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Self-reported Cancer History and the Risk of Uveal Melanoma

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Referat und bibliographische Beschreibung

Ziel der Studie war die Untersuchung des Zusammenhangs der Krebseigen- und Familienanamnese und dem Risiko des Uvealmelanoms. Die Arbeit basiert auf der RIFA Fall-Kontroll-Studie, die inzidente Uvealmelanomfälle und Bevölkerungskontrollen einschloss. Die Eigen- und Familienanamnese wurden durch computerunterstützte Telefoninterviews erhoben. Für die Abschätzung der Stärke des Zusammenhangs zwischen Expositionen (Anamnese und Familieanamnese der Tumoren) und dem Outcome (Uvealmelanom) wurden Odds Ratios (OR) als Schätzer des Relativen Risikos und 95% Konfidenzintervalle (KI) mit Hilfe der konditionalen logistischen Regression berechnet. Es wurden 455 Uvealmelanompatienten und 827 Bevölkerungkontrollen in die Analyse eingeschlossen. Die Ergebnisse der Studie zeigen, dass Krebs in der eigenen Vorgeschichte (OR=1.3; 95% KI: 0.9-2.0) und eine positive Familieanamnese für Krebserkrankungen (OR=1.3; 95% KI: 1.0-1.6) das Risiko des Uvealmelanoms um 30% erhöht. Das Risiko ist um 30% bzw. 80% erhöht, wenn ein Mitglied der Familie an Brustkrebs (OR=1.3; 95% KI: 0.8-2.1) bzw. an Prostatakrebs (OR=1.8; 95% KI: 0.9-3.6) erkrankte. Eine positive Familienanamnese für BRCA2-assoziierte Krebserkrankungen ist bei Männern mit einem erhöhten Uvealmelanomrisiko (OR=2.2; 95% KI: 1.3-3.7) assoziiert. Bei Frauen zeigte sich kein klarer Zusammenhang (OR=1.1; 95% KI: 0.7-1.8). Die Untersuchungen machen deutlich, dass bei Probanden mit positiver Familieanamnese für Bruskrebs, Prostatakrebs und BRCA2-assoziierten Tumoren speziell bei Männern ein erhöhtes Risiko für Uvealmelanome besteht.

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CONTENTS

ABBREVIATIONS

ATH	Apical Tumour Height
CI	Confidence Interval
CLR	Upper to lower 95% Confidence Limits Ratio
CT	Computerized Tomography
CMOS	Collaborative Ocular Melanoma Study
c-onc	Cellular Oncogene
OR	Odds Ratio
ICD 10	International Statistical Classification of Diseases and Related Health Problems, 10^{th} Revision
LBD	Largest Basal Diameter
LTD	Largest basal Tumour Diameter
MPY	Million Person Years
MRI	Magnetic Resonance Imaging
NMDE	Nondifferential Misclassification Error in a Dichotomous Exposure
SIR	Standardized Incidence Ratio
TSG	Tumor Suppressor Genes
UM	Uveal Melanoma
UV radiation	Ultraviolet radiation
v-onc	Viral Oncogene

1. Introduction

Uveal melanoma is a malignant neoplasm of the uveal tract, a pigmented layer of the eye that consists of the iris, ciliary body, and choroids. Most uveal melanomas (approximately 90%) originate from the choroids; the iris is the least common site of origin (2-3%) (Conway *et al*., 2001; Egan *et al*., 1988; Inskip *et al*. 2003).

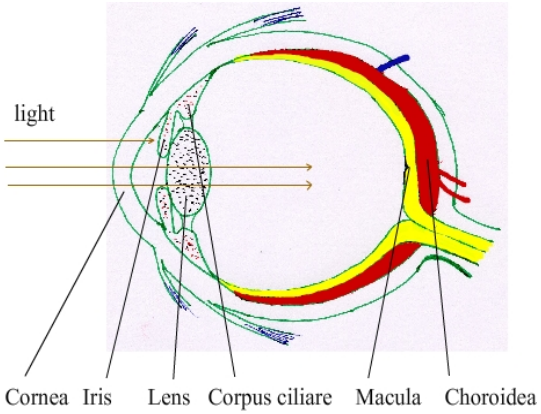

Figure 1. The uveal tract (iris, ciliary body and choroids) of the eye

Uveal melanoma was first reported by Georg Bartisch (1535-1606), a famous German ophthalmologist. However, Rudolf Virchow was the first to initiate detailed research of uveal melanoma in 1863. Thereafter, much effort has been spent on investigating uveal melanoma, particularly regarding the aetiology, but only a few risk factors or risk indicators have been identified until now.

The present study focusses on the potential association between uveal melanoma and some other cancers. The current knowledge about uveal melanoma will be reviewed first and will be followed by the questions of the study. A description of the study materials and statistical methods will then be presented. Finally, the main statistical results and a discussion will be presented.

1.1 Incidence

Uveal melanoma is the most common primary malignant intraocular tumour among adults. In an analysis of international cancer registers, uveal melanoma accounted for approximately

75% of all primary cancers of the eye in 1993-97 and was once as high as 82% in 1983-87 (Stang *et al*., 2005).

However, from a global perspective uveal melanoma is a rare disease. Reported age-standardized incidence rates of uveal melanoma vary in ethnic groups. The annual age-adjusted incidence estimated for ocular melanoma in the United States was 6.0 per million person years (MPY) from 1969 to 1971 (Hu *et al*., 2005; Scotto *et al*., 1976). In some European countries, the incidence was between 4.9 and 9.4 per MPY for the period from 1983 to 1998 (Stang *et al*., 2005; Bergman *et al*., 2002). The highest incidence is found in Sweden which has 9.4 per MPY for men and 8.9 per PMY for women (Bergman *et al*., 2002) (table 1).

1.2 Aetiology

Little is known about the causes of uveal melanoma. As intraocular melanoma and cutaneous melanoma share a common cell of origin, the melanocyte, they may have a similar aetiology. However, some risk factors of cutaneous melanoma, such as ultraviolet radiation, numerous freckles, exposure to chemicals, etc. (Klein-Szanto *et al*., 1994; Linet *et al*., 1995; Scotto *et al*., 1976), seem to be inconsistently associated with uveal melanoma. Generally, the risk factors of uveal melanoma will be classified into two classes in the present study. The first class of factors contains modifiable risk factors, which are something extrinsic to human beings that man can avoid; the second class are unmodifiable risk factors, which are something intrinsic that man can not change.

1.2.1 Modifiable Risk Factors

Most of the modifiable risk factors of uveal melanoma, including some environmental and occupational factors, are weakly or inconsistently associated with uveal melanoma. The most disputable one is solar ultraviolet (UV) radiation, which is a risk factor for both cutaneous melanoma and non-melanoma skin cancers (English *et al*., 1997; Gilchrest *et al*., 1999). Some studies have found a positive association between uveal melanoma and UV-radiation (UV-exposure, outdoor activities and expressed in terms of sunbathing) (Holly *et al*., 1990; Seddon *et al*., 1990; Tucker *et al*., 1985; Vajdic *et al*., 2002), whereas other studies produced conflicting results after evaluation of the association between uveal melanoma and temporal,

Table 1. Age-standardized incidence rate of uveal melanoma from published reports

Registry	Period	First Author	Year of Publication	Number of Cases	Incidence Rate**	
					Men	Women
Asia and Oceania						
Australia	83-97	Stang	2005	1603	6,2	5,2
Singapore	83-97	Stang	2005	9	0,3	0,1
Osaka	83-97	Stang	2005	28	0,2	0,2
North/Central America						
Canada	83-97	Stang	2005	2109	5,9	4,8
SEER(US)	73-97	Singh	2003	2493	4,9	3,7
SEER White(US)	83-97	Stang	2005	1759	5,1	4,2
SEER White***(US)	92-00	Hu	2005	1281	6,02	
SEER Black(US)	83-97	Stang	2005	10	0,4	0,2
SEER Black(US)	92-00	Hu	2005	9	0,31	
SEER Asian(US)	92-00	Hu	2005	10	0,38	
Costa Rica	83-97	Stang	2005	22	0,4	0,9
Europe						
Sweden	60-98	Bergman	2002	2997	9,4	8,9
Denmark	83-97	Stang	2005	815	7,5	6,3
UK Scotland	83-97	Stang	2005	696	6,9	6,3
Slovakia	83-97	Stang	2005	535	6,3	5,1
Czech	83-97	Stang	2005	919	5,6	4,6
France	83-97	Stang	2005	337	5,5	4,4
England	83-97	Stang	2005	1705	4,7	4,2
Switzerland	83-97	Stang	2005	81	4,2	4,0
Italy	83-97	Stang	2005	107	2,9	2,6
Spain	83-97	Stang	2005	99	2,6	1,7

* the table is modified from Stang etal. 2005, Hu et al. 2005, Singh et al. 2003 and Bergman et al.2002.

** Age-stadardized incidence rates (per million person yeras) from Stang et al. 2005 were age adjusted to the world standard population and rates from Hu et al. and Singh et al. were age adjusted to the 2000 and 1970 US standard population respectively; the rates from Hu et al. 2005 are not gender-specific. The rate from Bergman et al.2002 was age adjusted to the Swedish population during the period 1970 to 1974.

*** Non-Hispanic white

latitudinal and quantitative measures of UV-radiation (Gallagher *et al*., 1985; Pane & Hirst, 2000; Schwartz & Weiss, 1988).

There are also some other environmental risk factors reported, such as radio frequency radiation or sun lamp use (Stang *et al*., 2001; Tucker *et al*., 1985). However, consistent associations between uveal melanoma and environmental risk factors have not been established in epidemiological studies.

In the case of occupational risk factors, no strong evidence has been found to date to support their association with uveal melanoma. Although many studies have found some associations between uveal melanoma and welding, military service, farming, cooking or some chemical exposure (Albert *et al*., 1980; Ajani *et al*., 1992; Holly *et al*., 1996; Keller & Howe, 1994), there are also other studies with conflicting results (Holly *et al*., 1996; Pukkala & Notkola, 1997).

1.2.2 Unmodifiable Risk Factors

Potential unmodifiable risk factors for uveal melanoma are age, light skin and light iris colour. Most of them have been reported to be consistently associated with uveal melanoma. They are not risk factors rather risk indicators.

The risk of uveal melanoma increases by age. Its incidence usually peaks at 60-69 years (Mork, 1961; Raivio, 1977; Jensen, 1963). In Sweden, the peak incidence occurred at 65-74 years for females and 75-84 years for males from 1960 to 1998 (Bergman *et al*., 2002). Uveal melanoma is rarely observed among children (Barr *et al*., 1981). Only approximately 1% of uveal melanoma occurs in patients younger than 20 years (Barr *et al*., 1981; Singh *et al*., 2000), most of whom in contrast to adults with uveal melanoma are associated with oculodermal melanocytosis (Singh *et al*., 2000; Verdaguer, 1965).

The incidence of uveal melanoma among non-white populations is reported to be much lower than among white people. In a recent publication, Stang *et al.* reported age-standardized incidence rates of uveal melanoma among five Continents from 1983 to 1997, which included two countries in Asia. The age-standardized incidence in Singapore was 0.3 and 0.1 per PMY for men and women respectively; it was 0.2 per PMY for both men and women in Japan (Osaka) (Stang *et al*., 2005). Another publication, which compared the incidence rate of different racial groups in the U.S. from 1992 to 2000, reported age-standardized incidence rates to be 0.38 per MPY in Asian Americans and 0.31 per MPY in black Americans, which

was substantially lower than in non-Hispanic whites (6.02 per MPY) in the U.S. (Hu *et al*., 2005) (table 1).

Light iris colour has been consistently reported in many studies to be associated with the risk of uveal melanoma (Imesch *et al*., 1997; Saornil, 2004; Toivonen & Kivela, 200; Stang *et al*., 2001). Individuals with blue or gray eyes were observed to have a higher risk with a relative risk of 1.75 (95% CI: 1.31-2.34) as compared with individuals with brown eyes (Weis *et al*., 2006). Scandinavians, most of whom have light-coloured iris, have, out of all white races, a slightly increased risk of developing uveal melanoma (Bergman *et al*., 2002; Stang *et al*., 2005).

Atypical naevi appear to be associated with an increased risk of uveal melanoma depending on their number. However, Egan has argued that there is a weak association between naevi and uveal melanoma (Egan *et al*., 1988). In 1994, Van Hees *et al.* reported an increased odds ratio for 1-2 atypical naevi (OR=2.9; 95% CI: 1.2-6.7) and an even more increased odds ratio for 3 or more naevi (OR=5.3; 95% CI: 1.3-20.0) after adjustment for sex and age (Van Hees *et al*., 1994). Bataille *et al.* found an even stronger association between naevi and uveal melanoma (Bataille *et al*., 1995). In some reports, uveal naevi are also a precursor lesion for uveal melanoma because they may transform into melanoma (Augsburg *et al*., 1989). Tucker *et al.* found that iris naevi, not choroidal naevi, were related to intraocular melanoma (Tucker *et al*., 1985).

Since Silcock's report in 1802 of a London family with three generations suffering from uveal melanoma (also breast cancer or Li-Fraumeni syndrome in some individuals) (Silcock, 1892), more familial series have been described (Singh *et al*., 2005). The occurrence of familial uveal melanoma seems not to be coincidental (Singh *et al*., 1996; Van Hees *et al*., 1998), but suggests that uveal melanoma may develop on a genetic basis. Because uveal melanoma occurs sporadically and familial occurrence is very rare, accounting for only 0.6% of patients with uveal melanoma (Singh *et al*., 1996), little research has been done to establish an association between uveal melanoma and the family history.

The risks of other primary cancers in patients with uveal melanoma have been mentioned in many studies. In a recent study, Bergman *et al.* found elevated odds ratios for cutaneous melanoma (OR=1.75; 95% CI: 0.87-3.12), nervous system cancer (OR=1.49; 95% CI: 0.72-2.74), pancreatic cancer (OR=1.36; 95% CI: 0.74-2.28) and uterine cancer (OR=1.41; 95% CI: 0.68-2.59) (Bergman *et al*., 2006). Turner *et al.* found increased odds ratios for cutaneous melanoma (OR=6.97; 95% CI: 0.24-201.26), breast cancer (OR=1.8; 95% CI: 0.64-22.70 in females), colorectal cancer (OR=1.83; 95% CI: 0.48-6.95), cervix/uterine cancer (OR=3.63;

95% CI: 0.82-16.2) and bladder cancer (OR=3.8; 95% CI: 0.64-22.70) (Turner *et al*., 1989). Other studies evaluated these associations by standardized incidence ratio (SIR). An elevated SIR was found among patients with cutaneous melanoma (SIR=4.6; 95% CI: 2.9-6.8) by Shors *et al*. (Shors *et al*., 2002). Hemminki *et al.* found the same result with a very similar SIR (Hemminki *et al*., 2003). In a Canadian study, prostate cancer (SIR=1.48; 95% CI: 0.18-5.35 in males) and colorectal cancer (SIR=1.48; 95% CI: 0.18-5.35) showed an increased SIR in patients with uveal melanoma (Callejo *et al*., 2004).

However, the risk of uveal melanoma in patients with other previous cancers seems to be inconsistent within studies, cutaneous melanoma being an exception (SIR=1.4; 95% CI: 0.5-3.0 by Shors and OR=1.74; 95% CI: 0.78-3.89 by Bergman) (Bergman *et al*., 2006; Shors *et al*., 2002). In addition, Bergman *et al.* found also increased ORs for uveal melanoma among patients with prostate cancer (OR=1.52; 95% CI: 0.96-2.43), nonmelanoma skin cancer (OR=1.62; 95% CI: 0.76-3.35) and any cancer (OR=1.25; 95% CI: 0.98-1.59) (Bergman *et al*., 2006). Table 2 shows some studies focusing on the association between uveal melanoma and a number of other primary cancers.

There is only one study that examined the association between a family history of cancer and risk of uveal melanoma. In this study, Hemminki and Cheng assessed the family cancer history based on cancer history of parents and siblings and found that the sibling's breast cancer history was associated with an elevated risk for uveal melanoma (SIR=1.76; 95% CI: 1.00-2.87). Analyses based on the parental history of cancer showed that the increased risk of uveal melanoma was correlated to cancers in the site of upper aerodigestive tract (SIR=2.05; 95% CI: 0.97-3.78), left-side colon (SIR=1.83; 95% CI: 0.91-3.29), liver (SIR=1.32; 95% CI: 0.60-2.52), prostate (SIR=1.37; 95% CI: 0.99-1.87) and nervous system (SIR=1.86; 95% CI: 0.89-3.44). The breast cancer history of parents did not show a positive association with the risk of uveal melanoma (Hemminki & Chen, 2006).

