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Terhi Huttunen

Saccular Intracranial Aneurysm Disease in Eastern Finnish Population

Phenotype on Admission Long-term Excess Mortality Risk of Cancer

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EASTERN FINLAND

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ABSTRACT

Saccular intracranial aneurysms (sIAs) form during life at the branching sites of intracranial extracerebral arteries in the cerebrospinal fluid space. Rupture of the sIA wall is the most frequent cause of aneurysmal subarachnoid hemorrhage (aSAH), a devastating form of stroke that affects working aged population. Kuopio Neurosurgery sIA Database (www.uef.fi/ns) contains all cases of aSAH or unruptured sIAs admitted to the Kuopio University Hospital (KUH) since 1980 from the KUH catchment area in Eastern Finland. From 1980 to 2007, the geographic area remained the same, the population decreased from 863,726 to 851,066, the median age increased from 31 to 42 years in males and from 34 to 45 years in females, and the proportion of males remained at 49%. In the present study, we analysed (I) the phenotype, (II) long-term excess mortality, and (III) risk of cancer in 2904 consecutive sIA cases from 1980 to 2007, 618 unruptured (170 familial and 448 sporadic) and 2286 ruptured (aSAH) cases (308 familial and 1978 sporadic).

(I) From 1980 to 2007, familial and sporadic sIA patients aged along the catchment population. In familial sIA patients, the phenotype was modestly different from sporadic. The MCA bifurcation and the ACoA were almost as frequent for the ruptured sIAs, but the MCA bifurcation was clearly dominant among the unruptured ones, suggesting different etiologies for the sIA formation and rupture.

(II) The long term excess mortality of 244 familial and 1,502 sporadic one-year aSAH survivors was analysed as compared to the matched KUH catchment population. There was 12% excess mortality at 15 years. The causes of the long term excess mortality are heterogeneous, and more detailed analyses are required.

(III) The standardised incidence ratios (SIRs) of cancers after first diagnosis of sIA disease were calculated as against the matched KUH population. Lung cancer developed significantly more often in aSAH patients, SIR 2.4 for males and 2.5 for females. Long-term smoking habits of sIA disease carriers should be elucidated, and their abstinence from smoking should be supported and monitored.

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Medical Subject Headings: Intracranial Aneurysm; Subarachnoid Hemorrhage; Familial Disease; Phenotype on Admission; Excess Mortality; Cancer; Lung Neoplasms; Standardised Incidence Ratio.

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TIIVISTELMÄ

Sakkulaarinen intrakraniaalinen aneurysma (sIA) muodostuu kallonsisäisten, aivojen pinnalla likvoritilassa olevien valtimoiden haarautumiskohtiin. Aneurysmaattinen subaraknoidaalivuoto (aSAV), joka johtuu lähes aina sIA-seinämän puhkeamisesta, on hengenvaarallinen stroken muoto, joka kohdistuu työikäiseen väestöön. Kuopio Neurosurgery sIA Database (www.uef.fi/ns) sisältää kaikki aSAV- ja sIA-potilaat, jotka ovat tulleet hoitoon Kuopion yliopistollisen sairaalaan (KYS) 1980 lähtien KYSin vastuualueelta Keski- ja Itä-Suomesta. Ajanjaksolla 1980–2007 vastuualue on pysynyt samana, vastuuväestö hieman vähentynyt (863,726–851,066), keski-ikä selvästi lisääntynyt (miehillä 31–42; naisilla 34–45), ja miesten osuus pysynyt samana (49%). Tutkimme (I) sIA-taudin ilmiasua hoitoon tullessa sekä suhteellista (II) ylikuolleisuutta ja (III) syöpäriskiä verrattuna kaltaistettuun vastuuväestöön. Tutkimuskohortin muodosti 2904 sIA-potilasta (1980–2007), joista 618 vuotamattomia (170 familiaalista) ja 2286 vuotaneita (308 familiaalista).
(I) Ajanjaksolla 1980–2007 sekä familiaaliset että sporadiset sIA-potilaat ikääntyiväit vastuuväestön mukaisesti. Familiaaliset potilaat poikkesivat fenotyypiltään vain lievästi sporadisista. Keskimmäisen aivovaltimon haarautumiskohta ja etummainen yhdysvaltimo olivat lähes yhtä tavallisia puhjenneen aneurysman sijaintikohtia. Keskimmäisen aivovaltimon haarautumiskohta oli sen sijaan ylivoimaisesti tavallisin vuotamattomien aneurysmien sijainti. Löydös viittaa siihen, että aneurysman muodostumiseen ja puhkeamiseen vaikuttavat erilaiset riskitekijät.
(II) Suhteellista ylikuolleisuutta analysoitiin 1746 aSAV-potilaalla (244 familiaalista), jotka olivat hengissä 12 kuukautta vuodon jälkeen. Heidän ylikuolleisuutensa 15 vuoden seurannassa oli 12 %. Ylikuolleisuuden syyt ovat todennäköisesti monitekijäisiä, ja niitä on syytä analysoida tarkemmin.
(III) Potilailla laskettiin eri syöpien suhteellinen esiintyvyys (standardised incidence ratio, SIR) sIA-diagnoosin jälkeen verrattuna KYSin vastuuväestöön. Keuhkosyöpää esiintyi merkitsevästi enemmän aSAV-potilailla (SIR miehille 2.4 ja naisille 2.5). sIA-potilaiden tupakointia tulee tutkia tarkemmin ja lopettamista seurata ja tukea.

Luokitus: C10.228.140.300.510.600
Yleinen suomalainen asiasanasto: aivovaltimoaneurysma; lukinkalvon alainen aivoverenvuoto; familiaalinen tauti; pitkäaikaisylikuolleisuus; syövät; keuhkosyöpä; suhteellinen syövän esiintyvyys.

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Kuopio, June 2012

Terhi Huuskonen, née Huttunen

The list of original publications

This dissertation is based on the following original publications:

I Huttunen T, von und zu Fraunberg M, Frösen J, Lehecka M, Tromp G, Helin K, Koivisto T, Rinne J, Ronkainen A, Hernesniemi J, Jääskeläinen JE. Saccular intracranial aneurysm disease: distribution of site, size, and age suggests different etiologies for aneurysm formation and rupture in 316 familial and 1454 sporadic eastern Finnish patients. *Neurosurgery 66: 631-638, 2010.*

II Huttunen T, von und zu Fraunberg M, Koivisto T, Ronkainen A, Rinne J, Sankila R, Seppä K, Jääskeläinen JE. Long-term excess mortality of 244 familial and 1502 sporadic one-year survivors of aneurysmal subarachnoid hemorrhage compared with a matched Eastern Finnish catchment population. *Neurosurgery 68: 20-27, 2011.*

III Huttunen T, Riihinen A, Pukkala E, von und zu Fraunberg M, Koivisto T, Ronkainen A, Rinne J, Sankila R, Jääskeläinen JE. Increased relative risk of lung cancer in 2 904 patients with saccular intracranial aneurysm disease in Eastern Finland. *Neuroepidemiology 38: 93-99, 2012.*

Contents

Abbreviations

A1	Proximal segment of anterior cerebral artery
A2-5	A2-5 segment of anterior cerebral artery
ACA	Anterior cerebral artery
ADPKD	Autosomal dominant polycystic kidney disease
aSAH	Aneurysmal subarachnoid hemorrhage
ACoA	Anterior communicating artery
BA	Basilar artery
BAbif	Basilar bifurcation
CSF	Cerebrospinal fluid
CI	Confidence interval
CT	Computed tomography
CTA	Computed tomographic angiography
DSA	Digital substraction angiography
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Score
H&H	Hunt & Hess grade
ICA	Internal carotid artery
ICH	Intracerebral hematoma
ICP	Intracranial pressure
ISAT	International Subarachnoid Aneurysm Trial
ISUIA	International Study of Unruptured Intracranial Aneurysms
IVH	Intraventricular hemorrhage
KUH	Kuopio University Hospital
MCA	Middle cerebral artery
MBif	Middle cerebral artery bifurcation
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
OR	Odds ratio
PCA	Posterior cerebral artery
PCoA	Posterior communicating artery
PICA	Posterior inferior cerebellar artery
RER	Relative excess risk of death
RSR	Relative survival ratio
sIA	Saccular intracranial aneurysm
SIR	Standardised incidence ratio
SMR	Standardised mortality ratio
SNP	Single nucleotide polymorphism
VA	Vertebral artery
VBA	Vertebrobasilar artery

1 Introduction

Saccular intracranial aneurysms (sIAs) develop during life in some 2% of population (Ronkainen et al., 1998). Rupture of the sIA wall causes almost all cases of aneurysmal subarachnoid hemorrhage (aSAH) (van Gijn et al., 2007). Acute aSAH is a complex and critical systemic condition. Survivors of the primary bleed require multidisciplinary neurointensive care to prevent further damage, e.g., from rebleeding, hydrocephalus, increased intracranial pressure (ICP), delayed ischemic brain injury, seizures, electrolyte disturbances, cardiac and pulmonary dysfunction, and complications of the management (Bederson et al., 2009; Levine, 2009). There is a significant excess mortality for at least one year after acute aSAH (Guresir et al., 2008; Hernesniemi et al., 1993; Langham et al., 2009; Lehecka et al., 2008; Molyneux et al., 2005; O'Kelly et al., 2009; Rosengart et al., 2007; van der Bilt et al., 2009; Wartenberg et al., 2006). Sequelae of aSAH may cause long-term mortality, e.g., by predisposing to epilepsy, depression, dementia, shunt complications, hypothalamic and hypophyseal disorders, or cerebrovascular events.

The sIA disease is a complex trait, (Hardy and Singleton, 2009; Hindorff et al., 2009) affected by acquired risk factors and variants of the genome which may sensitize also to cardiovascular events in later life (Ronkainen et al., 2001). Its phenotypic tissue, branching site of major cerebral artery under hemodynamic stress (Alnaes et al., 2007), is poorly characterized in embryonic and adult cellular and molecular biology. Known risk factors include age, female sex, smoking, hypertension, and excess drinking (Feigin et al., 2005), and at least 10% of aSAH patients have a family history (Ronkainen et al., 1997; Ruigrok et al., 2005). In the Kuopio sIA Database, the criteria for an sIA family is at least two affected first-degree relatives. Mechanisms by which risk factors affect the formation of sIA pouch (primary phenotype) and the rupture of sIA wall (secondary phenotype) have to be elucidated for novel methods to identify sIA carriers and to occlude sIA pouches (Shi et al., 2009).

A variant on 9p21 associated with coronary artery disease, abdominal aortic aneurysm and sIA in 1,131 sIA patients from Finland, the Netherlands and Iceland (Helgadottir et al., 2008). In a genome-wide SNP association study, new loci on 2q33 and 8q11 and the previous one on 9p21 were identified in 2,045 sIA patients from Finland, the Netherlands and Japan (Bilguvar et al., 2008). For further genomic, and epigenomic, studies of the Finnish sIA disease, more data on the phenotype, acquired risk factors, and concomitant arterial diseases are required. In familial sIA patients from Southern Finland and Eastern Finland, genome-wide linkage analysis showed linkage to 19q13 (van der Voet et al., 2004) and Xp22 (Olson et al., 2002), both replicated in Japan (Yamada et al., 2004) as well as to kallikrein gene cluster (Weinsheimer et al., 2007). However, it is uncertain how relevant the linkage data is.

The Eastern Finnish gene pool has been particularly affected by a small number of founders, isolation, and major bottlenecks (Peltonen et al., 1999).

Neurosurgery of Kuopio University Hospital (KUH) has solely provided full-time acute and elective neurosurgical services for the KUH catchment area in Eastern Finland (Figure 1.1). KUH Neurosurgery maintains a database on all cases of aSAH or unruptured IAs admitted to the KUH since 1977, retrospectively from 1977 to 1989, and prospectively from 1990.

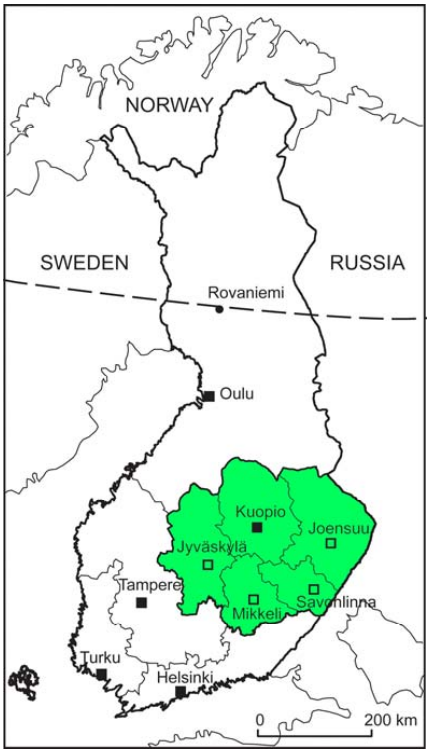

Figure 1.1 Map of the catchment area of Kuopio University Hospital (KUH), containing 4 central hospitals in Joensuu, Jyväskylä, Mikkeli, and Savonlinna. The areas of the 4 other university hospitals in Helsinki, Oulu, Tampere, and Turku are also delineated.

In the present study, we used an overall cohort of 2904 consecutive sIA cases from 1980 to 2007, 618 unruptured (170 familial and 448 sporadic) and 2286 ruptured (aSAH) cases (308 familial and 1978 sporadic). We analysed the following aspects of Eastern Finnish sIA disease:

(I) phenotype of sporadic and familial sIA patients and their unruptured and ruptured sIAs on admission,
(II) long-term excess mortality of aSAH patients as compared to matched KUH catchment population, and
(III) long-term relative risk of cancer as compared to matched KUH catchment population.

This study is a part of the long-term research efforts of the Kuopio sIA Database to characterize the Eastern Finnish sIA disease in terms of phenotypical distribution at first diagnosis, concomitant diseases, familial influence, and long-term outcome from the sIA disease and from concomitant diseases. This will serve two purposes. First, our data will support the design of preventive and follow-up actions to be implemented for sporadic and famial unruptured and ruptured sIA patients. Second, our data will support the long-term effort of disclosing familial and/or genomic background and molecular biology of the sIA formation and rupture.

2 Background of the study

2.1 SACCULAR INTRACRANIAL ANEURYSM (SIA) AND SUBARACHNOID HEMORRHAGE (ASAH)

2.1.1 Segmental anatomy of intracranial extracerebral arteries

The Circle of Willis is an anastomotic arterial polygon between the two internal carotid arteries (ICAs) and the vertebrobasilar system (Figure 2.1). The internal carotid artery (ICA) is divided into the C1 to C7 segments. The anterior cerebral artery (ACA) starts from the ICA bifurcation, and it is divided into the A1 to A5 segments. The proximal A1 segment is between the ICA bifurcation and the anterior communicating artery (ACoA). Traditionally, the distal part A2 to A5 is called the pericallosal artery. The middle cerebral artery (MCA) starts from the ICA bifurcation, and it is divided into the proximal M1 segment, the MCA bifurcation (Mbif), and the distal M2 to M4 segments. The posterior cerebral artery (PCA) starts from the distal bifurcation of the basilar artery (BA), which starts from the end fusion of the two vertrebral arteries (VAs). The two posterior communicating arteries (PCoA) between the ICAs and the PCAs complete the Circle of Willis.

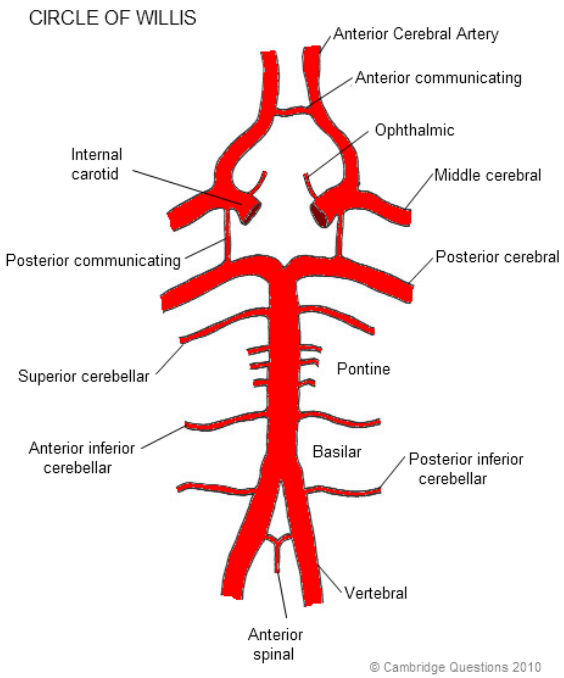

Figure 2.1 Circle of Willis

2.1.2 Definition of saccular intracranial extracerebral artery aneurysm

Saccular intracranial aneurysms (sIAs) are balloon-like dilatations that form during life at the branching sites of the intracranial extracerebral arteries in the cerebrospinal fluid (CSF) space in the proximity of the Circle of Willis (Figure 2.2). Rupture of the sIA wall is by far the most frequent cause of aneurysmal subarachnoid hemorrhage (aSAH), a devastating and third frequent form of stroke that affects working aged population (van Gijn et al., 2007; Bederson et al., 2009). At present, the diagnosis of unruptured and ruptured sIAs requires angiography (CTA, MRA, DSA).

Fusiform aneurysms, spindle shaped dilatations of the arterial trunk, are dominant, e.g., in the aorta. Fusiform aneurysms are uncommon in the intracranial extracerebral arteries, forming only 4% of all diagnosed aneurysms in the Kuopio sIA Database (Huttunen et al., 2010).

2.1.3 Incidence of sIA disease

Some 2% of population develops sIAs (Ronkainen et al., 1998; Feigin et al., 2005), i.e., some 108 000 of 5,4 million Finnish citizens. However, most sIA carriers do not have rupture during their life time as the general annual incidence of aSAH was 4-7 per 100 000 in the latest meta-analysis (Feigin et al., 2009). For unknown reasons, aSAH is thrice as frequent in Finland and Japan than elsewhere (de Rooij et al., 2007). In 2006 in Finland, there were 929 aneurysmal aSAH cases (I60.0-7) with 319 deaths (34%) within 12 months (Arto Pietilä and Veikko Salomaa www.ktl.fi/cvdr).

2.1.4 Medial gap

The phenotypic tissue of the sIA disease is very restricted, the medial gap (Canham and Finlay, 2004) (Figure 2.2) under hemodynamic stress at the branching sites of intracranial extracerebral arteries (Isaksen et al., 2008). The medial gap is a seal that forms between the medial bases of the two daughter branches that start from the mother branch during the embryonal morphogenesis. This is one manifestation of the embryonal branching morphogenesis seen in many other organs such as the bronchial tree or the bile ducts (Horowitz and Simons, 2008). The embryonal formation of the intracranial extracerebral artery system and the Circle of Willis has been amazingly poorly described in the medical literature on embryology.

