04-2.46	0.4	0.05-3.52
Wholesale traders and intermediates	6	10.2	32	10.2	1.0	0.40-2.49	1.3	0.49-3.54
Retail traders	6	10.2	33	10.5	1.0	0.38-2.40	0.8	0.27-2.26
Catering trade	4	6.8	16	5.1	1.3	0.44-4.18	1.5	0.44-5.07
Transport	9	15.3	43	13.7	1.1	0.52-2.46	1.4	0.58-3.22
Media industry	1	1.7	12	3.8	0.4	0.06-3.39	0.7	0.08-5.93
Credit and insurance business	2	3.4	17	5.4	0.6	0.14-2.72	0.6	0.12-3.18
Landed property services, business services	8	13.6	39	12.5	1.1	0.49-2.49	0.8	0.34-2.08
Health and veterinary sector	1	1.7	11	3.5	0.5	0.06-3.74	0.4	0.04-3.51
Church, trade unions	1	1.7	6	1.9	0.9	0.10-7.45	1.1	0.12-9.97
Other categories	44	74.6	204	65.2	1.6	0.83-2.94	0.8	0.38-1.63

[1] *According to the European Community Industrial Classification (NACE) for the main task performed*
[2] *No ORs were calculated for the following occupational branches, as no cases or controls were reported: Rubber and plastic production; Non-metal recycling, cleaning, drainage, trash; Construction industry; Reconstruction; Public administration, social security, defense, police; Education and social affaires; Culture, sport, entertainment; Other services; and House makers*
[3] *The reference group for all occupational branches was non-exposed men to the occupational group of interest*
[4] *Odds ratios were estimated from a conditional logistic-regression model including age and region of residence*
[*] *Statistically significant at P<0.05*

Table 18. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma the in pooled analysis by NACE occupational branches –main and secondary task–[1] among men

	Cases (N=59)		Controls (N=313)		Unadjusted		Adjusted[4]	
Occupational groups[2]	**n**	**%**	**n**	**%**	**OR**[3]	**95%-CI**	**OR**[3]	**95%-CI**
Agriculture, forestry; hunting; fishing	8	13.6	23	7.3	2.0	0.84-4.65	1.4	0.56-3.73
Mining	12	20.3	32	10.2	*2.2	1.08-4.64	2.0	0.87-4.78
Coal-mining, petroleum and gas production and manufacturing	4	6.8	4	1.3	*5.6	1.36-22.8	4.4	0.87-22.0
Food industry	7	11.9	12	3.8	*3.4	1.27-8.91	*3.4	1.08-10.5
Textile production and manufacturing	2	3.4	6	1.9	1.8	0.35-9.07	1.1	0.17-6.56
Leather and shoe production and manufacturing	1	1.7	2	0.6	2.7	0.24-29.7	0.8	0.05-11.2
Wood working (furniture, music instrument manufacturing)	4	6.8	21	6.7	1.0	0.33-3.06	0.9	0.26-2.86
Paper, editorial and printing industry	2	3.4	12	3.8	0.9	0.19-4.03	0.9	0.17-4.37
Chemical and pharmaceutical industry	9	15.3	16	5.1	*3.3	1.40-7.92	2.6	0.97-7.24
Rubber and plastic production	1	1.7	8	2.6	0.7	0.08-5.35	0.9	0.10-7.96
Glass, ceramic, and natural-stone working	1	1.7	19	6.1	0.3	0.04-2.04	0.4	0.04-2.84
Metal production, waste-metal-recycling	4	6.8	37	11.8	0.5	0.19-1.58	0.6	0.18-1.92
Metal manufacturing	3	5.1	49	15.7	*0.3	0.09-0.96	0.3	0.09-1.14
Machine production	4	6.8	46	14.7	0.4	0.15-1.22	0.4	0.14-1.32
Office-goods manuf, electrotech, precision-optic-jewel-toy work	6	10.2	28	8.9	1.2	0.46-2.91	1.5	0.52-4.60
Vehicle production	3	5.1	37	11.8	0.4	0.12-1.34	0.4	0.11-1.46
Provision of water and electricity	1	1.7	10	3.2	0.5	0.07-4.16	0.7	0.08-5.94
Construction industry	14	23.7	62	19.8	1.3	0.65-2.44	0.9	0.41-1.98
Reconstruction	8	13.6	49	15.7	0.8	0.38-1.89	0.9	0.36-2.02
Vehicle trade and repair	1	1.7	19	6.1	0.3	0.04-2.04	0.4	0.05-2.98
Wholesale traders and intermediates	8	13.6	34	10.9	1.3	0.56-2.93	1.8	0.72-4.38
Retail traders	9	15.3	35	11.2	1.4	0.65-3.15	1.4	0.55-3.38
Catering trade	4	6.8	17	5.4	1.3	0.41-3.90	1.5	0.44-4.99
Transport	9	15.3	45	14.4	1.1	0.49-2.33	1.3	0.55-3.04
Media industry	1	1.7	12	3.8	0.4	0.06-3.39	0.7	0.08-5.93
Credit and insurance business	2	3.4	17	5.4	0.6	0.14-2.72	0.6	0.12-3.18
Landed property services, business services	10	16.9	41	13.1	1.4	0.64-2.88	1.1	0.46-2.50
Public administration, social security, defense, police	21	35.6	114	36.4	1.0	0.54-1.72	1.0	0.50-1.99
Education and social affaires	5	8.5	23	7.3	1.2	0.43-3.20	2.0	0.63-6.37
Health and veterinary sector	1	1.7	11	3.5	0.5	0.06-3.74	0.4	0.04-3.51
Church, trade unions	1	1.7	8	2.6	0.7	0.08-5.35	0.5	0.05-4.13
Culture, sport, entertainment	1	1.7	16	5.1	0.3	0.04-2.46	0.2	0.03-1.97
Other categories	44	74.6	204	65.2	1.6	0.83-2.94	0.8	0.38-1.63