1.3 Tumourigenesis and Molecular Genetics of Uveal Melanoma

1.3.1 Melanocyte and Tumourigenesis

Uveal melanoma arises from the mutation of uveal melanocytes, which are pigment-producing cells that can also be found in the skin, hair and some mucosal surfaces. In fact, melanocytes are cells of neural-crest origin and migrate to their target organs at the early stage

Table 2 Studies focussing on the association between eye melanoma and other previous or subsequent primary cancers

Reference	Study design	Setting	Participants	Major findings related to eye melanoma
Bergman et al Invest Ophthalmol Vis Sci 2006	Case-control	Sweden	Swedish Cancer Registry, 2916 uveal melanoma patients and 14577 controls during the period 1960 to 1998	The OR for the risk of previous cancer was 1.25 (95% CI: 0.98-1.59). The risk of subsequent cancers was increased with SIR 1.13 (95% CI: 1.02-1.26). SIR of CM after UM was 1.75 (95% CI: 0.87-3.12)
Travis et al Cancer Res 1996	Cohort	USA	32251 women with ovarian cancer in 9 Cancer Registries during 1935-1972	Increased ratio of ocular melanoma after ovrian cancer (O/E: 4.45) Increased ratio of overall cancer after ovrian cancer (O/E: 1.28)
Osterlind et al Natl Cancer Inst Monogr 1985	Cohort	Denmark	25067 patients diagnosed with cancers (skin melanoma, cancers of brain, thyroid, connective tissue bone and eye) between 1943 and 1980	Patients were no found with increased incidence of second cancer than expected from compararison with the general population
Lischko et al Ophthalmol 1989	Case-control	England	197 cases and 385 RDD controls from England, 337 cases and 800 sibling controls from US	The association of previous malignancies with UM was weak. Only in female (case/RDD), previous cancer history was associated with a higher risk (OR=2.2, 95% CI: 0.97-5.1)
Turner et al Am J Ophthalmol 1989	Case-control	USA	400 uveal melanoma patients between 1984 and 1985, age and sex matching controls from Connecticut Tumor Registry	Gynecologic cancers tended to be more common among female uveal melanoma cases than among the controls. Prevalence of nonbasal cell cancers was over two times greater than the prevalence in controls.
Shors et al Int J Cancer 2002	Cohort	USA	63146 melanoma patients (60466 CM, 2525 UM and 155 conjunctiva)	Patients with UM went on to develop skin melanoma 4.6 times more often than the population at large.

* OR=odds ratio; CI=confidence interval; CM=cutaneous melanoma; UM=uveal melanoma; O=observed prrvalence; E=expected prevalence; RDD=random digit dialing

of fetal development. The uvea is the only site within the eye that contains melanocytes, which contribute to the iris colour. The key factor that determines the colour of the eye is not the number of melanocytes, rather their activity (Hu *et al*., 1995). The pigment that melanocytes synthesize is called melanin, which is an important protective factor for the posterior eye segment with regard to UV radiation and exists in two major forms ─ eumelanin and pheomelanin (Riley, 1997).

Melanocyte-stimulating hormone is a pituitary hormone; melatonin is an indole molecule that originates in the pineal gland. Both of these can affect the growth of melanocytes. The growth of melanocytes and production of melanin is related to these growth factors. Rodeck and Herlyn reported in 1991 that mutated melanocytes can produce growth factors themselves so that they may function in short autocrine loops to stimulate melanoma growth (Rodeck & Herlyn, 1991). Hanahan and Weinberg have also supposed this opinion (Hanahan & Weinberg, 2000). Hanahan and Weinberg deemed that most and perhaps all tumour cells would acquire six essential capabilities during the development of tumour, namely self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis and tissue invasion and metastasis (Hanahan & Weinberg, 2000). These six physiological changes are common in most tumours and elucidate the principles of transforming normal human cells into malignant cancers. The malignant transformation is regarded as a multistep process as genetic factors work in cooperation with external factors, in which genetic alternations seem to drive the mutation more progressively and make the neoplasm more malignant (Hanahan & Weinberg, 2000).

1.3.2 Molecular Genetics

It is currently believed that the molecular bases of tumourigenesis are mutations that produce oncogenes with dominant gain of function and tumour suppressor genes with recessive loss of function (Hanahan & Weinberg, 2000).

Oncogenes were initially recognized during research on viruses that cause mutations of their target cells (Bishop, 1983). These identified genes carried by viruses, are called oncogenes or viral oncogenes. The later findings have proved that most retroviral oncogenes have also cellular counterparts in normal cell functions, which are called proto-oncogenes or cellular oncogenes (Bishop, 1983; Bishop, 1985). The two different types of oncogenes can be

distinguished by using prefixes *c* for cellular (*c-onc*) and *v* for viral (*v-onc*) (Bishop, 1983; Varmus, 1984).

Tumour suppressor genes (TSG) are also called antioncogenes. Their activities converge on a few important cellular regulatory pathways that govern cell growth and homeostasis. One or more of these pathways have already been found to be disrupted in virtually all cancers (Harbour, 1999). The main function of antioncogenes is to regulate cell proliferation and prevent cell from dividing 'out of control' (Knudson, 1971). Once critical mutations of these antioncogenes occur, they are unable to prevent cells from neoplastically transforming. Epidemiological and biological studies have identified one type of mutation of antioncogenes that causes many different primary cancers (table 3). Because prototypic antioncogenes are recessive, they require "two-hit" inactivation of both alleles (Knudson, 1971; Knudson, 1973). In the hereditary case, because the first inactivation already exists in one of the alleles, the second "hit" will be sufficient to induce the occurrence of tumours (Knudson, 1993; Sherr, 2004). This theory explains the reason why higher prevalence of cancer has been observed among persons with a family history of cancer or previous cancer history.

Table 3 shows some selected tumour suppressor genes with their functions and associated neoplasms of the eye. Among them p53 pathway, Rb pathway, BRCA1 and BRCA2 are reported to be associated with uveal melanoma (Knudson, 1993; Harbour, 1999; Singh, 2005; Sherr, 2004).

Antioncogenes BRCA1 and BRCA2 are believed to be involved in many cancers (Struewing *et al*., 1997), especially in familial breast cancer (Antoniou *et al*., 2000; Easton *et al*., 1995; Easton *et al*., 1997; Ford *et al*., 1994; Struewing *et al*., 1997). The normal function of BRCA1/2 genes is to repair DNA. Mutations of BRCA1/2 contribute to the development of uveal melanoma in some reports (Easton *et al*., 1995; Ford *et al*., 1994; Liede *et al*., 2004). The BRCA1 gene was positionally cloned in 1994 (Miki *et al*., 1994) and its mutations confer a 45-87% risk of developing breast cancer and 36-66% risk of developing ovarian cancer in a woman's life time (up to age 70); it is also believed to play a role in colon, lung, pancreas, brain, prostate cancers and melanoma (Antoniou *et al*., 2000; the ABCSG, 2000; Easton *et al*., 1995; Ford *et al*., 1994; Struewing *et al*., 1997).

The BRCA2 was identified in 1995 (Wooster *et al*., 1995). Its mutations can prevent the production of tumour-suppression-proteins and lead to breast, pancreas, prostate cancers and melanoma (the ABCSG, 2000; Easton *et al*., 1997; Struewing *et al*., 1997; the Breast Cancer Linkage Consortium, 1999). In the report of the Breast Cancer Linkage Consortium, the relative risk for all malignant melanoma among the BRCA2 carriers is 2.58 (95% CI: 1.28-

Table 3 Some selected tumor suppressor genes in ophthalmology

Antioncogenes	Chromosome location	Protein function	Neoplasm	
			Familial cancer Association	Other major tumor types
RB	13q14	Arrest cell cycle	Retinoblastoma	Sarcomas, uveal melanoma
TP53	17p13	Detects cellular stresses or DNA damage	Li-Fraumeni Syndrome	more than half of human cancers (uveal melanoma?)
TSC1	9q34	Regulates vesicular trafficking	Tuberous sclerosis	Renal cell carcinoma, angiofibromas
TSC2	16p13	Inhibits GTP-binging proteins rap1A and rab5	Tuberous sclerosis	Renal cell carcinoma, angiofibromas
NF1	17q11	Inhibits *ras* activity	Neurofibromatosis type 1	Sarcomas, gliomas
NF2	22q12	Links cell membrane and cytoskeletal proteins	Neurofibromatosis type 2	Schwannoma
VHL	3p25	E3 ligase recognition factor for HIFα (Inhibits mRNA elongation)	Von Hippel-Lindau Syndrom	Renal cell carcinoma cerebellar hemangiosarcoma
INK4a (P16)	9p21	Cdk inhibitor (RB activation)	Melanoma of skin and eye(?)	Many (brain, lung, leukemias…cancer)
APC	5q21	Regulates ß catenin (Wnt/Wingless signaling)	Familial adenomatous polyposis	Colorectal cancer
BRCA1	17q21	DNA repair	Familial breast and ovarian cancer	Colon, pancreas, brain, prostate cancer skin melanoma
BRCA2	13q12-q13	DNA repair	Familial breast cancer	Prostate and pancreas cancer melanoma of skin and eye

* This table is modified from Knudson 1993, Harbour 1999, Singh 2005, Sherr 2004.

5.17) (the Breast Cancer Linkage Consortium, 1999). The BRCA2 mutations were first documented as a risk factor of uveal melanoma by Easton in 1997 (Easton, 1997). Thereafter, four additional studies have been conducted. The aim of these studies was to identify the risk of uveal melanoma due to BRCA2 germline mutations.

It was found that BRCA2 mutations accounted only for a small proportion of all uveal melanoma patients (Hearle *et al*., 2003; Iscovish *et al*., 2002; Sinilnikova *et al*., 1999; Scott *et al*., 2002). Table 4 summarizes the findings reported in previous studies regarding BRCA1/2 mutations linked to any cancer.

1.4 Clinical Aspects of Uveal Melanoma

1.4.1 Clinical Symptoms and Diagnosis

Uveal melanoma is an intraocular tumour that causes either dead or blindness among patients. It grows rather slowly before it is noticed and usually causes no symptom for many years. Some choroidal melanoma patients may complain about visual blur or field loss (Char *et al*., 1980).

Uveal melanoma is typically diagnosed by ophthalmoscopy, sometimes supplemented by slit lamp biomicroscopy, transocular fine-needle biopsy and ultrasound, and sometimes computer tomography scan (CT), magnetic resonance imaging scan (MRT) and fluorescein angiography (Tang *et al*., 1993). The transocular fine-needle biopsy can enable a cytological verification (Sensitivity: 84-100%; Specificity: 98%) (Shields *et al*., 1993); however, due to high complication rate, it has been reserved for selected cases where the diagnosis has not been established by a less-invasive technique.

1.4.2 Treatment

The treatment choices depend on a number of factors, such as the site of origin, the size and the location of the lesion, the age of the patient, whether extraocular invasion or distant metastasis has occurred (Gragoudas *et al*., 1991). Before radiation therapy was introduced, enucleation, the surgical removal of the eye, was the accepted standard treatment for uveal melanoma. During the past two decades radiation treatment, such as episcleral brachytherapy or external-beam radiation therapy, and charged-particle radiotherapy, has been refined and can destroy the growing tumour cells without causing substantial damage to healthy

Table 4 Studies focussing on the association between BRCA1/2 and some cancers

Reference	Study design	Setting	Participants	Major findings and conclusion
Hearle et al Inves Ophthalmol Vis Sci. 2003	Screen	England	385 uveal melanomas were screened for germline mutation in BRCA2, p16.	Less than 2% patients has BRCA2 mutations. Mutations in other genes contribute to an inherited predisposition to uveal melanoma
Iscovich et al Int J Cancer. 2002	Screen	Isael	153 uveal melanomas were screened for germline mutation BRCA2	The BRCA2 mutation accounts for only a small fraction of all Israeli UM cases.
Liede A, et al. Am J Hum Genet 2002	Case-Control	Pakistan	341 breast cancer cases, 120 ovarian cancer cases, and 200 female controls from two major cities in Pakistan	15 individuals with BRCA1 mutations and 8 individuals with BRCA2 mutations were found in breast cancer cases. 16 individuals with BRCA1 and 3 individuals with BRCA2 mutations were found in ovarian cancer cases. No mutations was found among controls. Overall, 9.1% cases had BRCA1/2 mutation; 74% of them were BRCA1 and 26% of them were BRCA2.
Thompson D, et al. Am J Hum Genet 2001	Screen	Europe North America	68 families from North America and 96 from Europe.	About 10% of male breast cancers were estimated to be associated with BRCA2 mutations.
Wooster, et al. Science. 1994	Linkage Analysis	UK		BRCA2 confers a high risk of breast cancer, but not ovarian cancer
Thompson D, et al J Natl Cancer Inst 2002	Cohort	Europe North America	11847 individuals were tested	BRCA1 mutation was associated with cancers (women: RR=2.3; men: RR=0.95), particularly with pancreas cancer (RR=2.26) cancer of uterine body and cervix (RR=2.65, RR=3.72)
Moslehi R, et al. Am J Hum Genet 2000	Cross-sectional	Israel	213 Jewish women with ovarian cancer and their first degree relatives	In total 86 individuals were found with mutations (57 BRCA1 and 29 BRCA2) in the first degree relatives, The risk of cancers would be increased in male BRCA2 mutations carriers before age of 65 years.
the BCLC J Natl Cancer Inst 1999	Cohort	Europe North America	3728 individuals (681 breast cancer or ovarian cancer, and 3047 unkonwn mutation carriers) were investigated.	Prostate cancer (RR=4.6), pancreas cancer (RR=3.5), melanoma (RR=2.58)

*RR=Relative Risk;

neighbouring tissue (Van Hees *et al*., 2003). Radiation therapy has been shown to be an effective and potentially alternative treatment to prevent tumours from spreading. It has been reported by the Collaborative Ocular Melanoma Study (COMS) that the effect and prognosis of I^{125} brachytherapy does not differ from that of enucleation (the COMS, 1997). However, 85% of the patients treated with I^{125} brachytherapy retained their eye for 5 years or more and 37% of patients treated with I^{125} brachytherapy had better visual acuity 5 years after treatment than patients' treated by irradiation (De Potter *et al*., 1996; Zimmerman *et al*., 1980). Transpupillary thermotherapy destroys small tumours through infrared laser light; photocoagulation burns small tumours with white or laser light; and cryo-therapy destroys small tumours by freezing them. However, enucleation is still the most common choice of therapy for large uveal melanomas (Seregard & Landau, 2001; the COMS, 1998; the COMS, 2001).

1.4.3 Prognosis and Prognostic Factors

Although the treatments mentioned above provide a good control of uveal melanoma, they are not the only prognostic factors. The prognosis of uveal melanoma is affected by the characteristics of uveal melanoma itself, such as tumour location, tumour size, tumour cell type and some cytogenetical factors.

Location

According to the location, uveal melanomas are classified as anterior uveal melanoma (located in the iris) and posterior uveal melanoma (located in the ciliary body or choroid). The ciliary body melanomas have the worst prognosis, whereas iris melanomas have the best (Mooy & de Jong, 1996; McLean *et al*., 1982; Schmittel *et al*., 2004; Seddon *et al*., 1983; Shields *et al*., 2001). The worse prognosis of ciliary body melanomas is not only due to typically late diagnosis and therefore larger size, but also because melanomas in the ciliary body consist of a great proportion of epithelioid cell (Klintworth & Scroggs, 1999; Scholes *et al*., 2003), which is regarded as a cellular type with the worst prognosis of uveal melanoma (Klintworth & Scroggs, 1999; McLean *et al*., 1995).

Cellular Type

The cellular types of uveal melanoma were first described by Callendar in 1931 (Callendar, 1931), modified by some pathologists in the Armed Forces Institute of Pathology in 1983 (McLean *et al*., 1983) and most recently revised by Grossniklaus and Green in 1994 into four distinct cellular types (Grossniklaus & Green, 1994). They are spindle A cells (spindle-shaped cells with slender nuclei and lacking distinct nucleoli), spindle B cells (spindle-shaped cells with larger nuclei and clear nucleoli), epithelioid cells (larger polygonal cells with one or more noticeable nucleoli) and intermediate cells (similar but smaller than epithelioid cells). Spindle A cell melanomas carry the best prognosis whereas epithelioid cell melanomas have the worst (Klintwoth & Scroggs, 1999; McLean, 1995).

Tumour Size

Tumour size is one of the most important predictors of survival and its classification is based on measurements of largest basal diameter (LBD) and apical tumour height (ATH). Occasionally LBD is also referred to as LTD (largest basal tumour diameter). Uveal melanomas are classified as small (1 <= ATH <= 3 mm and 16> LBD >= 5 mm), medium (3 < ATH <= 10 mm and LBD< 16 mm) and large (ATH > 10 mm and LBD >= 16 mm) (the COMS, 1998; Diener-West *et al*., 2001).

Many studies have shown that the greater the tumour size, the worse the prognosis (Diener-West *et al*., 1992; Hayton *et al*., 1989; McLean *et al*., 1982; Singh *et al*., 2001; Seregard & Kock, 1995; Seddon *et al*., 1983). In the Collaborative Ocular Melanoma Study, Diener-West *et al*. estimated a 5-year-all-cause-mortality of 16% for a small size choroidal melanoma, 32% for medium size choroidal melanoma and 53% for choroidal melanoma of large size (Diener-West *et al*., 1992).

