Studies on the Epidemiology of Open-angle Glaucoma

CURT EKSTRÖM
Dissertation presented at Uppsala University to be publicly examined in Enghoffsalen, Ingång 50, Akademiiska sjukhuset, 751 85 Uppsala, Thursday, December 13, 2007 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

Glaucoma is a common disease in the elderly population. Open-angle glaucoma (OAG) is the predominant form of glaucoma. Chronic simple glaucoma and capsular glaucoma, characterized by the occurrence of pseudoexfoliation in the anterior eye segment, are the most frequent types of OAG. The purpose of the present thesis was to study the epidemiology of OAG in the municipality of Tierp, whose population has a high exposure to pseudoexfoliation.

In a case-finding study, the prevalence of known cases of OAG by December 31, 1983 was estimated to 1.4% in people ≥45 years of age. Sixty-three percent of all cases had capsular glaucoma. Patients with advanced glaucoma were older, had had the disease for longer, had higher mean initial intraocular pressure, and had more extensive visual field defects at the time of diagnosis.

A population survey of people 65–74 years of age was conducted in 1984–86. The prevalence of OAG was 5.3%. Pseudoexfoliation was found in 17%, being more common in females. Pseudoexfoliation was associated with OAG only in people previously diagnosed with the disease (odds ratio = 16). In cases detected at the survey, an intraocular pressure ≥20 mmHg was a serious risk factor of having OAG (odds ratio = 9.7).

In a 5-year follow-up study of participants in the population survey, increased intraocular pressure and pseudoexfoliation were recognized as independent risk factors for the development of OAG (standardized risk ratios = 3.4 and 9.8, respectively). Interaction between increased intraocular pressure and pseudoexfoliation was indicated. By May 2006, the incidence of OAG was estimated to 7.1 per 1,000 person-years. The incidence of capsular glaucoma was more than twice that of chronic simple glaucoma.

The prevalence and incidence of OAG was higher than that reported from other studies conducted on Caucasian populations. The probable explanation for this finding is exposure to pseudoexfoliation.

Keywords: Open-angle glaucoma, Epidemiology, Capsular glaucoma, Chronic simple glaucoma, Normal tension glaucoma, Pseudoexfoliation, Pseudoexfoliation glaucoma, Prevalence, Incidence, Intraocular pressure

Curt Ekström, Department of Neuroscience, Box 593, Uppsala University, SE-75124 Uppsala, Sweden

© Curt Ekström 2007

ISSN 1651-6206
ISBN 978-91-554-7032-6
urn:nbn:se:uu:diva-8323 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-8323)
List of papers

This text is based on the following papers, which are referred to in the text by their Romans numerals:


IV. Ekström C. Incidence of open-angle glaucoma in Central Sweden. Submitted for publication.

V. Ekström C & Alm A. Pseudoexfoliation as a risk factor for prevalent open-angle glaucoma. The Tierp Glaucoma Survey. Submitted for publication.

Reprints were made with permission of the publisher.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>IOP</td>
<td>Intraocular pressure</td>
</tr>
<tr>
<td>OAG</td>
<td>Open-angle glaucoma</td>
</tr>
<tr>
<td>PEX</td>
<td>Pseudoexfoliation</td>
</tr>
</tbody>
</table>
Introduction

Glaucoma is a common disease, accounting for a substantial proportion of blindness in most parts of the world (Resnikoff et al. 2004). Open-angle glaucoma (OAG) is the predominant form of glaucoma. Glaucoma is of serious health concern, leading to loss of mobility and personal independence. Management of glaucoma takes a significant part of public health-care resources. At the Eye Department of Uppsala University Hospital, Sweden, glaucoma accounted for 26% of all outpatient visits in 1977 made by residents in the municipality of Tierp (Ekström 1983, unpublished).

Classification

The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (World Health Organization 1992) was used for classification purposes. In consequence, OAG with pseudoexfoliation (PEX) in the anterior eye segment was conceived as a form of primary glaucoma rather than a secondary glaucoma. Normal tension glaucoma was defined as a variant of OAG, with or without PEX. No cases of pigmentary glaucoma were included in the present studies. In the first papers, the term ‘chronic open-angle glaucoma’ was used to designate OAG.