2.1.5 Biology of sIA wall

Aneurysm wall lacks internal elastic lamina and normal intima-media-adventitia layers (Scanarini et al., 1978). The wall of unruptured sIAs is characterized by myointimal hyperplasia and organizing thrombus, whereas that of ruptured sIAs is characterized by a decellularized, degenerated matrix and a poorly organised luminal thrombus (Frosen et al., 2012). Vascular remodelling, increased inflammation, complement activation and apoptosis associate with the rupture of sIA wall (Frosen et al., 2012; Frosen et al., 2004; Tulamo et al., 2006). Cell-mediated and humoral inflammatory reaction is seen in both, but inflammation is clearly associated with degenerated and ruptured walls. The key event in the processes that lead to cell

death and subsequent matrix degeneration in the sIA wall may be the loss of functioning endothelium and subsequent thrombus formation on the luminal surface of the sIA wall. The dysfunction of the endothelium can be caused by the aberrant flow conditions in the sIA lumen caused by sIA geometry. This results in accumulation of cytotoxic and pro-inflammatory substances into the sIA wall, as well as thrombus formation. This may start the processes that eventually can lead to the decellularized and degenerated sIA wall that is prone to rupture (Frosen et al., 2012).

A recent study from our group compared the fresh samples of 11 ruptured and 8 unruptured sIAs, using whole genome microarray profiling (Kurki et al., 2011) – 799 genes were significantly upregulated and 421 downregulated in the ruptured sIA walls. Response to turbulent blood flow, chemotaxis, leukocyte migration, oxidative stress, vascular remodelling, and extracellular matrix degradation were active in the ruptured sIA walls. Pathway analysis and in silico transcription factor analysis suggested that TLR signalling and regulation by NF-κB, HIF1A and ETS transcription factors have key roles in the ruptured sIA walls.

2.1.6 Hemodynamics of sIA wall

Local hemodynamics and geometry of the bifurcation area are often implicated in the formation of saccular aneurysms and their rupture (Ingebrigtsen et al. 2004; Meng et al., 2007) (Figure 2.2). The carina of the bifurcation is thought to be exposed to the maximum impact of hemodynamic shear stress (van der Kolk et al., 2010). Bifurcations with sharp angles, significantly deviating the flow, may be in an increased risk for sIA formation (Bor et al., 2008). The hemodynamics and shear forces in the area of the Circle of Willis have been extensively mathematically modelled (Alnaes et al., 2007). A model based on patient specific CTA data and flexible sIA wall showed that high wall tension and wall displacement clustered at the aneurysm dome, the usual site of rupture (Isaksen et al., 2008). The geometry of sIA wall is not usually stable, many sIAs grow or change in shape during follow-up (Juvela et al., 2001). The shape and size of the sIA can change either by expansion of the wall due to proliferation of mural cells, or by distension due to hemodynamic stress or by the combination of these two mechanisms (Frosen et al., 2012).

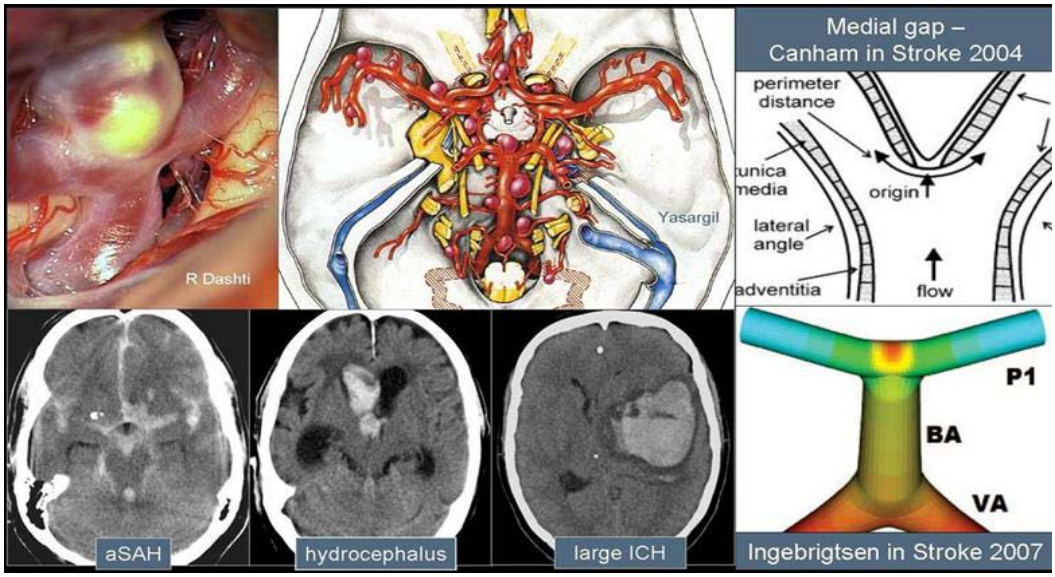

Figure 2.2 Saccular intracranial aneurysm (sIA) and subarachnoid hemorrhage (aSAH). Upper row from left to right. Unruptured sIA in the bifurcation of the internal carotid artery. The Circle of Willis connecting the intracranial extracerebral arteries with sIAs in the main branching sites. The medial gap area in the bifurcation.
Lower row from left to right. Typical acute aSAH in computed tomography (CT), blood in the CSF spaces appearing white. Acute aSAH with intraventricular hemorrhage and acute hydrocephalus. Acute aSAH with large intracerebral hemorrhage. Hemodynamic model of basilar artery bifurcation area.

2.1.7 Familial sIA disease

At least 10% of the aSAH patients have a familial background (Ruigrok et al., 2005; Ronkainen et al., 1997). The estimates of relative risks of familial aSAH varies from 4.1 to 6.6 (Ruigrok et al., 2001). A Danish population based cohort study of 9,367 patients and their 14,781 first degree relatives concluded that first degree relatives of patients with aSAH have a threefold to fivefold increased risk of aSAH as compared with the general population (Gaist et al., 2000). Another study looked at the cumulative incidence in 163 aSAH patients with 1290 first degree relatives and 3,588 second degree relatives. Ten first degree relatives and four second degree relatives had aSAH resulting in a hazard ratio of 6.6 (CI 2.0-21) (Bromberg, 1995). Familial clustering suggests that genomic variants – as well as epigenomic variation – are involved in the sIA disease. For previous phenotypic, outcome and genomic studies see the section Eastern Finnish sIA disease.

2.1.8 Genomics of sIA disease

The Finnish population is particularly prone to aSAH (de Rooij et al., 2007). The genetic homogeneity of Finns (Peltonen et al., 1999) may support the identification of genomic variants behind the complex sIA disease, affected by inherited as well as acquired risk factors. A variant on 9p21 associated with coronary artery disease, abdominal aortic aneurysm and sIA in 1131 sIA patients from Finland, the

Netherlands and Iceland (Helgadottir et al., 2008). LD block contains CDKN2A and CDKN2B with roles, e.g., in cancer and senescence (Helgadottir et al., 2008). In the first genome-wide SNP association study, new loci on 2q33 and 8q11 and the previous one on 9p21 were identified in 2045 sIA patients from Finland, the Netherlands and Japan (Bilguvar et al., 2008). In the follow up genomewide association study, loci 8q11.23-q12.1 and 9p21.3 were confirmed, and three new loci – 10q24.32 and CNNM2 – 13q13.1 and STARD13 – 18q11.2 and RBBP8 were identified (Yasuno et al., 2010). The functional significance of these loci is not known. One of the current trends is to find out large sIA families for exomic or genomic sequencing.

Certain inherited traits are associated with increased risk of the sIA disease, and may function as models in the molecular biology studies of the sIA disease. Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in the PKD1 or PKD2 genes (Mangos et al., 2010). About 1% of aSAH patients carry ADPKD, and 10% ADPKD patients develop sIAs (Ronkainen et al., 1997). Connective tissue syndromes Marfan (mutation in FBN1), Ehlers-Danlos type IV (COL3AI), and Loyes-Dietz (TGFBR1 and TGFBR2) predispose to vascular anomalies, including aortic and other arterial aneurysms and dissection, generalized arterial tortuosity, and fusiform aneurysm, but not saccular intracranial aneurysms (Loeys et al., 2005; Rodrigues et al., 2009; Oderich et al., 2005; Ruigrok et al., 2011).

2.2 RISK FACTORS OF SIA DISEASE

Age

Incidence of the sIA disease increases with age, being very low in the two first decades of life (Juvela, 2003; Inagawa, 2005; Rinkel et al., 1998). The median age for aSAH is in the fifth and sixth decades of life (Nieuwkamp et al., 2009).

Female gender

In general, females have sligthly dominated in the cohorts of unruptured and ruptured sIA disease (Rinkel et al., 1998). Reasons for the female dominance are not understood. It has been suggested that deacreased oestrogen production after the menopause would play a factor. In a meta-analysis (Feigin et al., 2005), hormone replacement therapy was associated with nonsignificantly reduced risk of SAH in one longitudinal study (Stampfer et al., 1991) and with 40% significantly reduced risk of SAH in two population-based case-control studies (Mhurchu et al., 2001) (Longstreth et al., 1994).

Hypertension

In a meta-analysis, hypertension increased the risk of SAH by ≈2.5× in longitudinal and case-control studies and was 30% more hazardous in women (Feigin et al., 2005).

Hypertension together with smoking are the most important modifiable risk factors of the sIA disease at population level.

A recent study found significant association of sIA disease with a risk allele at immediate proximity to endothelin receptor type A (ENDRA; 4q31.23) (Yasuno et al., 2011). ENDRA and ENDRB play key roles in the maintenance of the vasculature by controlling the balance between vasoconstriction and vasodilatation in response to hemodynamic stress. The endothelin system has been implicated in the pathogenesis of primary hypertension (Humbert et al., 2004). Hypertension and smoking, both well-established risk factors of IA pathogenesis, have been shown to alter the expression of endothelins (Xu et al., 2010). Furthermore, a variant in the suggestive IA locus at 5q23.2 (PRDM6) associated with increased systolic blood pressure in general European population (Yasuno et al., 2011; Gaál et al., 2012).

Smoking

In a Finnish single center series of 278 consecutive aneurysmal SAH patients and 314 hospitalized controls, published in 1993, the proportion of non-smokers were 12% vs. 41% in males and 47% vs. 61% in females (Juvela et al., 1993). Over 90% of male lung cancer patients are smokers (Tyczynski et al., 2003). Furthermore, smoking is a risk factor for cancers of the lung, upper aero-digestive tract (oral cavity, nasal cavity and sinuses, pharynx, larynx, oesophagus), pancreas, stomach, liver, lower urinary tract (renal pelvis and bladder), kidney and uterine cervix (Dreyer et al., 1997). In a meta-analysis, ever smoking was associated with a 2.2- to 3.1-fold increase when compared with never smoking, and current smoking had a 2.2- to 3.1-fold increased risk when compared with never and former smoking combined (Feigin et al., 2005).

Smoking alters the function of vascular endothelium, initiates the adhesion cascade and stimulates the vascular inflammatory events leading to atherosclerosis and hypertension (Balakumar and Kaur, 2009). However, the exact mechanisms by which smoking would affect the sIA wall are not known, but indirect evidence suggests inflammation and degradation of connective tissue.

Alcohol

Heavy (>150g/week) alcohol consumption (relative risk 1.5 to 2.1) is also a modifiable risk factor, accounting for 11% to 21% of the population-attributable risk for aSAH (Ruigrok et al., 2001). Data from several studies has demonstrated an increased risk od aSAH in relation to alcohol intoxication and binge drinking (Inagawa, 2001; Juvela et al., 1993; Kissela et al., 2002; Leppala et al., 1999; Longstreth et al., 1992; Feigin et al., 2005). Nonetheless, the mechanisms how alcohol predisposes to aSAH are not fully understood.

Weekly and seasonal variation in aSAH

Daily variation in hemorrhagic stroke has been analysed in several studies, with the peaks of SAH on the weekend (Juvela et al., 1993), on Sundays (Feigin et al., 2002), or on Mondays (Lin et al., 2008; Wang et al., 2002; Turin et al., 2007; Kelly-Hayes et al., 1995). Our group have showed that Sundays and Mondays are the most frequent and Saturdays the least frequent days of aSAH in Eastern Finnish population (Lindgren et al., 2011).

2.3 DIAGNOSIS, TREATMENT AND PREVENTION OF ASAH

2.3.1 Clinical appearance and diagnostics of aSAH

Symptoms and signs of aSAH include meningeal irritation (sudden and severe headache, vomiting, nuchal rigidity, photophobia), seizures and local neurological deficits (limb paresis, dysphasia, oculomotor palsy), intraocular hemorrhages, loss of consciousness, and sudden death.

Survivors of aSAH risk instant re-bleeding which indicates acute CT verification of SAH followed by CT and/or catheter angiography to verify or exclude a ruptured aneurysm or other neurovascular lesion (Figure 2.2). Negative CT should be followed by diagnostic lumbar puncture, including spectroscopy of CSF to diagnose earlier SAH. In about 15% of SAH cases, no other neurovascular lesion, or other etiology is detected, even with high quality four vessel DSA (Pyysalo et al., 2011).

The most common system for grading the clinical condition after aSAH is the Hunt and Hess (H&H) scale, (0) No SAH, (I) Asymptomatic or mild headache, mild nuchal rigidity, (II) moderate to severe headache, nuchal rigidity, no neurological deficit, except cranial nerve palsy, (IV) stupor or mild to moderate hemiparesis; possible early decerebrate rigidity, and (V) deep coma, decebral posturing, moribund. In addition, the presence of intracerebral hematoma, intraventricular hematoma and hydrocephalus are evaluated on admission.

2.3.2 Neurointensive care of aSAH

Acute aSAH is a complex systemic condition that requires multidisciplinary neuroICU care. The management aims to prevent further damage from rebleeding, hydrocephalus, increased ICP, acute ischemic brain injury, seizures, electrolyte disturbances, cardiac and pulmonary dysfunction, and subacute ischemic brain injury (Levine, 2009; Bederson et al., 2009; Diringer et al., 2011).

The ruptured sIA should be occluded in the acute phase to prevent re-bleeding (Diringer et al., 2011). Immediate repair of the ruptured sIA by either coil embolisation or microsurgical clip ligation reduces the risk of re-bleeding, with microsurgical exclusion being slightly more efficacious (Molyneux et al., 2005).

A prospective study of treatment of acute ruptured sIA showed that the outcome was not significantly different between these treatment groups at three (Vanninen et al., 1999) or 12 months (Koivisto et al., 2000).

From Kuopio Database, Karamanakos et al. concluded that coil embolisation has not improved the overall outcome of aSAH in the elderly in Eastern Finland (Karamanakos et al., 2010).

2.3.3 Diagnosis and treatment of unruptured sIAs

Unruptured IA(s) are mainly detected as occult findings in neuroimaging for other symptoms, and in a few cases by screening sIA family members. The detection rate has increased due to the availability of non-invasive brain imaging methods, particularly MRI and MR angiography. Furthermore, in patients who have been treated for a ruptured sIA, the annual rate of new sIA formation is 1% per year to 2% per year (Bederson et al., 2009; Rinne and Hernesniemi, 1993).

The decision to prophylatically occlude unruptured sIAs should be based on the estimation of life-long risk of rupture, on the other hand, and the potential risks of occlusive therapy, either microsurgical clipping or endovascular techniques.

According to the International Study of Unruptured Intracranial Aneurysms (ISUIA), 5-year cumulative rupture rates for patients who did not have a history of subarachnoid haemorrhage with aneurysms located in internal carotid artery, anterior communicating or anterior cerebral artery, or middle cerebral artery were 0%, 2.6%, 14.5%, and 40% for aneurysms less than 7 mm, 7-12 mm, 13-24 mm, and 25 mm or greater, respectively, compared with rates of 2.5%, 14.5%, 18.4%, and 50%, respectively, for the same size categories involving posterior circulation and posterior communicating artery aneurysms (Wiebers et al., 2003).

2.3.4 Prevention of aSAH

MR angiography screenings of unselected populations for incidental sIAs may not be feasible due to high cost and problems of achieving full coverage.

The most effective way to prevent sIA formation and/or rupture is to reduce modifiable risk factors, of which smoking and hypertension are the two most important ones (Feigin et al., 2005). In a recent multi-centre, population-based, case-control study, information on smoking status, history of hypertension, physical activity, dietary intake, alcohol consumption, body mass index, and family history of aSAH, were obtained from 432 aSAH cases and 473 matched community-based aSAH-free controls. A recent population-based case-control study confirmed that smoking cessation (OR 3.69) and blood pressure control (1.79) are the most important strategies to prevent aSAH (Shiue et al., 2012). In a large cohort study (475 734 Korean men) smoking cessation was associated with reduced risk of aSAH (hazard ratio of 0.58) (Song and Cho, 2008).

2.4 OUTCOME AFTER ASAH

2.4.1 Short-term outcome of aSAH

In our recent review of multivariate analyses of large (> 500 patients) aneurysmal SAH cohorts (Karamanakos et al., 2011), the subsequent outcome and mortality have mainly been reported at 2 months, 3 months, or 6 months after aneurysmal aSAH (Coghlan et al., 2009; Frontera et al., 2008; Guresir et al., 2008; Langham et al., 2009; Molyneux et al., 2005; O'Kelly et al., 2010; Rosengart et al., 2007; Wartenberg et al. 2006; Zacharia et al., 2009).

Unfavourable outcome at three months was associated with increasing age, WFNS, posterior circulation sIA, large sIA, IVH, ICH, elevated systolic blood pressure on admission, history of hypertension, prior aSAH, myocardial infarctation and liver disease, fever, anemia, hyperglycemia, poor admission H&H, amount of blood on CT. Variables present during hospitalization associated with poor outcome were temperature >38 degrees C 8 days after aSAH, use of anticonvulsants, symptomatic vasospasm, and cerebral infarction.

2.4.2 Long-term excess mortality aSAH

There are few published population based studies analysing long-term excess mortality after aSAH (Ronkainen et al., 2001; Lehecka et al., 2007; Molyneux et al., 2009; Nieuwkamp et al., 2011; Olafsson et al., 1997). In the International Subarachnoid Aneurysm Trial (ISAT) cohort, 1,413 one year survivors of aSAH from U.K. were followed up for a mean of 9 years (Molyneux et al., 2009). Their long-term death rates were increased as compared to the general population of U.K. (Molyneux et al., 2009). A recent study of 17,705 aSAH patients implicated a mortality rate of a 35.4% at 15 years, with overall standardised mortality ratio of 1.57 in a mean follow up time of 6.8 years (Nieuwkamp et al., 2011). Several studies have addressed cardiovascular complications after acute aSAH and in the long run, including myocardiac injury (Diringer et al., 2011; Ronkainen et al., 2001). Cardiovascular causes may explain at least partially the long-term excess mortality after aSAH, in a disease strongly associated with hypertension and smoking.