Cytogenetical Factors

Some cytogenetical factors have been associated with a poor outcome of uveal melanoma. A frequently studied chromosomal abnormality in uveal melanoma is the deletion of chromosome 3 (monosomy 3) (Hoesman *et al*., 1990; Prescher *et al*., 1990; Prescher *et al*., 1996; Singh *et al*., 1994; Sisley *et al*., 1993), which is an important cytogenetical predictor of survival and is associated with metastasis. After adjustment for prognostic factors, the relative

risk of dying due to uveal melanoma is 4 for UM patients with monosomy 3 as compared with those without monosomy 3 (Sandinha *et al*., 2004). Another gene defect associated with worse prognosis is abnormality of chromosome 8, which involves amplifications or an extra copy of chromosome 8, or isochromosome 8q (replacement of short arms by long arms) (Sisley *et al*., 1997). These abnormalities are associated with large tumour size and aggressive histology (Sisley *et al*., 2000).

Some other findings include chromosome 1 changes and chromosome 6 gains. Chromosome 1 changes seem to be associated with worse prognosis (Aalto *et al*., 2000) whereas chromosome 6 gains on the short arm seem to have a protective effect associated with a better prognosis (White *et al*., 1998).

Metastasis

Metastasis of uveal melanoma is difficult to be detected. Less than 3% of patients can be found with evidence of metastasis at the time of diagnosis (Damato, 2004; Pach & Robert, 1986). In fact, metastases can occur several years before diagnosis (Eskelin *et al*., 2000; Singh, 2001; Singh *et al*., 2004). UM cells spread through blood (hematogenous spread) and most often produce liver metastases (Rietschel *et al*., 2005; the COMS, 2001). Cervical lymph node metastases were reported to occur in 6.5% of all uveal melanomas within 15 years after diagnosis (Tojo *et al*., 1995).

The metastasis of uveal melanoma is the leading cause of death of UM patients (Kujala *et al*., 2003). The relative 5-year survival rates were about 70% between 1960 and 1998 in Sweden (Bergman *et al*., 2003) and ranged from 77% to 82% between 1973 and 1993 in the United States (Singh & Topham, 2003). The relative 10-year survival rates were undetermined due to imprecise estimates in both studies (Bergman *et al*., 2003; Singh & Topham, 2003).

2. Objective

As the aetiology of uveal melanoma remains largely unknown, a study to investigate potential risk factors for uveal melanoma is essential. The present report aims to study the association of uveal melanoma with own history and family history of cancer. Based on a review of the literature, the following hypotheses are studied:

- Whether an own cancer history of selected types (any cancer, breast cancer (Silcock, 1892; Turner *et al*., 1989), renal cancer (Scelo *et al*., 2006), cutaneous melanoma (Hemminki *et al*., 2003; Shors *et al*., 2002), prostate cancer (Bergman *et al*., 2006; Scelo *et al*., 2006), colorectal cancer (Callejo *et al*., 2004; Turner *et al*., 1989), BRCA1-related cancers (Antoniou *et al*., 2000; the ABCSG, 2000; Easton *et al*., 1995; Ford *et al*., 1994; Struewing *et al*., 1997) and BRCA2-related cancers (the ABCSG, 2000; Easton *et al*., 1997; Struewing *et al*., 1997; the BCLC, 1999)) is associated with the risk of uveal melanoma
- Whether a family history of selected types (any cancer, breast, renal, prostate, colorectal cancer or cutaneous melanoma (Hemminki & Chen, 2006), BRCA1-related cancers (Antoniou *et al*., 2000; the ABCSG, 2000; Easton *et al*., 1995; Ford *et al*., 1994; Struewing *et al*., 1997) and BRCA2-related cancers (the ABCSG, 2000; Easton *et al*., 1997; Struewing *et al*., 1997; the BCLC, 1999)) is associated with the risk of uveal melanoma

3 Materials and Methods

3.1 Case Recruitment

The present study is a matched case-control study with incidence density sampling and was carried out by an epidemiological working group led by Prof. Stang at the University of Essen from Feb. 2002 to Mar. 2005 in Germany. The hospital-based recruitment of cases was carried out in the Department of Ophthalmology, University of Duisburg-Essen, which is a referral centre for eye cancer in Germany and yearly treats approximately 400-500 patients with ocular neoplasms from all over Germany and other countries (Schmidt-Pokrzywniak *et al.*, 2004).

The following types of eye melanomas (International Statistical Classification of Diseases and Related Health Problems, 10th Revision) were included as intraocular melanoma: topography codes C69.3, C69.4 and C69.9 for sites of melanoma in the choroids, iris, ciliary body and unspecific location of the eyes respectively. Eligible cases of uveal melanoma had to fulfill the following five requirements (Schmidt-Pokrzywniak *et al.*, 2004).

- The cases must be new patients diagnosed as primary melanoma located in the choroid, iris, and /or ciliary body.
- The date of the diagnosis must be during the recruitment period from Sep. 25th 2002 to Sep. 24th 2004.
- The cases must be in a range of 20-74 years at the time of diagnosis.
- The cases must be living in Germany.
- The cases must be able to complete an interview in the German language.

A definite diagnosis of uveal melanoma in this study was determined by the unambiguous results of clinical examination of the eye (ophthalmoscopy) and ultrasound (or fluorescence angiography, computer tomography or magnetic resonance imaging). The sensitivity of the diagnosis on uveal melanoma in this referral centre is reported to be satisfactory (Stang *et al.*, 2001). During the recruitment period, an overall total of 486 eligible cases were identified in the referral centre and 455 cases participated in the study.

3.2 Control Recruitment

The recruitment of controls was based on the population of Germany. The controls were matched individually to cases by sex, age and region of residence (Schmidt-Pokrzywniak *et al.*, 2004). Eligible controls were randomly sampled from mandatory lists of residence that cover the residential population of Germany. They were required to be the same gender as the case and their age had to be within the same 5-year age band compared to the age at diagnosis of cases and they were recruited from the population in a city of comparable size within a radius of 60 km around the case's place of residence. The controls were required to have no medical history of uveal melanoma and to be capable of completing the interview in the German language. They are referred to as "population controls".

To improve the statistical power, two controls were recruited per case (Schmidt-Pokrzywniak *et al.*, 2004) and a total of 972 controls were required accordingly to this matching ratio (2:1). In previous studies, the control response proportions in population-based studies in Germany have been always about 60% (36-74%) (Stang *et al.*, 1999). In this regard, the study design required 1527 eligible controls to receive the questionnaire via post.

3.3 Data Collection

Computer-assisted telephone interviews were conducted by trained interviewers in this study and included questions concerning demographic characteristics, own cancer history, family history of cancer and so on. Only invasive cancers were included into the own and family history of cancer. The own cancer history and family cancer history were reported by participants and were classified by ICD-10 according to the site of cancers. During the recruitment period, interviewers were regularly monitored and received regular training courses after the initial training course for them.

3.4 Sample Size Calculation

Sample size calculation of the study was driven by the formula suggested by Woodward in 1992 (Wooster, 1992). The type I error (α) was set to be 5% and the type II error was set to be 10%. A two-sided hypothesis was assumed.

However, the study was basically planned to answer the question whether the use of mobile phones is associated with an increased risk of uveal melanoma. In the present report, the exposure prevalence is not related to mobile phone usage, but related to the own cancer history or family cancer history. The statistical power has differed from cancer to cancer because of their varying prevalence. According to the table by Schmidt-Pokrzywniak *et al.* (Schmidt-Pokrzywniak *et al.*, 2004), the statistical power will be 90% if the exposure prevalence and odds ratios are 0.05 and 2.0 respectively, or 0.1 and 1.7 respectively, or 0.2 and 1.5 respectively, and so on.

3.5 Exposure Assessment

Demographic Factors

In the present report, most of the demographic factors are the matching factors. To explore effect modification by age, age was divided into two groups: 1 = "older than 59 years" and 0 = "not older than 59 years". Sex has two categories: 1 = "female" and 2 = "male".
Family size is the number of all family members including parents, siblings, children and the index person. It is used to adjust the effect estimates of family cancer history and divided into 4 categories: 1 = "3 or 4 family members", 2 = "5 or 6 family members", 3 = "7 or 8 family members" and 4 = "more than 8 family members".

Self-reported Family Cancer History and Own Previous Cancer History

All of the independent variables about self-reported cancer history are binary variables with two categories (yes and no) and the category "no" is the reference group. A self-reported history of uveal melanoma was excluded because some cases reported their current diagnosis.
The cancers of interest were classified into 25 groups containing upper aerodigestive tract cancers (C00-C14 & C32), upper digestive organ cancers (C15-C17), colorectal cancers (C18-C20 & C26), cancers of liver-biliary system (C22-C24), pancreas cancer (C25), lung cancer (C34), cancers of bone and articular cartilage (C40-C41 & C49), skin cancer (C43 & C44), cutaneous melanoma (C43), nonmelanoma skin cancer (C44), breast cancer (C50), cancers of female genital organ except ovary (C51, C53, C55 & C57), ovarian cancer (C56), prostate cancer (C61), testicular cancer (C62), cancers of urinary system (C64-C68), cancers of nervous system (C70 & C71), cancer of thyroid (C73), cancers of ill-defined sites (C76-C80),

lymphoid and haematopoietic cancers (C81-C96), cancers of multiple sites (C97), BRCA1-related cancers (C18-C20, C25, C26, C34, C43, C50, C56, C61, C70 & C71) and BRCA2-related cancers (C25, C43, C50 & C61). Table 5 shows all cancers or cancer groups assessed in the study as based on self-reported own and family history cancer.

Cancers known to be related to BRCA1 mutations include breast cancer (C50), pancreatic cancer (C25), ovarian cancer (C56), colorectal cancers (C26, C18-C20), lung cancer (C34), nervous system cancers (C70-C71), prostate cancer (C61), and cutaneous melanoma (C43) (Antoniou *et al*., 2000; the ABCSG, 2000; Easton *et al*., 1995; Ford *et al*., 1994; Struewing *et al*., 1997).

Cancers related to BRCA2 mutations include breast cancer (C50), pancreatic cancer (C25), prostate cancer (C61), and cutaneous melanoma (C43) (the ABCSG, 2000; Easton *et al*., 1997; Struewing *et al*., 1997; the BCLC, 1999). Although it was proposed that colon cancer was related to BRCA2 mutations, later studies that attempted to establish an association between them have found no relevant association (Lieder *et al*., 2004; the BCLC, 1999; Niell *et al*., 2004).

The cancers were identified for both own cancer history and family cancer history. To obtain a further estimate of the risk related to family cancer history, histories were categorized according to the relationship. From this point of view, there are overall four types of family cancer histories and they are i) family cancer history of parents, ii) siblings, iii) parents and siblings and iv) all first-degree relatives. The effect of cancer history among different relations of family members has been analyzed independently and compared with each other in this study.

3.6 Statistical Methods

Conditional logistic regression accounting for the matching factors gender, age and region was used to calculate odds ratios. Due to the incidence density sampling of controls, the odds ratio estimates the incidence rate ratio (IRR). 95% confidence intervals are given as a measure of statistical precision of the effect estimates. For the comparison of the precision of effect estimates, confidence limit ratios (CLR) were used to quantify the precision of effect estimates in this study.

To adjust the effect estimates of family cancer history, family size would be taken into account as a covariate. All data were analyzed using the statistical software SAS for windows version 9.1.

Table 5. Definition and ICD 10 code of cancers assessed in the RIFA study

Cancer name	Definition	ICD 10 code
Cancer of upper aerodigestive tract	malignant neoplasms of lip, oral cavity, pharynx and larynx	C00-C14 and C32
Cancers of digestive tract	malignant neoplasms of oesophagus, stomach	C15-C17
Colorectal cancer	malignant neoplasms of colon, rectum, rectosigmoid junction and ill-defined digestive organs	C18-C20 and C26
Cancer of liver-biliary system	malignant neoplasms of liver, gallbladder and biliary tract	C22 -C24
Pancreas cancer	malignant melanoma of pancreas	C25
Lung cancer	malignant neoplasm of lung and bronchus	C34
Cancer of bone and articular cartilage	malignant neoplasms of bone, articular cartilage and some connective and soft tissue	C40-C41 and C49
Skin cancer	melanoma and other malignant neoplasm of skin	C43 and C44
Cutaneous melanoma	malignant melanoma of skin	C43
Nonmelanoma skin cancer	other nonmelanoma skin cancer	C44
Breast cancer	malignant neoplasm of breast and connective tissue of breast (exclude skin of breast)	C50
Female genital organ cancer	malignant neoplasms of female genital organs except ovary	C51, C53, C55 and C57
Ovarian cancer	malignant neoplasm of ovary	C56
Prostate cancer	malignant neoplasm of prostate	C61
Testicular cancer	malignant neoplasm of testis	C62
Urinary tract cancer	malignant neoplasm of urinary tract	C64-C68
Uveal melanoma	malignant melanoma of uveal tract	C69
Cancer of the nervous system	malignant neoplasms of brain and meninges	C70 and C71
Cancer of the thyroid	malignant neoplasm of thyroid	C73
Cancer of ill-defined sites	malignant neoplasms of ill-defined, secondary and unspecified sites	C76-C80
Lymphoid, haematopoietic cancer	malignant neoplasms, stated to be primary, of lymphoid, haematopoietic and related tissue	C81-C96
Cancer of multiple sites	malignant neoplasms of independent (primary) multiple sites	C97
BRCA2 Group	breast, pancreas, prostate cancer and skin melanoma	C25, C50, C61, C43
BRCA1 Group	breast, pancreas, colorectal, ovarian, lung, prostate and nervous system cancer, skin melanoma	C25, C50, C56, C34, C61 C43,C70-C71,C18-C20,C26

4. Results

A total number of 1282 participants have been interviewed, including 455 cases and 827 population controls from thirteen Federal States of Germany. The response proportion was 94% among cases and 55% among population controls.

4.1 Own Previous Cancer History

The risk of uveal melanoma after diagnosis of another cancer was increased by 30% (OR=1.3; 95% CI: 0.9-2.0; CLR=2.2). The risk of UM after diagnosis of renal cancer could not be estimated because of zero exposed controls. Patients who reported a previous cutaneous melanoma history had an increased risk of 70% (OR=1.7; 95% CI: 0.3-10.2; CLR=34). An elevated risk was observed for patients who reported a previous colorectal cancer (OR=1.4; 95% CI: 0.5-4.2; CLR=8.4). There was no association between UM and own history of BRCA1/2-related cancers. The increased odds ratios were also observed among participants who reported a previous cancer of the skin (nonmelanoma), thyroid, bladder or lymphoid and haematopoietic tissue (**table 6**).

The risk of UM after diagnosis of another cancer was not elevated among men, nor was any increased risk observed after diagnosis of prostate cancer, renal cancer, skin melanoma or BRCA1/2-related cancers. The risk of UM after diagnosis of bladder cancer was increased by 90% (OR=1.9; 95% CI: 0.3-13.8; CLR=46) among men (**table 7**).

Table 8 presents the odds ratios of own cancer history among women. The risk of UM after diagnosis of another cancer was increased by 90% (OR=1.9; 95% CI: 1.1-3.2; CLR=2.9), and the risk after a history of colorectal cancer was increased by 70% (OR=1.7; 95% CI: 0.3-9.1; CLR=30.3). There was no marked risk increase for UM among women with a history of breast cancer (OR=0.6; 95% CI: 0.2-1.7). The risk of UM after diagnosis of skin melanoma or renal cancer was not estimated. However, women with an own history of nonmelanoma skin cancer were found to be at elevated risk for UM (OR=5.5; 95% CI: 1.1-27.5; CLR=25), as were those with an own history of skin cancer (including melanoma and nonmelanoma). Increased odds ratios were observed among women with a previous cancer of the ovary, thyroid, lymphoid and haematopoietic tissue.