[1] *According to the European Community Industrial Classification (NACE) for the main and secondary task performed*
[2] *No ORs were calculated for the following occupational branches, as no cases or controls were reported: Non-metal recycling, cleaning, drainage, trash; Other services; and House makers*
[3] *The reference group for all occupational branches was non-exposed men to the occupational group of interest*
[4] *Odds ratios were estimated from a conditional logistic-regression model including age and region of residence*
[*] *Statistically significant at P<0.05*

Table 19. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma in the pooled analysis by NACE occupational branches –main task–[1] among women

	Cases (N=59)		Controls (N=162)		Unadjusted		Adjusted[4]	
Occupational groups[2]	**n**	**%**	**n**	**%**	**OR**[3]	**95%-CI**	**OR**[3]	**95%-CI**
Agriculture, forestry; hunting; fishing	6	10.2	14	8.6	1.2	0.44-3.26	1.1	0.39-3.25
Mining	1	1.7	3	1.9	0.9	0.09-8.92	1.2	0.12-12.1
Coal-mining, petroleum and gas production and manufacturing	2	3.4	3	1.9	1.9	0.30-11.3	3.1	0.43-21.8
Food industry	4	6.8	23	14.2	0.4	0.15-1.33	0.6	0.18-1.87
Textile production and manufacturing	10	16.9	21	13.0	1.4	0.60-3.10	1.6	0.66-3.93
Leather and shoe production and manufacturing	2	3.4	4	2.5	1.4	0.25-7.73	1.7	0.28-9.82
Wood working (furniture, music instrument manufacturing)	2	3.4	2	1.2	2.8	0.39-20.1	1.8	0.21-14.6
Paper, editorial and printing industry	5	8.5	11	6.8	1.3	0.42-3.81	1.8	0.55-5.71
Chemical and pharmaceutical industry	3	5.1	8	4.9	1.0	0.27-4.01	1.1	0.27-4.51
Glass, ceramic, and natural-stone working	1	1.7	3	1.9	0.9	0.09-8.92	0.7	0.07-6.96
Metal manufacturing	2	3.4	11	6.8	0.5	0.10-2.24	0.3	0.07-1.65
Machine production	6	10.2	8	4.9	2.2	0.72-6.52	3.2	0.96-10.7
Office-goods manuf, electrotech, precision-optic-jewel-toy work	5	8.5	13	8.0	1.1	0.36-3.11	1.3	0.40-3.89
Vehicle production	2	3.4	5	3.1	1.1	0.21-5.81	1.6	0.28-9.29
Provision of water and electricity	1	1.7	2	1.2	1.4	0.12-15.3	1.9	0.16-23.7
Wholesale traders and intermediates	10	16.9	17	10.5	1.7	0.75-4.03	1.7	0.68-4.31
Retail traders	18	30.5	55	34.0	0.9	0.45-1.62	0.8	0.41-1.64
Catering trade	8	13.6	12	7.4	2.0	0.76-5.04	2.3	0.85-6.19
Transport	1	1.7	7	4.3	0.4	0.05-3.17	0.8	0.09-7.27
Credit and insurance business	2	3.4	16	9.9	0.3	0.07-1.44	0.3	0.06-1.49
Landed property services, business services	11	18.6	17	10.5	1.9	0.86-4.44	2.1	0.83-5.40
Health and veterinary sector	12	20.3	16	9.9	*2.3	1.03-5.24	2.4	0.97-5.71
Church, trade unions	1	1.7	3	1.9	0.9	0.09-8.92	0.4	0.04-4.75
Other services	3	5.1	13	8.0	0.6	0.17-2.24	0.3	0.07-1.75
House makers	12	20.3	26	16.0	1.3	0.62-2.85	1.5	0.64-3.50
Other categories	53	89.8	137	84.6	1.6	0.63-4.13	1.3	0.50-3.64

[1] According to the European Community Industrial Classification (NACE) for the main task performed
[2] No ORs were calculated for the following occupational branches, as no cases or controls were reported: Rubber and plastic production; Metal production, waste-metal-recycling; Non-metal recycling, cleaning, drainage, trash; Construction industry; Reconstruction; Vehicle trade and repair; Media industry; Public administration, social security, defense, police; Education and social affaires; and Culture, sport, entertainment
[3] The reference group for all occupational branches was non-exposed women to the occupational group of interest
[4] Odds ratios were estimated from a conditional logistic-regression model including age and region of residence
[*] Statistically significant at P<0.05

Table 20. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma in the pooled analysis by NACE occupational branches –main and secondary task–[1] among women