In the previous study from the Kuopio Database, Ronkainen et al. observed that 900 aSAH patients with good outcome (GOS 5) at 12 months had a mortality rate twice that of the Eastern Finnish general population in a median follow up time of 7.5 years (Ronkainen et al., 2001). Systemic cardiovascular disease appeared to be the most important cause of death, responsible for 60% of cases (Ronkainen et al., 2001). They concluded that aSAH is one aspect of chronic general vascular disease, and more attention should be paid to the reduction of risk factors, and the long-term follow up of aSAH survivors.

A recent study made from the Kuopio sIA Database (1980-2007) showed 29% mortality in 1657 patients at 12-months. Of 13 variables available on admission,

independent risk factors were: age; Hunt&Hess grades IV-V; acute hydrocephalus; intraventricular hemorrhage (IVH); and intracerebral hemorrhage (ICH). The sequelae of aneurysmal SAH were the leading cause of death for about 12 months, after which other causes became dominant. H&H grades IV (flexion reaction) and especially V (extension reaction) were strong indicators of acute mortality, whereas age was not. Patients in good condition on admission had a very low mortality rate at 12 months, regardless of age. The mode of occlusive therapy was not an independent risk factor of 12-month mortality (Karamanakos et al., 2011).

2.4.3 Long-term neurological outcome after aSAH

The life expectancy is reduced for patients who survived aSAH (Ronkainen et al., 2001; Molyneux et al., 2009; Wermer et al., 2009). The various neurological deficits, like epilepsy, dementia, shunt-dependent hydrocephalus, depression, cognitive impairment, decreased quality of life, post traumatic distress syndrome are involved both in the increased mortality and morbidity of aSAH patients (Hart et al., 2011; O'Kelly et al., 2009; Al-Khindi et al., 2010; Greebe et al., 2010; Hedlund et al., 2011).

2.5 EASTERN FINNISH SIA DISEASE

Is Finnish sIA disease a definable entity, because aSAH is clearly more frequent in Finland (Ingall et al., 2000)? There seems to be at least one phenotypic difference, increased proportion of sIAs at the MCA bifurcation (Rinne et al., 1994). In the two whole genome SNP association studies (Yasuno et al., 2010; Bilguvar et al. 2008), the profile of associated loci was partially different in Finnish sIA patients from the Kuopio and Helsinki sIA Registries.

Is Eastern Finnish sIA disease a subtype of Finnish sIA disease? Single nucleotide polymorphism association (Salmela et al., 2008) studies and Y-chromosomal variations (Lappalainen et al., 2006) suggest that Western and Eastern Finland have partially different population histories. Eastern Finland offers an opportunity to study familial sIA disease (Ronkainen et al., 1997; Ronkainen et al., 1998). Small founder population may support the identification of genomic variants behind the complex sIA disease, affected by inherited as well as acquired risk factors.

2.5.1 Catchment population of Kuopio University Hospital (KUH)

The geographic area has remained the same, but the population has decreased from 863,726 in 1980 to 851,066 in 2007. During the same period, the median age increased from 31 to 42 years in males and from 34 to 45 years in females, but the proportion of males has remained unchanged at 49%.

2.5.2 Kuopio Neurosurgery sIA Database (www.uef.fi/ns)

Since 1977, Neurosurgery of KUH has solely provided full-time (7 days, 24 hours) acute and elective neurosurgical services for the KUH catchment area in Eastern Finland (Figure 1.1). The KUH area contains four central hospitals with catchment

areas of their own. CT was available since 1980 in Kuopio, 1983 in Mikkeli, 1985 in Jyväskylä, 1988 in Savonlinna and 1989 in Joensuu.

Patients with acute SAH have been acutely admitted to the KUH for angiography and treatment if not moribund or very aged. Cases with unruptured IA(s) detected have also had a neurosurgical consultation for elective occlusion. In both instances, exact numbers of rejection are not available.

KUH Neurosurgery maintains a database on all cases of aSAH or unruptured IAs admitted to the KUH since 1977, retrospective from 1977 to 1989, and prospective from 1990. The Database was created by Juha Hernesniemi, since 1997 Professor and Head of Helsinki Neurosurgery. A dedicated full-time nurse has interviewed all new cases of sIA and aSAH, and collected detailed information, including family history for the sIA disease. Clinical data from the hospital periods and follow-up visits have also been entered. The criteria for a sIA family is at least two affected first-degree relatives. The phenotype, genetics, and outcome of Eastern Finnish sIA disease have been analysed in many local and collaborative studies (Ronkainen et al., 1998; Ronkainen et al., 2001; Ronkainen et al., 1999; Ronkainen et al., 1997; Hernesniemi et al., 1993; Lehecka et al., 2007; van der Voet et al., 2004; Helgadottir et al., 2008; Bilguvar et al., 2008; Fogelholm et al., 1993).

2.5.3 Genomic studies of sIA disease in KUH catchment population

A variant on 9p21 associated with coronary artery disease, abdominal aortic aneurysm and sIA in 1.131 sIA patients from Finland, the Netherlands and Iceland (Helgadottir et al., 2008). LD block contains CDKN2A and CDKN2B with roles, e.g., in cancer and senescence (Helgadottir et al., 2008). In the first genome-wide SNP association study, new loci on 2q33 and 8q11 and the previous one on 9p21 were identified in 2.045 sIA patients from Finland, the Netherlands and Japan (Bilguvar et al., 2008). In the follow up Genome-wide association study, loci 8q11.23-q12.1 and 9p21.3 were confirmed, and three new loci –10q24.32 and CNNM2 – 13q13.1 and STARD13 – 18q11.2 and RBBP8 were identified (Yasuno et al., 2010). The functional significance of these loci is not known. One of the current trends is to find out large sIA families for exomic or genomic sequencing. Another lead for the identification of genetic components behind the sIA disease is to study associated genetic diseases.

2.5.4 Vascular diseases in KUH population

Cardiovascular events and their risk factors have been monitored carefully in Eastern Finland since the 1970s. The area has been subjected to population based interventions to reduce cardiovascular risk factors. The decline in the incidence and mortality of cardiovascular events coincides with decrease in risk factors. Between 1972 and 2007, the coronary mortality was decreased by 80 %. Diastolic blood pressure decreased by 8.7 mmHg, smoking by 15 percentage points, and cholesterol level by1.54 mmol/ml (Vartiainen et al., 2010).

2.5.5 Familial disease

Ronkainen et al. started analysing the familial sIA disease in the Kuopio sIA Database. In Eastern Finland, approximately 10% of aSAH patients have a familial background of aSAH or incidental sIAs, with at least two affected first-degree family members (Ronkainen et al., 1993). Within sIA families, the risk for harbouring sIAs among asymptomatic family members is at least four times higher than in sporadic aSAH patients (Ronkainen et al., 1997).

The largest twin study to date with 79,664 twin pairs (0.29% monozygotic) and 509 aSAH cases during a follow-up of 6.01 million person-years did not show significant genomic contribution to aSAH (Korja et al., 2010). Familial clustering of risk factors (smoking, hypertension, alcohol) may significantly explain the familial clustering of the sIA disease.

Among familial aSAH patients there was a slight female predominance, the males tended to have aSAH at significantly younger age than the females. The rupture of sIA was at a younger age in familial patients than in sporadic ones. The ruptured familial sIAs were smaller, and they were more often multiple, and located in middle cerebral artery as compared with sporadic aSAH patients (Ronkainen et al., 1995).

Ronkainen et al. concluded that screening of first-degree relatives in familial sIA families constitute a high-risk group for incidental sIAs, and that this group would benefit from screening for asymtomatic sIAs (Ronkainen et al., 1998).

The outcome was similar in the familial and sporadic aSAH groups in the Finnish population (Ronkainen et al., 2001). This might suggest that in both familial and sporadic cases the basic pathological reason for the formation of sIA could be the same.

2.5.6 Concomitant diseases

The occurrence of concomitant diseases has not been comprehensively studied in the Eastern Finnish sIA cohort.

2.5.7 Previous PhD theses on Eastern Finnish sIA disease

Antti Tapaninaho – Non-Ischemic Complications after Subarachnoid Hemorrhage and Aneurysm Surgery (1994).

Jaakko Rinne – Multiple Intracranial Aneurysms: Kuopio Experience on 302 of 1.314 Patients (1996).

Antti Ronkainen – Familial Intracranial Aneurysms (1997).

Timo Koivisto – Prospective Outcome Study of Aneurysmal Subarachnoid Hemorrhage: Endovascular versus Surgical Therapy (2002).

Liu Yawu – MRI Characterization of Human Acute Ischemic Stroke: Diffusion and Perfusion Weighted Imaging and Phase Contrast Angiography (2003).

Paula Bendel – Imaging of the Brain after Aneurysmal Subarachnoid Hemorrhage – One-Year MRI Outcome of Surgical and Endovascular Treatment (2009).

Stepani Bendel – Pituitary and Adrenal Response to Critical Illness (2010).

Petros Karamanakos – In progress.

3 Aims of the study

3.1 PHENOTYPE OF SIA DISEASE ON ADMISSION

To study the phenotype of saccular intracranial aneurysm disease in 1770 patients on admission to the Kuopio University Hospital from the Eastern Finnish catchment population and time trends from 1980 to 2007.

3.2 LONG-TERM OUTCOME AFTER ASAH

To analyse the long-term excess mortality and causes of death of familial and sporadic one-year aSAH survivors as compared to the matched Eastern Finnish catchment population.

3.3 IMPACT OF RISK FACTORS ON LONG-TERM OUTCOME AFTER ASAH

To study the incidence of cancer after the sIA diagnosis from 1980 to 2007 in 2904 patients as compared to the KUH catchment population. We hypothesised that a) sIA patients would be predisposed to tobacco related cancers, and that b) familial sIA patients would have different risks of cancer.

4 Saccular intracranial aneurysm disease – distribution of site, size and age suggest different etiologies for aneurysm formation and rupture in 316 familial and 1454 sporadic Eastern Finnish patients[1]

Abstract. Finnish saccular intracranial aneurysm (sIA) disease associates to 2q33, 8q11, and 9p21 loci, and links to 19q13, Xp22 and kallikrein cluster in sIA families. Detailed phenotyping of familial and sporadic sIA disease is required for fine mapping of the Finnish sIA disease. Eastern Finland, particularly isolated genetically, is served by Kuopio Neurosurgery. We studied the site and size distribution of unruptured and ruptured sIAs in correlation to age and sex in 316 familial and 1454 sporadic sIA patients on first admission from 1993 to 2007. The familial and sporadic aSAH patients had slightly different median ages (46 vs. 51 years in males; 50 vs. 57 years in females), different proportion of males (50% vs. 42%), equal median diameter of ruptured sIAs (7mm vs. 7mm) with no correlation to age, and equally unruptured sIAs (30% vs. 28%). The unruptured sIAs were most frequent at MCA bifurcation (44% vs. 39 %) and ACoA (12% vs. 13 %) in contrast to the ruptured sIAs at ACoA (37% vs. 29%) and MCA bifurcation (29% vs. 29%). The size of unruptured sIAs increased by age in the sporadic group.The MCA bifurcation was most prone to develop unruptured sIAs, suggesting that MCA branching during embryonic period might be involved. Different site distribution of ruptured and unruptured sIAs suggests different etiologies for sIA formation and rupture. No correlation of size and age at rupture (exposure to risk factors) suggest that the size at rupture is more dependent on hemodynamic stress.

[1]Adapted with permission of the Neurosurgery from: **Huttunen T., von und zu Fraunberg M., Frösen J., et al. Distribution of site, size and age in saccular intracranial aneurysm disease suggest different risk factors for formation and rupture – analysis of 316 familial and 1454 sporadic patients, Neurosurgery. 2010;66(4):631-638; discussion 638.**

4.1 INTRODUCTION

Subarachnoid hemorrhage (aSAH) from ruptured saccular intracranial aneurysm (sIA) is a devastating form of stroke that affects working age population (van Gijn et al., 2007; Bederson et al., 2009). The sIA disease is a complex trait. Its phenotypic tissue, branching site of major cerebral artery under hemodynamic stress (Alnaes et al., 2007), is poorly characterized in embryonic and adult cellular and molecular biology. Some 2% of population develops sIAs (Ronkainen et al., 1998; Feigin et al., 2005) but most do not rupture during life as the general annual incidence of SAH is 9 per 100 000 (de Rooij et al., 2007). Risk factors include age, female sex, smoking, hypertension, and excess drinking (Feigin et al., 2005), and at least 10% of aSAH patients have a family history (Ronkainen et al., 1997; Ruigrok et al., 2005). Mechanisms by which risk factors affect the formation of sIA pouch (primary phenotype) and the rupture of sIA wall (secondary phenotype) have to be elucidated for novel methods to identify sIA carriers and to occlude sIA pouches (Shi et al., 2009).

Our concortium (www.fiarc.fi) studies the genetics of sIA disease (Ronkainen et al., 1997; van der Voet et al., 2004; Helgadottir et al., 2008; Bilguvar et al., 2008; Ronkainen et al., 1999) and the biology of sIA wall (Frosen et al., 2004; Frosen et al., 2006; Tulamo et al., 2006; Laaksamo et al., 2008) in the Finnish population, particularly prone to aSAH (de Rooij et al., 2007). The genetic homogeneity of Finns (Laaksamo et al., 2008) may support indentification of genetic variants behind the sIA disease. In familial sIA patients from Southern Finland and Eastern Finland, genome-wide linkage analysis showed linkage to 19q13 (van der Voet et al., 2004) and Xp22 (Olson et al., 2002), both replicated in Japan (Yamada et al., 2004) as well as to kallikrein gene cluster (Weinsheimer et al., 2007). A variant on 9p21 associated with coronary artery disease, abdominal aortic aneurysm and sIA in 1.131 sIA patients from Finland, the Netherlands and Iceland (Helgadottir et al., 2008). In a genome-wide SNP association study, new loci on 2q33 and 8q11 and the previous one on 9p21 were identified in 2.045 sIA patients from Finland, the Netherlands and Japan (Bilguvar et al., 2008). For further mapping of the Finnish sIA disease, more data on the phenotype, acquired risk factors, and concomitant arterial diseases are required.

The Eastern Finnish gene pool has been particularly affected by a small number of founders, isolation, and major bottlenecks (Peltonen et al., 1999). In the present study, we analysed the phenotype on admission in the sIA Registry of Kuopio Neurosurgery, serving solely Eastern Finland. We studied the size and site distribution of unruptured and ruptured sIAs in correlation to age and sex in 316 familial and 1454 sporadic sIA patients from 1993 and 2007. Furthermore, we analysed the changes of age and sex distribution in an extended recruitment period from 1980 and 2007 in comparison to ageing catchment population.

4.2 MATERIALS AND METHODS

4.2.1 Catchment population of Kuopio University Hospital

During the study period from 1980 to 2007, Neurosurgery of Kuopio University Hospital (KUH) solely provided full-time (7 days, 24 hours) acute and elective neurosurgical services for the KUH catchment area in Eastern Finland (Figure 4.1). The KUH area contains four central hospitals with catchment areas of their own. CT was available since 1980 in Kuopio, 1983 in Mikkeli, 1985 in Jyväskylä, 1988 in Savonlinna and 1989 in Joensuu. From 1980 to 2007, the geographic area remained the same. The population decreased from 863,726 to 851,066 while the median age increased from 31 to 42 years in males and from 34 to 45 years in females. The proportion of males remained unchanged at 49% (Figure 4.2).

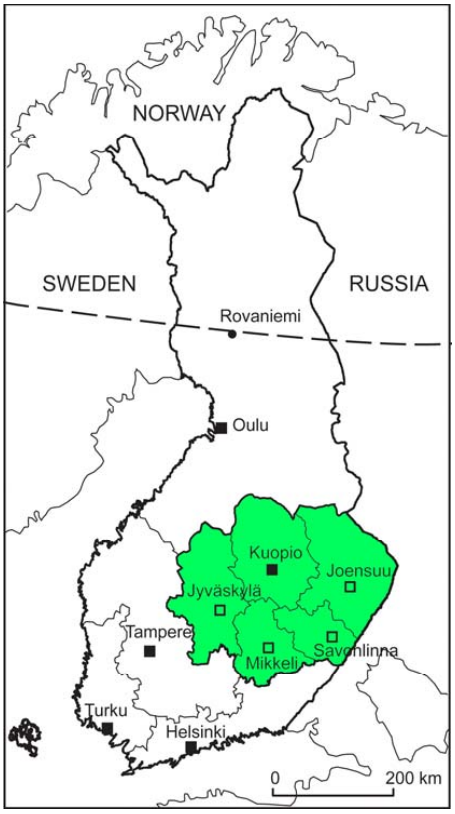

Figure 4.1. Map of the catchment area of Kuopio University Hospital (KUH), containing 4 central hospitals in Joensuu, Jyväskylä, Mikkeli, and Savonlinna. The areas of the 4 other university hospitals in Helsinki, Oulu, Tampere, and Turku are also delineated.

4.2.2 Cases of subarachnoid hemorrhage or unruptured intracranial aneurysm in the KUH area

Patients with acute SAH have been acutely admitted to the KUH for angiography and treatment if not moribund or very aged. Cases with unruptured IA(s) detected have also had a neurosurgical consultation for elective occlusion. In both instances, exact numbers of rejection are not available.

4.2.3 Kuopio IA Database

KUH Neurosurgery maintains a database on all cases of aSAH or unruptured IAs admitted to the KUH since 1977, retrospective from 1977 to 1989, and prospective from 1990. The database is run by a dedicated full-time nurse who interviews all new cases of IA and aSAH, and collects detailed information, including family history for sIA disease. Clinical data from the hospital periods and follow-up visits are also entered. The criteria for an sIA family was at least two affected first-degree relatives. Several genetic studies of Eastern Finnish sIA disease have been published (Ronkainen et al., 1998; Ronkainen et al., 1997; van der Voet et al., 2004; Olson et al., 2002; Helgadottir et al., 2008; Bilguvar et al. 2008; Ronkainen et al., 1999; Weinsheimer et al., 2007).

4.2.4 Study population

The inclusion criteria were:

1. citizen of Finland and resident of the KUH catchment area at the time of diagnosis of sIA disease between January 1, 1980 and December 31, 2007.

2. admission to the KUH and verification of sIA(s) by angiography or at autopsy.

The exclusion criteria were:

1. patients with other forms of IA(s) (e.g., fusiform, traumatic or mycotic) but no saccular IA(s).

4.2.5 Variables

The variables were: age at first diagnosis of sIA disease; sex; family history; number of sIAs; exact site of each sIA; ruptured or unruptured sIA; the longest of three perpendicular measures of sIA lumen; and year of first diagnosis from 1980 to 2007. The sIA variables were analysed in detail from 1993 to 2007, the period of routine imaging of both carotid and vertebral arteries as well as MRA at KUH.