Table 6. Distribution of own history of any cancer except uveal melanoma and matched OR*

Cancer and ICD10 code		Cases N=455		Population controls N=827		OR (95% CI)
		N	%	N	%	
Any cancer except UM						
	Yes	49	10,8	69	8,3	1.3 (0.9, 2.0)
	No	406	89,2	758	91,7	1,0
Colorectal cancer (C18-C20, C26)						
	Yes	6	1,3	8	1,0	1.4 (0.5, 4.2)
	No	449	98,7	819	99,0	1,0
Skin cancer (C43, C44)						
	Yes	10	2,2	9	1,1	2.2 (0.9, 5.4)
	No	445	97,8	818	98,9	1,0
Skin melanoma (C43)						
	Yes	2	0,4	3	0,4	1.7 (0.3, 10.2)
	No	453	99,6	824	99,6	1,0
Nomelanoma skin cancer (C44)						
	Yes	7	1,5	6	0,7	2.0 (0.7, 6.3)
	No	448	98,5	821	99,3	1,0
Breast cancer** (C50)						
	Yes	6	2,8	17	4,6	0.6 (0.2, 1.7)
	No	208	97,2	356	95,4	1,0
Female genital organ cancer** (C51,C53,C55,C57)						
	Yes	5	2,3	7	1,9	1.2 (0.4, 4.1)
	No	209	97,7	366	98,1	1,0
Ovarian cancer** (C56)						
	Yes	1	0,5	1	0,3	2.4 (0.2, 39.7)
	No	213	99,5	372	99,7	1,0
Prostate cancer** (C61)						
	Yes	3	1,2	12	2,6	0.5 (0.1, 1.7)
	No	238	98,8	442	97,4	1,0
Renal cancer (C64,C65)						
	Yes	1	0,2	0	0,0	+∞
	No	454	99,8	827	100,0	1,0
Bladder cancer (C67)						
	Yes	3	0,7	2	0,2	3.1 (0.5, 19.3)
	No	452	99,3	825	99,8	1,0
Cancer of thyroid (C73)						
	Yes	2	0,4	2	0,2	1.7 (0.2, 12.2)
	No	453	99,6	825	99,8	1,0
Cancers of ill-defined, unspecified sites (C76-C80)						
	Yes	4	0,9	7	0,8	1.2 (0.4, 4.3)
	No	451	99,1	820	99,2	1,0
Lymphoid, haematopoietic tissue cancer (C81-C96)						
	Yes	6	1,3	1	0,1	9.9 (1.2, 85.1)
	No	449	98,7	826	99,9	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	20	4,4	42	5,1	0.9 (0.5, 1.6)
	No	435	95,6	785	94,9	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	11	2,4	32	3,9	0.6 (0.3, 1.3)
	No	444	97,6	795	96,1	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account;**These cancers are only estimated among participants of related gender respectively.
*** The cancers with zero exposed subjects are not shown.

Table 9 shows the risk of UM after an own history of cancer among participants aged 60 years or more. No increased risk of UM was observed after an own history of overall, breast, renal, colorectal, prostate, BRCA1/2-related cancer or cutaneous melanoma.

Among those participants under the age of 60 years, the risk of UM after diagnosis of another cancer was increased 2.3-fold (OR=2.3; 95% CI: 1.1-4.8; CLR=4.3). Subjects who reported a BRCA1/2-related cancer history had an increased odds ratios of 2.6 (95% CI: 0.7-10.0) and 2.4 (95% CI: 0.5-12.2) respectively. Increased OR were also observed among patients with previous cutaneous melanomas or colorectal cancers. However, participants having previously suffered renal, breast or prostate cancer were not found to have an increased OR for UM. An own history of bladder or skin cancer (including melanoma and nonmelanoma) was found to have an increased OR (**table 10**).

4.2 Family Cancer History

The risk of UM was increased by 30% when one of the first-degree relatives was reported with any cancer (OR=1.3; 95% CI: 1.0-1.6; CLR=1.6). Those who reported a family history of renal, breast, prostate, BRCA2-related cancer or skin melanoma were found to have increased odds ratios of 1.5, 1.3, 1.8 or 1.5 respectively. Family histories of colorectal and BRCA1-related cancers were not observed with any increase in odds ratios. The risk of UM was increased by a factor of 2.0 and 3.4 among people who reported a family history of pancreatic cancer (OR=2.0; 95% CI: 0.8-4.7; CLR=5.9), bone and articular cartilage cancer (OR=3.4; 95% CI: 1.0-11.6; CLR=11.6) respectively. Patients with a family history of cancers in the testis, nervous system, unspecified sites or lymphoid and haematopoietic tissue had increased odds ratios of 1.4 (95% CI: 0.4-5.1; CLR=12.7), 1.7 (95% CI: 0.6-4.5), 1.9 (95% CI: 1.1-3.3) and 1.7 (95% CI: 0.9-3.2) respectively (**table 11)**.

Males with any family history of cancers were found to be at an increased risk of UM (OR=1.4; 95% CI: 1.0-2.0; CLR=2.0). Family histories of breast or BRCA1-related cancers were observed with increased odds ratios of 1.9 and 1.3 respectively. Males with a family history of renal or colorectal cancers were not observed with any increased odds ratios. The risk of UM was increased when one of the first-degree relatives was reported with BRCA2-related cancers (OR=2.2; 95% CI: 1.3-3.7; CLR=2.8), prostate cancer (OR=2.3; 95% CI: 0.8-6.3; CLR=7.9), nervous system cancers (OR=2.3; 95% CI: 0.8-7.1; CLR=8.8) and pancreatic cancer (OR=2.5; 95% CI: 0.7-9.4; CLR=13.4). The risk of UM was found to be increased

among males with a family history of nonmelanoma skin cancer or unspecified site cancers (**table 12).**

Among females, any family history of cancer was not observed with increased OR but, the risk of UM was increased by 40%, 90% and 90% when one of the first-degree relatives was reported with prostate cancer (OR=1.4; 95% CI: 0.5-3.7; CLR=7.4), renal cancer (OR=1.9; 95% CI: 0.5-6.8; CLR=13.6) or skin melanoma (OR=1.9; 95% CI: 0.3-11.8; CLR=39.3) respectively. The risk of UM was not observed to be increased among females with a family history of breast, colorectal or BRCA1/2-related cancers. Females with a family history of pancreas or lymphoid and haematopoietic tissue cancer had increased odds ratios of 1.6 (95% CI: 0.5-5.1) and 2.6 (95% CI: 1.1-6.3) respectively (**table 13**).

Table 14 presents the odds ratios of family cancer history among participants aged 60 years or more. Any family history of cancer was observed to increase the risk of UM by up to 40% (OR=1.4; 95% CI: 1.0-1.9; CLR=1.9) among these participants. The patients with family history of breast, prostate, BRCA2-related cancers or skin melanoma had an elevated odds ratio of 1.5 (95% CI: 0.9-2.6; CLR=2.9), 2.8 (95% CI: 1.1-7.2; CLR=6.5), 1.9 (95% CI: 1.2-3.1; CLR=2.6) and 5.6 (95% CI: 0.5-57.3; CLR=114.6) respectively. The risk of UM was not found to be increased among these participants with a family history of renal or colorectal cancers. An increased risk of UM was observed among participants with a family history of cancer of the bone and articular cartilage or lymphoid and haematopoietic tissue.

Among the participants younger than 60 years, no risk of UM was observed when one of the first-degree relatives was reported with any history of cancer. Family histories of renal, nervous system cancers and nonmelanoma skin cancer were observed with increased odds ratios of 2.9 (95% CI: 0.8-10.4; CLR=13), 3.6 (95% CI: 0.6-21.0; CLR=35) and 2.6 (95% CI: 0.6-11.4; CLR=19) respectively (**table 15**).

Table 16 presents the effect estimates of family history of cancer among the males aged 60 years or more. The risk of UM was increased by 80% (OR=1.8; 95% CI: 1.1-2.7; CLR=2.5) when one of the first-degree relatives was reported with any cancer. The family histories of breast, prostate or BRCA1/2-related cancers were observed with increased odds ratios of 2.3 (95% CI: 1.0-5.1), 4.8 (95% CI: 1.2-19.2; CLR=16), 1.5 (95% CI: 0.9-2.5; CLR=2.8) and 3.0 (95% CI: 1.5-5.9; CLR=4.0) respectively. Increased odds ratios were observed among those with a family history of cancer of the liver-biliary system or unspecific sites.

In general, the risk of UM was not observed to be increased among male participants under the age of 60 years with a family history of cancer. Family history of renal or pancreas cancer however was an exception and showed elevated OR of 2.1 (95% CI: 0.4-10.6; CLR=26.5) and

Table 11 Distribution of any family cancer history of all first degree relatives and matched OR

Cancer and ICD10 code		Cases N=455		Population controls N=827		OR (95% CI)
		N	%	N	%	
Any cancer						
	Yes	192	42,2	306	37,0	1.3 (1.0, 1.6)
	No	259	56,9	514	62,2	1,0
Cancer of upper aerodigestive tract (C00-C14 & C32)						
	Yes	3	0,7	5	0,6	0.9 (0.2, 4.1)
	No	448	98,5	815	98,5	1,0
Upper digestive tract cancer (C15-C17)						
	Yes	21	4,6	37	4,5	0.8 (0.5, 1.2)
	No	430	94,5	783	94,7	1,0
Colorectal cancer (C18-C20,C26)						
	Yes	23	5,1	55	6,7	0.7 (0.4, 1.2)
	No	428	94,1	765	92,5	1,0
Cancer of liver-biliary system (C22-C24)						
	Yes	9	2,0	17	2,1	0.8 (0.4, 1.8)
	No	442	97,1	803	97,1	1,0
Pancreatic cancer (C25)						
	Yes	14	3,1	14	1,7	2.0 (0.8, 4.7)
	No	437	96,0	806	97,5	1,0
Lung cancer (C34)						
	Yes	22	4,8	57	6,9	0.7 (0.4, 1.2)
	No	429	94,3	763	92,3	1,0
Cancer of bone and articular cartilage (C40-C41, C49)						
	Yes	8	1,8	4	0,5	3.4 (1.0, 11.6)
	No	443	97,4	816	98,7	1,0
Skin cancer (C43, C44)						
	Yes	13	2,9	13	1,6	1.7 (0.8, 3.8)
	No	438	96,3	807	97,6	1,0
Skin melanoma (C43)						
	Yes	4	0,9	3	0,4	2.2 (0.5, 10.3)
	No	447	98,2	817	98,8	1,0
Nomelanoma skin cancer (C44)						
	Yes	7	1,5	6	0,7	1.8 (0.6, 5.5)
	No	444	97,6	814	98,4	1,0
Breast cancer (C50)						
	Yes	39	8,6	55	6,7	1.3 (0.8, 2.1)
	No	412	90,5	765	92,5	1,0
Female genital organ cancer** (C51,C53,C55,C57)						
	Yes	19	4,2	34	4,1	0.9 (0.5, 1.7)
	No	432	94,9	784	94,8	1,0
Ovarian cancer (C56)						
	Yes	1	0,2	1	0,1	1.7 (0.1, 30.8)
	No	450	98,9	819	99,0	1,0
Prostate cancer (C61)						
	Yes	16	3,5	20	2,4	1.8 (0.9, 3.6)
	No	435	95,6	800	96,7	1,0
Testicular cancer (C62)						
	Yes	5	1,1	5	0,6	1.4 (0.4, 5.1)
	No	446	98,0	815	98,5	1,0
Renal cancer (C64-C65)						
	Yes	9	2,0	12	1,5	1.5 (0.6, 3.6)
	No	442	97,1	808	97,7	1,0
Bladder cancer (C67)						
	Yes	5	1,1	9	1,1	0.8 (0.3, 2.5)
	No	450	98,9	811	98,1	1,0
Nervous system cancer (C70, C71)						
	Yes	8	1,8	9	1,1	1.7 (0.6, 4.5)
	No	443	97,4	811	98,1	1,0
Cancer of thyroid (C73)						
	Yes	1	0,2	3	0,4	0.5 (0.0, 5.0)
	No	450	98,9	817	98,8	1,0
Cancers of ill-defined, unspecified sites (C76-C80)						
	Yes	27	5,9	28	3,4	1.9 (1.1, 3.3)
	No	424	93,2	792	95,8	1,0
Lymphoid, haematopoietic tissue cancer (C81-C96)						
	Yes	19	4,2	26	3,1	1.7 (0.9, 3.2)
	No	432	94,9	794	96,0	1,0
Cancers of independent multiple sites (C97)						
	Yes	1	0,2	1	0,1	3.0 (0.2, 48.0)
	No	450	98,9	819	99,0	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	107	23,5	189	22,9	1.0 (0.8, 1.4)
	No	344	75,6	631	76,3	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	67	14,7	86	10,4	1.5 (1.1, 2.2)
	No	384	84,4	734	88,8	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account; **excluding ovarian cancer;
*** The missing values (4 cases and 7 controls) are not shown in table.

2.3 (95% CI: 0.4-14.9; CLR=37.2) respectively (**table 17**).

Table 18 presents the odds ratios of family cancer history among females aged 60 years or more. The risk of UM was not observed among the participants with a family history of cancer, nor was it observed for women with a family history of renal, breast, prostate, colorectal, BRCA1/2-related cancers or skin melanoma. Family history of cancer of the pancreas, unspecific sites or lymphoid and haematopoietic tissue showed increased odds ratios of 3.6 (95% CI: 0.6-20.8; CLR=34.7), 2.4 (95% CI: 0.9-6.4; CLR=7.1) and 3.3 (95% CI: 1.0-11.4) respectively.

Table 19 presents the effect estimates of family cancer history among younger females aged <60 years. No risk of UM was observed among the participants with a family history of any cancer, nor was it observed for women with a family history of breast, prostate, colorectal, BRCA1/2-related cancers or skin melanoma. The risk of UM was increased when an index person reported a family history of cancer of the kidney (OR=5.0; 95% CI: 0.5-50.0; CLR=100), skin (nonmelanoma) (OR=3.6; 95% CI: 0.6-21.0; CLR=35), lymphoid and haematopoietic tissue (OR=2.1; 95% CI: 0.6-7.3; CLR=12.2).

Table 20 presents the odds ratios of family cancer histories adjusted by family size. Family size has virtually no effect on the risk of uveal melanoma with the OR of approximately 1.0. The adjusted odds ratios of any cancer were similar to the unadjusted odds ratios.

Table 21 presents the effect estimates of family cancer history by four different definitions of a positive family history. The risk of UM was identical when any family cancer history was reported from the sources of parents or siblings, so was the risk for index persons with a family history of breast, prostate, BRCA2-related, testis, bone and articular cartilage or lymphoid and haematopoietic tissue cancers. The increased risk of UM was observed among persons with a family history of skin cancer (both for skin melanoma and nonmelanoma skin cancer). The effect of family history of skin cancer appears to be linked to the siblings' history of cancer. The association between UM and a family history of pancreatic, nervous system, unspecific sites or multiple sites cancers appears to be attributed to the parents' history of cancer.

The stratified analysis by gender is presented in **table 22** and **23**. Among males, the effects of a family history of any cancer, particularly of breast, nervous system, testicular, BRCA2-related and liver-biliary system cancers were found to be similar between the family history of parents and siblings. The contribution of a family history of skin cancer (both for skin melanoma and nonmelanoma skin cancer) seems to be owed to siblings' history of cancer. A

history of pancreatic, nervous system, unspecific sites or multiple sites cancers among the parents was found to occur consistently with UM (**table 22**).

Among females, the effects of a history of pancreatic, prostate, renal, bone, articular cartilage or unspecific sites cancers among parents was found to occur consistently with UM. The risk of UM was increased by 70% among females who reported a family cancer history among the parents. No risk of UM was observed among females with family cancer history among her siblings. The risks of UM due to family history of lymphoid and haematopoietic tissue cancers were not observed to vary between the family history of parents and siblings (**table 23**).