Occupational groups[2]	Cases (N=59)		Controls (N=162)		Unadjusted		Adjusted[4]	
	n	%	n	%	OR[3]	95%-CI	OR[3]	95%-CI
Agriculture, forestry; hunting; fishing	6	10.2	16	9.9	1.0	0.38-2.77	1.1	0.37-3.04
Mining	1	1.7	4	2.5	0.7	0.07-6.20	0.9	0.09-7.92
Coal-mining, petroleum and gas production and manufacturing	2	3.4	3	1.9	1.9	0.30-11.3	3.1	0.43-21.8
Food industry	6	10.2	25	15.4	0.6	0.24-1.60	0.9	0.32-2.49
Textile production and manufacturing	10	16.9	22	13.6	1.3	0.58-2.93	1.5	0.63-3.60
Leather and shoe production and manufacturing	3	5.1	5	3.1	1.7	0.39-7.22	1.8	0.39-8.48
Wood working (furniture, music instrument manufacturing)	2	3.4	2	1.2	2.8	0.39-20.1	1.8	0.21-14.6
Paper, editorial and printing industry	5	8.5	11	6.8	1.3	0.42-3.81	1.8	0.55-5.71
Chemical and pharmaceutical industry	3	5.1	8	4.9	1.0	0.27-4.01	1.1	0.27-4.51
Rubber and plastic production	1	1.7	2	1.2	1.4	0.12-15.3	0.8	0.06-11.5
Glass, ceramic, and natural-stone working	1	1.7	3	1.9	0.9	0.09-8.92	0.7	0.07-6.96
Metal manufacturing	4	6.8	11	6.8	1.0	0.31-3.26	0.7	0.21-2.50
Machine production	6	10.2	10	6.2	1.7	0.60-4.94	2.4	0.72-8.12
Office-goods manuf, electrotech, precision-optic-jewel-toy work	5	8.5	13	8.0	1.1	0.36-3.11	1.3	0.40-3.89
Vehicle production	2	3.4	6	3.7	0.9	0.18-4.64	1.3	0.23-7.82
Provision of water and electricity	1	1.7	2	1.2	1.4	0.12-15.3	1.9	0.16-23.7
Construction industry	1	1.7	6	3.7	0.4	0.05-3.80	0.6	0.07-5.69
Reconstruction	1	1.7	4	2.5	0.7	0.07-6.20	0.9	0.09-8.98
Wholesale traders and intermediates	10	16.9	17	10.5	1.7	0.75-4.03	1.7	0.68-4.31
Retail traders	19	32.2	56	34.6	0.9	0.48-1.69	0.9	0.44-1.76
Catering trade	8	13.6	15	9.3	1.5	0.62-3.82	1.7	0.68-4.46
Transport	1	1.7	7	4.3	0.4	0.05-3.17	0.8	0.09-7.27
Credit and insurance business	2	3.4	16	9.9	0.3	0.07-1.44	0.3	0.06-1.49
Landed property services, business services	11	18.6	18	11.1	1.8	0.81-4.13	2.1	0.81-5.25
Public administration, social security, defense, police	5	8.5	12	7.4	1.2	0.39-3.43	1.2	0.39-3.86
Education and social affaires	9	15.3	26	16.0	0.9	0.41-2.14	0.9	0.38-2.33
Health and veterinary sector	12	20.3	16	9.9	*2.3	1.03-5.24	2.4	0.97-5.71
Church, trade unions	1	1.7	3	1.9	0.9	0.09-8.92	0.4	0.04-4.75
Other services	3	5.1	14	8.6	0.6	0.16-2.05	0.1	0.02-1.33
House makers	13	22.0	28	17.3	1.4	0.65-2.82	1.6	0.69-3.65
Other categories	53	89.8	138	85.2	1.5	0.59-3.95	1.2	0.45-3.31

[1] According to the European Community Industrial Classification (NACE) for the main and secondary task performed
[2] No ORs were calculated for the following occupational branches, as no cases or controls were reported: Metal production, waste-metal-recycling; Non-metal recycling, cleaning, drainage, trash; Vehicle trade and repair; Media industry; and Culture, sport, entertainment
[3] The reference group for all occupational branches was non-exposed women to the occupational group of interest
[4] Odds ratios were estimated from a conditional logistic-regression model including age and region of residence
[*] Statistically significant at P<0.05

Table 21. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma in the pooled analysis by JSQ occupational classification –main task–[1] including men and women

Occupational groups[2]	Cases (N=118)		Controls (N=475)		Unadjusted		Adjusted[4]	
	n	%	n	%	OR[3]	95%-CI	OR[3]	95%-CI
Health care	10	8.5	29	6.1	1.4	0.67-3.01	1.3	0.55-2.86
Dentistry	1	0.8	1	0.2	4.0	0.25-64.8	1.4	0.08-23.5
Cooking	17	14.4	37	7.8	*2.0	1.08-3.67	*2.1	1.04-4.29
Textile dry cleaning	1	0.8	3	0.6	1.3	0.14-13.0	0.9	0.06-12.6
Farming	13	11.0	36	7.6	1.5	0.77-2.94	1.2	0.57-2.46
Working with farm animals	11	9.3	27	5.7	1.7	0.82-3.54	1.2	0.54-2.72
Metal smelting	1	0.8	30	6.3	*0.1	0.02-0.94	0.2	0.03-1.73
Wood working	6	5.1	27	5.7	0.9	0.36-2.20	0.9	0.35-2.48
Pulp, paper production	4	3.4	6	1.3	2.7	0.76-9.84	3.2	0.75-13.6
Slaughtering	2	1.7	15	3.2	0.5	0.12-2.34	0.4	0.09-2.00
Shoe, leather	5	4.2	5	1.1	*4.1	1.18-14.5	2.6	0.68-10.0
Electricians	4	3.4	47	9.9	*0.3	0.11-0.91	0.5	0.16-1.54
Welding, brazing, soldering	15	12.7	105	22.1	*0.5	0.29-0.92	0.9	0.48-1.79
Plastic production	3	2.5	8	1.7	1.5	0.40-5.82	1.3	0.26-6.91
Painting	3	2.5	34	7.2	0.3	0.10-1.12	0.6	0.16-1.93
Builder, stonemason, plasterer	14	11.9	47	9.9	1.2	0.65-2.31	1.3	0.62-2.82
Railway working	2	1.7	12	2.5	0.7	0.15-3.01	1.3	0.27-6.64
Chemical industry	5	4.2	16	3.4	1.3	0.46-3.53	1.7	0.51-5.36
Automobile repair and construction	4	3.4	27	5.7	0.6	0.20-1.70	1.1	0.34-3.27
Metal working	13	11.0	107	22.5	*0.4	0.23-0.79	0.7	0.34-1.32

[1] *According to the Job Specific Questionnaire Occupational Classification (JSQ) for the main task performed (ever vs. never worked)*
[2] *No ORs were calculated for the following occupational branches, as no cases or controls were reported: Forestry; Foundries; Electro plating; Textile working; Tanneries; Glass industry; Pottery, ceramic industry; Rubber industry; Painting manufacturing; and Air and spaceship construction*
[3] *The reference group for all occupational branches was non-exposed individuals (men/women) to the occupational group of interest*
[4] *Odds ratios were estimated from a conditional logistic-regression model including age, gender and region of residence*
[*] *Statistically significant at P<0.05*