Prevalence

OAG is an affliction of old age. In addition to age, the prevalence of OAG is dependent on the diagnostic criteria used. With this in mind, it is remarkable how consistent the estimates are for studies carried out on Asian and Caucasian populations. About 2% in the age range 40 years and older have OAG (Table 1). Studies in Baltimore and Barbados suggest that the disease is more common in black people.
Table 1. Prevalence of definite open-angle glaucoma in various studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Age (years)</th>
<th>Prevalence (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baltimore, USA 1</td>
<td>Tielsch et al. 1991</td>
<td>≥40</td>
<td>1.29</td>
</tr>
<tr>
<td>Baltimore, USA 2</td>
<td>Tielsch et al. 1991</td>
<td>≥40</td>
<td>4.74</td>
</tr>
<tr>
<td>Beaver Dam, USA</td>
<td>Klein et al. 1992</td>
<td>≥43</td>
<td>2.1</td>
</tr>
<tr>
<td>Roscommon, Ireland</td>
<td>Coffey et al. 1993</td>
<td>≥50</td>
<td>2</td>
</tr>
<tr>
<td>Barbados, West Indies</td>
<td>Leske et al. 1994</td>
<td>40–84</td>
<td>7.0</td>
</tr>
<tr>
<td>Rotterdam, The Netherlands</td>
<td>Dielemans et al. 1994</td>
<td>≥55</td>
<td>1.10</td>
</tr>
<tr>
<td>Blue Mountains, Australia</td>
<td>Mitchell et al. 1996</td>
<td>≥49</td>
<td>3.0</td>
</tr>
<tr>
<td>Melbourne, Australia</td>
<td>Wensor et al. 1998</td>
<td>≥40</td>
<td>1.7</td>
</tr>
<tr>
<td>Kongwa, Tanzania</td>
<td>Buhrmann et al. 2000</td>
<td>≥40</td>
<td>3.1</td>
</tr>
<tr>
<td>Andhra Pradesh, India</td>
<td>Dandona et al. 2000</td>
<td>≥40</td>
<td>2.56</td>
</tr>
<tr>
<td>Temba, South Africa</td>
<td>Rotchford et al. 2003a</td>
<td>≥40</td>
<td>2.9</td>
</tr>
<tr>
<td>Tamil Nadu, India</td>
<td>Ramakrishnan et al. 2003</td>
<td>≥40</td>
<td>1.7</td>
</tr>
<tr>
<td>Reykjavik, Iceland 3</td>
<td>Jonasson et al. 2003</td>
<td>≥50</td>
<td>4.0</td>
</tr>
<tr>
<td>Tajimi, Japan</td>
<td>Iwase et al. 2004</td>
<td>≥40</td>
<td>3.9</td>
</tr>
<tr>
<td>Segovia, Spain</td>
<td>Antón et al. 2004</td>
<td>40–79</td>
<td>2.1</td>
</tr>
<tr>
<td>Wroclaw, Poland 3</td>
<td>Nizankowska et al. 2005</td>
<td>40–79</td>
<td>1.53</td>
</tr>
<tr>
<td>Tamil Nadu, India</td>
<td>Vijaya et al. 2005</td>
<td>≥40</td>
<td>1.62</td>
</tr>
<tr>
<td>Thessaloniki, Greece 3</td>
<td>Topouzis et al. 2007</td>
<td>≥60</td>
<td>3.8</td>
</tr>
</tbody>
</table>

1 White population, adjusted for non-participation
2 Black population, adjusted for non-participation
3 Including capsular glaucoma

A common feature of many published glaucoma surveys is the high percentage of previously undiagnosed disease among all cases. In the industrialized countries, about half of all subjects with OAG are unaware that they have the disease (Hollows & Graham 1966; Sommer et al. 1991; Coffey et al. 1993; Dielemans et al. 1994; Topouzis et al. 2007). In contrast, of those identified with OAG in rural populations of southern India, more than 90% had not been diagnosed before the study (Ramakrishnan et al. 2003; Vijaya et al.)
As a consequence of the high proportion of undiagnosed cases, prevalence rates are higher in population surveys than in health care based studies.

**Incidence**

While there are numerous estimates of OAG prevalence from varying populations, information on its incidence is sparse. Some of these studies are presented in Table 2. Nelander (1933) studied the morbidity of primary glaucoma in the city of Uppsala, Sweden between 1922 and 1932. The incidence increased from 0.4 per 1,000 person-years in people 50–59 years of age to 2.7 per 1,000 in people 80–89 years of age. More than 80% of the patients were classified as chronic simple glaucoma cases.