Table 21. Estimated OR* for family cancer histories by different definition of a positive family history

Cancer and ICD10 code	Family history							
	All 1st degree relatives		Parents +Sibling		Sibling only		Parents only	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Any cancer	1,3	1.0-1.5	1,3	1.0-1.7	1,3	0.9-1.9	1,3	1.0-1.7
Cancer of upper aerodigestive tract (C00-C14, C32)	0,9	0.2-4.1	0,9	0.2-4.1	2,2	0.3-16.8	0,4	0.0-3.8
Some digestive tract cancer (C15-C17)	0,8	0.5-1.2	1,1	0.6-2.0	0,7	0.2-2.7	1,3	0.7-2.4
Colorectal cancer (C18-C20, C26)	0,7	0.4-1.2	0,7	0.4-1.1	0,5	0.2-1.5	0,7	0.4-1.3
Cancer of liver-biliary system (C22-C24)	0,8	0.4-1.8	0,8	0.3-1.9	0,6	0.1-3.1	0,9	0.3-2.5
Pancreatic cancer (C25)	2,0	0.8-4.7	2,0	0.8-4.7	0,2	0.0-1.7	3,3	1.3-8.5
Lung cancer (C34)	0,7	0.4-1.2	0,7	0.4-1.2	1,3	0.6-3.6	0,5	0.3-1.0
Cancer of bone and articular cartilage (C40-C41, C49)	3,4	1.0-11.6	3,4	1.0-11.6	3,8	0.3-43.7	3,2	0.8-13.5
Skin cancer (C43, C44)	1,7	0.8-3.8	2,0	0.9-4.7	6,5	1.3-33.0	1,1	0.4-3.3
Skin Melanoma (C43)	2,2	0.5-10.3	3,0	0.5-19.0	+∞		0,7	0.1-8.0
Nonmelanoma Skin Cancer (C44)	1,8	0.6-5.5	2,3	0.7-7.4	3,0	0.3-35.8	2,1	0.5-8.1
Breast cancer (C50)	1,3	0.8-2.1	1,3	0.8-2.1	1,4	0.7-2.7	1,3	0.7-2.3
Female genital organ cancer** (C51,C53,C55,C57)	0,9	0.5-1.7	0,9	0.5-1.7	0,8	0.2-3.0	1,1	0.6-2.1
Ovarian cancer (C56)	1,7	0.1-30.8	1,7	0.1-30.8	+∞		0,0	
Prostate cancer (C61)	1,8	0.9-3.6	1,8	0.9-3.6	1,9	0.5-7.0	1,7	0.7-3.9
Testicular cancer (C62)	1,4	0.4-5.1	2,0	0.4-9.5	1,6	0.2-11.7	3,0	0.3-35.8
Renal cancer (C64-C65)	1,5	0.6-3.6	1,5	0.7-3.6	0,8	0.2-3.4	2,3	0.7-7.6
Cancer of bladder (C67)	0,8	0.3-2.5	0,8	0.3-2.5	1,1	0.1-12.7	0,7	0.2-2.6
Nervous system cancer (C70, C71)	1,7	0.6-4.5	2,0	0.7-5.4	0,3	0.0-2.9	7,0	1.4-34.9
Cancer of thyroid (C73)	0,5	0.0-5.0	0,9	0.1-10.3	+∞		0,0	
Cancer of unspecified sites (C76-C80)	1,9	1.1-3.3	1,9	1.1-3.3	1,2	0.5-2.7	2,5	1.2-5.4
Lymphoid, haematopoietic tissue cancer (C81-C96)	1,7	0.9-3.2	1,7	0.9-3.3	1,4	0.6-3.5	1,9	0.7-5.0
Cancer of multiple siyes (C97)	3,0	0.2-48.0	3,0	0.2-48.0	0,0		3,0	0.2-48.0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)	1,0	0.8-1.4	1,1	0.8-1.4	1,3	0.8-2.0	1,0	0.7-1.4
BRCA2-related cancers (C25,C43, C50, C61)	1,5	1.1-2.2	1,6	1.1-2.3	1,5	0.8-2.5	1,7	1.1-2.7

* OR=Odds Ratio; all ORs were estimated by conditional logistic regression taking the matching factors into account; **excluding ovarian cancer;

5 Discussion

This report, based on the RIFA case-control study that included 455 cases and 827 population controls, focussed on the association between UM risk and the history of cancer, especially own or family history of breast, renal, colorectal, prostate, BRCA1/2-related cancers or cutaneous melanoma.

The results show that both a family history of any cancer and own previous cancer history are positively associated with the risk of uveal melanoma. A family history of breast, prostate or BRCA2-related cancers was found to be positively associated with the risk of UM.

In this study, an association between one's own history of cancers and uveal melanoma has been suggested (OR=1.3; 95% CI: 0.9-2.0) and is quite similar to the result obtained by Bergman *et al.* (OR=1.25; 95% CI: 0.98-1.59) (Bergman *et al.*, 2006) and Scelo *et al.* (OR=1.25; 95% CI: 1.02-1.51) (Scelo *et al.*, 2006). After stratifying by gender, the risk of UM is not observed among males having suffered a prior cancer, but is found to be increased by up to 90% among females with any own history of cancers (OR=1.9; 95% CI: 1.1-3.2; CLR=2.9). Among participants aged 60 years or more, the risk of UM is increased by a factor of 2.3 (OR=2.3; 95% CI: 1.1-4.8; CLR=4.4) when they have reported to have already suffered any cancer.

Although an association between own history of breast cancer and UM has been suggested in some other studies, no increased risk of UM was observed among participants having previously had breast cancer. The exposure prevalence of own history of breast cancer among female controls was even found to be higher than that among female cases. Bergman *et al.* and Scelo *et al.* also did not observed an association between own history of breast cancer and UM (Bergman *et al.*, 2006; Scelo *et al*., 2006).

In two recent studies no association between UM and cutaneous melanoma was reported (Bergman *et al.*, 2006; Scelo *et al*., 2006). In the current study the exposure prevalence of own history of skin melanoma was observed to be higher among cases than that among controls. Though a precise estimate is not observed in this study, it is suggested that the association between skin melanoma and UM should be studied further.

An association between one's own history of renal cancer and UM is not found in the present study. An increased risk of UM after diagnosis of renal cancer was reported by Scelo *et al*.

and Bergman *et al*., whereas an association between renal cancer and UM was suggested only by Scelo *et al*., the proposed linkage through chromosome 3 monosomy (Bergman *et al.*, 2006; Scelo *et al*., 2006). In the present study the OR of own history of renal cancer was not estimated because there was only one case with renal cancer and no control was reported with previous renal cancer.

Reports on the association between own history of prostate cancer and UM are not consistent. Scelo *et al.* recently found an association between them while Bergman *et al.* did not find any relation (Bergman *et al.*, 2006; Scelo *et al*., 2006). The current study identified no increased risk of UM among participants with an own history of prostate cancer. The exposure prevalence of one's own history of prostate cancer was observed to be higher among controls than that of cases. No association between own history of prostate cancer and UM is suggested.

An association between own history of colorectal cancer and UM was not observed (Bergman *et al.*, 2006; Scelo *et al*., 2006). In this study an increased OR was found among the participants having had a colorectal cancer. After stratifying by gender and age, the increased OR was only observed among women or participants younger than 60 years. Due to the low exposure prevalence of own history of colorectal cancers (1.3% in cases and 1.0% in controls), the effect estimates for colorectal cancers are too imprecise to allow a firm conclusion to be reached regarding any association between UM and own history of colorectal cancers.

The present study indicates that a family history of any cancer is associated with the risk of UM, particularly among males aged 60 years or more (OR=1.8; 95% CI: 1.1-2.7; CLR=2.5). After stratification by origin of family history (from parents or from siblings or both), the effect estimates for overall family cancer history did not vary. However, Hemminki and Chen did not find the same trend between eye melanoma and family history of any cancer (SIR=1.0; 95% CI: 0.85-1.17) (Hemminki & Chen, 2006). In their study, Hemminki and Chen, based on the Swedish Family-Cancer Database, studied the association between eye melanoma and family history of cancers and found an elevated risk of eye melanoma when one of the sisters of the index person was diagnosed with breast cancer (SIR=1.76; 95% CI: 1.00-2.87). The risk of UM is positively associated with familial breast cancer as well (Singh *et al.*, 2005). In the present analysis, the risk of UM was increased when one family member was reported with breast cancer and the risk did not vary with the origin of family history, and was observed to be much higher among male participants.

The analysis shows, a family history of prostate cancer appears to increase the risk of UM by 80% (OR=1.8; 95% CI: 0.9-3.6). The increased risk was not changed after stratifying by sex and origin of family history. Hemminki and Chen also found increased risks (SIR=1.37; 95% CI: 0.99-1.87) of eye melanoma among people whose father was diagnosed with prostate cancer.

No association was found between UM and family history of renal or colorectal cancer in this study. These findings are consistent with the study by Hemminki and Chen (Hemminki & Chen, 2006). Although an increased OR was found among participants with a family history of skin melanoma, the effect estimate was quite imprecise.

In this study, cancers have been grouped by presumed association with mutations of BRCA1/2 according to the reports in the literatures. An association between UM and family history of BRCA1-related cancers was not found. However, the results suggest that family history of BRCA2-related cancers is associated with the risk of UM (OR=1.5; 95% CI: 1.1-2.2). Furthermore, this association appears to be specific among men. Although it is believed that BRCA2 mutations contribute to no more than 5% of all occurrences of UM (Liede *et al*., 2004), a stronger association has been observed between UM and family history of BRCA2-related cancers in the present study. After stratification by sex, the association between UM and family history of BRCA2-related cancers is only observed among males. Although both BRCA1 and BRCA2 have been reported to be genetic risk factors for UM, it appears that BRCA2 plays a greater role in increasing the risk of UM.

In this report, the family history of lymphoid, haematopoietic tissue or unspecified sites cancers (C76-C96) was associated with an increased risk of UM. An increased risk of UM has been previously noted with a family history of unspecified sites cancers. Until now, no similar observation has been made regarding lymphoid and haematopoietic tissue cancers.

In sum, this study suggests a positive association between UM and a family history of prostate, breast or BRCA2-related cancers. An association between UM and a family history or own history of cancer was also suggested, but the strength of the association was weak. Consistent estimates between family and own history for some cancers were not obtained, which possibly suggests a differing pathogenesis of UM for mutations of germline and somatic origin.

From a molecular genetics perspective, the host, based on the first mutations being germline in the former or somatic in the latter, will get a second “hit” for some cancer under a certain condition. If they have any association between the first hits (like sharing some tumour

suppressor genes), there must be some association between phenotypes (UM and other cancers).

BRCA1, BRCA2, p53 pathway and Rb pathway are reported to be associated with uveal melanoma (Knudson, 1993; Harbour, 1999; Singh, 2005; Sherr, 2004). These genetic factors do not only increase the risk of UM, but also increase the risk of some other cancers. The disruption of p53 pathway due to p53 mutations can be observed in more than half of human cancers (Singh, 2005). BRCA2 mutations are also observed in several cancers including breast cancer, skin melanoma, prostate cancer and uveal melanoma (the ABCSG, 2000; Easton *et al*., 1997; Struewing *et al*., 1997; the BCLC, 1999).

Moreover, one cancer can be induced by two or more genetic factors, such as prostate cancer. BRCA2 mutations are reported to be consistently associated with the risk of prostate cancer (Liede *et al*., 2004). In addition to the BRCA2 mutations shared by prostate cancer and UM as a genetic risk factor, both neoplasms have been associated with chromosome 3 abnormalities during the development of a tumour. As already known, chromosome 3 monosomy is a relevant indicator of poor prognosis for UM. However, until 2005 no association between chromosome 3 and prostate cancer had been identified. Larson *et al*. reported a more specific association of prostate cancer with germline mutations on the chromosome 3 region bearing the *FHIT* gene (Larson *et al*., 2005). Altered cellular functions due to chromosome 3 abnormalities might be shared in UM and prostate cancer.

Strengths and Limitations

The study has limitations that deserve consideration. First, the response proportions in this study were 94% among cases and 55% among controls. The low response proportion among the controls introduces uncertainty into the results. The lack of any information related to the cancer history (own and family history) among the nonresponding controls makes it impossible to estimate whether nonresponse bias has occurred. The comparison of the lifetime prevalences of a cancer history by age and sex among controls of the RIFA study with the German Examination Health Survey from 1998 shows that these prevalences are quite comparable suggesting that a heavy nonresponse bias among the controls is not very likely (figure 2).

Another limitation is related to the exposure misclassification. All exposure information, i.e., cancer history information, is based on self-reports. From validation studies it is well known

that self-reported cancer histories suffer from misclassification depending on the site of cancer and other factors (Douglas *et al.*, 1999). It is difficult to speculate in which direction misclassification errors might have biased the study results because the magnitude of misclassification among uveal melanoma cases is virtually unknown.

A third limitation of the study is related to the low prevalences of several tumor sites that resulted in uninformative effect estimates. Although the power is limited for some cancers of lower prevalence reported among the participants own history, the statistical power is acceptable to get precise effect estimates for most cancers reported in the family history.

Use of a case-control study design is always advantageous in probing into rare diseases like uveal melanoma. Being a rare tumour with little aetiological information, uveal melanoma has been described consistently to be associated with age, possibly gender too. In the present study, cases and controls were matched by age, gender and region of residence, thus own history and family history of cancer could be studied without heavy confounding by those factors. The interviewers had been well trained to be capable of performing highly standardized interviews, and regular monitoring and training were undertaken after an initial interviewer training course. The cancer history was assessed in a detailed way and was coded according to ICD10. Moreover, as based on the total number of interviewed cases in this study, the RIFA case-control study is so far the largest case-control study on uveal melanoma in the world.

Conclusion

In the present study, cancers were regarded as complex phenotypes of some genes; the self-reported own cancer history and family history were regarded as evidence of occurrence of cancer. Cases and population controls were matched by sex, age and region of residence. The own cancer history and family cancer history in the first degree relatives were collected through computer assisted telephone interviews.

Women who reported a history of previous cancer have an increased risk of UM. People younger than 60 years seem to have an increased risk of UM when he or she has already suffered any cancer. One major finding is that a family history of prostate or breast cancer may increase the risk of UM. BRCA2-related cancers seem to be associated with an elevated risk of UM. These findings indicate that a routine ocular examination among people with a

family history of breast, prostate or BRCA2-related cancers could lead to the early diagnosis of UM and thus, deliver an improved prognosis.

Skin melanoma is the only neoplasm that the effect estimates between own and family history are consistent for. This observation suggests that the association between skin melanoma and UM should be more closely examined in larger studies to reach a conclusion on the nature of this association.

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Table 7 Distribution of own history of any cancer except uveal melanoma and matched OR* among males

Cancer and ICD10 code		Cases N=241		Population controls N=454		OR (95% CI)
		N	%	N	%	
Any cancer except UM						
	Yes	17	7,1	35	7,7	0.9 (0.5, 1.6)
	No	224	92,9	419	92,3	1,0
Colorectal cancer (C18-C20, C26)						
	Yes	3	1,2	5	1,1	1.2 (0.3, 5.3)
	No	238	98,8	449	98,9	1,0
Skin cancer (C43, C44)						
	Yes	1	0,4	7	1,5	0.3 (0.0, 2.7)
	No	240	99,6	447	98,5	1,0
Skin melanoma (C43)						
	Yes	0	0,0	3	0,7	0,0
	No	241	100,0	451	99,3	1,0
Nomelanoma skin cancer (C44)						
	Yes	0	0,0	4	0,9	0,0
	No	241	100,0	450	99,1	1,0
Prostate cancer (C61)						
	Yes	3	1,2	12	2,6	0.5 (0.1, 1.7)
	No	238	98,8	442	97,4	1,0
Renal cancer (C64,C65)						
	Yes	1	0,4	0	0,0	+∞
	No	240	99,6	454	100,0	1,0
Bladder cancer (C67)						
	Yes	2	0,8	2	0,4	1.9 (0.3, 13.8)
	No	239	99,2	452	99,6	1,0
Cancer of ill-defined sites (C76-C80)						
	Yes	3	1,2	6	1,3	1.0 (0.2, 4.1)
	No	238	98,8	448	98,7	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	3	1,2	15	3,3	0.4 (0.1, 1.3)
	No	238	98,8	439	96,7	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	7	2,9	20	4,4	0.7 (0.3, 1.6)
	No	234	97,1	434	95,6	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account;** The cancers with zero exposed subjects are not shown.

Table 8 Distribution of own history of any cancer except uveal melanoma and matched OR* among females

Cancer and ICD10 code		Cases N=214		Population controls N=373		OR (95% CI)
		N	%	N	%	
Any cancer except UM						
	Yes	32	15,0	34	9,1	1.9 (1.1, 3.2)
	No	182	85,0	339	90,9	1,0
Colorectal cancer (C18-C20, C26)						
	Yes	3	1,4	3	0,8	1.7 (0.3, 9.1)
	No	211	98,6	370	99,2	1,0
Skin cancer (C43, C44)						
	Yes	9	4,2	2	0,5	7.9 (1.7, 37.3)
	No	205	95,8	371	99,5	1,0
Skin melanoma (C43)						
	Yes	2	0,9	0	0,0	+∞
	No	212	99,1	373	100,0	1,0
Nomelanoma skin cancer (C44)						
	Yes	7	3,3	2	0,5	5.5 (1.1, 27.5)
	No	207	96,7	371	99,5	1,0
Breast cancer (C50)						
	Yes	6	2,8	17	4,6	0.6 (0.2, 1.7)
	No	208	97,2	356	95,4	1,0
Female genital organ cancer (C51,C53,C55,C57)						
	Yes	5	2,3	7	1,9	1.2 (0.4, 4.1)
	No	209	97,7	366	98,1	1,0
Ovarian cancer (C56)						
	Yes	1	0,5	1	0,3	2.4 (0.2, 39.7)
	No	213	99,5	372	99,7	1,0
Cancer of thyroid (C73)						
	Yes	2	0,9	1	0,3	3.2 (0.3, 36.6)
	No	212	99,1	372	99,7	1,0
Lymphoid, haematopoirtic tissue cancer (C81-C96)						
	Yes	4	1,9	1	0,3	7.7 (0.8, 71.3)
	No	210	98,1	372	99,7	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	8	3,7	17	4,6	0.9 (0.4, 2.1)
	No	206	96,3	356	95,4	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	18	8,4	22	5,9	1.1 (0.6, 2.3)
	No	196	91,6	351	94,1	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account;** The cancers with zero exposed subjects are not shown.