Table 22. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) for uveal melanoma in the pooled analysis by JSQ occupational classification –main task–[1] stratifying by gender

Occupational groups	Cases		Controls		Unadjusted		Adjusted[5]	
	n	%	n	%	OR[4]	95%-CI	OR[4]	95%-CI
Men[2]	**(N=59)**		**(N=313)**					
Health care	1	1.7	13	4.2	0.4	0.05-3.10	0.6	0.06-5.07
Cooking	6	10.2	8	2.6	*4.3	1.44-12.8	*5.6	1.66-19.1
Farming	7	11.9	21	6.7	1.9	0.76-4.61	1.4	0.50-3.77
Working with farm animals	6	10.2	14	4.5	2.4	0.89-6.54	1.5	0.47-4.54
Metal smelting	1	1.7	28	8.9	0.2	0.02-1.32	0.2	0.03-1.92
Wood working	4	6.8	26	8.3	0.8	0.27-2.39	0.7	0.23-2.31
Pulp, paper production	1	1.7	4	1.3	1.3	0.15-12.0	1.6	0.13-18.3
Slaughtering	1	1.7	4	1.3	1.3	0.15-12.0	2.6	0.24-27.5
Shoe, leather	3	5.1	1	0.3	*16.5	1.69-160	5.7	0.48-66.9
Electricians	4	6.8	45	14.4	0.4	0.15-1.26	0.5	0.17-1.67
Welding, brazing, soldering	13	22.0	101	32.3	0.6	0.31-1.15	0.9	0.43-1.76
Plastic production	1	1.7	8	2.6	0.7	0.08-5.35	0.6	0.05-6.25
Painting	3	5.1	32	10.2	0.5	0.14-1.59	0.6	0.17-2.15
Builder, stonemason, plasterer	14	23.7	46	14.7	1.8	0.92-3.54	1.4	0.64-2.99
Railway working	2	3.4	12	3.8	0.9	0.19-4.03	1.3	0.27-6.64
Chemical industry	5	8.5	15	4.8	1.8	0.64-5.25	1.9	0.57-6.34
Automobile repair and construction	3	5.1	25	8.0	0.6	0.18-2.11	0.9	0.26-3.33
Metal working	11	18.6	101	32.3	*0.5	0.24-0.97	0.6	0.30-1.29
Women[3]	**(N=59)**		**(N=162)**					
Health care	9	15.3	16	9.9	1.6	0.68-3.93	1.5	0.60-3.76
Cooking	11	18.6	29	17.9	1.1	0.49-2.26	1.4	0.58-3.19
Textile dry cleaning	1	1.7	2	1.2	1.4	0.12-15.3	1.0	0.06-16.6
Farming	6	10.2	15	9.3	1.1	0.41-3.00	1.0	0.36-2.91
Working with farm animals	5	8.5	13	8.0	1.1	0.36-3.11	1.0	0.32-3.19
Wood working	2	3.4	1	0.6	5.6	0.50-62.5	2.6	0.23-29.1
Pulp, paper production	3	5.1	2	1.2	4.3	0.70-25.9	5.1	0.75-34.2
Slaughtering	1	1.7	11	6.8	0.2	0.03-1.88	0.2	0.02-1.70
Shoe, leather	2	3.4	4	2.5	1.4	0.25-7.73	1.7	0.30-9.97
Welding, brazing, soldering	2	3.4	4	2.5	1.4	0.25-7.73	1.4	0.24-8.61
Automobile repair and construction	1	1.7	2	1.2	1.4	0.12-15.3	1.9	0.16-22.7
Metal working	2	3.4	6	3.7	0.9	0.18-4.64	1.1	0.21-5.87

[1] *According to the Job Specific Questionnaire Occupational Classification (JSQ) for the main task performed (ever vs. never worked)*
[2] *No ORs were calculated for the following occupational branches, as no cases or controls were reported: Dentistry; Textile dry cleaning; Forestry; Foundries; Electro plating; Textile working; Tanneries; Glass industry; Pottery, ceramic industry; Rubber industry; Painting manufacturing; Air and spaceship construction*
[3] *No ORs were calculated for the following occupational branches, as no cases or controls were reported: Dentistry; Forestry; Metal Smelting; Foundries; Electro plating; Textile working; Tanneries; Electricians; Glass industry; Pottery, ceramic industry; Rubber industry; Plastic production; Painting; Painting manufacturing; Builder, stonemason, plasterer; Railway working; Chemical industry; and Air and spaceship construction*
[4] *The reference group for all occupational branches was non-exposed men or women to the occupational group of interest*
[5] *Odds ratios were estimated from a conditional logistic-regression model including age and region of residence*
[*] *Statistically significant at P<0.05*

Table 23. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) in the pooled analysis for the principal jobs positively associated to Uveal Melanoma based on the ISCO[1] occupational groups for *main task* and *main and secondary task*, stratifying by gender