4.2.6 Ethical aspects

The study was approved by the Ethics Committee of the Kuopio University Hospital.

4.2.7 Statistical analysis

The subjects were either patients or sIAs. Discrete variables were expressed in proportions and continuous variables in medians and ranges. Groups were compared using the Fisher exact test, Chi-square test, Mann-Whitney U-test or Kruskal-Wallis test when appropriate. Continuous variables were correlated using the Spearman rank correlation test. P-values less than 0.05 were considered significant. SPSS 14.0 statistical software (SPSS Inc., Chicago, IL) was used.

4.3 RESULTS

4.3.1 Familial and sporadic sIA patients from 1980 to 2007 in Eastern Finland

The entire study population was 2899 consecutive sIA patients diagnosed between 1980 and 2007, inclusive, 474 familial patients from 294 families, and 2.425 sporadic patients. Time trends are demonstrated in Figure 4.2. Cases with unruptured sIA(s) only increased dramatically since about 1993.

4.3.2 Familial and sporadic sIA patients at first aSAH - trends from 1980 to 2007

From 1980 to 2007, there were 2.285 sIA patients with aSAH at first diagnosis, 307 (13%) familial and 1.979 (87%) sporadic (Table 4.1). In the catchment population, the proportion of males remained unchanged (49%), but the median ages of males (31 vs. 42 years) and females (34 years vs. 45 years) increased remarkably (Figure 4.2). From the first 5-year period (1980-1984) to the last (2003-2007), male aSAH patients

increased slightly in the familial group (42% vs. 50%; p=0.285) but decreased in the sporadic group (54% vs. 43%; p=0.004) (Table 4.1). The median age of male aSAH patients increased both in the familial group (39 years vs. 51 years; p=0.003) and in the sporadic group (45 years vs. 51 years; p<0.0001). The median age of female aSAH patients increased both in the familial group (47 years to 52 years; p=0.074) and in the sporadic group (50 years vs. 56 years; p<0.0001).

Table 4. 1. Characteristics of 307 familial and 1978 sporadic Eastern Finnish patients with first subarachnoid hemorrhage (aSAH) from saccular intracranial aneurysm (sIA) between 1980 and 2007.

	Patients		**Females vs. males**			**Median age at aSAH**
	n	%		n	%	yr
Entire period 1980-2007						
Familial aSAH patients	307	13	F	150	49	50 (40-61)
			M	157	51	45 (37-53)
Sporadic aSAH patients	1979	87	F	1071	54	55 (45-65)
			M	908	46	49 (40-58)
Time period 1980-1984						
Familial aSAH patients	55	15	F	32	58	47 (30-60)
			M	23	42	39 (32-49)
Sporadic aSAH patients	307	85	F	140	46	50 (42-57)
			M	167	54	45 (42-57)
Time period 2003-2007						
Familial aSAH patients	38	10	F	19	50	52 (45-59)
			M	19	50	51 (43-58)
Sporadic aSAH patients	339	90	F	193	57	56 (48-69)
			M	146	43	51 (44-58)

sIA, saccular intracranial aneurysm; aSAH, subarachnoid hemorrhage from ruptured sIA; F female, M male. For age distribution, 25% and 75% percentiles are also given in parentheses.

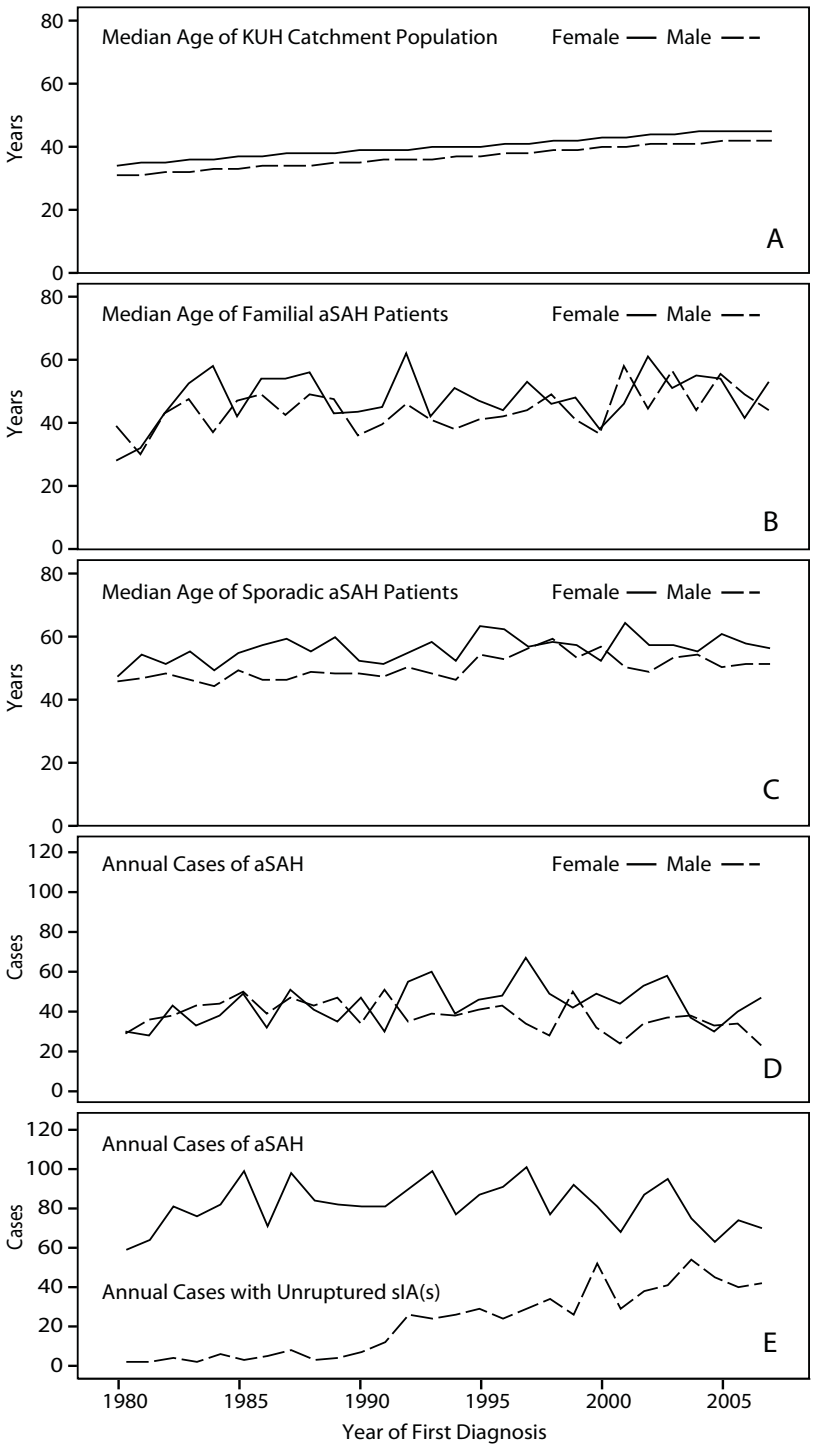

Figure 4.2. Median ages of familial and sporadic aSAH patients admitted to Kuopio University Hospital between 1980 and 2007 as compared to the catchment population (A-C). Gender distribution of aSAH patients (D). Annual numbers of ruptured and unruptured sIA cases (E).

4.3.3 Familial and sporadic sIA patients at first aSAH (1993-2007)

During the last 15 years, there were 168 (14%) familial and 1069 (86%) sporadic patients with first aSAH (Table 4.2). The familial aSAH patients had equal sex distribution and were 5 to 8 years younger than the sporadic ones. The most frequent sites of the ruptured sIAs were ACoA (37% vs. 29%; p=0.048), MCA bifurcation (29% vs. 29%), and PCoA (11% vs. 12%) (Table 4.3). Gender and age did not correlate to the site distribution of ruptured familial or sporadic sIAs. Their median diameters were equal at 7 mm (Table 4.3). Age did not correlate to the diameter of ruptured familial or sporadic sIAs either (Figure 4.3).

Table 4.2. Characteristics of 316 familial and 1454 sporadic Eastern Finnish patients with saccular intracranial aneurysm (sIA) disease first diagnosed between 1993 and 2007, the period of routine imaging of both carotid and vertebral arteries.

	Patients		**Females vs. males**			**Median age at diagnosis**	**Median size of ruptured sIAs**
	n	%		n	%	yr	mm
Familial sIA patients	316	18	F	167	53	49 (44-59)	6 (4-8)
			M	149	47	47 (40-56)	6 (4-8)
Patients with aSAH	168		F	84	50	50 (44-61)	7 (5-9)
			M	84	50	46 (38-57)	7 (5-10)
with one or more associated sIAs	51	30	F	32	63	50 (45-61)	7 (6-10)
			M	19	37	47 (43-59)	7 (5-8)
Patients with no aSAH	148		F	83	56	49 (44-56)	-
			M	65	44	49 (43-55)	-
two or more sIAs	48	32	F	26	54	52 (46-60)	-
			M	22	46	46 (40-54)	-
Sporadic sIA patients	1454	82	F	839	58	57 (48-68)	6 (4-10)
			M	615	42	52 (44-61)	7 (4-10)
Patients with aSAH	1069		F	625	58	57 (47-67)	6 (4-10)
			M	444	42	51 (43-59)	8 (5-10)
with one or more associated sIAs	294	28	F	180	61	56 (47-66)	7 (5-10)
			M	114	39	51 (45-59)	8 (6-12)
Patients with no ASAH	385		F	214	56	58 (49-69)	-
			M	171	44	55 (48-64)	-
two or more sIAs	97	25	F	55	57	58 (47-69)	-
			M	42	43	50 (47-60)	-

sIA, saccular intracranial aneurysm; aSAH, subarachnoid hemorrhage from ruptured sIA; F female; M male.
For age and size distributions, 25% and 75% percentiles are also given in parentheses.

Table 4.3. Characteristics of 489 familial and 2065 sporadic saccular intracranial aneurysms (sIAs) at first diagnosis of sIA disease in Eastern Finland between 1993 and 2007, the period of routine imaging of both carotid and vertebral arteries.

	Familial sIAs									**Sporadic sIAs**								
	In patients with aSAH						**In patients with no SAH**			**In patients with aSAH**						**In patients with no aSAH**		
	Ruptured sIAs			Unruptured sIAs			Unruptured sIAs			Ruptured sIAs			Unruptured sIAs			Unruptured sIAs		
	N	%	Size mm	N	%	Size mm	N	%	Size mm	N	%	Size mm	N	%	Size mm	N	%	Size mm
Total	**168**	**100**	**7**	**96**	**100**	**3**	**225**	**100**	**4**	**1061**	**100**	**7**	**457**	**100**	**3**	**540**	**100**	**5**
Female	84	50	7	63	66	3	123	55	4	625	59	8	289	63	3	302	56	5
Male	84	50	7	33	34	3	102	45	4	436	41	6	168	37	3	238	44	5
ICA all*	**29**	**17**	**6**	**21**	**22**	**2**	**47**	**21**	**4**	**240**	**22**	**7**	**104**	**23**	**4**	**143**	**26**	**5**
ICA PCoA	18	11	7	5	5	3	9	4	4	135	12	7	39	9	4	40	7	5
ICAbif	5	3	7	3	3	3	8	4	4	36	3	6	13	3	4	26	5	4
ACA all	**68**	**41**	**6**	**21**	**22**	**3**	**37**	**17**	**5**	**377**	**35**	**6**	**91**	**20**	**3**	**90**	**17**	**4**
A1	0	-	-	2	2	2	1	0.4	3	8	1	4	6	1	2	1	0.2	2
ACoA	62	37	6	10	10	2	26	12	5	307	29	6	47	10	3	69	13	4
A2 – A5	6	4	4	9	10	4	10	4	3	62	6	5	38	8	3	20	4	5
MCA all	**62**	**37**	**9**	**51**	**53**	**4**	**128**	**57**	**4**	**342**	**32**	**8**	**226**	**48**	**3**	**246**	**45**	**6**
M1	12	7	6	13	14	4	21	9	3	25	2	6	39	9	2	23	4	4
Mbif	48	29	10	31	32	4	99	44	5	311	29	8	169	35	3	209	38	6
M2 - M5	2	1	10	7	7	2	8	4	3	6	1	4	18	4	3	14	3	4
VA all*	**4**	**2**	**4**	**1**	**1**	**2**	**3**	**1**	**2**	**35**	**3**	**4**	**5**	**1**	**6**	**13**	**2**	**4**
VA PICA	1	1	4	1	1	2	2	1	2	31	3	4	4	1	4	10	2	4
BA all*	**5**	**3**	**9**	**2**	**2**	**2**	**10**	**4**	**5**	**67**	**7**	**8**	**28**	**6**	**2**	**46**	**9**	**8**
BAbif	2	1	21	1	1	2	9	4	6	55	5	8	11	2	5	34	6	8
PCA all	**0**	**-**	**-**	**0**	**-**	**-**	**0**	**-**	**-**	**7**	**1**	**5**	**3**	**2**	**2**	**2**	**1**	**4**

[a]sIA, saccular intracranial aneurysm; aSAH, aneurysmal subarachnoid hemorrhage; ICA, internal carotid artery; PCoA, posterior communicating artery; ICAbif, ICA bifurcartion; ACA, anterior cerebral artery; A1-A5, A1-A5 segments of ACA; ACoA, anterior communicating artery; MCA, middle cerebral artery; M1-M5, M1-M5 segments of MCA; Mbif, MCA bifurcation; VA, vertebral artery; PICA, posterior inferior cerebellar artery; BA, basilar artery; BAbif, BA bifurcation; PCA posterior cerebral artery. All sizes are medians.

* All locations are not presented because of small numbers.

4.3.4 Unruptured sIAs in familial and sporadic sIA patients at first aSAH (1993-2007)

During the last 15 years, 30% of the familial and 28% of the sporadic aSAH patients presented with associated unruptured sIAs (Table 4.2). Associated sIAs were less frequent in males in the familial aSAH group (23% vs. 38%; p=0.044) and the sporadic aSAH group (26% vs. 29%) (Table 4.2). Age did not correlate with the presence of associated sIAs in either group. The median numbers of associated sIAs per patient were 3 (range 2 to 7) and 3 (range 2 to 6), respectively. Age and gender did not correlate with the number of associated sIAs. The most frequent sites in the familial and sporadic groups were Mbif (32% vs. 35%); M1 (14% vs. 9%) and ACoA 10% vs. 10% (Table 4.3). The median diameters were equal at 3 mm, with no correlation with age and gender (Table 4.2, Figure 4.3).

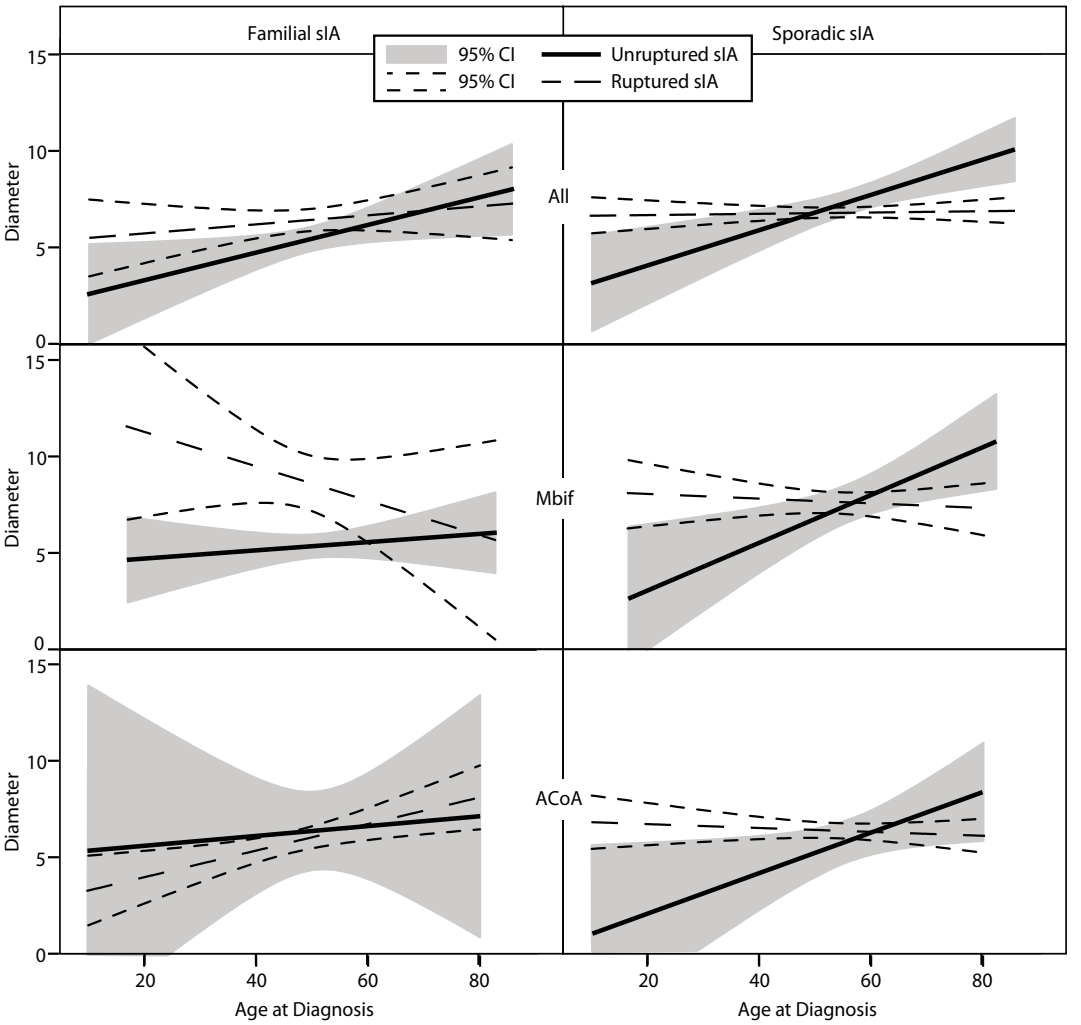

Figure 4.3. Correlation of age at diagnosis and diameter of unruptured and ruptured familial and sporadic sIAs. Regression lines and 95% confidence intervals are shown. All sIAs (upper), middle cerebral artery bifurcation (Mbif) sIAs (middle) and anterior communicating artery (ACoA) sIAs (lower).