Table 9 Distribution of own history of any cancer except uveal melanoma and matched OR* among participants aged 60 years or more

Cancer and ICD10 code		Cases N=257		Population controls N=474		OR (95% CI)
		N	%	N	%	
Any cancer history except UM						
	Yes	31	12,1	54	11,4	1.1 (0.7, 1.7)
	No	226	87,6	420	88,6	1,0
Colorectal cancer (C18-C20, C26)						
	Yes	4	1,6	7	1,5	1.2 (0.4, 4.1)
	No	253	98,1	467	98,5	1,0
Skin cancer (C43, C44)						
	Yes	5	1,9	8	1,7	1.2 (0.4, 3.8)
	No	252	97,7	466	98,3	1,0
Skin melanoma (C43)						
	Yes	0	0,0	2	0,4	0,0
	No	257	99,6	472	99,6	1,0
Nonmelanoma skin cancer (C44)						
	Yes	4	1,6	6	1,3	1.1 (0.3, 4.5)
	No	253	98,1	468	98,7	1,0
Breast cancer** (C50)						
	Yes	5	1,9	15	3,2	0.6 (0.2, .1.7)
	No	252	97,7	459	96,8	1,0
Female genital organ cancer** (C51,C53,C55,C57)						
	Yes	3	1,2	3	0,6	1.3 (0.3, 6.9)
	No	254	98,4	471	99,4	1,0
Ovarian cancer** (C56)						
	Yes	1	0,4	1	0,2	2.4 (0.2, 39.7)
	No	256	99,2	473	99,8	1,0
Prostate cancer** (C61)						
	Yes	3	1,2	12	2,5	0.5 (0.1, 1.7)
	No	254	98,4	462	97,5	1,0
Bladder cancer (C67)						
	Yes	2	0,8	1	0,2	5.3 (0.5, 58.7)
	No	255	98,8	473	99,8	1,0
Cancer of thyroid (C73)						
	Yes	2	0,8	2	0,4	1.7 (0.2, 12.2)
	No	254	98,4	472	99,6	1,0
Lymphoid, haematopoirtic tissue cancer (C81-C96)						
	Yes	3	1,2	1	0,2	5.0 (0.5, 50.0)
	No	254	98,4	473	99,8	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	15	5,8	38	8,0	0.7 (0.4, 1.4)
	No	242	93,8	436	92,0	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	8	3,1	29	6,1	0.5 (0.2, 1.1)
	No	249	96,5	445	93,9	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account; ** these cancers are only estimated among participants of related gender respectively.
***The cancers with zero exposed subjects are not shown.

Table 10 Distribution of own history of any cancer except uveal melanoma and matched OR* among participants younger than 60 years

Cancer and ICD10 code		Cases N=198		Population controls N=353		OR (95% CI)
		N	%	N	%	
Any cancer except UM						
	Yes	18	9,1	15	4,2	2.3 (1.1, 4.8)
	No	180	89,6	338	95,8	1,0
Colorectal cancer (C18-C20, C26)						
	Yes	2	1,0	1	0,3	3.0 (0.3, 35.8)
	No	196	97,5	352	99,7	1,0
Skin cancer (C43, C44)						
	Yes	5	2,5	1	0,3	9.7 (1.1, 85.4)
	No	193	96,0	352	99,7	1,0
Skin melanoma (C43)						
	Yes	2	1,0	1	0,3	5.3 (0.5, 58.7)
	No	196	97,5	352	99,7	1,0
Nomelanoma skin cancer (C44)						
	Yes	3	1,5	0	0,0	+∞
	No	194	96,5	353	100,0	1,0
Breast cancer** (C50)						
	Yes	1	0,5	2	0,6	1.1 (0.1, 12.7)
	No	197	98,0	351	99,4	1,0
Female genital organ cancer** (C51,C53,C55,C57)						
	Yes	1	0,5	3	0,8	0.7 (0.1, 7.4)
	No	197	98,0	350	99,2	1,0
Bladder cancer (C67)			0,0			
	Yes	1	0,5	1	0,3	1.4 (0.1, 23.6)
	No	197	98,0	352	99,7	1,0
Cancers of unspecified sites (C76-C80)						
	Yes	3	1,5	3	0,8	2.2 (0.4, 11.2)
	No	195	97,0	350	99,2	1,0
Lymphoid and haematopoietic tissue cancer (C81-C96)						
	Yes	3	1,5	3	0,8	+∞
	No	195	97,0	350	99,2	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	5	2,5	4	1,1	2.6 (0.7, 10.0)
	No	193	96,0	349	98,9	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	3	1,5	3	0,8	2.4 (0.5, 12.2)
	No	195	97,0	350	99,2	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account;** These cancers are only estimated among participants of related gender respectively.

*** The cancers with zero exposed subjects are not shown.

Table 12. Distribution of any family cancer history of all first degree relatives and matched OR* among males

Cancer and ICD10 code		Cases N=241		Population controls N=454		OR (95% CI)
		N	%	N	%	
Any cancer						
	Yes	95	39,4	150	33,0	1.4 (1.0, 2.0)
	No	144	59,8	299	65,9	1,0
Cancer of upper aerodigestive tract (C00-C14 & C32)						
	Yes	1	0,4	4	0,9	0.4 (0.0, 3.7)
	No	238	98,8	445	98,0	1,0
Upper digestive tract cancer (C15-C17)						
	Yes	12	5,0	19	4,2	1.0 (0.6, 1.8)
	No	227	94,2	430	94,7	1,0
Colorectal cancer (C18-C20,C26)						
	Yes	13	5,4	26	5,7	0.9 (0.5, 1.9)
	No	226	93,8	423	93,2	1,0
Cancer of liver-biliary system (C22-C24)						
	Yes	5	2,1	5	1,1	1.8 (0.5, 6.4)
	No	234	97,1	444	97,8	1,0
Pancreas cancer (C25)						
	Yes	6	2,5	5	1,1	2.5 (0.7, 9.4)
	No	233	96,7	444	97,8	1,0
Lung cancer (C34)						
	Yes	8	3,3	29	6,4	0.5 (0.2, 1.1)
	No	231	95,9	420	92,5	1,0
Cancer of bone and articular cartilagen (C40-C41, C49)						
	Yes	4	1,7	1	0,2	7.7 (0.8, 71.3)
	No	235	97,5	448	98,7	1,0
Skin cancer (C43, C44)						
	Yes	4	1,7	8	1,8	0.9 (0.3, 3.2)
	No	235	97,5	441	97,1	1,0
Skin melanoma (C43)						
	Yes	1	0,4	1	0,2	3.0 (0.2, 48.0)
	No	238	98,8	448	98,7	1,0
Nomelanoma skin cancer (C44)						
	Yes	2	0,8	4	0,9	0.7 (0.1, 3.9)
	No	237	98,3	445	98,0	1,0
Breast cancer (C50)						
	Yes	21	8,7	21	4,6	1.9 (1.0, 3.8)
	No	218	90,5	428	94,3	1,0
Female genital organ cancer** (C51,C53,C55,C57)						
	Yes	7	2,9	15	3,3	0.8 (0.3, 2.2)
	No	232	96,3	434	95,6	1,0
Prostate cancer (C61)						
	Yes	9	3,7	9	2,0	2.3 (0.8, 6.3)
	No	230	95,4	440	96,9	1,0
Testicular cancer (C62)						
	Yes	3	1,2	3	0,7	1.5 (0.3, 7.8)
	No	236	97,9	446	98,2	1,0
Renal cancer (C64-C65)						
	Yes	4	1,7	7	1,5	1.1 (0.3, 4.0)
	No	235	97,5	442	97,4	1,0
Bladder cancer (C67)						
	Yes	1	0,4	3	0,7	0.4 (0.0, 3.8)
	No	238	98,8	446	98,2	1,0
Nervous system cancer (C70, C71)						
	Yes	7	2,9	6	1,3	2.3 (0.8, 7.1)
	No	232	96,3	443	97,6	1,0
Cancers of ill-defined, unspecified sites (C76-C80)						
	Yes	10	4,1	11	2,4	2.0 (0.8, 5.0)
	No	229	95,0	438	96,5	1,0
Lymphoid, haematopoietic tissue cancer (C81-C96)						
	Yes	6	2,5	15	3,3	1.0 (0.4, 2.7)
	No	233	96,7	435	95,8	1,0
Cancers of independent multiple sites (C97)						
	Yes	1	0,4	0	0,0	+∞
	No	238	98,8	449	98,9	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	56	23,2	84	18,5	1.3 (0.9, 2.0)
	No	183	75,9	365	80,4	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	35	14,5	33	7,3	2.2 (1.3, 3.7)
	No	204	84,6	416	91,6	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account;

**excluding ovarian cancer;

*** The missing values (2 casesand 5 controls) are not showed in table.

Table 13. Distribution of any family Cancer history of all first degree relatives and matched OR* among females

Cancer and ICD10 code		Cases N=214		Population controls N=373		OR (95% CI)
		N	%	N	%	
Any cancer						
	Yes	97	45,3	156	41,8	1.1 (0.8, 1.6)
	No	115	53,7	215	57,6	1,0
Cancer of upper aerodigestive tract (C00-C14 & C32)						
	Yes	2	0,9	1	0,3	3.0 (0.3, 35.8)
	No	210	98,1	370	99,2	1,0
Upper digestive tract cancer (C15-C17)						
	Yes	9	4,2	18	4,8	1.0 (0.4, 2.3)
	No	203	94,9	353	94,6	1,0
Colorectal cancer (C18-C20,C26)						
	Yes	10	4,7	29	7,8	0.5 (0.2, 1.1)
	No	202	94,4	342	91,7	1,0
Cancer of liver-biliary system (C22-C24)						
	Yes	4	1,9	12	3,2	0.5 (0.2, 1.7)
	No	208	97,2	359	96,2	1,0
Pancreatic cancer (C25)						
	Yes	8	3,7	9	2,4	1.6 (0.5, 5.1)
	No	204	95,3	362	97,1	1,0
Lung cancer (C34)						
	Yes	14	6,5	28	7,5	0.9 (0.4, 1.8)
	No	198	92,5	343	92,0	1,0
Cancer of bone and articular cartilagen (C40-C41, C49)						
	Yes	4	1,9	3	0,8	1.2 (0.2, 6.8)
	No	208	97,2	368	98,7	1,0
Skin cancer (C43, C44)						
	Yes	9	4,2	5	1,3	2.9 (0.9, 9.0)
	No	203	94,9	366	98,1	1,0
Skin melanoma (C43)						
	Yes	3	1,4	2	0,5	1.9 (0.3, 11.8)
	No	209	97,7	369	98,9	1,0
Nomelanoma skin cancer (C44)						
	Yes	5	2,3	2	0,5	4.3 (0.8, 23.1)
	No	207	96,7	369	98,9	1,0
Breast cancer (C50)						
	Yes	18	8,4	34	9,1	1.0 (0.5, 1.8)
	No	194	90,7	337	90,3	1,0
Female genital organ cancer** (C51,C53,C55,C57)						
	Yes	12	5,6	19	5,1	0.9 (0.4, 2.1)
	No	200	93,5	352	94,4	1,0
Ovarian cancer (C56)						
	Yes	1	0,5	1	0,3	1.7 (0.1, 30.8)
	No	211	98,6	370	99,2	1,0
Prostate cancer (C61)						
	Yes	7	3,3	11	2,9	1.4 (0.5, 3.7)
	No	205	95,8	360	96,5	1,0
Testicular cancer (C62)						
	Yes	2	0,9	2	0,5	1.3 (0.2, 9.8)
	No	210	98,1	369	98,9	1,0
Renal cancer (C64-C65)						
	Yes	5	2,3	5	1,3	1.9 (0.5, 6.8)
	No	207	96,7	366	98,1	1,0
Bladder cancer (C67)						
	Yes	4	1,9	6	1,6	1.1 (0.3, 4.1)
	No	208	97,2	365	97,9	1,0
Nervous system cancer (C70, C71)						
	Yes	1	0,5	3	0,8	0.5 (0.1, 5.5)
	No	211	98,6	368	98,7	1,0
Thyroid cancer (C73)						
	Yes	1	0,5	1	0,3	1.4 (0.1, 23.6)
	No	211	98,6	370	99,2	1,0
Cancers of ill-defined, unspecified sites (C76-C80)						
	Yes	17	7,9	17	4,6	1.8 (0.8, 3.7)
	No	195	91,1	354	94,9	1,0
Lymphoid, haematopoietic tissue cancer (C81-C96)						
	Yes	13	6,1	11	2,9	2.6 (1.1, 6.3)
	No	199	93,0	360	96,5	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	51	23,8	105	28,2	0.8 (0.5, 1.2)
	No	161	75,2	266	71,3	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	32	15,0	53	14,2	1.1 (0.7, 1.8)
	No	180	84,1	318	85,3	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account;
**excluding ovarian cancer;
*** The missing values (2 casesand 5 controls) are not showed in table.

Table 14 Distribution of any family ancer history of all first degree relatives and matched OR[1] among participants aging 60 years or more

Cancer and ICD10 code		Cases N=257		Population controls N=474		OR (95% CI)
		N	%	N	%	
Any cancer						
	Yes	118	45,9	183	38,6	1.4 (1.0, 1.9)
	No	136	52,9	285	60,1	1,0
Cancer of upper aerodigestive tract (C00-C14 & C32)						
	Yes	2	0,8	1	0,2	5.8 (0.5, 65.9)
	No	252	98,1	467	98,5	1,0
Upper digestive tract cancer (C15-C17)						
	Yes	16	6,2	26	5,5	1.3 (0.7, 2.5)
	No	238	92,6	442	93,2	1,0
Colorectal cancer (C18-C20, C26)						
	Yes	14	5,4	38	8,0	0.6 (0.3, 1.2)
	No	240	93,4	430	90,7	1,0
Cancer of liver-biliary system (C22-C24)						
	Yes	8	3,1	10	2,1	1.4 (0.5, 3.5)
	No	246	95,7	458	96,6	1,0
Pancreatic cancer (C25)						
	Yes	8	3,1	7	1,5	3.2 (0.9, 11.2)
	No	246	95,7	461	97,3	1,0
Lung cancer (C34)						
	Yes	12	4,7	34	7,2	0.6 (0.3, 1.3)
	No	242	94,2	434	91,6	1,0
Cancer of bone and articular cartilagen (C40-C41, C49)						
	Yes	5	1,9	2	0,4	4.0 (0.7, 21.4)
	No	249	96,9	466	98,3	1,0
Skin cancer (C43, C44)						
	Yes	6	2,3	6	1,3	1.8 (0.6, 5.7)
	No	248	96,5	462	97,5	1,0
Skin melanoma (C43)						
	Yes	3	1,2	1	0,2	5.6 (0.5, 57.3)
	No	251	97,7	467	98,5	1,0
Nomelanoma skin cancer (C44)						
	Yes	2	0,8	3	0,6	1.0 (0.2, 6.3)
	No	252	98,1	465	98,1	1,0
Breast cancer (C50)						
	Yes	27	10,5	33	7,0	1.5 (0.9, 2.6)
	No	227	88,3	435	91,8	1,0
Female genital organ cancer (C51,C53,C55,C57)						
	Yes	10	3,9	20	4,2	1.0 (0.3, 2.9)
	No	244	94,9	448	94,5	1,0
Ovarian cancer (C56)						
	Yes	1	0,4	0	0,0	+∞
	No	253	98,4	468	98,7	1,0
Prostate cancer (C61)						
	Yes	10	3,9	9	1,9	2.8 (1.1, 7.2)
	No	244	94,9	459	96,8	1,0
Testicular cancer (C62)						
	Yes	3	1,2	3	0,6	1.5 (0.3, 7.8)
	No	251	97,7	465	98,1	1,0
Renal cancer (C64-C65)						
	Yes	3	1,2	8	1,7	0.7 (0.2, 2.9)
	No	251	97,7	460	97,0	1,0
Bladder cancer (C67)						
	Yes	3	1,2	4	0,8	1.6 (0.3, 8.1)
	No	251	97,7	464	97,9	1,0
Nervous system cancer (C70, C71)						
	Yes	4	1,6	7	1,5	1.1 (0.3, 3.9)
	No	250	97,3	461	97,3	1,0
Thyroid cancer (C73)						
	Yes	1	0,4	1	0,2	1.0 (0.1, 16.0)
	No	253	98,4	467	98,5	1,0
Cancers of unspecified sites (C76-C80)						
	Yes	21	8,2	18	3,8	2.4 (1.2, 4.7)
	No	233	90,7	450	94,9	1,0
Lymphoid, haematopoietic tissue cancer (C81-C96)						
	Yes	13	5,1	16	3,4	1.9 (0.8, 4.3)
	No	241	93,8	452	95,4	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	65	25,3	112	23,6	1.1 (0.8, 1.6)
	No	189	73,5	356	75,1	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	44	17,1	48	10,1	1.9 (1.2, 3.1)
	No	210	81,7	420	88,6	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account; **excluding ovarian cancer;
*** The missing values (2 casesand 5 controls) are not showed in table.