When, 50 years later, Lindblom & Thorburn (1984a) reported on glaucoma detected during a 3-year period in Hälsingland, Sweden, the incidence of OAG was 1.3 per 1,000 person-years at the age of 45 years and older (own calculations). In another health care based study, spanning 15 years, conducted in Olmsted County, Minnesota, USA (Schoff et al. 2001), the highest age-specific incidence, 0.94 per 1,000 person-years, was found in the eighth decade.

Data on the incidence of OAG are also available from follow-up studies. The incidence in a population aged 55 years and older in Dalby, Sweden, was 2.4 per 1,000 person-years (Bengtsson 1989a). Follow-up of an Australian population revealed a 5-year cumulative incidence of 0.5% (0.1% per year) in people aged 40 years and older (Mukesh et al. 2002). Participants in the Rotterdam Study were re-examined 6 years later (de Voogd et al. 2005), when the incidence was estimated to 1.2 per 1,000 person-years. OAG was the leading cause of visual field loss in all age categories (Skenduli-Bala et al. 2005).

The cumulative incidence in the Barbados Eye Studies was higher than the estimates for comparable studies on Caucasian populations. Recently, a 9-year risk of OAG in the black population aged 40 years and older of 4.4%, or an average of 0.5% per year, was reported (Leske et al. 2007).
Table 2. Incidence rate of definite open-angle glaucoma per 1,000 person-years in Hälsingland, Dalby, Olmsted County, and the Rotterdam Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Age (years)</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hälsingland, Sweden</td>
<td>Health care based</td>
<td>≥45</td>
<td>1.3</td>
</tr>
<tr>
<td>Dalby, Sweden</td>
<td>All residents</td>
<td>55–80</td>
<td>2.4</td>
</tr>
<tr>
<td>Olmsted, USA</td>
<td>Health care based</td>
<td>All ages</td>
<td>0.145 ¹</td>
</tr>
<tr>
<td>Rotterdam, The Netherlands</td>
<td>All residents</td>
<td>≥55</td>
<td>1.2</td>
</tr>
</tbody>
</table>

¹ Adjusted to the 1990 white U.S. population

Risk factors

Demographic risk factors
Every population-based study that has investigated the effect of age has found an increasing risk for OAG with increasing age. In the Barbados study (Leske et al. 1994), OAG was 11-fold more prevalent in people 70–79 years of age than 40–49 years. There is no certain association with gender. Compared with Caucasians, Afro-Americans have an increased risk of OAG. In the Baltimore Eye Study, black Americans were 3–4 times more likely to have OAG than their white neighbours (Tielsch et al. 1991).

Increased intraocular pressure
Increased intraocular pressure (IOP) is recognized as a risk factor for OAG (Sommer 1989; Anderson 1989). An association between increased IOP and OAG has been demonstrated in a number of cross-sectional studies (Bengtsson 1980; Sommer et al. 1991; Leske et al. 1995). In experimental ophthalmology, a causal relationship between extended IOP increase and glaucoma-like degeneration at the optic nerve head has been established (Quigley et al. 1987).

The pressure theory has been questioned, however (Krakau 1981; Krakau et al. 1983). The finding of optic disc haemorrhages early in the course of the disease has favoured a vasogenic theory of visual field loss, the pressure
increase being secondary (Bengtsson 1981a; Sonnsjö & Krakau 1993). In later years, the promising results of randomized trials on the effect of pressure-reducing therapy in ocular hypertension (Kass et al. 2002) and early glaucoma (Heijl et al. 2002) have increased the acceptance of a pressure theory of optic nerve damage in OAG.

Pseudoexfoliation

PEX is an age-related disorder of unknown aetiology, characterized by the production and accumulation of a fibrillar material in the anterior segment of the eye (Ritch & Schlötzer-Schrehardt 2001). Recently, common sequence variants in the LOXL1 gene, involved in elastin formation, were found to confer susceptibility to capsular glaucoma (Thorleifsson et al. 2007). The exact composition of the exfoliative material is unknown. Mucopolysaccharide-containing fibrils is produced and accumulated extracellularly close to the cell surface, disrupting the normal function of the cell. Basement membranes and other structures are damaged followed by degeneration of surrounding tissues.