	Exposure	Cases		Controls		Adjusted [2]	
		n	%	n	%	OR	95% CI
Main task							
Men							
Clerical workers	No	42	71.2	256	81.8	1.0	
	Yes	17	28.8	57	18.2	1.8	0.86-3.78
General farmers	No	52	88.1	298	95.2	1.0	
	Yes	7	11.9	15	4.8	1.7	0.60-4.95
Miners	No	49	83.1	292	93.3	1.0	
	Yes	10	16.9	21	6.7	2.3	0.92-5.99
Food, beverage, and tobacco processors	No	55	93.2	308	98.4	1.0	
	Yes	4	6.8	5	1.6	4.7	0.99-22.1
Women							
Service workers	No	32	54.2	101	62.3	1.0	
	Yes	27	45.8	61	37.7	1.8	0.86-3.80
Medical, dental, pharmaceutical and veterinary workers	No	51	86.4	152	93.8	1.0	
	Yes	8	13.6	10	6.2	2.1	0.71-6.02
Station, engine, heavy equipment operators, and freight handlers	No	50	84.7	150	92.6	1.0	
	Yes	9	15.3	12	7.4	2.5	0.94-6.58
Main and secondary task							
Men							
Clerical workers	No	41	69.5	238	76.0	1.0	
	Yes	18	30.5	75	24.0	1.4	0.70-2.94
General farmers	No	52	88.1	295	94.2	1.0	
	Yes	7	11.9	18	5.8	1.5	0.53-4.13
Miners	No	49	83.1	292	93.3	1.0	
	Yes	10	16.9	21	6.7	2.3	0.92-5.99
Food, beverage, and tobacco processors	No	54	91.5	306	97.8	1.0	
	Yes	5	8.5	7	2.2	3.7	0.94-14.1
Women							
Service workers	No	30	50.8	89	54.9	1.0	
	Yes	29	49.2	73	45.1	1.5	0.73-2.95
Medical, dental, pharmaceutical and veterinary workers	No	51	86.4	152	93.8	1.0	
	Yes	8	13.6	10	6.2	2.1	0.71-6.02
Station, engine, heavy equipment operators, and freight handlers	No	49	83.1	140	86.4	1.0	
	Yes	10	16.9	22	13.6	1.5	0.63-3.70

[1] *International Standard Classification of Occupations*
[2] *Odds ratios were estimated from a conditional logistic-regression model including age and region of residence*
[*] *Statistically significant at P<0.05*

Table 24. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) in the pooled analysis for the principal branches positively associated to Uveal Melanoma based on the NACE[1] industrial branches for *main task* and *main and secondary task*, stratifying by gender

	Exposure	Cases		Controls		Adjusted [2]	
		n	%	n	%	OR	95% CI
Main task							
Men							
Mining	No	48	81.4	282	90.1	1.0	
	Yes	11	18.6	31	9.9	1.9	0.81-4.66
Coal-mining, petrol/gas production and manufacturing	No	56	94.9	310	99.0	1.0	
	Yes	3	5.1	3	1.0	4.8	0.67-33.6
Food industry	No	52	88.1	301	96.2	1.0	
	Yes	7	11.9	12	3.8	*3.4	1.08-10.5
Chemical and pharmaceutical industry	No	50	84.7	298	95.2	1.0	
	Yes	9	15.3	15	4.8	*2.8	1.01-7.78
Women							
Machine production	No	53	89.8	154	95.1	1.0	
	Yes	6	10.2	8	4.9	3.2	0.96-10.7
Catering trade	No	51	86.4	150	92.6	1.0	
	Yes	8	13.6	12	7.4	2.3	0.85-6.19
Landed property services and business services	No	48	81.4	145	89.5	1.0	
	Yes	11	18.6	17	10.5	2.1	0.83-5.40
Health and veterinary sector	No	47	79.7	146	90.1	1.0	
	Yes	12	20.3	16	9.9	2.4	0.97-5.71
Main and secondary task							
Men							
Mining	No	47	79.7	281	89.8	1.0	
	Yes	12	20.3	32	10.2	2.0	0.87-4.78
Coal-mining, petrol/gas production and manufacturing	No	55	93.2	309	98.7	1.0	
	Yes	4	6.8	4	1.3	4.4	0.87-22.0
Food industry	No	52	88.1	301	96.2	1.0	
	Yes	7	11.9	12	3.8	*3.4	1.08-10.5
Chemical and pharmaceutical industry	No	50	84.7	297	94.9	1.0	
	Yes	9	15.3	16	5.1	2.6	0.97-7.24
Women							
Machine production	No	53	89.8	152	93.8	1.0	
	Yes	6	10.2	10	6.2	2.4	0.72-8.12
Catering trade	No	51	86.4	147	90.7	1.0	
	Yes	8	13.6	15	9.3	1.7	0.68-4.46
Landed property services and business services	No	48	81.4	144	88.9	1.0	
	Yes	11	18.6	18	11.1	2.1	0.81-5.25
Health and veterinary sector	No	47	79.7	146	90.1	1.0	
	Yes	12	20.3	16	9.9	2.4	0.97-5.71

[1] *European Community Industrial Classification*
[2] *Odds ratios were estimated from a conditional logistic-regression model including age and region of residence*
[*] *Statistically significant at P<0.05*

Table 25. Distribution of subjects, odds ratios (OR) and 95% confidence intervals (CI) in the pooled analysis for the principal branches positively associated to Uveal Melanoma based on the JSQ[1] classification system for *main task*, stratifying by gender

	Exposure	Cases		Controls		Adjusted [2]	
		n	%	n	%	OR	95% CI
Main task							
Men							
Cooking	No	53	89.8	305	97.4	1.0	
	Yes	6	10.2	8	2.6	*5.6	1.66-19.1
Farmer	No	52	88.1	292	93.3	1.0	
	Yes	7	11.9	21	6.7	1.4	0.50-3.77
Builder, stonemason, and plasterer	No	45	76.3	267	85.3	1.0	
	Yes	14	23.7	46	14.7	1.4	0.64-2.99
Chemical industry	No	54	11.5	298	95.2	1.0	
	Yes	5	8.5	15	4.8	1.9	0.57-6.34
Women							
Health care	No	50	84.7	146	90.1	1.0	
	Yes	9	15.3	16	9.9	1.5	0.60-3.76
Cooking	No	48	81.4	133	82.1	1.0	
	Yes	11	18.6	29	17.9	1.4	0.58-3.19

[1] *Job-specific questionnaire*
[2] *Odds ratios were estimated from a conditional logistic-regression model including age and region of residence*
[*] *Statistically significant at P<0.05*

Table 26. Comparison between the principal associations previously published regarding potential occupational risks for uveal melanoma and those found in the pooled analysis