Table 15 Distribution of any family cancer history of all first degree relatives and matched OR* among participants younger than 60 years

Cancer and ICD10 code		Cases N=198		Population controls N=353		OR (95% CI)
		N	%	N	%	
Any cancer						
	Yes	74	37,4	123	34,8	1.1 (0.7, 1.6)
	No	123	62,1	229	64,9	1,0
Cancer of upper aerodigestive tract (C00-C14 & C32)						
	Yes	1	0,5	4	1,1	0.3 (0.0, 2.5)
	No	196	99,0	348	98,6	1,0
Upper digestive tract cancer (C15-C17)						
	Yes	5	2,5	11	3,1	0.8 (0.3, 2.5)
	No	192	97,0	341	96,6	1,0
Colorectal cancer (C18-C20, C26)						
	Yes	9	4,5	17	4,8	0.9 (0.4, 2.0)
	No	188	94,9	335	94,9	1,0
Cancer of liver-biliary system (C22-C24)						
	Yes	1	0,5	7	2,0	0.2 (0.0, 2.0)
	No	196	99,0	345	97,7	1,0
Pancreatic cancer (C25)						
	Yes	6	3,0	7	2,0	1.2 (0.4, 4.2)
	No	191	96,5	345	97,7	1,0
Lung cancer (C34)						
	Yes	10	5,1	23	6,5	0.8 (0.4, 1.6)
	No	187	94,4	329	93,2	1,0
Cancer of bone and articular cartilagen (C40-C41, C49)						
	Yes	3	1,5	2	0,6	2.7 (0.4, 17.3)
	No	194	98,0	350	99,2	1,0
Skin cancer (C43, C44)						
	Yes	7	3,5	7	2,0	1.7 (0.6, 5.0)
	No	190	96,0	345	97,7	1,0
Skin melanoma (C43)						
	Yes	1	0,5	2	0,6	0.7 (0.1, 8.0)
	No	196	99,0	350	99,2	1,0
Nomelanoma skin cancer (C44)						
	Yes	5	2,5	3	0,8	2.6 (0.6, 11.4)
	No	192	97,0	349	98,9	1,0
Breast cancer (C50)						
	Yes	12	6,1	22	6,2	1.0 (0.4, 2.2)
	No	183	92,4	330	93,5	1,0
Female genital organ cancer (C51,C53,C55,C57)						
	Yes	9	4,5	14	4,0	0.9 (0.3, 2.8)
	No	188	94,9	338	95,8	1,0
Prostate cancer (C61)						
	Yes	6	3,0	11	3,1	1.0 (0.3, 2.9)
	No	191	96,5	341	96,6	1,0
Testicular cancer (C62)						
	Yes	2	1,0	2	0,6	1.3 (0.2, 9.8)
	No	195	98,5	350	99,2	1,0
Renal cancer (C64-C65)						
	Yes	6	3,0	4	1,1	2.9 (0.8, 10.4)
	No	191	96,5	348	98,6	1,0
Bladder cancer (C67)						
	Yes	2	1,0	5	1,4	0.4 (0.1, 2.3)
	No	195	98,5	347	98,3	1,0
Nervous system cancer (C70, C71)						
	Yes	4	2,0	2	0,6	3.6 (0.6, 21.0)
	No	193	97,5	350	99,2	1,0
Cancers of unspecified sites (C76-C80)						
	Yes	6	3,0	10	2,8	1.1 (0.4, 3.1)
	No	191	96,5	342	96,9	1,0
Lymphoid, haematopoietic tissue cancer (C81-C96)						
	Yes	6	3,0	10	2,8	1.4 (0.5, 4.0)
	No	191	96,5	342	96,9	1,0
Cancer of multiple sites (C97)						
	Yes	1	0,5	1	0,3	3.0 (0.2, 48.0)
	No	196	99,0	351	99,4	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	42	21,2	77	21,8	0.9 (0.6, 1.4)
	No	155	78,3	275	77,9	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	23	11,6	38	10,8	1.0 (0.6, 1.8)
	No	174	87,9	314	89,0	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account; **excluding ovarian cancer;

*** The missing values (2 casesand 5 controls) are not showed in table.

Table 16. Distribution of any family cancer history of all first degree relatives and matched OR* among males aged 60 years or more

Cancer and ICD10 code		Cases N=144		Population controls N=280		OR (95% CI)
		N	%	N	%	
Any cancer						
	Yes	65	45,1	95	33,9	1.8 (1.1, 2.7)
	No	78	54,2	181	64,6	1,0
Cancer of upper aerodigestive tract (C00-C14)						
	Yes	1	0,7	1	0,4	2.8 (0.2, 47.1)
	No	142	98,6	275	98,2	1,0
Upper digestive tract cancer (C15-C17)						
	Yes	10	6,9	15	5,4	1.4 (0.6, 3.3)
	No	133	92,4	261	93,2	1,0
Colorectal cancer (C18-C20,C26)						
	Yes	7	4,9	17	6,1	0.8 (0.3, 2.0)
	No	136	94,4	259	92,5	1,0
Cancer of liver-biliary system (C22-C24)						
	Yes	5	3,5	3	1,1	3.3 (0.7, 14.2)
	No	138	95,8	273	97,5	1,0
Pancreas cancer (C25)						
	Yes	3	2,1	3	1,1	2.7 (0.4, 17.3)
	No	140	97,2	273	97,5	1,0
Lung cancer (C34)						
	Yes	3	2,1	18	6,4	0.2 (0.1, 1.1)
	No	140	97,2	258	92,1	1,0
Cancer of bone and articular cartilagen (C40-C41, C49)						
	Yes	4	2,8	0	0,0	+∞
	No	139	96,5	276	98,6	1,0
Skin cancer (C43, C44)						
	Yes	2	1,4	5	1,8	0.8 (0.1, 4.3)
	No	141	97,9	271	96,8	1,0
Skin melanoma (C43)						
	Yes	1	0,7	0	0,0	+∞
	No	142	98,6	276	98,6	1,0
Nomelanoma skin cancer (C44)						
	Yes	1	0,7	3	1,1	0.5 (0.1, 5.5)
	No	142	98,6	273	97,5	1,0
Breast cancer (C50)						
	Yes	16	11,1	14	5,0	2.3 (1.0, 5.1)
	No	127	88,2	262	93,6	1,0
Female genital organ cancer** (C51,C53,C55,C57)						
	Yes	4	2,8	11	3,9	0.6 (0.2, 2.3)
	No	139	96,5	265	94,6	1,0
Prostate cancer (C61)						
	Yes	7	4,9	4	1,4	4.8 (1.2, 19.2)
	No	136	94,4	272	97,1	1,0
Testicular cancer (C62)						
	Yes	2	1,4	2	0,7	1.9 (0.3, 13.8)
	No	141	97,9	274	97,9	1,0
Renal cancer (C64-C65)						
	Yes	1	0,7	4	1,4	0.4 (0.0, 4.2)
	No	142	98,6	272	97,1	1,0
Bladder cancer (C67)						
	Yes	1	0,7	0	0,0	+∞
	No	142	98,6	276	98,6	1,0
Nervous system cancer (C70, C71)						
	Yes	4	2,8	6	2,1	1.3 (0.3, 4.6)
	No	139	96,5	270	96,4	1,0
Cancers of ill-defined, unspecified sites (C76-C80)						
	Yes	9	6,3	9	3,2	2.3 (0.9, 6.1)
	No	134	93,1	267	95,4	1,0
Lymphoid, haematopoietic tissue cancer (C81-C96)						
	Yes	5	3,5	10	3,6	1.1 (0.4, 3.6)
	No	138	95,8	266	95,0	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	37	25,7	54	19,3	1.5 (0.9, 2.5)
	No	106	73,6	222	79,3	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	26	18,1	20	7,1	3.0 (1.5, 5.9)
	No	117	81,3	256	91,4	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account;
**excluding ovarian cancer;
*** The missing values (1 cases and 4 controls for each cancer) are not showed in table.
****The cancers with zero exposed subjects are not shown.

Table 17. Distribution of any family cancer history of all first degree relatives and matched OR* among males younger than 60 years

Cancer and ICD10 code		Cases N=97		Population controls N=174		OR (95% CI)
		N	%	N	%	
Any cancer						
	Yes	30	30,9	55	31,6	1.0 (0.6, 1.7)
	No	66	68,0	118	67,8	1,0
Cancer of upper aerodigestive tract (C00-C14)						
	Yes	0	0,0	3	1,7	0,0
	No	96	99,0	170	97,7	1,0
Upper digestive tract cancer (C15-C17)						
	Yes	2	2,1	4	2,3	0.8 (0.1, 4.4)
	No	94	96,9	169	97,1	1,0
Colorectal cancer (C18-C20,C26)						
	Yes	6	6,2	9	5,2	1.3 (0.4, 3.9)
	No	90	92,8	164	94,3	1,0
Cancer of liver-biliary system (C22-C24)						
	Yes	0	0,0	2	1,1	0,0
	No	96	99,0	171	98,3	1,0
Pancreas cancer (C25)						
	Yes	3	3,1	2	1,1	2.3 (0.4, 14.9)
	No	93	95,9	171	98,3	1,0
Lung cancer (C34)						
	Yes	5	5,2	11	6,3	0.8 (0.3, 2.3)
	No	91	93,8	162	93,1	1,0
Cancer of bone and articular cartilagen (C40-C41, C49)						
	Yes	0	0,0	1	0,6	0,0
	No	96	99,0	172	98,9	1,0
Skin cancer (C43, C44)						
	Yes	2	2,1	3	1,7	1.2 (0.2, 7.3)
	No	94	96,9	170	97,7	1,0
Skin melanoma (C43)						
	Yes	0	0,0	1	0,6	0,0
	No	96	99,0	172	98,9	1,0
Nomelanoma skin cancer (C44)						
	Yes	1	1,0	1	0,6	1.0 (0.1, 16.0)
	No	95	97,9	172	98,9	1,0
Breast cancer (C50)						
	Yes	5	5,2	7	4,0	1.2 (0.3, 4.5)
	No	91	93,8	166	95,4	1,0
Female genital organ cancer** (C51,C53,C55,C57)						
	Yes	3	3,1	4	2,3	1.3 (0.3, 6.1)
	No	93	95,9	169	97,1	1,0
Prostate cancer (C61)						
	Yes	2	2,1	5	2,9	0.7 (0.1, 3.9)
	No	94	96,9	168	96,6	1,0
Testicular cancer (C62)						
	Yes	1	1,0	1	0,6	1.0 (0.1, 16.0)
	No	95	97,9	172	98,9	1,0
Renal cancer (C64-C65)						
	Yes	3	3,1	3	1,7	2.1 (0.4, 10.6)
	No	93	95,9	170	97,7	1,0
Bladder cancer (C67)						
	Yes	0	0,0	3	1,7	0,0
	No	96	99,0	170	97,7	1,0
Nervous system cancer (C70, C71)						
	Yes	3	3,1	0	0,0	+∞
	No	93	95,9	173	99,4	1,0
Cancers of ill-defined, unspecified sites (C76-C80)						
	Yes	1	1,0	2	1,1	1.0 (0.1, 11.0)
	No	95	97,9	171	98,3	1,0
Lymphoid, haematopoietic tissue cancer (C81-C96)						
	Yes	1	1,0	5	2,9	0.6 (0.1, 5.4)
	No	95	97,9	168	96,6	1,0
Cancers of independent multiple sites (C97)						
	Yes	1	1,0	0	0,0	+∞
	No	95	97,9	173	99,4	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	20	20,6	33	19,0	1.1 (0.6, 2.0)
	No	76	78,4	140	80,5	1,0
BRCA2-related Cancers (C25, C43, C50, C61)						
	Yes	9	9,3	13	7,5	1.2 (0.5, 3.0)
	No	87	89,7	160	92,0	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account;
**excluding ovarian cancer;
*** The missing values (1 cases and 4 controls for each cancer) are not showed in table.
****The cancers with zero exposed subjects are not shown.

Table 18. Distribution of any family cancer history of all first degree relatives and matched OR* among females aged 60 years or more

Cancer and ICD10 code		Cases N=113		Population controls N=194		OR (95% CI)
		N	%	N	%	
Any cancer						
	Yes	53	46,9	88	45,4	1.1 (0.7, 1.7)
	No	58	51,3	104	53,6	1,0
Cancer of upper aerodigestive tract (C00-C14)						
	Yes	1	0,9	0	0,0	+∞
	No	110	97,3	192	99,0	1,0
Upper digestive tract cancer (C15-C17)						
	Yes	6	5,3	11	5,7	1.1 (0.4, 3.2)
	No	105	92,9	181	93,3	1,0
Colorectal cancer (C18-C20,C26)						
	Yes	7	6,2	21	10,8	0.5 (0.2, 1.2)
	No	104	92,0	171	88,1	1,0
Cancer of liver-biliary system (C22-C24)						
	Yes	3	2,7	7	3,6	0.7 (0.2, 2.6)
	No	108	95,6	185	95,4	1,0
Pancreas cancer (C25)						
	Yes	5	4,4	4	2,1	3.6 (0.6, 20.8)
	No	106	93,8	188	96,9	1,0
Lung cancer (C34)						
	Yes	9	8,0	16	8,2	1.0 (0.4, 2.5)
	No	102	90,3	176	90,7	1,0
Cancer of bone and articular cartilagen (C40-C41, C49)						
	Yes	1	0,9	2	1,0	0.7 (0.1, 8.0)
	No	110	97,3	190	97,9	1,0
Skin cancer (C43, C44)						
	Yes	4	3,5	1	0,5	6.1 (0.7, 56.8)
	No	107	94,7	191	98,5	1,0
Skin melanoma (C43)						
	Yes	2	1,8	1	0,5	3.0 (0.3, 35.8)
	No	109	96,5	191	98,5	1,0
Nomelanoma skin cancer (C44)						
	Yes	1	0,9	0	0,0	+∞
	No	110	97,3	192	99,0	1,0
Breast cancer (C50)						
	Yes	11	9,7	19	9,8	1.0 (0.5, 2.2)
	No	100	88,5	173	89,2	1,0
Female genital organ cancer** (C51,C53,C55,C57)						
	Yes	6	5,3	9	4,6	1.0 (0.3, 2.9)
	No	105	92,9	183	94,3	1,0
Ovarian cancer (C56)						
	Yes	1	0,9	0	0,0	+∞
	No	110	97,3	192	99,0	1,0
Prostate cancer (C61)						
	Yes	3	2,7	5	2,6	1.5 (0.3, 6.3)
	No	108	95,6	187	96,4	1,0
Testicular cancer (C62)						
	Yes	1	0,9	1	0,5	1.0 (0.1, 16.0)
	No	110	97,3	191	98,5	1,0
Renal cancer (C64-C65)						
	Yes	2	1,8	4	2,1	1.1 (0.2, 6.0)
	No	109	96,5	188	96,9	1,0
Bladder cancer (C67)						
	Yes	2	1,8	4	2,1	1.0 (0.2, 6.1)
	No	109	96,5	188	96,9	1,0
Nervous system cancer (C70, C71)						
	Yes	0	0,0	1	0,5	0,0
	No	111	98,2	191	98,5	1,0
Cancers of ill-defined, unspecified sites (C76-C80)						
	Yes	12	10,6	9	4,6	2.4 (0.9, 6.4)
	No	99	87,6	183	94,3	1,0
Lymphoid, haematopoietic tissue cancer (C81-C96)						
	Yes	8	7,1	6	3,1	3.3 (1.0, 11.4)
	No	103	91,2	186	95,9	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	30	26,5	61	31,4	0.8 (0.5, 1.4)
	No	81	71,7	131	67,5	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	18	15,9	28	14,4	1.2 (0.6, 2.4)
	No	93	82,3	164	84,5	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account;
excluding ovarian cancer;* The missing values (2 cases and 2 controls for each cancer) are not showed in table.
****The cancers with zero exposed subjects are not shown.