An increased IOP is believed to mediate the effect of PEX, exfoliative material and pigment causing obstruction of the trabecular meshwork by deposits from the aqueous humor. In addition, exfoliative material appears to be produced locally in connection with the trabecular cells (Ritch & Schlötzer-Schrehardt 2001). Rather than the amount of exfoliation, the main risk factor for OAG seems to be the degree of chamber-angle pigmentation (Puska 1995; Shuba et al. 2007).

PEX is closely related to age and rarely seen before 45 years of age. The prevalence varies widely between different populations, the highest frequency usually being reported from the Nordic countries. A selection of prevalence studies is presented in Table 3. PEX is a common finding in black South Africans, but is extremely rare in the black population of Barbados (Leske et al. 2002a).

Several studies have demonstrated a connection between PEX and increased IOP (Aasved 1971; Hiller et al. 1982; Davanger et al. 1991). In hospital-based studies in the Nordic countries, PEX was found in at least half of the prevalent cases of OAG (Forsius 1988). Two Australian studies (Mitchell et al. 1997b; McCarty & Taylor 2000), a South Indian study (Krishnadas et al. 2003), and a South African study (Rotchford et al. 2003b) all revealed an association between PEX and OAG. In fact, PEX has been suggested to be ‘the most common identifiable cause of open-angle glaucoma’ (Ritch 1994).

Previously, PEX was thought to be restricted to the eye. In the 1970s, however, exfoliative fibrils were demonstrated in the conjunctiva and extraocular structures (Ringvold 1972; 1973; Eagle et al. 1979). More recently, exfoliation has been observed in skin, visceral organs, blood vessels and intracranial structures (Streeten et al. 1990; Schlötzer-Schrehardt et al. 1992;
Streeten et al. 1992). A possible connection between exfoliation and circulatory disorders has been suggested (Naumann et al. 1998). In a Swedish study of dementia patients, PEX was found in a greater proportion than expected (Linnér et al. 2001).

Table 3. Prevalence of pseudoexfoliation in various studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Age (years)</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham, USA</td>
<td>Hiller et al. 1982</td>
<td>52–85</td>
<td>1.8%</td>
</tr>
<tr>
<td>Sør-Trøndelag, Norway</td>
<td>Ringvold et al. 1988</td>
<td>≥65</td>
<td>16.9%</td>
</tr>
<tr>
<td>Roscommon, Ireland</td>
<td>Coffey et al. 1993</td>
<td>≥50</td>
<td>1.33%</td>
</tr>
<tr>
<td>Blue Mountains, Australia</td>
<td>Mitchell et al. 1997b</td>
<td>≥49</td>
<td>2.3%</td>
</tr>
<tr>
<td>Victoria, Australia</td>
<td>McCarty et al. 2000</td>
<td>≥40</td>
<td>0.98%</td>
</tr>
<tr>
<td>Tamil Nadu, India</td>
<td>Krishnadas et al. 2003</td>
<td>≥40</td>
<td>6.0%</td>
</tr>
<tr>
<td>Hlabisa, South Africa</td>
<td>Rotchford et al. 2003b</td>
<td>≥40</td>
<td>7.7%</td>
</tr>
<tr>
<td>Temba, South Africa</td>
<td>Rotchford et al. 2003b</td>
<td>≥40</td>
<td>6.0%</td>
</tr>
<tr>
<td>Reykjavik, Iceland</td>
<td>Jonasson et al. 2003</td>
<td>≥50</td>
<td>10.3%</td>
</tr>
<tr>
<td>Segovia, Spain</td>
<td>Antón et al. 2004</td>
<td>40–79</td>
<td>1.2%</td>
</tr>
<tr>
<td>Hisayama, Japan</td>
<td>Miyazaki et al. 2005</td>
<td>≥50</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

Other ocular risk factors

There is a close connection between optic disc haemorrhages and OAG (Bengtsson 1989b). In view of all the unanswered questions regarding haemorrhages of the optic nerve head, they should be conceived of as a sign of the disease rather than a risk factor for the disease. Thinner central corneal thickness has been identified as a predictor of OAG (Gordon et al. 2002). The correlation between OAG and thinner corneas is, however, biased by the effect of corneal thickness on IOP measurements. In applanation tonometry, a low value of central corneal thickness induces an underestimation and a high value an overestimation of the IOP (Ehlers et al. 1975).
**Myopia**, on the other hand, is thought to be a true risk factor for OAG. In a Swedish study (Grødum et al. 2001), myopia was identified as an independent risk factor for OAG. The effect of myopia increased with the magnitude of the refractive error. In addition, myopia was a stronger risk factor among individuals with lower IOP level.