Principal associations reported in previous published studies by chronological order (author, year)	Major associations (adjusted OR-95%CI) found in the pooled analysis for selected occupations, main task
Ref. 1: Increased incidence in workers of a chemical plant. Possible human carcinogens identified were: Dimethylsulfate, hydrazine, 4,4´-methylene dianiline (Albert DM et al, 1980)	**Chemical workers *(see Ref. 1, 6 , 12 and 16)*** Chemical and pharmaceutical industry; NACE, men, 9 cases and 15 controls: 2.8 (1.01-7.78). Chemical industry, JSQ, men, 5 cases and 15 controls: 1.9 (0.57-6.34)
Ref. 2: In a proportional registration ratios study for eye cancer in England and Wales, higher PRR in non-manual vs. manual social classes were seen. Notably high for electrical and electronic workers (Swerdlow A, 1983)	**Farmers *(see Ref. 5, 7, 10, 11, 14 and 17)*** General farmers; ISCO, men, 7 cases and 15 controls: 1.7 (0.60-4.95). Agriculture, forestry, hunting, and fishing; NACE, men, 7 cases and 23 controls: 1.4 (0.51-3.60). Farmers; JSQ, men, 7 cases and 21 controls: 1.4 (0.50-3.77)
Ref. 3: Increased risk for welders in a case-control study, OR 10.9 (2.1-56.5) (Tucker MA et al, 1985)	**Welders *(See Ref. 3, 9, 16 and 18)*** Welding, brazing, and soldering; JSQ, men/women, 15 cases and 105 controls: 0.9 (0.48-1.79)
Ref. 4: A population-based case-control study showed a significant OR for governmental workers (indoor managerial group) of 3.5 (p=0.006) after controlling for hair and eye color (Gallagher RP et al, 1985)	**Construction workers *(see Ref. 10)*** Bricklayers, roofers, and other construction workers; ISCO, men, 12 cases and 42 controls: 1.3 (0.57-2.98). Construction industry; NACE, men, 14 cases and 58 controls: 1.0 (0.44-2.13). Builder, stonemason, and plasterer; JSQ, men, 14 cases and 46 controls: 1.4 (0.64-2.99)
Ref. 5: In a proportion mortality study for eye cancer, white male farmers presented a significant PMR of 3.75. The cohorts 1869-89, 1890-1904, and 1905-58 showed a significant PCMR of 3.43 (Saftlas AF et al, 1987)	**Clerical workers *(see Ref. 2 and 8)*** Clerical workers; ISCO, men, 17 cases and 57 controls: 1.8 (0.86-3.78)
Ref. 6: A historical cohort of retired asbestos workers showed a SMR for eye cancer of 15.4 (Enterline PE et al, 1987)	**Managerial group *(see Ref. 2, 4 and 7)*** Managers and managerial employees; ISCO, men/women, 27 cases and 118 controls: 1 (0.57-1.64)
Ref. 7: The Danish register linkage study showed the highest rates for males working in financial institutions. High rates also for male farmers (Lynge E and Thygesen L, 1990)	**Wood workers *(see Ref. 8)*** Wood workers; ISCO, 7 cases and 26 controls: 1.1 (0.43-2.97). Wood working, furniture, music instrument manufacturing; NACE, 6 cases and 19 controls: 1.2 (0.41-3.27). Wood working; JSQ, 6 cases and 27 controls: 0.9 (0.35-2.48)
Ref. 8: A cancer registration study from England, Wales, and Sweden, showed the following PRR for UM: laborers 48 (30-73); clerical workers 138 (103-181); woodworkers 155 (90-248); administrative and managers 137 (97-188) (Vagerö D et al, 1990)	**Livestock workers *(see. Ref. 13)*** Working with farm animals; JSQ, men, 6 cases and 14 controls: 1.5 (0.47-4.54)
Ref. 9: In a case-control study, having ever workee with welding arcs, showed an OR of 1.3 (0.5-3.1) (Seddon JM et al, 1990)	**Metal workers *(see Ref. 15)*** Metal production, waste-metal recycling; NACE, men/women, 4 cases and 41 controls: 0.5 (0.15-1.48). Metal manufacturing; NACE, men/women: 0.4 (0.14-0.99). Metal working; JSQ, men, 11 cases and 101 controls: 0.6 (0.30-1.29)
Ref. 10: The cross-linkage system to explore occupational risks for UM showed positive risks for agriculture and negative for construction (Ajani et al, 1992)	**Health workers *(see 13 and 16)*** Medical, dental, pharmaceutical, and veterinary workers; ISCO, women, 8 cases and 10 controls: 2.1 (0.71-6.02). Health and veterinary sector; NACE, women, 12 cases and 16 controls: 2.4 (0.97-5.71). Health care; JSQ, women, 9 cases and 16 controls: 1.5 (0.60-3.76)
Ref. 11: The Illinois Farmers case-control study showed a significant OR for eye cancer, 6.49 (1.78-23.71) (Keller JE and Howe HL, 1994)	**Electric and electronic workers *(see Ref. 2)*** Electric and electronic workers, broadcasting-cinema operators; ISCO, men, 3 cases and 47 controls: 0.4 (0.10-1.25). Electricians; JSQ, men, 4 cases and 45 controls: 0.5 (0.17-1.67)
Ref. 12: A study on conjuntival melanosis showed and elevated RR of 1.5 (1.1-2.2) for chemical industrial workers (Bulbulia A et al, 1995)	
Ref. 13: A finish retrospective cohort showed the following SIR: goldsmiths repairing watches 13.5 (1.63-48.6), plumbers 3.82 (1.40-8.29), auxiliary nurses 2.94 (1.08-6.40), female livestock workers 0.35 (0.11-0.82) (Pukkala E, 1995)	
Ref. 14: A Swedish cohort among male agricultural workers showed a SIR for eye cancer of 1.09 (0.81-1.43) (Wiklund K and Dich J, 1995)	
Ref. 15: A population-based case-control study for eye cancer among women in the workplace showed an elevated OR for fabricated metal products manufacturing 2.9 (1-8.6) (Swanson M and Brissette, 1995)	
Ref. 16: Population-based case-control study in US: asbestos exposure (1.8; 1.1-3.1); welding exposure (2.2; 1.3-3.5); chemists-chemical engineers-chemical technicians (5.8; 1.6-22.7); health-related occupations (3.3; 1.3-8.2) (Holly EA et al, 1996)	
Ref. 17: Norwegian cohort among agricultural workers showed standardized mortality rates for eye cancer of 0.8 (0.5-1.4) for men; and 1.6 (0.7-3) for women (Kristensen P et al, 1996)	
Ref. 18: An elevated risk for ocular melanoma in male welders (7.3;2.6-20.1) in a population-based case-control study; dose-response relationship with job duration (Guenel et al, 2001)	