4.3.5 Unruptured sIAs in familial and sporadic sIA patients with no aSAH (1993-2007)

During the last 15 years, there were 148 familial and 385 sporadic patients with 225 and 540 unruptured sIA(s) but no aSAH at first diagnosis. The proportions of males were 44% and 44%, and the median ages 49 years vs. 55 years for males ($p<0.0001$) and 49 years vs. 58 years for females ($p<0.0001$), respectively. The median numbers of associated sIAs per patient were 2 (range, 1 to 6) and 1 (range, 1 to 6). Age or gender did not correlate to the number of associated sIAs. The most frequent sites in the familial and sporadic groups were MCA bifurcation (44% vs. 39 %) and ACoA (12% vs. 13 %) (Table 4.3). The median diameters were 4 mm vs. 5 mm ($p=0.0001$), respectively. The diameter increased by age in the sporadic group ($p=0.001$) but not in the familial group (Figure 4.3). Gender did not correlate with the diameter (Table 4.2).

4.4 DISCUSSION

Our concortium (www.fiarc.fi) studies the genetics of sIA disease (Ronkainen et al., 1997; van der Voet et al., 2004; Helgadottir et al., 2008; Bilguvar et al., 2008; Ronkainen et al., 1999) and the biology of sIA wall tissue (Frosen et al., 2004; Frosen et al., 2006; Tulamo et al., 2006; Laaksamo et al., 2008) in the Finnish population with high incidence of aSAH (de Rooij et al., 2007). Finland has long been isolated for geographic, linguistic, and cultural reasons (Peltonen et al., 1999). Mitochondrial DNA indicates that Finns do not significantly differ from other European populations (Lahermo et al., 1996). SNP association analyses (Salmela et al., 2008) and Y-chromosomal variations (Lappalainen et al., 2006) suggest that Western and Eastern Finland have partly different population histories. The Eastern Finnish gene pool has been affected by a small number of founders, isolation, and major bottlenecks (Peltonen et al., 1999).

4.4.1 Eastern Finnish familial and sporadic sIA cohort

The impact of familial background on Eastern Finnish sIA disease at first diagnosis was modest in this study and in the previous one (Ronkainen et al., 1999; Ronkainen et al., 1995). The Kuopio sIA registry now consists of 294 sIA families with at least two affected first-degree relatives, but many families share a common ancestry in the 16th to 20th centuries due to small number of founders (Peltonen et al., 1999). Next, we will analyse the occurrence of concomitant diseases during long-term follow up in our sIA cohort as compared to the matched catchment population because sIA candidate genes or variants might act indirectly, e.g., through hypertension or atherosclerosis. Improved neuroimaging and aging of the population clearly affected our cohort, showing that time trends matter if large sIA cohorts are compared (van Munster et al., 2008; Mahindu et al., 2008).

4.4.2 Multiple sIAs

One would expect that familial background predisposes to multiple sIAs (Ruigrok et al., 2004), and they were more frequent in the familial non-aSAH patients (32% vs. 25%) but not in the aSAH patients (30% vs. 28%) (Ronkainen et al., 1995).

4.4.3 Age and gender at first diagnosis

Familial patients were a few years younger than the sporadic ones, but the ages in both groups reflected that of the catchment population. This would suggest that familial patients had also been affected by acquired risk factors. In the entire cohort, male sporadic aSAH patients reduced from slight dominance to minority, possibly due to reduced cardiovascular risk factors among Eastern Finnish males (Vartiainen et al., 2000; Broderick et al., 2003). For unknown reasons, females have dominated sIA cohorts more than catchment populations (Weir et al., 2002; Carter et al., 2006) and this was seen also in our familial non-aSAH patients but not in the aSAH patients.

4.4.4 Site distribution of unruptured and ruptured sIAs

We divided sIAs into (a) ruptured sIAs, (b) unruptured sIAs in aSAH patients, and (c) unruptured sIAs without aSAH. The MCA bifurcation and the ACoA were almost equal sites for the ruptured sIAs, but the MCA bifurcation was dominant among the unruptured ones (Carter et al., 2006; Rinne et al., 1994), even more so in the sIA carriers without aSAH (40% vs. 12%), regardless of familial background. The different site distribution of unruptured and ruptured sIAs (Carter et al., 2006) suggests different risk factors for the sIA pouch formation (primary phenotype) and for the sIA wall rupture (secondary phenotype). This finding is crucial for molecular biology studies of the sIA disease but its significance has not been stressed. It is amazing that the distal bifurcation of the M1 trunk is more prone to develop sIAs that the more proximal bifurcations of the carotid and basilar arteries. Unfavourable ratio of hemodynamic stress to arterial wall thickness at the MCA bifurcation might be a factor. We hypothesise, however, that molecular biology of MCA branching during embryonic period is also involved. To our knowledge, this has not been discussed and no data are available.

4.4.5 Diameter of sIAs

One would expect that familial background predisposes to larger sIAs (Ruigrok et al., 2004), but the median diameters of ruptured familial and sporadic sIAs were equal (7 mm), also at the ACoA (6mm) but slightly different at the MCA bifurcation (10mm vs. 8mm). One would also expect that the diameters of sIAs increase by age due to longer exposure to risk factors. Importantly, Carter et al showed that the unruptured sIAs increased in size by age but the ruptured sIAs did not (Carter et al., 2006). Our study confirms this crucial finding for molecular biology of the sIA disease, more in sporadic sIAs than in familial ones. Carter et al found, as in our study, that the distal sIAs were smaller at rupture than the proximal ones (Table 3). We hypothesise that some aneurysms become rupture prone, and their diameter at rupture is more dependent on hemodynamic stress and site than other risk factors.

4.5 CONCLUSIONS

1. From 1980 to 2007 the median age of the KUH catchment population increased from 33 years to 44 years. Familial and sporadic sIA patients aged with the catchment population which should be noted when large cohorts with long recruitment time are compared.

2. The phenotype at first diagnosis was only modestly different in the familial variant of Eastern Finnish sIA disease.

3. The MCA bifurcation is more prone to develop unruptured sIAs where as the anterior communicating artery ruptures most frequently. We hypothesise that branching morphogenesis (Horowitz and Simons, 2008) of the MCA bifurcation during embryonic period would be involved.

4. Differences between the distribution of ruptured and unruptured sIA sites suggest different etiologies for sIA formation and rupture.

5. No correlation between diameter at rupture and time of exposure to risk factors suggest that the diameter at rupture is more dependent on hemodynamic stress and site than other risk factors.

5 Long-term excess mortality of 244 familial and 1,502 sporadic one-year survivors of aneurysmal subarachnoid hemorrhage as compared to matched Eastern Finnish catchment population[2]

Abstract. We analysed the long term excess mortality of 244 familial and 1,502 sporadic one-year survivors of subarachnoid hemorrhage (aSAH) from saccular intracranial aneurysm (sIA) as compared to a matched Eastern Finnish catchment population. Kuopio Neurosurgery Database contains 1,746 one-year survivors of aSAH (1980-2007) from a defined population. The median follow-up time, until death (n=494) or the end of 2008, was 12 years. Relative survival ratios (RSR) were calculated as compared to the matched (gender, age, calendar time) catchment population. Relative excess risks of death (RER) were estimated for variables known on admission for aSAH as well as Glasgow Outcome Scale at 12 months. There was 12% excess mortality at 15 years (cumulative RSR 0.88 (CI 95% 0.85-0.91)). Independent risk factors were male gender (RER 1.6), age over 64 years (2.9), ruptured basilar tip sIA (4.5), severe hydrocephalus on admission (3.6), no occlusive therapy (6.0), and GOS 2, 3 or 4 at 12 months (23, 4.1, 2.1), but not familial sIA disease. There were lethal rebleeds from 13 of the 1.440 clipped sIAs, two of the 265 coiled sIAs, and two from the 17 non-occluded sIAs, and 14 new lethal bleeds from other sIAs. The impact of both sporadic and familial aSAH and their sequelae in the central nervous and cardiovascular system may cause long-term morbidity and mortality. The complex sIA disease may predispose to other vascular events in later life. The causes of the long term excess mortality are heterogeneous, and more detailed analyses are required.

[2] Adapted with permission of the Neurosurgery from: **Huttunen T, von und Zu Fraunberg M, Koivisto T, et al. Long-term excess mortality of 244 familial and 1502 sporadic one-year survivors of aneurysmal subarachnoid hemorrhage compared with a matched Eastern Finnish catchment population.** *Neurosurgery*. 2011;68(1):20-27.

5.1 INTRODUCTION

Saccular intracranial aneurysms (sIAs) develop during life in some 2% of population (Ronkainen et al., 1998). Rupture of the sIA wall causes almost all cases of aneurysmal subarachnoid hemorrhage (aSAH)(van Gijn et al., 2007). Acute aSAH is a complex and critical systemic condition. Survivors of the primary bleed require multidisciplinary neurointensive care to prevent further damage, e.g., from rebleeding, hydrocephalus, increased ICP, delayed ischemic brain injury, seizures, electrolyte disturbances, cardiac and pulmonary dysfunction, and complications of the management (Bederson et al., 2009; Levine, 2009). There is a significant excess mortality for at least one year after acute aSAH (Guresir et al., 2008; Wartenberg et al., 2006; Hernesniemi et al., 1993; Langham et al., 2009; Lehecka et al., 2008; Molyneux et al., 2005; O'Kelly et al., 2009; Rosengart et al., 2007; van der Bilt et al., 2009; Wartenberg et al., 2006).

Sequelae of aSAH may cause long-term mortality, e.g., by predisposing to epilepsy, depression, dementia, shunt complications, hypothalamic and hypophyseal disorders, or cerebrovascular events. The sIA disease is a complex trait (Hardy and Singleton, 2009; Hindorff et al., 2009), affected by acquired risk factors and variants of the genome which may sensitize also to cardiovascular events in later life (Ronkainen et al., 2001). Population-based studies of the long-term excess mortality and its causes after aSAH are few (Lehecka et al., 2007; Wermer et al., 2009). In the ISAT cohort, 1.413 one year survivors of aSAH from U.K. presented with 144 deaths in a mean of 9 years against 92 expected deaths from the standard death rates of England and Wales (Molyneux et al., 2009).

Our consortium (www.fiarc.fi) studies the sIA disease in the Finnish population (Bilguvar et al., 2008; van der Voet et al., 2004; Frosen et al., 2004; Frosen et al., 2006; Helgadottir et al., 2008; Laaksamo et al., 2008; Ronkainen et al., 1997; Ronkainen et al., 1999; Tulamo et al., 2006), particularly prone to aSAH (de Rooij et al., 2007). Kuopio Neurosurgery serves an Eastern Finnish catchment population, genetically characterized by a small number of founders, isolation, and major bottlenecks (Peltonen et al., 1999). In the previous study using the Kuopio sIA Database, 900 aSAH patients with good outcome (GOS 5) at 12 months had a mortality rate twice (SMR 1.96) that of the Eastern Finnish population in a median of 7.5 years (Ronkainen et al., 2001). In the present study, we analyse the long-term excess mortality of 244 familial and 1,502 sporadic one-year aSAH survivors as compared to the same catchment population matched by gender, age, and calendar time.

5.2 MATERIALS AND METHODS

5.2.1 Catchment population of Kuopio University Hospital

During the study period from 1980 to 2007, Neurosurgery of Kuopio University Hospital (KUH) solely provided full-time acute and elective neurosurgical services for the KUH catchment population in Eastern Finland (Huttunen et al., 2010) The KUH area contains four central hospitals with neurological units and catchment areas of their own. From 1980 to 2007, the geographic area remained the same, the population decreased from 863,726 to

851,066, the median age increased from 31 to 42 years in males and from 34 to 45 years in females, and the proportion of males remained unchanged at 49% (Huttunen et al., 2010).

5.2.2 Admission of SAH patients

All cases of SAH diagnosed by spinal tap or CT at the KUH catchment area were acutely admitted to KUH for angiography and treatment if not moribund or very aged. The exact number of rejected SAH patients are not available.

5.2.3 Kuopio Intracranial Aneurysm Database

KUH Neurosurgery maintains a database (Access) on all cases of unruptured and ruptured intracranial aneurysms admitted to the KUH since 1977. The database has been prospective since 1990, and earlier cases have been entered from the hospital records. The database is run by a dedicated full-time nurse, who interviews all new cases, and collects and codes into variables detailed information, including family history. The criteria for a sIA family is at least two affected first-degree relatives (Huttunen et al., 2010). Clinical data from the hospital periods and follow-up visits are entered. The use of prescribed medicines (1994-2008) by the patients before and after the sIA diagnosis, occurrence of cancer and other diseases, and causes of death have been entered from the national registries. The phenotype, genetics, and outcome of Eastern Finnish sIA disease has been analysed in many local and collaborative studies (Ronkainen et al., 1998; Hernesniemi et al., 1993; Ronkainen et al., 2001; Bilguvar et al., 2008; Helgadottir et al., 2008; Ronkainen et al., 1997; Ronkainen et al., 1999; van der Voet et al., 2004; Fogelholm et al. 1993; Huttunen et al., 2010; Lehecka et al., 2007).

5.2.4 Study population

The inclusion criteria were:

1. Citizen of Finland and resident of the KUH catchment area at the time of first aSAH between January 1, 1980 and December 31, 2007.

2. Admission alive to the KUH, and verification of sIA(s) by angiography or at autopsy.

The exclusion criteria were:

1. Rupture of an intracranial aneurysm other than a saccular one (e.g., fusiform, traumatic, or mycotic).

5.2.5 Follow up data

The death certificates with the ICD-9 or ICD-10 codes, were obtained from Statistics Finland. All patients were followed up until death or December 31, 2008, and no patient was lost from the follow up.

5.2.6 Variables in survival analysis

The prognostic variables were divided into four categories: sIA disease carrier (gender; age at aSAH; sporadic vs. familial sIA patient; GOS until 12 months); sIA disease (location

and diameter of the ruptured sIA; condition on admission for aSAH (Hunt & Hess grade; ICH; IVH; acute hydrocephalus); and treatment (year of aSAH; clipping vs. coiling vs. no occlusion of the ruptured sIA) (Table 5.1).

5.2.7 Statistical analysis

Groups were compared using non-parametric statistics, and p-values less than 0.05 were considered significant. SPSS 16.0 statistical software (SPSS Inc., Chicago, IL) was used.

The relative survival ratio (RSR) was calculated by dividing the observed survival proportion by the expected survival proportion (Ederer et al., 1961). The observed survival was estimated by the actuarial method (Cutler and Ederer, 1958) using annual intervals. The estimates of the expected survival were derived according to the Hakulinen method (Hakulinen, 1982) using the life tables of the KUH catchment population stratified by gender, 1-year age groups, and 1-year calendar periods. Annual and cumulative RSRs with 95% confidence intervals (CIs) were calculated from one year after aSAH (Table 5.1).

For multivariate analysis of risk factors potentially associated with mortality one year after aSAH, a relative survival regression model was fitted to the individual-level data with exact survival times using the maximum likelihood approach (Esteve et al., 1990; Dickman et al., 2004). The 11 covariates included in this model were: gender; age at aSAH; location and diameter of the ruptured sIA; Hunt & Hess grade; ICH; IVH; acute hydrocephalus; clipping vs. coiling vs. no occlusion of the ruptured sIA; year of aSAH; GOS until 12 months. These covariates were selected on the basis of prior knowledge of their effects on one-year mortality (Lehecka et al., 2008; Ronkainen et al., 2001; Lehecka et al., 2007). In the model, the observed hazard of death is assumed to be a sum of the catchment population hazard and a non-negative excess hazard, which is modelled as a multiplicative function of covariates. The baseline excess hazard was assumed to be constant within three intervals: 1 to 4 years, 4 to 10 years and after 10 years from admission. The covariates were divided in subgroups (Table 1), and the excess hazards for any two patient subgroups were assumed to be proportional over follow-up time. The relative excess risk (RER) of death was estimated for each subgroup with one subgroup as a reference (Table 5.3). The goodness of fit of the model was assessed using partial residuals, defined similarly to Schoenfeld residuals (Stare et al., 2005), and the assumptions of the model were tested to be appropriate. The 'relsurv' package (Pohar and Stare, 2006) in R(R Development Core Team, 2009) was used to fit the regression model and to assess the goodness of the fit.

5.2.8 Ethical aspects

The study was approved by the Ethics Committee of the Kuopio University Hospital. The causes of deaths were obtained with the permission from the Statistics Finland and the Ministry of Social Affairs and Health of Finland.

5.3 RESULTS

5.3.1 One-year mortality of 2,286 sIA patients admitted for aSAH

Between 1980 and 2007, 307 familial and 1,979 sporadic sIA patients had been admitted alive after aSAH to KUH. During the first 12 months after admission, 64 familial and 476 sporadic patients had died, resulting in 12-month mortality of 21% for the familial patients and 24% for the sporadic ones, respectively (Figures 5.1A and 5.1B).

5.3.2 Long-term excess mortality of 1,746 sIA patients alive one year after aSAH

The long-term excess mortality and the causes of death were analysed for the 1,746 sIA patients alive at 12 months after aSAH (Table 5.1). The median follow-up time until death or the end of 2008 was 12 years. Overall, 494 patients had died: 24 females and 27 males of the 244 familial patients, and 202 females and 241 males of the 1,502 sporadic patients, respectively (Table 5.2). The 15-year cumulative relative survival ratio (RSR) was 0.88 (CI 95% 0.85-0.91), implying 12% excesss mortality as compared to the matched Eastern Finnish catchment population of KUH (Table 5.1). Figures 5.1C and 5.1D show the cumulative relative survival ratios according to gender and familial sIA disease.