Table 19. Distribution of any family cancer history of all first degree relatives and matched OR* among females younger than 60 years

Cancer and ICD10 code		Cases N=101		Population controls N=179		OR (95% CI)
		N	%	N	%	
Any cancer						
	Yes	44	43,6	68	38,0	1.2 (0.7, 2.1)
	No	57	56,4	111	62,0	1,0
Cancer of upper aerodigestive tract (C00-C14)						
	Yes	1	1,0	1	0,6	1.0 (0.1, 16.0)
	No	100	99,0	178	99,4	1,0
Upper digestive tract cancer (C15-C17)						
	Yes	3	3,0	7	3,9	0.9 (0.2, 3.5)
	No	98	97,0	172	96,1	1,0
Colorectal cancer (C18-C20,C26)						
	Yes	3	3,0	8	4,5	0.5 (0.1, 2.0)
	No	98	97,0	171	95,5	1,0
Cancer of liver-biliary system (C22-C24)						
	Yes	1	3,0	5	2,8	0.4 (0.0, 3.3)
	No	100	97,0	174	97,2	1,0
Pancreas cancer (C25)						
	Yes	3	3,0	5	2,8	0.7 (0.1, 4.1)
	No	98	97,0	174	97,2	1,0
Lung cancer (C34)						
	Yes	5	5,0	12	6,7	0.7 (0.3, 2.2)
	No	96	95,0	167	93,3	1,0
Cancer of bone and articular cartilagen (C40-C41, C49)						
	Yes	3	3,0	1	0,6	5.0 (0.5, 50.0)
	No	98	97,0	178	99,4	1,0
Skin cancer (C43, C44)						
	Yes	5	5,0	4	2,2	2.1 (0.5, 8.1)
	No	96	95,0	175	97,8	1,0
Skin melanoma (C43)						
	Yes	1	1,0	1	0,6	1.0 (0.1, 16.0)
	No	100	99,0	178	99,4	1,0
Nomelanoma skin cancer (C44)						
	Yes	4	4,0	2	1,1	3.6 (0.6, 21.0)
	No	97	96,0	177	98,9	1,0
Breast cancer (C50)						
	Yes	7	6,9	15	8,4	0.8 (0.3, 2.4)
	No	94	93,1	164	91,6	1,0
Female genital organ cancer** (C51,C53,C55,C57)						
	Yes	6	5,9	10	5,6	0.9 (0.3, 2.8)
	No	95	94,1	169	94,4	1,0
Prostate cancer (C61)						
	Yes	4	4,0	6	3,4	1.3 (0.3, 5.1)
	No	97	96,0	173	96,6	1,0
Testicular cancer (C62)						
	Yes	1	1,0	1	0,6	1.7 (0.1, 30.8)
	No	100	99,0	178	99,4	1,0
Renal cancer (C64-C65)						
	Yes	3	3,0	1	0,6	5.0 (0.5, 50.0)
	No	98	97,0	178	99,4	1,0
Bladder cancer (C67)						
	Yes	2	2,0	2	1,1	1.2 (0.2, 8.6)
	No	99	98,0	177	98,9	1,0
Nervous system cancer (C70, C71)						
	Yes	1	1,0	2	1,1	0.7 (0.1, 8.0)
	No	100	99,0	177	98,9	1,0
Cancers of ill-defined, unspecified sites (C76-C80)						
	Yes	5	5,0	8	4,5	1.1 (0.3, 3.6)
	No	96	95,0	171	95,5	1,0
Lymphoid, haematopoietic tissue cancer (C81-C96)						
	Yes	5	5,0	5	2,8	2.1 (0.6, 7.3)
	No	96	95,0	174	97,2	1,0
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)						
	Yes	22	21,8	44	24,6	0.8 (0.4, 1.5)
	No	79	78,2	135	75,4	1,0
BRCA2-related cancers (C25, C43, C50, C61)						
	Yes	14	13,9	25	14,0	0.9 (0.4, 2.0)
	No	87	86,1	154	86,0	1,0

* All ORs were estimated by conditional logistic regression taking the matching factors into account;
**excluding ovarian cancer;

***The cancers with zero exposed subjects are not shown.

Table 20. Distribution of any family cancer history of all first degree relatives and adjusted OR*

Cancer and ICD10 code		Cases N=459		Population controls N=827		OR (95% CI)
		N	%	N	%	
Any cancer						
	Yes	192	41,8	306	37,0	1.3 (1.0, 1.6)
	No	263	57,3	514	62,2	1,0
Cancer of the upper aerodigestive tract (C00-C14, C32)						
	Yes	3	0,7	5	0,6	0.9 (0.2, 4.1)
	No	452	98,5	815	98,5	1,0
Upper digestive tract cancer (C15-C17)						
	Yes	40	8,7	87	10,5	0.8 (0.5, 1.2)
	No	415	90,4	733	88,6	1,0
Colorectal cancer (C18-C20, C26)						
	Yes	19	4,1	52	6,3	0.6 (0.3, 1.0)
	No	436	95,0	768	92,9	1,0
Cancer of liver-biliary system (C22-C24)						
	Yes	9	2,0	17	2,1	0.8 (0.4, 1.8)
	No	442	97,1	803	97,1	1,0
Pancreatic cancer (C25)						
	Yes	14	3,1	14	1,7	2.0 (0.8, 4.7)
	No	441	96,1	806	97,5	1,0
Lung cancer (C34)						
	Yes	22	4,8	57	6,9	0.7 (0.4, 1.2)
	No	433	94,3	763	92,3	1,0
Cancer of bone and articular cartilage (C40-C41, C49)						
	Yes	8	1,7	4	0,5	3.4 (1.0, 11.6)
	No	447	97,4	816	98,7	1,0
Skin cancer (C43, C44)						
	Yes	13	8,5	13	6,7	1.7 (0.8, 3.8)
	No	442	90,6	807	92,5	1,0
Skin melanoma (C43)						
	Yes	4	0,9	3	0,4	2.2 (0.5, 10.3)
	No	451	98,3	817	98,8	1,0
Nonmelanoma skin cancer (C44)						
	Yes	7	1,5	6	0,7	1.8 (0.6, 5.6)
	No	448	97,6	814	98,4	1,0
Breast cancer (C50)						
	Yes	39	8,5	55	6,7	1.4 (0.9, 2.1)
	No	416	90,6	765	92,5	1,0
Female genital organ cancer** (C51,C53,C55,C57)						
	Yes	20	4,4	35	4,2	1.0 (0.5, 1.8)
	No	435	94,8	785	94,9	1,0
Ovarian cancer (C56)						
	Yes	1	0,2	1	0,1	+∞
	No	454	98,9	819	99,0	1,0
Prostate cancer (C61)						
	Yes	16	3,5	20	2,4	1.7 (0.9, 3.5)
	No	439	95,6	800	96,7	1,0
Testicular cancer (C62)						
	Yes	5	1,1	5	0,6	1.4 (0.4, 5.1)
	No	450	98,0	815	98,5	1,0
Renal cancer (C64-C65)						
	Yes	9	2,0	12	1,5	1.5 (0.6, 3.5)
	No	446	97,2	808	97,7	1,0
Bladder cancer (C67)						
	Yes	5	1,1	9	1,1	0.8 (0.3, 2.5)
	No	450	98,0	811	98,1	1,0
Nervous system cancer (C70, C71)						
	Yes	8	1,7	9	1,1	1.7 (0.6, 4.5)
	No	447	97,4	811	98,1	1,0
Cancer of the thyroid (C73)						
	Yes	1	0,2	3	0,4	0.5 (0.0, 4.9)
	No	454	98,9	817	98,8	1,0
Cancers of unspecified sites (C76-C80)						
	Yes	27	5,9	28	3,4	1.9 (1.1, 3.4)
	No	428	93,2	792	95,8	1,0
Lymphoid, haematopoietic cancer (C81-C96)						
	Yes	19	4,1	26	3,1	1.7 (0.9, 3.2)
	No	436	95,0	794	96,0	1,0
Cancers of multiple sites (C97)						
	Yes	1	0,2	1	0,1	3.0 (0.2, 47.8)
	No	454	98,9	819	99,0	1,0
BRCA1-related cacners (C50,C25,C56,C44, C18,C34,C71,C61)						
	Yes	107	23,3	189	22,9	1.0(0.8, 1.4)
	No	348	75,8	631	76,3	1,0
BRCA2-related cancers (C25, C50, C61)						
	Yes	67	14,6	86	10,4	1.5 (1.1, 2.2)
	No	388	84,5	734	88,8	1,0

* All ORs were estimated by conditional logistic regression and adjusted by family size. **excluding ovarian cancer
*** The missing values (4 cases and 7 controls) are not shown in table.

Table 22. Estimated OR* for family cancer histories by different definition of a positive family history among males

Cancer and ICD10 code	Family history							
	All 1st degree relatives		Parents +Sibling		Sibling only		Parents only	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Any cancer	1,4	1.0-2.0	1,4	1.0-2.0	1,6	1.0-2.7	1,4	0.9-2.0
Cancer of upper aerodigestive tract (C00-C14, C32)	0,4	0.0-3.7	0,4	0.0-3.7	0,9	0.1-11.4	0,0	
Upper digestive tract cancer (C15-C17)	1,3	0.6-2.7	1,3	0.6-2.7	1,7	0.2-13.2	1,2	0.5-2.7
Colorectal cancer (C18-C20, C26)	0,9	0.5-1.9	0,9	0.5-1.9	0,7	0.2-2.8	1,2	0.5-2.7
Cancer of liver-biliary system (C22-C24)	1,8	0.5-6.4	1,8	0.5-6.4	1,7	0.1-30.8	1,8	0.4-7.5
Pancreatic cancer (C25)	2,5	0.7-9.4	2,5	0.7-9.4	1,0	0.1-16.0	3,2	0.7-14.1
Lung cancer (C34)	0,5	0.2-1.1	0,5	0.2-1.1	3,2	0.7-14.9	0,3	0.1-0.9
Cancer of bone and articular cartilage (C40-C41, C49)	7,7	0.8-71.3	7,7	0.8-71.3	+∞		4,4	0.4-51.2
Skin cancer (C43, C44)	0,9	0.3-3.2	1,2	0.3-4.1	5,3	0.5-58.7	0,6	0.1-3.0
Skin melanoma (C43)	3,0	0.2-48.0	3,0	0.2-48.0	+∞		0,0	
Nonmelanoma skin cancer (C44)	0,7	0.1-3.9	1,0	0.2-6.3	0,0		1,0	0.2-6.3
Breast cancer (C50)	1,9	1.0-3.8	1,9	1.0-3.8	2,4	1.0-6.2	1,5	0.6-3.4
Female genital organ cancer** (C51,C53,C55,C57)	0,8	0.3-2.2	0,8	0.3-2.2	0,8	0.1-4.8	1,0	0.3-3.0
Ovarian cancer (C56)	0,0		0,0		0,0		0,0	
Prostate cancer (C61)	2,3	0.8-6.3	2,3	0.8-6.3	5,3	0.6-49.4	1,7	0.5-5.7
Testicular cancer (C62)	1,5	0.3-7.8	1,6	0.2-11.7	1,4	0.1-23.6	1,7	0.1-30.8
Renal cancer (C64-C65)	1,1	0.3-4.0	1,1	0.3-4.0	0,7	0.1-6.6	1,5	0.3-6.9
Cancer of bladder (C67)	0,4	0.0-3.8	0,4	0.0-3.8	0,0		0,4	0.0-3.8
Nervous system cancer (C70, C71)	2,3	0.8-7.1	2,3	0.8-7.1	0,4	0.0-3.4	12,4	1.5-106.6
Cancer of thyroid (C73)	0,0		0,0		0,0		0,0	
Cancer of unspecified sites (C76-C80)	2,0	0.8-5.0	2,0	0.8-5.0	1,2	0.3-4.4	3,1	0.9-10.4
Lymphoid, haematopoietic tissue cancer (C81-C96)	1,0	0.4-2.7	0,9	0.3-2.7	0,8	0.2-3.4	1,0	0.2-5.1
Cancer of multiple siyes (C97)	+∞		+∞		0,0		+∞	
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)	1,3	0.9-1.9	1,3	0.9-1.9	1,9	1.0-3.4	1,1	0.7-1.8
BRCA2-related cancers (C25, C43, C50, C61)	2,2	1.3-3.7	2,2	1.3-3.7	3,1	1.3-7.1	1,8	1.0-3.5

* OR=Odds ratios; all ORs were estimated by conditional logistic regression taking the matching factors into account; **excluding ovarian cancer;

Table 23. Estimated OR* for family cancer histories by different definition of a positive family history among females

Cancer and ICD10 code	Family history							
	All 1st degree relatives		Parents +Sibling		Sibling only		Parents only	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Any cancer	1,1	0.8-1.6	1,2	0.8-1.7	1,1	0.7-1.8	1,2	0.8-1.8
Cancer of upper aerodigestive tract (C00-C14, C32)	3,0	0.3-35.8	3,0	0.3-35.8	+∞		1,0	0.1-16.0
Some digestive tract cancer (C15-C17)	1,0	0.4-2.3	1,0	0.4-2.3	0,3	0.0-2.7	1,4	0.5-3.7
Colorectal cancer (C18-C20, C26)	0,5	0.2-1.1	0,5	0.2-1.0	0,2	0.0-2.0	0,5	0.2-1.1
Cancer of liver-biliary system (C22-C24)	0,5	0.2-1.7	0,4	0.1-1.5	0,3	0.0-3.1	0,5	0.1-2.3
Pancreatic cancer (C25)	1,6	0.5-5.1	1,6	0.5-5.1	0,0		3,3	1.0-11.5
Lung cancer (C34)	0,9	0.4-1.8	0,9	0.4-1.8	0,9	0.3-2.9	0,7	0.3-1.6
Cancer of bone and articular cartilage (C40-C41, C49)	2,0	0.4-9.5	2,0	0.4-9.5	0,0		2,8	0.5-15.7
Skin cancer (C43, C44)	2,9	0.9-9.0	3,5	1.0-12.1	7,7	0.8-71.3	2,2	0.5-10.3
Skin melanoma (C43)	1,9	0.3-11.8	3,0	0.3-35.8	+∞		1,0	0.1-16.0
Nonmelanoma skin cancer (C44)	4,3	0.8-23.1	4,3	0.8-23.1	3,0	0.3-35.8	5,6	0.5-57.3
Breast cancer (C50)	1,0	0.5-1.8	0,9	0.5-1.8	0,8	0.3-2.2	1,2	0.6-2.6
Female genital organ cancer** (C51,C53,C55,C57)	0,9	0.4-2.1	0,9	0.4-2.1	0,9	0.1-5.3	1,2	0.5-2.6
Ovarian cancer (C56)	1,7	0.1-30.8	1,7	0.1-30.8	+∞		0,0	
Prostate cancer (C61)	1,4	0.5-3.7	1,4	0.5-3.7	0,8	0.1-6.7	1,7	0.5-5.5
Testicular cancer (C62)	1,3	0.2-9.8	3,0	0.3-35.8	1,7	0.1-30.8	+∞	
Renal cancer (C64-C65)	1,9	0.5-6.8	1,9	0.5-6.8	1,0	0.2-5.8	5,2	0.5-50.4
Cancer of bladder (C67)	1,1	0.3-4.1	1,1	0.3-4.1	1,1	0.1-12.7	1,1	0.2-4.9
Nervous system cancer (C70, C71)	0,5	0.1-5.5	1,0	0.1-11.9	0,0		1,7	0.1-30.8
Cancer of thyroid (C73)	1,4	0.1-23.6	1,4	0.1-23.6	+∞		0,0	
Cancer of unspecified sites (C76-C80)	1,8	0.8-3.8	1,8	0.8-3.7	1,3	0.5-3.5	2,2	0.9-5.8
Lymphoid, haematopoietic tissue cancer (C81-C96)	2,6	1.1-6.3	2,7	1.1-6.7	2,2	0.7-7.5	3,0	0.8-10.8
Cancer of multiple siyes (C97)	0,0		0,0		0,0		0,0	
BRCA1-related cancers (C18, C25,C34, C43,C50,C56, C61,C71)	0,8	0.6-1.2	0,9	0.6-1.3	0,8	0.4-1.6	0,9	0.6-1.4
BRCA2-related cancers (C25,C43, C50, C61)	1,1	0.7-1.8	1,2	0.7-1.9	0,8	0.3-1.7	1,7	0.9-3.0

* OR=Odds ratios; all ORs were estimated by conditional logistic regression taking the matching factors into account; **excluding ovarian cancer;

Theses

1. Although a rare disease, uveal melanoma is the most common malignant intraocular tumour among adult. Its incidence rates have been observed between 4.9 and 9.4 per million person year for the period from 1983 to 1988 in Europe.
2. The relative 5-year survival rates were approximately 70% in 1960 and increased to 82% in 1998 in the world.
3. However, little is known about its aetiology. Besides some risk indicators like age, light iris colour and light skin, most of risk factors are weakly or inconsistently associated with UM.
4. Family history and own history of cancer have been reported to be associated with an increased risk of some cancers. However, there are only few studies focusing on the association between uveal melanoma and family history and own history of cancer.
5. The aim of this study was to estimate the risk of uveal melanoma among persons who reported a family history or own history of cancer.
6. This study is referred to as RIFA case-control study and carried out from Feb. 1$^{st.}$ 2002 to Mar. 14th. 2005 in Germany. A total of 455 cases and 827 population controls were recruited, matching on sex, age and region of residence. The own cancer history and family cancer history in the first degree relatives were collected through computer assisted telephone interviews.
7. An increased risk was found among participants with a family history or own history of any cancer and this risk was observed to be increased by 90% among females having suffered any cancer. An increased risk was also observed among participants younger than 60 years.
8. Participants who reported to have a family history of breast cancer were observed to have a 30% increased risk of UM. An 80% increased risk was also found among participant with a family history of prostate cancer.
9. A family history of any BRCA2-related cancer is observed to be positively associated with the risk of UM, specifically among males only. This association is not found among females.

10. There are various potential limitations in this study that need to be taken into account. The analytical results are based on the recollection of cancer history, and the response proportion among the controls was low. To minimize information bias, lots of methods were used, such as questionnaire-techniques, training of interviewers, etc. .
11. Although the statistical power is limited for some cancers of lower prevalence reported in own history or family history, the present results contribute to the underestimating of the association between cancer history and risk of uveal melanoma.

Lebenslauf

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Selbständigkeitserklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritte und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quellen gekennzeichnet.

Halle, 14.01.2007 Hui Zhang

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