Table 27. Consistency between the hospital and population-based studies according to the ISCO classification system for the main task, through comparison of the adjusted odds ratios (Adj. OR)

ISCO Job group (main task)[2]	Hospital-based				Population-based		
	Cases n (%)	Controls n (%)	Adj. OR[1] (95%CI)		Cases n (%)	Controls n (%)	Adj. OR[1] (95%CI)
Architects, engineers, air-ship craft, office, production supervisors	*8 (9.9)*	*20 (13.5)*	*0.9 (0.36-2.27)*	≠	*5 (13.5)*	*46 (14.1)*	*1.1 (0.39-3.07)*
Medical, dental, pharmaceutical and veterinary workers	*5 (6.2)*	*9 (6.1)*	*0.8 (0.23-2.87)*	≠	*4 (10.8)*	*14 (4.3)*	*2.7 (0.80-9.10)*
Managers, managerial employees	*15 (18.5)*	*30 (20.3)*	*0.7 (0.33-1.43)*	≠	*12 (32.4)*	*88 (26.9)*	*1.4 (0.68-3.02)*
Clerical workers	*27 (33.3)*	*39 (26.4)*	*1.3 (0.65-2.45)*	=	*9 (24.3)*	*71 (21.7)*	*1.2 (0.51-2.73)*
Sales workers	*19 (23.5)*	*34 (23.0)*	*0.9 (0.46-1.87)*	=	*5 (13.5)*	*59 (18.0)*	*0.6 (0.21-1.62)*
Service workers	*27 (33.3)*	*31 (20.9)*	*2.8 (1.28-5.98)*	≠	*8 (21.6)*	*64 (19.6)*	*0.8 (0.29-2.01)*
Miners	*6 (7.4)*	*10 (6.8)*	*1.5 (0.45-4.93)*	=	*4 (10.8)*	*13 (4.0)*	*2.9 (0.79-10.3)*
Machinery fitters and assemblers and precision-instrument makers	*4 (4.9)*	*15 (10.1)*	*0.6 (0.18-1.96)*	≠	*4 (10.8)*	*37 (11.3)*	*1.3 (0.43-4.17)*
Bricklayers, roofers and other construction workers	*8 (9.9)*	*13 (8.8)*	*1.1 (0.37-3.34)*	=	*4 (10.8)*	*29 (8.9)*	*1.6 (0.49-5.27)*
Station/engine/heavy equipment operators, freight handlers	*10 (12.3)*	*16 (10.8)*	*1.2 (0.53-2.88)*	=	*4 (10.8)*	*34 (10.4)*	*1.1 (0.36-3.34)*

[1] Odds ratios were estimated from a conditional logistic-regression model including age and region of residence
[2] Consistency was assessed only in those occupational groups with more than three cases and controls in each analyzed study. Consistency was not evaluated when one of the adjusted OR presented the null value
≠ INCONSOSTENCY between studies: The adjusted OR from the hospital and population-based studies point at different directions
= CONSOSTENCY between studies : The adjusted OR from the hospital and population-based studies point at the same direction

Table 28. Consistency between the hospital and population-based studies according to the NACE classification system for the main task, through comparison of the adjusted odds ratios (Adj. OR)

NACE industry branches (main task)[2]	Hospital-based				Population-based		
	Cases n (%)	Controls n (%)	Adj. OR[1] (95%CI)		Cases n (%)	Controls n (%)	Adj. OR[1] (95%CI)
Mining	15 (10.1)	7 (8.6)	1.2 (0.42-3.56)	=	19 (5.8)	5 (13.5)	3.1 (0.94-10.2)
Food industry	9 (6.1)	7 (8.6)	1.5 (0.52-4.44)	=	26 (8.0)	4 (10.8)	1.1 (0.33-3.66)
Textile production and manufacturing	11 (7.4)	8 (9.9)	1.6 (0.57-4.79)	=	15 (4.6)	4 (10.8)	1.5 (0.44-5.25)
Chemical and pharmaceutical industry	11 (7.4)	8 (9.9)	1.6 (0.56-4.51)	=	12 (3.7)	4 (10.8)	2.8 (0.80-9.89)
Machine production	13 (8.8)	6 (7.4)	0.9 (0.33-2.69)	≠	37 (11.3)	4 (10.8)	1.1 (0.37-3.55)
Wholesale traders and intermediates	12 (8.1)	10 (12.3)	1.7 (0.65-4.57)	=	37 (11.3)	6 (16.2)	1.3 (0.52-3.44)
Retail traders	29 (19.6)	19 (23.5)	1.0 (0.51-2.13)	=	59 (18.0)	5 (13.5)	0.5 (0.17-1.42)
Transport	10 (6.8)	4 (4.9)	0.8 (0.22-2.60)	≠	40 (12.2)	6 (16.2)	1.9 (0.69-5.14)
Landed property services, business services	20 (13.5)	13 (16.0)	1.1 (0.47-2.49)	=	36 (11.0)	6 (16.2)	1.6 (0.63-4.30)
Public administration, social security, defense, police	32 (21.6)	20 (24.7)	1.4 (0.64-3.25)	≠	94 (28.7)	6 (16.2)	0.7 (0.28-1.82)