Table 5.1. Long-term cumulative relative survival of the 1.746 sIA patients alive at 12 months after admission for aSAH to the Kuopio University Hospital between 1980-2007 as compared to the matched Eastern Finnish catchment population[a]

	Patients alive at one year after aSAH		**Cumulative relative survival ratio at 5 yrs**		**Deaths at 1 to 5 years**	**Cumulative relative survival ratio at 10 yrs**		**Deaths at 5 to 10 years**	**Cumulative relative survival ratio at 15 yrs**		**Deaths at 10 to 15 years**
	N	%			N			N			N
All patients	1746	100	0.97	0.96-0.98	125	0.92	0.90-0.94	137	0.88	0.85-0.91	235
females	917	53	0.98	0.96-0.99	54	0.94	0.91-0.96	64	0.91	0.87-0.95	110
males	830	47	0.97	0.94-0.98	71	0.91	0.87-0.94	73	0.84	0.80-0.89	125
familial	244	14	1.00	0.97-1.02	11	0.99	0.93-1.02	11	0.89	0.80-0.96	30
sporadic	1502	86	0.97	0.95-0.98	114	0.91	0.89-0.93	126	0.87	0.84-0.90	205
Age at aSAH (years)											
0 - 34	216	12	0.95	0.91-0.98	12	0.92	0.87-0.95	7	0.90	0.85-0.95	10
35 - 64	1268	73	0.98	0.96-0.99	72	0.93	0.91-0.95	83	0.88	0.85-0.91	175
> 65	263	15	0.96	0.90-1.01	41	0.86	0.76-0.95	47	0.77	0.62-0.93	50
Site of ruptured sIA											
ACoA	563	32	0.97	0.95-0.99	42	0.93	0.89-0.96	43	0.87	0.82-0.92	71
Mbif	521	30	0.98	0.95-1.00	29	0.94	0.90-0.97	36	0.90	0.84-0.94	86
BAbif	49	3	0.85	0.70-0.93	8	0.78	0.59-0.91	4	0.65	0.41-0.83	5
Size of ruptured sIA (mm)											
< 7	607	35	0.99	0.97-1.00	43	0.95	0.91-0.98	52	0.94	0.88-0.98	66
7 - 14	867	50	0.96	0.94-0.98	61	0.91	0.87-0.94	56	0.85	0.81-0.89	108
> 14	176	10	0.98	0.93-1.01	15	0.92	0.84-0.98	17	0.83	0.72-0.92	48
Hunt&Hess grade on admission											
1 - 2	1073	62	0.97	0.95-0.99	74	0.94	0.91-0.96	76	0.89	0.85-0.93	133
3	476	27	0.98	0.95-1.00	35	0.90	0.85-0.94	50	0.86	0.80-0.92	78
4 - 5	198	11	0.96	0.91-0.99	16	0.92	0.83-0.98	11	0.80	0.67-0.91	24
ICH on admission											
yes	359	21	0.97	0.94-0.99	25	0.93	0.87-0.97	28	0.84	0.76-0.91	69
no	1379	79	0.97	0.96-0.98	98	0.92	0.90-0.94	108	0.88	0.85-0.92	163
IVH on											

admission											
yes	371	22	0.96	0.93-0.99	28	0.89	0.84-0.94	38	0.83	0.76-0.89	60
no	1367	78	0.97	0.96-0.99	95	0.94	0.91-0.96	97	0.89	0.86-0.92	173
Hydrocephalus on admission											
none	1101	63	0.98	0.97-1.00	66	0.95	0.92-0.97	73	0.91	0.87-0.94	151
moderate	547	31	0.96	0.93-0.98	47	0.90	0.86-0.94	48	0.85	0.79-0.91	65
severe	85	5	0.92	0.82-0.97	10	0.80	0.67-0.89	13	0.68	0.52-0.81	16
Ruptured sIAs on ACoA											
with ICH	67	12	0.94	0.83-0.99	8	0.88	0.73-0.97	5	0.86	0.68-0.99	8
without ICH	494	88	0.97	0.95-0.99	33	0.93	0.89-0.97	38	0.87	0.81-0.92	62
Ruptured sIAs on Mbif											
with ICH	208	60	0.98	0.93-1.00	12	0.93	0.86-0.99	16	0.83	0.73-0.92	46
without ICH	311	40	0.98	0.94-1.00	17	0.94	0.89-0.98	20	0.93	0.86-0.99	38
Occlusion of ruptured sIA											
microsurgical	1440	82	0.97	0.96-0.98	101	0.93	0.90-0.95	117	0.88	0.85-0.91	226
endovascular	265	15	0.99	0.95-1.02	13	0.94	0.86-1.00	16	0.91	0.74-1.03	4
other	24	2	0.95	0.72-1.02	3	0.71	0.43-0.90	4	0.77	0.46-0.98	3
none	17	1	0.77	0.43-0.95	7	0.71	0.33-0.97	0	0.59	0.18-0.95	2
GOS at one year											
5	1242	71	0.99	0.97-1.00	55	0.95	0.93-0,97	85	0.91	0.88-0.94	70
4	346	20	0.96	0.92-0.99	26	0.90	0.84-0.94	32	0.84	0.76-0.90	24
3	151	9	0.88	0.80-0.94	24	0.78	0.67-0.86	21	0.68	0.55-0.79	16
2	7	0.4	0.76	0.27-0.97	2	0.43	0.07-0.82	2	-	-	-

[a]sIA, saccular intracranial aneurysm; aSAH, subarachnoid hemorrhage from ruptured sIA; ACoA, anterior communicating artery; Mbif, middle cerebral artery bifurcation; BAbif, basilar artery bifurcation; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage. In parentheses 95% confidence intervals.

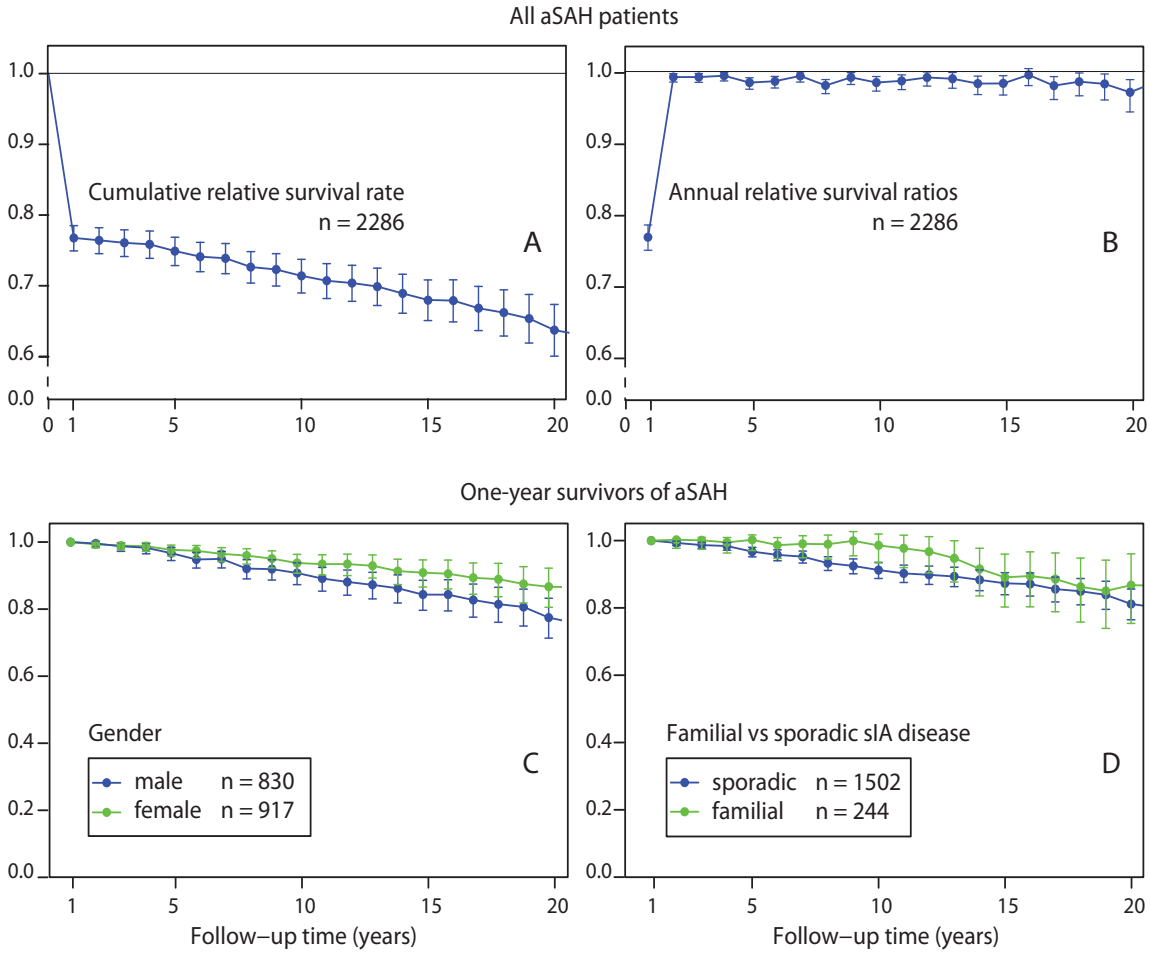

Figure 5.1 Excess mortality of the aSAH patients as compared to the matched Eastern Finnish catchment population. Cumulative (A) and annual (B) relative survival ratios of 2.286 patients after admission for aSAH. Cumulative relative survival ratios of the1,746 one-year survivors of aSAH by gender (C), and familial vs. sporadic sIA disease (D). The horizontal line at 100% represents the survival of the matched catchment population and curves below that line represent excess mortality of the study population. 95% confidence intervals are indicated by vertical bars.

Table 5.2. Causes of deaths until the end of 2008 of the 1.746 sIA patients alive at 12 months after admission for aSAH from 1980 to 2007.

	Sporadic		**Familial**		
	Females	**Males**	**Females**	**Males**	**Total**
	N (%)				
All patients	798	704	118	126	1746
Median follow-up time	11	12	12	12	12
Number of deaths	202*	241*	24*	27*	494*
Neurological deaths					
sequelae of aSAH	23 (11)	19 (8)	1 (4)	1 (4)	44 (9)
recurrent aSAH	7 (4)	8 (3)	1 (4)	1 (4)	17 (3)
new aSAH	8 (4)	5(2)	1 (4)	0 (0)	14 (3)
ICH	5 (3)	8 (3)	2(9)	2 (7)	17 (3)
brain infarction	18 (9)	9 (4)	4 (18)	1 (4)	32 (7)
dementia	11 (5)	4 (2)	1 (4)	0 (0)	6 (1)
other	4 (2)	2 (1)	0 (0)	0 (0)	6 (1)
Cardiovascular deaths					
ischemic cardiac disease	31 (15)	60 (25)	5 (23)	1 (4)	97 (20)
other	19 (9)	10 (4)	2 (9)	2 (7)	33 (7)
Cancer					
pulmonary	6 (3)	21 (9)	1 (4)	1 (4)	29 (6)
gastric	6 (3)	15 (6)	1 (4)	6 (21)	28 (6)
kidney	3 (2)	3 (1)	0 (0)	0 (0)	6 (1)
other	13 (6)	16 (7)	2 (9)	1 (4)	32 (7)
Gastric disease	10 (5)	18 (7)	1 (4)	1 (4)	30 (6)
Pulmonary disease	16 (8)	15 (6)	1 (4)	1 (4)	33 (7)
Kidney disease	6 (3)	5 (2)	1 (4)	0 (0)	12 (2)
Other disease	6 (3)	5 (2)	0 (0)	1 (4)	12 (2)
Trauma	8 (4)	8 (3)	0 (0)	5 (18)	21 (5)
Suicide	0 (0)	6 (3)	0 (0)	1 (4)	7 (2)
Intoxication	2 (1)	4 (2)	0 (0)	2 (7)	8 (2)

sIA, saccular intracranial aneurysm; aSAH, subarachnoid hemorrhage from ruptured sIA; ICH, intracranial hemorrhage.
*The percentages of different causes of death are presented in paranthesis in the column.

5.3.3 Causes of death one year after aSAH

In the familial group, the most frequent causes of deaths for the females were ischemic cardiac disease (5 / 24 deaths) and brain infarction (4 / 24), and for the males gastric cancer (6 / 27) and trauma (5 / 27) (Table 5.2). In the sporadic group, the leading causes of death among the females were ischemic cardiac disease (31 / 202) and sequelae of aSAH (23 / 202), for the males ischemic cardiac disease (60 / 241) and pulmonary cancer (21 / 241) (Table 5.2).

Figure 5.2 shows the ages at death plotted against the ages at aSAH according to three vascular causes of death. Lethal brain infarctions and lethal ischemic cardiac events occurred in later life, at the median ages of 78 and 73 years in females and 79 and 66 years in males, respectively (Figures 5.2B and 5.2C). Instead, lethal cases of recurrent or new aSAH occurred earlier ($p<0.001$), irrespective of age after the first aSAH, at the median age of 67 in females and 52 in males, respectively (Figure 5.2A).

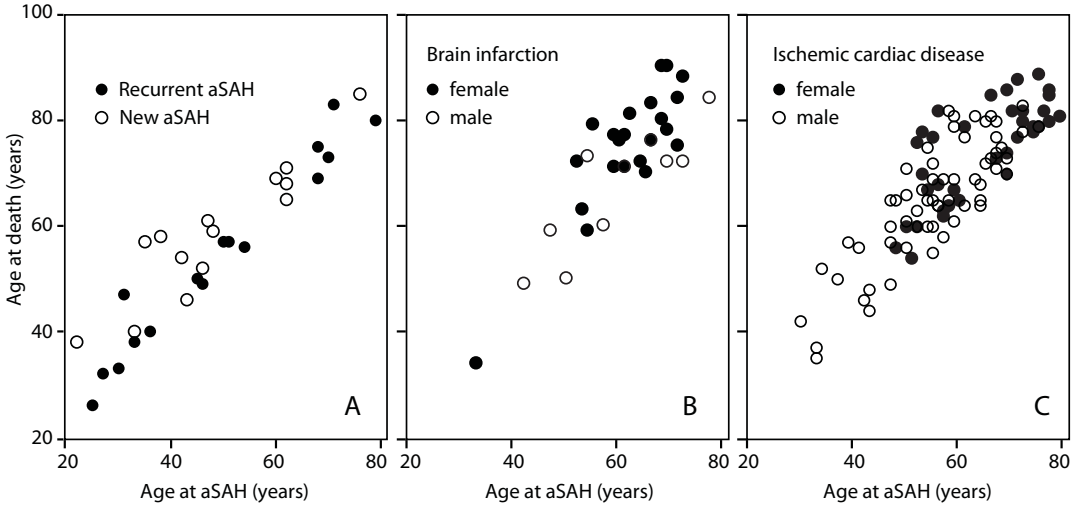

Figure 4.2 Age at aSAH (x-axis) vs age at death (y-axis) according to three vascular causes of death. Recurrent aSAH from previously ruptured sIA vs. new aSAH from another sIA (A). Brain infarction (B), and ischemic cardiac events (C) according to gender.

5.3.4 Recurrent or new aSAH during follow up

The 1,440 clipped cases (1980 – 2007) and the 265 endovascularly treated cases (1992-2007) did not differ in the long-term excess mortality (Table 5.3). There were 13 lethal re-bleeds from the clipped sIAs, two lethal re-bleeds from the coiled sIAs, and two lethal re-bleeds from the untreated ruptured sIAs at the median times of 4.9, 6.8, and 3.2 years, respectively. In addition, there were 14 new lethal bleeds from other sIAs at a median of 9.1 years. Removing the 31 lethal re-bleeds or new bleeds, the 15-year cumulative relative survival ratio (RSR) was still 0.89 (CI 95% 0.86-0.92), implying 11% excess mortality. There were no differences in the rates of re-bleeds or new bleeds between the familial and sporadic patients.

5.3.5 Independent risk factors for long-term excess mortality

In the multivariate regression model for relative excess risk (RER) of death, the male gender (RER 1.6; CI 95% 1.0 -2.7), age over 64 years at aSAH (2.9; 1.2 – 6.9), ruptured basilar tip sIA (4.5; 2.0 – 10), severe hydrocephalus on admission (3.6; 1.8-7), no occlusion of the ruptured sIA (6.0; 1.7-21), and the condition at 12 months after the primary aSAH, GOS 4 (2.2; 1.2-4), GOS 3 (4.1; 2.1-8), and GOS 2 (23;5.7-90) were significantly associated with the increased long-term excess mortality (Table 5.3). Instead, familial sIA disease (Figure 5.1C), and the mode of occlusive therapy, either microsurgical or endovascular were not considered risk factors.

Table 5.3. Relative excess risks (RERs) of death for the 1.746 patients alive one year after aSAH

	RER	**95% CI**
Gender		
Female	1	reference
Male	1.63	0.98 - 2.71
Age at aSAH (years)		
0 - 34	1	reference
35 - 64	1.00	0.51 - 1.96
> 65	2.88	1.19 - 6.94
Familial sIA disease		
yes	1	reference
no	1.80	0.76 - 4.28
Size of ruptured sIA (mm)		
< 7	1	reference
7 - 14	1.37	0.75 - 2.49
> 15	1.85	0.84 - 4.08
Site of ruptured sIA		
ACoA	1	reference
Mbif	1.14	0.61 - 2.14
BAbif	4.48	2.01 - 9.99
Other	1.00	0.55 - 1.83
Hunt&Hess Grade on admission		
1 - 2	1	reference
3	0.66	0.36 - 1.22
4 - 5	0.77	0.35 - 1.67
ICH on admission		
no	1	reference
yes	1.13	0.57 - 2.23
IVH on admission		
no	1	reference
yes	1.03	0.57 - 2.23
Hydrocephalus on admission		
none	1	reference
moderate	1.69	1.01 - 2.83
severe	3.59	1.81 - 7.13
Occlusion of ruptured sIA		
microsurgical	1	reference
endovascular	0.79	0.32 - 1.92
other	1.22	0.26 - 5.72
none	6.02	1.70 - 21.3
GOS at one year		
5	1	reference
4	2.15	1.12 - 4.10
3	4.13	2.11 - 8.09
2	22.6	5.66 - 90.2

sIA, saccular intracranial aneurysm; aSAH, subarachnoid hemorrhage from ruptured sIA; ACoA, anterior communicating artery; MCA, middle cerebral artery; BAbif, BA bifurcation; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage

5.4 DISCUSSION

This cohort of 1,746 one-year survivors of aSAH from the Kuopio sIA Database presented with a long term excess mortality of 12% at 15 years as compared to the Eastern Finnish catchment population matched by gender, age at aSAH, and calendar time. Independent patient-related risk factors for the excess mortality were male gender and age over 64 years at aSAH, but not the familial sIA disease. Independent sIA disease related risk factors were the ruptured basilar tip sIA, severe hydrocephalus on admission, no occlusion of the ruptured sIA, and GOS 2-4 at 12 months. In the median follow up time of 12 years, there were 494 deaths of which 17 were caused by a recurrent aSAH and 14 by a new aSAH from another sIA. These 31 aSAH deaths only partially explain the excess mortality of 12% at 15 years.

There are few published population based studies of the long-term excess mortality after aSAH (Ronkainen et al., 2001; Lehecka et al., 2007; Molyneux et al., 2009; Olafsson et al., 1997; Wermer et al., 2009). In Eastern and Southern Finland, 280 patients with a ruptured distal ACA aneurysm did not present with excess mortality after 3 years (Lehecka et al., 2007), possibly because of the distal site of the ruptured aneurysm and the unique location between the cerebral hemispheres. In the previous study from the Kuopio Database, Ronkainen et al. (Ronkainen et al., 2001) observed that 900 aSAH patients with good outcome (GOS 5) at 12 months had a mortality rate twice that of the Eastern Finnish general population in a median follow up time of 7.5 years. There were 14 deaths caused by a new aSAH. Standardised mortality ratios (SMRs) were calculated according to age, sex, and year of admission. They concluded that aSAH is one aspect of chronic general vascular disease, and more attention should be paid to the reduction of risk factors, and the long term follow up of aSAH survivors. In the International Subarachnoid Aneurysm Trial (ISAT) cohort, 1.413 one year survivors of aSAH from U.K. were followed up for a mean of 9 years (Molyneux et al., 2009). They presented with an increased SMR (1.57; 144 observed vs. 92 expected deaths) as compared to the standard death rates of England and Wales. There were 17 re-bleeds from the clipped or coiled aneurysms causing 9 deaths, and 6 cases of aSAH from de novo aneurysms causing 3 deaths. In a Dutch cohort of 752 clipped aSAH survivors discharged to home, the SMR was 1.7 overall and 3.2 for the patients under 40 years of age (Wermer et al., 2009).