**Family history**

A positive family history has long been recognized as a risk factor for OAG, indicating that specific gene defects contribute to the pathogenesis of the disorder. Chromosomal defects responsible for autosomal-dominant or recessive traits have been identified. Adult-onset OAG, however, is a complex disease, and only on rare occasions does it follow a Mendelian inheritance pattern, suggesting that inherited risk factors confer a susceptibility to the disease but separately are not necessarily causative (Wiggs 2007).

As could be expected, the bearing of a family history on the risk of developing OAG varies between different studies and different populations. In the Rotterdam Study (Wolfs et al. 1998), relatives of patients with glaucoma were found to be at greater risk (risk ratio, 9.2), than relatives of controls. A positive family history was identified as the strongest risk factor for glaucoma (adjusted odds ratio, 3.1) in one of the Australian studies, referred to in Table 1 (Weih et al. 2001). In a follow-up study of ocular hypertension, however, Bengtsson & Heijl (2005) were unable to confirm any effect of a positive family history among first-degree relatives.

The Barbados Family Study is a part of the ongoing epidemiological studies on OAG in Barbados. In this black population of West-African origin, approximately one-fourth of the siblings of OAG patients had the disease (or were suspected cases), despite their relatively young age (Leske et al. 2001). Risk factors for OAG in siblings were similar to those in unrelated individuals.

**Other risk factors**

There has been a widely held belief that *diabetes mellitus* is a risk factor for OAG. A connection with diabetes has been described in some studies (Klein et al. 1994; Dielemans et al. 1996; Mitchell et al. 1997a; Pasquale et al. 2006), but not in others (Tielsch et al. 1995a; Leske et al. 1995; de Voogd et al. 2006). At present, there is no consensus regarding an association between diabetes and OAG.

The question of *systemic hypertension* and OAG is controversial. A positive correlation with increased IOP has been known for years (Bengtsson 1972). In addition, some cross-sectional studies have found an association between hypertension and OAG (Tielsch et al. 1995b; Dielemans et al. 1995). In the Barbados Eye Studies, Leske et al. (2002b) investigated the
covariation between hypertension, increased IOP, and the 4-year incidence of OAG. Interestingly, individuals with lower ocular perfusion pressure, defined as the difference between mean arterial pressure and IOP, ran a greater risk of OAG than individuals with higher perfusion pressure. The result was thought to be consistent with the vascular theory of OAG pathogenesis.

Health-care based studies

Lindblom & Thorburn (1982) studied the occurrence of previously diagnosed glaucoma in the Hälsingland population, Sweden. OAG was found at a prevalence of 1.2% in people 45 years and older (own calculation). Two-thirds of the patients had PEX. In a study in Iceland, Viggósson et al. (1986) applied the method of using prescription data to the consumption of glaucoma drugs. The prevalence of OAG was estimated at 1.9% in those aged 50 years and older. Blika & Ringvold (1987) reported a prevalence of 1.3% in the population of Sør-Trøndelag, Norway, 50 years and older. PEX involved nearly 60% of all OAG. The diagnostic criteria were, however, more liberal than in the other studies.

In population surveys, the equal proportions of normal tension glaucoma and high tension glaucoma are a common finding in newly detected cases. More than half of all glaucomatous eyes in the Baltimore survey (Sommer et al. 1991) had a screening IOP below 21 mmHg, whether these eyes were receiving treatment or not. In the Dalby study, southern Sweden (Bengtsson 1981b), approximately half of the patients had an IOP within the normal range at the survey, whereas increased IOP at first presentation was a characteristic finding in health care-based studies carried out in Central Sweden. In the incidence study in Hälsingland (Lindblom & Thorburn 1984a; 1984b), three out of four patients had PEX. Only 8 (3%) of the 248 cases of OAG had an IOP below 20 mmHg at the time of diagnosis.

In a study of incident OAG, PEX was detected in more than 60% of all patients (Ekström 1985). Four (6%) of the 68 consecutive cases of OAG were classified as normal tension glaucoma. Two-thirds of the patients presented with eye symptoms related to disturbed visual function; in a substantial proportion, the symptoms could be attributed to glaucoma damage. Berggren & Widengård (1993) described patients with OAG attending an eye department in the preceding 3 years; PEX was found in two out of three. Five (4%) of the 128 patients were diagnosed as having normal tension glaucoma. One in three was thought to have a handicapping visual field defect in the worse eye.