[1] Odds ratios were estimated from a conditional logistic-regression model including age and region of residence
[2] Consistency was assessed only in those occupational groups with more than three cases and controls in each analyzed study. Consistency was not evaluated when one of the adjusted OR presented the null value
≠ INCONSOSTENCY between studies: The adjusted OR from the hospital and population-based studies point at different directions
= CONSOSTENCY between studies : The adjusted OR from the hospital and population-based studies point at the same direction

Table 29. Consistency between the hospital and population-based studies according to the JSQ classification system for the main task, through comparison of the adjusted odds ratios (Adj. OR)

JSQ job groups (main task)[2]	Hospital-based				Population-based		
	Cases n (%)	Controls n (%)	Adj. OR[1] (95%CI)		Cases n (%)	Controls n (%)	Adj. OR[1] (95%CI)
Health care*	6 (7.4)	11 (7.4)	0.9 (0.30-2.81)	≠	4 (10.8)	18 (5.5)	1.8 (0.57-5.77)
Cooking**	12 (14.8)	16 (10.8)	2.2 (0.89-5.39)	=	5 (13.5)	21 (6.4)	2.0 (0.63-6.36)
Welding, brazing, soldering*	7 (8.6)	19 (12.8)	0.8 (0.30-2.03)	≠	8 (21.6)	86 (26.3)	1.1 (0.44-2.69)
Builder, stonemason, plasterer**	10 (12.3)	16 (10.8)	1.2 (0.46-3.31)	=	4 (10.8)	31 (9.5)	1.5 (0.45-4.67)
Metal working**	7 (8.6)	25 (16.9)	0.6 (0.23-1.46)	=	6 (16.2)	82 (25.1)	0.8 (0.31-2.13)

[1] Odds ratios were estimated from a conditional logistic-regression model including age and region of residence
[2] Consistency was assessed only in those occupational groups with more than three cases and controls in each analyzed study. Consistency was not evaluated when one of the adjusted OR presented the null value
≠ INCONSOSTENCY between studies: The adjusted OR from the hospital and population-based studies point at different directions
= CONSOSTENCY between studies : The adjusted OR from the hospital and population-based studies point at the same direction

Table 30. Consistency of results between the hospital (H) and population-based (P) studies for selected occupational categories according to ISCO, NACE, and JSQ in both sexes, through comparison of the adjusted odds ratios (Adj. OR)

Occupational category	Adjusted OR* (No. of cases-controls)					
	ISCO		NACE		JSQ	
	P	H	P	H	P	H
Chemical[1]	No cases	**3.0** (3-2)	**2.8** (4-12)	**1.6** (8-11)	No cases	**4.0** (5-4)
Farming[2]	**1.1** (2-14)	**1.8** (10-10)	**1.4** (3-20)	**1.2** (10-17)	**0.8** (2-20)	**1.3** (11-16)
Food[3]	**2.5** (1-5)	**2.8** (3-3)	**1.1** (4-26)	**1.5** (7-9)	**2.0** (5-21)	**2.2** (12-16)
Mining[4]	**2.9** (4-13)	**1.5** (6-10)	**3.1** (5-19)	**1.2** (7-15)	.	.
Health[5]	**2.7** (4-14)	**0.8** (5-9)	**0.7** (2-18)	**1.2** (10-16)	**1.8** (4-18)	**0.9** (6-11)

** Conditional logistic regression model included age and region of residence*
[1] Chemical, rubber and plastic workers (ISCO); chemical and pharmaceutical industry (NACE); chemical industry (JSQ)
[2] General farmers (ISCO); agriculture, forestry, hunting and fishing (NACE); farming (JSQ)
[3] Food, beverage and tobacco processors (ISCO); food industry (NACE); cooking (JSQ)
[4] Miners (ISCO); mining (NACE); no mining category (JSQ)
[5] Medical, dental, pharmaceutical and veterinary workers (ISCO); Health and veterinary sector (NACE); Health care (JSQ)

Table 31. Consistency across the three categorization methods in the pooled analysis for the main task, stratifying by gender, through comparison of the adjusted odds ratios (OR)[1]

ISCO job group	JSQ job group	NACE industrial branch
Men		
General farmers	Farming	Agriculture, forestry, hunting, fishing
1.7 (0.60-4.95)(7)	1.4 (0.50-3.77)(7)	1.4 (0.51-3.6)(7)
Miners	--	Mining
2.3 (0.92-5.99)(10)		1.9 (0.81-4.66)(11)
Food, beverage, and tobacco processors	Cooking	Food industry
4.7 (0.99-22.05)(4)	5.6 (1.66-19.1)(6)	3.4 (1.08-10.57)(7)
Bricklayers, roofers, and other construction workers	Builder, stonemason, plasterer	Construction industry
1.3 (0.57-2.98)(12)	1.4 (0.64-2.99)(14)	1.0 (0.44-2.13)(14)
Plumbers, welders, sheet-structural metal workers	Welding, brazing, soldering	--
0.7 (0.27-1.85)(6)	0.9 (0.48-1.79)(15)	
Wood workers	Wood working	Wood working, furniture, music-inst. manuf.
1.1 (0.43-2.97)(7)	0.9 (0.35-2.48)(6)	1.2 (0.41-3.27)(6)
Chemical, rubber and plastic workers	Chemical industry	Chemical and pharmaceutical industry
1.2 (0.24-6.33)(2)	1.9 (0.57-6.34)(5)	2.8 (1.01-7.78)(9)
Women		
General farmers	Farming	Agriculture, forestry, hunting, fishing
1.4 (0.41-4.78)(57)	1.0 (0.36-2.91)(6)	1.1 (0.39-3.25)(6)
Medical, dental, pharmaceutical, veterinary workers	Health care	Health and veterinary sector
2.1 (0.71-6)(8)	1.5 (0.60-3.76)(9)	2.4 (0.97-5.71)(12)

[1] *Adjusted OR (95% confidence interval)(number of cases)*

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