The strength of the present study is derived from the Finnish health care system. Finland is divided into mutually exclusive geographical catchment areas between the 5 university hospitals. A catchment population served solely by a single neurosurgical unit allows the creation of disease cohorts that are unselected and unbiased to the minimum. Very accurate population and mortality statistics of the stable population, e.g., with causes registered for virtually all deaths, allow the comparison of a defined disease cohort to the catchment population. The expertise of the Finnish Cancer Registry has allowed to calculate the relative mortality ratios, e.g., for intracranial meningiomas (Kallio et al., 1992) distal ACA aneurysms (Lehecka et

al., 2007) and AVMs (Laakso et al., 2008). Unlike the standardised mortality ratio (SMR), a ratio of the observed and expected numbers of deaths, (Ronkainen et al., 2001; Molyneux et al., 2009) the relative survival ratio (RSR) takes into account possible temporal variations in the excess mortality. The annual and cumulative relative survival ratios allow a more comprehensive presentation of the data in the course of follow up time in the form of survival time plots (Figure 5.1).

The covariates tested (gender; age at aSAH, location and diameter of the ruptured sIA, Hunt & Hess grade, ICH; IVH; acute hydrocephalus, clipping vs. coiling vs. no occlusion of the ruptured sIA, year of aSAH, GOS until 12 months) were selected on the basis of prior knowledge of their effects on one-year mortality (Lehecka et al., 2008; Ronkainen et al., 2001; Lehecka et al., 2007). The outcome of familial and sporadic aSAH patients has not been compared previously. The multivariable analyses should be interpreted with caution. The covariates investigated may be thought to be important risk factors because they are associated with a small P value, and other covariates may be thought not to be risk factors because of larger P values, but both opinions may be erroneous (type I and type II statistical errors, respectively). Additional studies are necessary to address the reliability of these exploratory findings.

The present study is based on the rather homogeneous Eastern Finnish population, and our results require replication in unselected multi-ethnic populations. For centuries, Finland had been long been isolated for geographic, linguistic, and cultural reason.(Peltonen et al., 1999) Mitochondrial DNA indicates that Finns do not significantly differ from other European populations (Lahermo et al., 1996). SNP association analyses (Salmela et al., 2008) and Y-chromosomal variations (Lappalainen et al., 2006) suggest that Western and Eastern Finland have partly different population histories. The Eastern Finnish gene pool has been affected by a small number of founders, isolation, and major bottlenecks (Peltonen et al., 1999). There were 244 familial aSAH patients in the present cohort, and many of them must share a common ancestry in the 16th to 20th centuries due to small number of founders (Peltonen et al., 1999).

The familial sIA disease did not associate with the long term excess mortality (Figure 1C). In our previous study of the sIA phenotype on admission, the familial males and females were only a few years younger than the sporadic ones, and the proportions of multiple sIAs were equal at 30% and 28% (Huttunen et al., 2010). These findings indicate that the the familial sIA disease is not particularly grave as compared to the sporadic sIA disease, at least when the minimum requirement for an sIA family is two affected first degree relatives. For comparison, the differences in the age of onset and proportion of multiple meningiomas and schwannomas are remarkable between sporadic and neurofibromatosis type 2 type patients.

The causes of the long term excess mortality after aSAH are heterogeneous, and more detailed analyses are required. The UK cohort (Molyneux et al., 2009) and the present cohort of 1,413 and 1,746 one year aSAH survivors, respectively, were not analysed for the relative distribution of the causes of deaths as compared to that of the corresponding catchment populations. New cases of aSAH, from previously occluded, untreated, or de novo aneurysms, caused more deaths than would be expected in general population. Instead, it is difficult to pinpoint which other causes of deaths were truly overrepresented among the one year survivors of aSAH.

The impact of aSAH and its sequelae in the central nervous system and the cardiovascular system may cause long-term morbidity and mortality. Survivors of aSAH are potentially at risk to neurological morbidity from, e.g., epilepsy, depression, dementia, shunt complications, hypothalamic and hypophyseal disorders, and ischemic cerebrovascular events. All these may add to the excess mortality. The sIA disease is a complex trait, like diabetes type 2 or Alzheimer's disease, affected by acquired risk factors and variants of the genome, and by their interactions (Hardy and Singleton, 2009; Hindorff et al., 2009). The genomic variants behind the sIA disease might sensitize the sIA patients to neurovascular and cardiovascular events in later life as well. It is not known, so far, whether the sIA disease is restricted to the forks of intracranial extracerebral arteries only.

5.5 CONCLUSIONS

The impact of both sporadic and familial aSAH and their sequelae in the central nervous and cardiovascular system may cause long-term morbidity and mortality. The complex sIA disease may predispose to other vascular events in later life. The causes of the long term excess mortality are heterogeneous, and more detailed analyses are required.

6 Increased relative risk of lung cancer in 2 904 patients with secular intracranial aneurysm disease in Eastern Finland[3]

Abstract. To analyse long-term incidence of cancer after the first diagnosis of saccular intracranial aneurysm (sIA) disease. Neurosurgery of Kuopio University Hospital (KUH) solely serves a defined Eastern Finnish population. Kuopio sIA Database contains 2904 consecutive sIA cases from 1980 to 2007, 618 unruptured (170 familial and 448 sporadic) and 2286 ruptured (aSAH) cases (308 familial and 1978 sporadic). They were followed for cancer incidence (Finnish Cancer Registry) until death (n=1176) or December 31, 2008, a total of 26,844 person-years. Their standardised incidence ratios (SIRs) of different cancers were calculated as against corresponding (year of follow-up, gender, age) KUH population. Lung cancer after the first sIA diagnosis occurred in 30 of the 1340 male patients (SIR 2.0; 95% confidence interval [CI] 1.4 - 2.9), and in 10 of the 1564 female patients (SIR 2.6; 95% CI 1.2 - 4.7). Poisson regression analysis identified male gender and increasing diameter of the ruptured sIA as independent risk factors for the lung cancer, while the familial sIA disease, age at aSAH, site of ruptured sIA, or the presence of associated unruptured sIAs had no significant effect. Carriers of sIA disease have an increased risk of developing lung cancer. Their long-term smoking habits after the sIA diagnosis should be elucidated for preventive purposes

[3] Adapted with permission of the Neurosurgery from: **Huttunen T, von und zu Fraunberg M, Koivisto T, et al. Long-term excess mortality of 244 familial and 1502 sporadic one-year survivors of aneurysmal subarachnoid hemorrhage compared with a matched Eastern Finnish catchment population.** Neurosurgery. 2011;68(1):20-27.

6.1 INTRODUCTION

Some 2% of population develops during life saccular intracranial aneurysms (sIAs) at the branching sites of major intracranial extracerebral arteries (Ronkainen et al., 1998). Rupture of the sIA wall causes almost all cases of aneurysmal subarachnoid hemorrhage (aSAH) (van Gijn et al., 2007), but most sIAs do not rupture as the annual incidence of SAH is about 6 per 100,000 (Feigin et al., 2009). Acute aSAH is a critical condition, a devastating form of stroke that affects working age population (van Gijn et al., 2007; Bederson et al., 2009; Levine, 2009). The sIA disease is a complex trait. Known risk factors include age, female sex, hypertension, smoking, and excess drinking (Feigin et al., 2005), and at least 10% of aSAH patients have a family history (Ronkainen et al., 1997; Huttunen et al., 2010).

A large multinational genomewide association study of intracranial aneurysm identified five susceptibility loci, among them 9p21.3 (Helgadottir et al., 2008) close to the CDKN2A and CDKN2B genes that are involved in many types of cancer (Kamb et al., 1994). Furthermore, smoking is a common risk factor for both the sIA disease and cancers of the lung, upper aero-digestive tract (oral cavity, nasal cavity and sinuses, pharynx, larynx, oesophagus), pancreas, stomach, liver, lower urinary tract (renal pelvis and bladder), kidney and uterine cervix (Dreyer et al., 1997) Population-based studies of the long-term outcome of sIA patients are few (Lehecka et al., 2007; Molyneux et al., 2009; Olafsson et al., 1997; Wermer et al., 2009; Huttunen et al., 2011; Nieuwkamp et al., 2011), and it has not been established whether the sporadic or familial sIA disease carriers are predisposed also to other phenotypes, including cancer (Nieuwkamp et al., 2011; Huttunen et al., 2011; Ronkainen et al., 2001; Bilguvar et al., 2008).

Neurosurgery of Kuopio University Hospital (KUH) serves solely an Eastern Finnish catchment population, and Kuopio sIA Database (www.uef.fi/crc/ns) contains all sIA patients admitted since 1980 (Huttunen et al., 2011; Huttunen et al., 2010). In the present study, we analyse the long-term incidence of cancer in 2904 sIA patients from 1980 to 2007 as compared to the KUH catchment population.

6.2 MATERIALS AND METHODS

6.2.1 Catchment population of Kuopio University Hospital (KUH)

During the study period from 1980 to 2007, Neurosurgery of KUH solely provided full-time acute and elective neurosurgical services for the KUH catchment population in Eastern Finland (Huttunen et al., 2010; Huttunen et al., 2011). The KUH area contains four central hospitals with neurological units and catchment areas of their own. From 1980 to 2007, the geographic area remained the same, the population decreased from 864,000 to 851,000, and the median age increased from 31 to 42 years in males and from 34 to 45 years in females, but the proportion of males remained at 49%.

6.2.2 Kuopio Intracranial Aneurysm Database

All cases of SAH diagnosed by spinal tap or CT at the KUH catchment area were acutely admitted to KUH for angiography and treatment if not moribund or very aged. Cases with unruptured IA(s) detected either as occult findings in neuroimaging for other symptoms, or by screening sIA family members, have also had a neurosurgical consultation for elective occlusion. The findings were confirmed with 4-vessel catheter angiography, MRA or CTA. In both instances, exact numbers of rejection are not available. KUH Neurosurgery maintains a database on all cases of unruptured and ruptured intracranial aneurysms admitted to the KUH since 1980 (Huttunen et al., 2011; Huttunen et al., 2010). The database has been prospective since 1990, and earlier cases have been entered from the hospital records. The database is run by a dedicated full-time nurse, who interviews all new cases, and collects and codes into variables detailed information, including family history. The criteria for an sIA family is at least two affected first-degree relatives (Huttunen et al., 2010). Clinical data from the hospital periods and follow-up visits are entered. The use of prescribed medicines since 1994, the diagnoses of other diseases, including cancer, and the causes of death have been entered from the national registries. The phenotype, genetics, and outcome of Eastern Finnish sIA disease has been analysed in many local and collaborative studies (Ronkainen et al., 1998; Ronkainen et al., 1999; Helgadottir et al., 2008; Lehecka et al., 2007; Bilguvar et al., 2008; Fogelholm et al., 1993; Hernesniemi et al., 1993; van der Voet et al., 2004).

6.2.3 Study population

In overall, 308 familial and 1978 sporadic patients with a ruptured sIA and 170 familial and 448 sporadic patients with unruptured sIA(s) fulfilled the following inclusion criteria:

1. Citizen of Finland and resident of the KUH catchment area at the time of diagnosis of the sIA disease between January 1, 1980 and December 31, 2007.

2. Admission alive to the KUH and verification of sIA by angiography or at autopsy.

6.2.4 Follow up for cancer incidence

The information of the cancer diagnoses was obtained from the Finnish Cancer Registry. The patients were followed up for the cancer diagnoses from the date of first diagnosis of sIA disease between 1980 and 2007 until death (n=1176) or December 31, 2008. No patient was lost from the follow up.

6.2.5 Statistical analysis

The number of observed cancer cases and person-years at risk were calculated by gender, 5-year age groups, three calendar periods (1980-1989, 1990-1999 and 2000-2007), and time since the diagnosis of sIA disease (<1, 1-9.9, ≥10 years). The expected number of cases for all cancers combined and for site specific cancers was calculated by multiplying the number of person-years in each stratum by the corresponding

cancer incidence rate in KUH catchment area. To calculate the standardised incidence ratio (SIR), the observed number of cases was divided by the expected number. The 95% confidence intervals (CIs) were based on the assumption that the number of observed cases followed a Poisson distribution.

Logistic regression was used to analyse which of the variables (gender, familial or sporadic disease, age at aSAH, diameter and site of ruptured sIA, multiple sIAs) independently associated to the occurrence of lung cancer after aSAH.

6.2.6 Ethical aspects

The study was approved by the Ethics Committee of the Kuopio University Hospital. The cases of cancer and causes of death were obtained with the permission from the Statistics Finland and the Ministry of Social Affairs and Health of Finland.

6.3 RESULTS

6.3.1 Observed and expected cases of cancer

The entire study population was 2904 consecutive sIA patients first diagnosed between 1980 and 2007, inclusive (Table 6.1). There were 2286 aSAH cases, 308 (13.5%) familial and 1978 (86.5%) sporadic ones. There were 618 unruptured sIA cases, 170 (27.5%) familial and 448 (72.5%) sporadic ones. The total follow-up time was 26844 person-years. After the first diagnosis of sIA disease, 218 cases of cancer were detected as against 183 expected ones (SIR 1.19; 95% CI 1.04-1.35; p=0.05). Table 6.2 presents the observed and expected cases of cancer according to the rupture status and gender.

6.3.2 Familial sIA disease and cancer

There were 39 cancers in the 477 familial patients (SIR 1.5; 95% CI 1.0-2.0) and 179 in the 2426 sporadic patients (SIR 1.1; 95% CI 1.0-1.3), with no significant difference in the overall cancer incidence. In the familial sIA cohort, no significant overrepresentations were found in any cancer site or type.

6.3.3 Lung cancer

Lung cancer was diagnosed in five of the 273 males with unruptured sIA(s) (SIR 1.8; 95% 0.6-4.2) and in 25 of the 1066 males with a ruptured sIA (SIR 2.4; 95% 1.3-3.0) (Table 6.2). Lung cancer was diagnosed in two of the 344 females with unruptured sIA(s) (SIR 2.6; 95% 0.3-9.5) and in 8 of the 1.220 females with a ruptured sIA (SIR 2.5; 95% 1.1-5.0) (Table 6.2). In the 2.285 aSAH patients, multivariate logistic regression analysis showed that male gender and increasing diameter of the ruptured sIA were independently associated to the lung cancer. Instead, the familial or sporadic sIA disease, age at aSAH, site of ruptured sIA, or presence of associated unruptured sIAs were not significant (Table 6.3).

Table 6.1. Characteristics of 2904 patients with saccular intracranial aneurysm (sIA) disease first diagnosed between 1980 and 2007 in Eastern Finland.

	Patients	**Median age at sIA diagnosis**	**Follow up time**
	n	years	person years
sIA patients	2904	52 (43-62)	26844
Familial	478 (16%)	48 (39-56)	4733
Ruptured sIA disease	308	47 (38-57)	3219
Females	150	50 (40-61)	1619
Males	158	45 (37-53)	1600
Unruptured sIA disease	170	49 (42-55)	1514
Females	97	49 (43-56)	881
Males	73	48 (40-55)	633
Sporadic	2426 (84%)	53 (43-63)	22111
Ruptured sIA disease	1978	52 (43-62)	18915
Females	1070	55 (45-65)	9818
Males	908	49 (40-58)	9097
Unruptured sIA disease	448	57 (44-66)	3196
Females	247	59 (49-69)	1718
Males	201	54 (48-63)	1478

sIA, saccular intracranial aneurysm; 25% and 75% percentiles for age distributions

Table 6.2. Site-specific standardised incidence ratios (SIRs) and their 95% confidence intervals (CIs) after the diagnosis of saccular intracranial aneurysm (sIA) disease in 2285 ruptured and 618 unruptured cases by gender and site.