High pressures at first presentation characterized all of the Swedish studies. The predominance of PEX could explain this finding. On average, OAG patients with PEX had higher IOP than patients without PEX. Old age was
another characteristic finding. More than half of the patients were older than 70 years.

Grødum et al. (2002) studied differences between OAG patients identified in the Early Manifest Glaucoma Trial in Malmö, southern Sweden, and patients previously diagnosed in clinical practice. Normal tension glaucoma was four times as common in the former category. Patients detected at the population survey had lower IOP, lower prevalence of PEX and better visual fields than self-selected patients.
The objective of the present thesis was to study the epidemiology of OAG in a defined population with a high frequency of PEX. The specific aims were:

I. To estimate the prevalence and incidence of OAG, and subgroups of the disease, with respect to age and gender

II. To study increased IOP and PEX as risk factors for prevalent OAG in a population survey of people 65–74 years of age

III. To evaluate the effect of increased IOP and PEX on the risk for developing OAG in a 5-year follow-up study of people 65–74 years of age

IV. To study differences between OAG cases detected in a population survey and in health-care services
Methods

Study area

The study area was the municipality of Tierp in the north of Uppsala County, south Central Sweden. At the outset of the population survey, there were 20,078 inhabitants in Tierp, of whom 2,377 were 65–74 years of age (Official Statistics of Sweden 1984). Eye health care is provided at the Primary Health Care Centre in Tierp, the chief town in the municipality. The University Hospital at Uppsala, 60 km south of Tierp, cares for ophthalmic in-patients. Eye health care provided for Tierp residents at the Eye Department in Gävle, 35 km north of Tierp, is of insignificant proportion. Since the 1980s, at least 3 ophthalmologists have been in private practice in the city of Uppsala.

Glaucoma population

Tierp residents, diagnosed with glaucoma, have been registered in special glaucoma case records, kept at the Eye Department in Tierp, since 1978. To complete the information, three different kinds of computer files at the Department of Social Medicine (now Public Health and Caring Sciences), Uppsala University was used to search for patients with a missing case record.

First, outpatient visits and in-patient care at Uppsala University Hospital have been registered for Tierp residents since 1977. At present, the files cover visits up to 2003. Second, information on purchases of prescribed drugs from the pharmacies in Tierp has been collected from 1972 to 1998. Finally, visits to physicians at the Primary Health Care Centre in Tierp have been registered along with the diagnoses since 1976. Altogether 354 residents, diagnosed in health care services between 1980 and 1985 as having glaucoma, were found. The source of information is presented in Fig. 1. Most patients were covered by all of the sources; 7 were detected only by searching hospital records, and 9 with the help of registers of prescribed drugs for the treatment of glaucoma.
Fig. 1. Tierp residents diagnosed with glaucoma 1980–85, by source of information. Tierp = patients with consultations for glaucoma at the Eye Department in Tierp. Prescriptions = patients with prescription(s) for anti-glaucoma drugs dispensed at Tierp pharmacies. Uppsala = patients with consultations for glaucoma at Uppsala University Hospital. Cases detected at the population survey are not included.

Concepts and definitions

Chronic simple glaucoma and capsular glaucoma were classified as OAG; i.e. signs of angle-closure glaucoma or secondary glaucoma were missing. Capsular glaucoma was characterized by the presence of PEX in the anterior eye segment. Normal tension glaucoma was defined as a variant of OAG, having no more than one registered pressure reading above 21 mmHg and none above 24 mmHg.

Each patient is represented by one eye only, designated the ‘first eye’. If there was glaucoma in both eyes, this was the eye first diagnosed with glaucoma. If both eyes received the diagnosis at the same time, the ‘first eye’ was the one that had OAG, or the most extensive glaucoma damage, in that order.
For a diagnosis of definite OAG, a reproducible visual field defect was required, consistent with glaucoma and not explainable on other grounds, in at least one eye.

**Visual field testing**

Visual fields were tested on the Competer 350 automated perimeter, measuring the sensitivity at 68 locations in the central 20°. Supraliminal threshold-related (screening) test logic or threshold test logic was used (Heijl 1985). In the early 1980s, however, visual fields were examined on Competer 250. The main difference between the two machines is that Competer 350 has four additional test points at 2.5° eccentricity. Manual visual fields were recorded on the Goldmann perimeter.

**Screening test logic**

The criteria applied by Bengtsson & Krakau (1979) were used to designate abnormal screening fields on the Competer. A visual field defect was defined as the occurrence of at least one abnormal test point outside the blind-spot area. A test point was deemed abnormal if the test procedure had concluded on a level of sensitivity \( g \leq 2 \) steps below the starting level. To be accepted as a blind spot, a scotoma was required in at least one of the two points on the visual field chart where the blind spot is usually found. In the population survey, a scotoma of the blind spot was defined as a reduced sensitivity of \( g \leq 2 \) steps compared to the starting level; otherwise, an absolute scotoma was required.

If the Competer failed to identify the blind spot during the testing procedure and, in addition, the blind-spot check light was seen in \( \geq 30\% \) of all exposures, the test was deemed unreliable. In the population survey, a more liberal criterion was applied; fixation losses up to one-third of all exposures were accepted.

**Threshold test logic**

The criteria suggested by Heijl et al. (1980) were applied to identify abnormal threshold fields, provided that the abnormal test points were found outside the blind spot area. These criteria are presented in Table 4.

A blind spot was defined as an absolute scotoma in at least one of the two points on the visual field chart where the blind spot is usually found. If the Competer failed to identify the blind spot and, in addition, the blind-spot check light was seen in \( \geq 30\% \) of all exposures, the test was deemed as unreliable.
Table 4. Classification criteria for abnormal threshold fields (Competer 350)

1. At least one test point with a threshold of $-4$ or less, numerically
2. One test point with a threshold of $-3$ with at least two adjacent points of $-2$ or less
3. At least two adjacent test points with a threshold of $-3$
4. At least four adjacent test points with a threshold of $-2$, when the corresponding points in the other half of the visual field (up or down) do not show more than one test point of $-2$ or less
5. A threshold difference of $\geq 6$ between the sum of the five nasal test points above the horizontal meridian, compared with the five nasal points below
6. The measured threshold value is increased by one step, when rules 1–4 are applied to test points $20^\circ$ from fixation, and to test points up to $60^\circ$ above and down to $60^\circ$ below the blind spot $15^\circ$ from fixation

Goldmann perimetry

Manual visual fields were tested using the Haag-Streit Goldmann perimeter according to a modified Armaly-Drance technique (Rock et al. 1971). In the first study (Paper I), 24% of all perimetries at the time of diagnosis were carried out using kinetic isoptre perimetry only, which was applied before 1974. The criteria for visual field loss were consistent with those used in the Framingham Eye Study (Leibowitz et al. 1980). However, instead of $\geq 10^\circ$, the limit for nasal steps was set at $>5^\circ$ (Werner & Drance 1977; Drance 1978). Definitions of visual field defects, thought to be compatible with glaucoma damage, are listed in Table 5.

Table 5. Classification criteria for abnormal Goldmann visual fields

1. A nasal step of $>5^\circ$ in one or more isoptres
2. A paracentral scotoma of $>5^\circ$ extension in the narrowest dimension and $>5$ dB deep
3. A more extensive defect in the peripheral isoptre than those listed above
Eye examinations

Intraocular pressure

IOP was measured using a Goldmann applanation tonometer mounted on a Haag-Streit slit-lamp after instilling a drop of Fluress (oxybuprocain chloride 4 mg/ml, fluorescein sodium 2.5 mg/ml) into each eye. Calibration of the two tonometers used in the studies revealed a deviation of 1–2 mmHg above the true value for pressures taken up to 1987. To compensate for the error, pressure readings from 1978 to 1987 were reduced by one unit. Since 1988, the tonometers presented a correct value.

Anterior segment

All participants underwent biomicroscopy at the Haag-Streit slit-lamp to determine the presence or absence of PEX, defined as white flakes on the anterior lens capsule or on the pupillary border. Before the examination, the eyes were dilated with one drop of Mydriacyl (tropicamide 5 mg/ml).

Optic disc

Assessment of the optic disc in both eyes was performed at the slit-lamp using a Goldmann one-mirror contact lens or a Volk 90D lens, after pupillary dilatation. In accordance with a modification of the scheme recommended by Shaffer et al. (1975), a drawing of the optic disc was made in the glaucoma case record (Fig. 2). The drawings were made on the basis of shape rather than colour. The disc margin was defined as the inner margin of the scleral ring, and the size of the cup was estimated from the point at which the disc surface makes its first definite transition posteriorly.