			Patients with ruptured sIA disease				Patients with unruptured sIA disease			
Primary site		**ICD-10**	**Observed**	**Expected**	**SIR**	**95% CI**	**Observed**	**Expected**	**SIR**	**95% CI**
All sites	M	C00-96	93	68.3	1.36	1.1-1.66**	15	16.82	0.89	0.50-1.47
	F		80	79.5	1.01	0.8-1.25	30	18.71	1.60	1.08-2.28*
Mouth, pharynx										
Lip	M	C00	1	0.77	1.30	0.03-7.22		0.15	0.00	0.00-24.6
	F			0.32	0.00	0.00-11.4		0.08	0.00	0.00-44.5
Tongue	M	C01-02		0.32	0.00	0.00-11.7		0.07	0.00	0.00-50.5
	F		2	0.24	8.33	1.01-30.1*		0.06	0.00	0.00-62.3
Mouth, other	M	C03-06		0.31	0.00	0.00-12.1		0.07	0.00	0.00-51.4
	F		2	0.28	7.03	0.85-25.4		0.06	0.00	0.00-57.1
Pharynx	M	C09-14	2	0.32	6.32	0.77-22.8		0.07	0.00	0.00-49.6
	F			0.13	0.00	0.00–27.4		0.03	0.00	0.00-111
Digestive organs										
Oesophagus	M	C15	2	0.88	2.26	0.27-8.17		0.21	0.00	0.00-17.7
	F			0.62	0.00	0.00-5.92		0.13	0.00	0.00-28.7
Stomach	M	C16	4	2.95	1.36	0.37-3.47	1	0.67	1.50	0.04-8.35
	F		1	2.82	0.35	0.01-1.97	2	0.61	3.29	0.40-11.9
Colon	M	C18	2	3.63	0.55	0.07-1.98		0.92	0.00	0.00-4.01
	F		2	5.19	0.39	0.05–1.39	3	1.21	2.47	0.51-7.23
Rectum, rectosigmoid, anus	M	C19-21	4	2.88	1.39	0.38-3.55	1	0.71	1.41	0.04-7.85
	F		3	2.89	1.04	0.21-3.03	2	0.67	2.99	0.36-10.8
Liver	M	C22	5	1.08	4.65	1.51-10.8**		0.28	0.00	0.00-13.0
	F			0.84	0.00	0.00-4.41		0.19	0.00	0.00-19.1
Gallbladder, bile ducts	M	C23-24	2	0.52	3.88	0.47-14.0		0.13	0.00	0.00-29.0
	F		1	1.39	0.72	0.02–3.99		0.30	0.00	0.00-12.3
Pancreas	M	C25	7	2.46	2.84	1.14-5.86*	1	0.60	1.68	0.04-9.35
	F		2	3.09	0.65	0.08-2.33		0.71	0.00	0.00-5.20
Respiratory organs										
Larynx, epiglottis	M	C32	2	0.76	2.63	0.32-9.50		0.16	0.00	0.00-22.9
	F			0.08	0.00	0.00-44.6		0.02	0.00	0.00-168
Lung, trachea	M	C33-34	25	12.3	2.04	1.32-3.01**	5	2.75	1.82	0.59-4.23
	F		8	3.15	2.54	1.10-5.0*	2	0.76	2.62	0.32-9.46

Skin										
Melanoma	M	C43	1	2.03	0.49	0.01-2.74	1	0.47	2.12	0.05-11.8
	F		1	2.03	0.49	0.01-2.74		0.48	0.00	0.00-7.76
Soft tissues										
	M	C48-49		0.48	0.00	0.00-7.70		0.11	0.00	0.00-32.5
	F			0.51	0.00	0.00-7.20		0.12	0.00	0.00-31.0
Lymphoid and haematopoietic tissue										
Hodgkin lymphoma	M	C81		0.31	0.00	0.00-11.8		0.06	0.00	0.00-64.1
	F			0.21	0.00	0.00-17.6		0.04	0.00	0.00-85.4
Non-Hodgkin lymphoma	M	C82-85,C96	4	2.89	1.38	0.38-3.53		0.68	0.00	0.00-5.38
	F		1	3.37	0.30	0.01-1.65	1	0.79	1.26	0.03-7.02
Multiple myeloma	M	C90		0.83	0.00	0.00-4.41		0.20	0.00	0.00-18.2
	F			1.09	0.00	0.00-3.37	1	0.24	4.13	0.10-23.0
Leukaemia	M	C91-95	2	1.48	1.35	0.16-4.87		0.34	0.00	0.00-11.0
	F		1	1.53	0.65	0.02-3.64		0.34	0.00	0.00-10.9
Brain, central nervous system										
	M	C70-72	3	1.99	1.51	0.31-4.40	1	0.43	2.35	0.06-13.1
	F		2	3.16	0.63	0.08-2.28	4	0.71	5.60	1.52-14.3*
Urinary organs										
Kidney	M	C64-65	6	2.75	2.18	0.80-4.74		0.65	0.00	0.00-5.67
	F		6	2.71	2.21	0.81-4.81	1	0.63	1.58	0.04-8.78
Bladder, ureter, urethra	M	C66-68	2	3.78	0.53	0.06-1.91		0.92	0.00	0.00-4.02
	F		3	1.48	2.03	0.42-5.93	1	0.33	3.01	0.08-16.8
Prostate		C61	14	16.9	0.83	0.45-1.38	3	4.79	0.63	0.13-1.83
Female breast		C50	27	22.8	1.18	0.78-1.72	7	5.70	1.23	0.49-2.52
Female reproductive organs										
Cervix uteri		C53	2	0.97	2.07	0.25-7.47		0.20	0.00	0.00-18.3
Corpus uteri		C54	6	5.54	1.08	0.40-2.35	2	1.30	1.54	0.19-5.57
Ovary		C56	2	3.64	0.55	0.07-1.98		0.83	0.00	0.00-4.43

Levels of significance: * p<0.05; ** p<0.01

Table 6.3. Characteristics of aSAH patients with lung cancer, with odds ratios (ORs) from logistic regression analysis.

	Lung cancer / total	**OR**	**95% CI**	**P-value**
sIA patients	35 / 2285			
Females	9 / 1220	1		
Males	26 / 1065	3.8	1.7-8.4	0.001
Sporadic	31 / 1978	1		
Familial	4 / 307	0.9	0.3-2.7	0.87
Age at aSAH (years)				
≤ 45	5 / 777	1		
46 - 59	16 / 855	1.5	0.5-4.7	0.54
≥ 60	14 / 653	0.9	0.2-4.1	0.87
Diameter of ruptured sIA (mm)				
≤ 7	4 / 390	1		
8 - 14	12 / 427	2.9	1.02-7.9	0.05
≥ 15	9 / 161	4.4	1.4-13	0.01
Site of ruptured sIA (mm)				
AcoA	5 / 684	1		
Mbif	15 / 703	2.85	1.02-7.93	0.05
Other	15 / 898	4.35	1.42-13.34	0.01
Multiple sIAs				
Yes	18 / 807	1		
No	8 / 268	1.3	0.6-2.7	0.43

All values adjusted for year of birth

6.3.4 Other smoking related cancers

Pancreatic cancer (SIR 2.8; 95% CI 1.1-5.9) and liver cancer (SIR 4.6; 95% CI 1.5-10.8) were significantly overrepresented in the male patients with the ruptured sIA disease (Table 6.2). Instead, other smoking-related cancers (tongue, mouth, pharynx, larynx, oesophagus, stomach, bladder and kidney) were not.

6.3.5 Other cancers

There were four central nervous system tumours as against one expected in the female patients with unruptured sIA(s) (SIR 5.6; 95% CI 1.5-14.3) (Table 6.2), all of them meningiomas. No other sites or types of cancers were overrepresented in the study cohort.

6.4 DISCUSSION

To our knowledge, this is the first population based study on the relative incidence of cancers in the carriers of saccular intracranial aneurysm (sIA) disease. PubMed lists only case reports on the coexistence of CNS tumours and sIA disease. The study cohort consisted of 2904 sIA patients admitted alive between 1980 and 2007 to the Kuopio University Hospital (KUH) from its geographically defined Eastern Finnish catchment population (Huttunen et al., 2011). Our new findings were: lung cancer was significantly overrepresented in the aSAH patients; the ruptured sIA were larger in the aSAH patients who developed lung cancer; the familial sIA disease did not increase the risk of any type of cancer.

Known risk factors for the sIA disease include age, gender, hypertension, smoking, excess alcohol consumption, and familial background (Feigin et al., 2005). Smoking

is a common avoidable risk factor for both the sIA disease (Feigin, et al. 2005) and lung cancer (Dreyer et al., 1997). In a Finnish single center series of 278 consecutive aneurysmal SAH patients and 314 hospitalized controls, published in 1993, the proportion of non-smokers were 12% vs. 41% in males and 47% vs. 61% in females (Juvela et al., 1993). Over 90% of male lung cancer patients are smokers (Tyczynski et al., 2003). In the second genome-wide SNP association study with extended cohorts from Europe and Japan, 5,891 cases and 14,181 controls, five loci were identified: RBBP8 on 18q11.2; STARD13-KL on 13q13.1; a gene-rich region on 10q24.32; SOX17 on 8q11.23-q12.1; and CDKN2A-CDKN2B on 9p21.3 (Yasuno et al., 2010). However, none of these loci have emerged in the GWAS studies of lung cancer (www.genome.gov/gwastudies).

A larger diameter of the ruptured sIA independently associated to the lung cancer. In a Finnish cohort of 87 patients with 111 unruptured sIAs, smoking was an independent risk factor for further aneurysm growth in a mean follow-up time of 18.9 years (Juvela et al., 2001). In a Japanese cohort of 285 aSAH patients, smoking was independently associated with aneurysms $\geq$5mm in diameter (Inagawa, 2010). In a prospective cohort of 298 aSAH patients, smoking at any time independently associated with large ($\geq$13 mm) aneurysms (Qureshi et al., 2000). The sIA pouches are under hemodynamic stress and shearing forces in the turbulent blood flow at the intracranial artery forks, but many additional factors may predispose the sIA pouches to dilation and/or rupture. Smoking alters the function of vascular endothelium, initiates the adhesion cascade and stimulates the vascular inflammatory events leading to atherosclerosis and hypertension (Balakumar and Kaur, 2009). The exact mechanisms of smoking on the sIA wall are not known, but indirect evidence suggest inflammation and degradation of connective tissue.

No overrepresentations were found by the cancer type or site in the familial patients. In the Kuopio sIA Database (www.uef.fi/ns), 14% of the aSAH patients belonged to an sIA family (Huttunen et al., 2010). The familial sIA disease has an undefined genomic background, and there is no evidence on manifestations in other tissues than the forks of the intracranial arteries. In Finnish familial sIA patients, genome-wide linkage analysis showed linkage to 19q13 (van der Voet et al., 2004) and Xp22 (Olson et al., 2002), both replicated in Japan (Yamada et al., 2004) as well as to kallikrein gene cluster (Weinsheimer et al., 2007). Their significance, if any, in the sIA formation or rupture remains unresolved. In a cohort of 79,644 complete twin pairs of Danish, Finnish, and Swedish origin with 6.01 million person-years of follow up, there only 6 concordant twin pairs in a total of 504 SAH cases, suggesting at most a modest role for genetic factors in SAH (Korja et al., 2010).

The strength of this study derives from the accurate population and cancer statistics (Teppo et al., 1994) of the stable Finnish population. The weakness of the study is that information about the smoking status at the time of aSAH patients was not available. In addition, the present study is based on the rather homogeneous Eastern Finnish population (Peltonen et al., 1999), and our results require replication in unselected multi-ethnic populations.

6.5 CONCLUSIONS

Smoking is a modiable risk factor that is important in the prevention of aSAH as well as for further understanding of the pathogenesis of sIA formation and sIA wall rupture. The long-term smoking habits of the carriers of unruptured sIAs as well as survivors of aSAH after the first diagnosis should be elucidated. Their permanent abstinence from smoking should be supported and monitored.

7 Summary and future perspectives

Saccular intracranial aneurysms (sIAs) form during life at the branching sites of intracranial extracerebral arteries in the cerebrospinal fluid space. Rupture of the sIA wall is the most frequent cause of aneurysmal subarachnoid hemorrhage (aSAH), a devastating form of stroke that affects working aged population.

Kuopio Neurosurgery sIA Database (www.uef.fi/ns) contains all cases of aSAH or unruptured sIAs admitted to the Kuopio University Hospital (KUH) since 1980 from the KUH catchment area in Eastern Finland (Figure 1.1). From 1980 to 2007, the geographic area remained the same, the population decreased from 863,726 to 851,066, the median age increased from 31 to 42 years in males and from 34 to 45 years in females, and the proportion of males remained at 49%.

In the present study, we analysed (I) the phenotype, (II) long-term excess mortality, and (III) risk of cancer in 2904 consecutive sIA cases from 1980 to 2007, 618 unruptured (170 familial) and 2286 ruptured (aSAH) cases (308 familial).

(I) From 1980 to 2007, familial and sporadic sIA patients aged along the catchment population, important to notice in large study cohorts with long recruitment periods. In familial sIA patients, the phenotype at first diagnosis was modestly different from that of sporadic patients. Since the familial background is a known risk factor for the sIA disease, slight differences in the age at aSAH, gender distribution, and size distribution of sIAs were unexpected. The reason most probably is the liberal definition of familial sIA disease in this study cohort: two or more first degree relatives carrying sIA disease. Consequently, further genealogical and genomic studies of the present 300 sIA families in the Kuopio sIA Database are required.

In the present study, 308 aSAH patients were familial (13%) of the 2286 aSAH patients, when the criteria of sIA family was one first degree relative carrying sIA disease in addition to the patient. This definition of an sIA family is rather liberal. On the other hand, geneological analysis of sIA families in the Kuopio sIA Database has revealed megapedigrees with ancestry in the 16th century, with 59 sIA patients in the largest one, so far. In addition, there were nine sIA families with both parents carrying the sIA disease, and in one of them all six children developed the sIA disease (unpublished data). These findings demonstrate that there are some forms of genetic transmission of the sIA disease, so far unknown. On the other hand, the largest twin study of aSAH by Dr. Miikka Korja showed that the classic inheritance is rather low: only five concordant aSAH cases among 152 monozygotic twin pairs with aSAH. This study has obviously missed cases of unruptured sIA carriers among the 147 disconcordant monozygotic pairs. Anyhow, the data suggests that classic genetic factors such as mutations of genes do not play an important role in the genesis on the sIA disease. In complex diseases, the concordance between monozygotic twins is far

less than 100%, suggesting that epigenomic changes such as methylation profiles of the DNA may play a significant role. This raises the question how to define the sporadic form and the familial form of a complex disease, or how to differentiate inherited and environmental risk factors. Genomic variants and epigenomic profiles may predispose to acquired risk factors of the sIA disease, including desire for smoking or alcohol, or individual sensitivity for their adverse effects. To conclude, epigenome brings huge variability and its role in human disease is just starting to unravel.

We support the Finnish guidelines (Lääkärin käsikirja, 2010) that members of sIA families should be screened by non-invasive angiography from the age of 30 years and advised for non-smoking, screening of blood pressure, and avoidance of heavy alcohol use. They should also be informed that no genetic predisposition tests are available, so far.

Mechanisms by which risk factors affect the formation of sIA pouch and the rupture of sIA wall have to be elucidated for novel methods to identify sIA carriers and to occlude sIA pouches. The MCA bifurcation and the ACoA were almost equal sites for the ruptured sIAs, but the MCA bifurcation was clearly dominant among the unruptured ones. This suggests different etiologies for the sIA formation and the sIA wall rupture. The MCA bifurcation was most prone to develop unruptured sIAs, suggesting that MCA branching during embryonic period might be involved. The phenotypic tissue of the sIA disease is very restricted, the medial gap under hemodynamic stress at the branching sites of intracranial extracerebral arteries. The medial gap is a seal that forms between the medial bases of the two daughter branches that start from the mother branch during the embryonal branching morphogenesis. The embryonal formation of the intracranial extracerebral artery system and the Circle of Willis has been amazingly poorly described in the medical literature on embryology.

(II) The long term excess mortality of 244 familial and 1,502 sporadic one-year aSAH survivors was analysed as compared to the matched KUH catchment population. There was 12% excess mortality at 15 years. The sIA disease is a complex trait, affected by acquired risk factors and variants of the genome which may sensitize also to cardiovascular events in later life. Sequelae of aSAH may cause long-term mortality, e.g., by predisposing to epilepsy, depression, dementia, shunt complications, hypothalamic and hypophyseal disorders, or cerebrovascular events. The causes of the long term excess mortality are heterogeneous, and more detailed analyses are required. Consequently, one important line of further reasearch is to study the risks of various concomitant diseases, including hypertension and diabetes type II that affect the arterial wall, in the familial and sporadic sIA patients in the Kuopio sIA Database.

Furthermore, the long-term psychosocial outcome has not been comprehensively studied in Finland or elsewhere of the survivors of aSAH. These psychosocial outcome measures include anxiety, fatigue, depression, sleep disturbances, cognitive disturbances, post traumatic distress syndrome, divorce, alcoholism or substance abuse, unemployment, reduced income level, and suicide. For instance, fatigue in a systemic review of literature occurred in 31 to 90%, and other psychosocial problems could not explain all cases of fatigue. Fatigue reduces quality of life and life satisfaction in patients after SAH (Kutlubaev, 2012). On the other hand, the Utrecht group, led by Professor Gabriel Rinkel, has also shown that between 5 and 12.5 years after aSAH, the improvement in modified Ranking Scale had decreased but patients reported overall a better Quality of Life (Greebe, 2010). This suggests that aSAH survivors continue to adapt and improve while coping with restrictions in functioning. We propose that units providing neurocare for aSAH patients would also organise multidisciplinary neuropoliclinics for long-term follow up of the patients.

(III) The standardised incidence ratios (SIRs) of cancers after first diagnosis of sIA disease were calculated as against the matched KUH population. Lung cancer developed significantly more often in the aSAH patients, SIR 2.4 for males and 2.5 for females. Unfortunately, this retrospective study could not use smoking information because that not been reliably registered at the first diagnosis and follow up of the sIA patients. However, increased occurrence of lung cancer suggests that the patients continued smoking even after the aSAH diagnosis. In a Finnish single center series of 278 consecutive aneurysmal SAH patients and 314 hospitalized controls, published in 1993, the proportion on admission of non-smokers were 12% vs. 41% in males and 47% vs. 61% in females (Juvela et al., 1993). The most effective way to prevent sIA formation and/or rupture is to reduce modifiable risk factors, of which smoking and hypertension are the two most important ones. Long-term smoking habits of sIA disease carriers should be elucidated, and their abstinence from smoking should be supported and monitored. Health counseling to reduce known risk factors of sIA disease would be one form of the activities of proposed aSAH policlinics.

These results will primarily serve the Eastern Finnish population and its sIA patients, in terms of future preventation, earlier diagnosis, optimisation of therapeutic measures, screening and treatment of concomitant diseases, and design of long-term follow up. Naturally, many more aspects of the Eastern Finnish sIA disease have to be disclosed for a complete clinical picture, modifying factors, and outcome of the disease. These results cannot be wholly transferred to other and more heterogeneous populations in developed countries such as Scandinavia or the rest of Europe. This is not necessarily a handicap, because this data will primarily serve the population from which it was extracted.

8 Conclusions

8.1 PHENOTYPE OF SIA DISEASE ON ADMISSION

A) From 1980 to 2007 the median age of the KUH catchment population increased from 33 years to 44 years. Familial and sporadic sIA patients aged with the catchment population which should be noted when large cohorts with long recruitment time are compared.

B) The phenotype at first diagnosis was only modestly different in the familial variant of Eastern Finnish sIA disease.

C) The MCA bifurcation is more prone to develop unruptured sIAs where as the anterior communicating artery ruptures most frequently. We hypothesise that branching morphogenesis of the MCA bifurcation during embryonic period would be involved.

D) Differences between the distribution of ruptured and unruptured sIA sites suggest different etiologies for sIA formation and rupture.

E) No correlation between diameter at rupture and time of exposure to risk factors suggest that the diameter at rupture is more dependent on hemodynamic stress and site than other risk factors.

8.2 LONG-TERM OUTCOME AFTER ASAH

The impact of both sporadic and familial aSAH and their sequelae in the central nervous and cardiovascular system may cause long-term morbidity and mortality. The complex sIA disease may predispose to other vascular events in later life. The causes of the long term excess mortality are heterogeneous, and more detailed analyses are required.

8.3 IMPACT OF RISK FACTORS ON LONG-TERM OUTCOME AFTER ASAH

Smoking is a modifiable risk factor that is important in the prevention of aSAH as well as for further understanding of the pathogenesis of sIA formation and sIA wall rupture. The long-term smoking habits of the carriers of unruptured sIAs as well as survivors of aSAH after the first diagnosis should be elucidated. Their permanent abstinence from smoking should be supported and monitored.

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Saccular Intracranial Aneurysm Disease in Eastern Finnish Population

Phenotype on Admission Long-term Excess Mortality Risk of Cancer

Saccular intracranial aneurysms (sIAs) form during life at the branching sites of intracranial extracerebral arteries in the cerebrospinal fluid space. Rupture of the sIA wall is the most frequent cause of aneurysmal subarachnoid hemorrhage aSAH, a devastating form of stroke that affects working aged population. In the present study, we analysed the phenotype, long-term excess mortality, and risk of cancer in 2904 consecutive sIA cases from 1980 to 2007 from the Kuopio Neurosurgery sIA Database.

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