Fig. 2. Drawing of the optic discs in a glaucoma patient (cover illustration)
R = right eye (normal)
L = left eye (glaucoma)
The optic discs were graded into the following categories: (1) non-glaucomatous disc; (2) glaucomatous discs, not excavated to the disc margin; (3) glaucomatous disc, excavated to the disc margin at any part of the circumference. The characteristics of the glaucomatous optic nerve head referred to by Spaeth (1978) were used in the grading. Thus, excavation to the disc margin, localized notching or pallor of the neural rim, saucerization, or marked asymmetry of the optic cup between the two eyes were regarded as clinical signs of optic nerve damage.

Optic disc haemorrhages were defined as superficial linear and flame-shaped or splinter-shaped haemorrhages on or adjacent to the optic disc, as well as round and blotchy haemorrhages in the deeper part of the disc.

Chamber angle
Gonioscopy was carried out at the slit-lamp with the Goldmann one-mirror lens after local anaesthesia with Tetrakain (tetracaine chloride 10 mg/ml) eye-drops. The Scheie method (1957) for grading of angle width and pigmentation was applied. As a rule, gonioscopy was done after pupillary dilatation.

Chronic open-angle glaucoma in a defined population (Paper I)

Identification of cases
The glaucoma population in Tierp (see Fig. 1) was searched for patients diagnosed with OAG on December 31, 1983. The cases of disease were subsequently classified using information from patient records as a basis. Patients with a reproducible visual field defect in either eye were designated cases of prevalent OAG.

Mean initial intraocular pressure
The IOP readings that were recorded were the two most recent on an outpatient basis at the time of diagnosis, without pressure-reducing therapy. The mean of these readings was used in the calculations. To get integers, rounding was made to the first pressure reading.
Grading of visual fields

The Goldmann perimeties of the ‘first eye’ at diagnosis were classified jointly in a ‘masked’ fashion by two ophthalmologists, unconnected with the study, as follows: Stage I. No certain signs of visual field defect. Stage II. Definite signs of visual field defect, but lacking Bjerrum scotoma with nasal breakthrough. Stage III. Bjerrum scotoma with nasal breakthrough or more extensive visual field defect. In the analysis, consideration was only given to whether or not the patient had a stage III visual field defect.

Advanced visual field defect was defined as a reduction in the visual field for the largest and brightest test object on the Goldmann perimeter to a diameter corresponding to a visual angle of 20° or less around central fixation.

Population survey (Papers III and V)

The sample

From March 1984 to March 1986, a glaucoma survey was conducted, the target population being Tierp residents, 65–74 years old. In addition to a random sample of the selected age group, the study included patients previously diagnosed with glaucoma. For practical reasons, the extent of the study was limited to one-third of the target population. The Department of Social Medicine at Uppsala University provided two lists of eligible residents, whose date of birth was divisible by the figure 3. The first list comprised subjects born between 1910 and 1914; the second comprised subjects born between 1916 and 1920. The lists were updated twice.

In 1984–85, 406 residents born in 1910–14 were invited. No appointments were sent until those invited had had their birthday. In this way, all participants were 70–74 years old at the time of the examination. Ten persons who died in 1984 were excluded, and 3 persons who moved into the area in 1984 were examined in 1985. Thus, the 70–74-year age group comprised 399 individuals registered in Tierp on December 31, 1984.

Next, in 1985–86, 449 residents born in 1916–20 were invited. These were 65–69 years old in 1985. The same procedures were repeated as for the older age group. Meanwhile 13 persons had died or left the area, and 3 had moved into the area. Thus, the 65–69-year age group comprised 439 individuals registered in Tierp on December 31, 1985. In all, the population survey involved 838 individuals aged 65–74 years.
Previously diagnosed glaucoma

The glaucoma population in Tierp (see Fig. 1) was searched for patients diagnosed between 1984 and 1985 as having glaucoma. Sixty of the 354 patients had a diagnosis of OAG, and were 65–74 years old at the time of the population survey.

Thirty-one patients, born in 1910–14, were resident in Tierp on December 31, 1984, and 29 patients born in 1916–20 were resident on December 31, 1985. Owing to the randomization process, 23 of the 60 patients were included in the population sample. Patients diagnosed with glaucoma underwent a complete examination in the same way as those who participated in the screening study. One patient with OAG, unknown in Tierp, was not examined until 1987.

Screening pressure

An assistant measured the IOP. If the difference in IOP between the two eyes exceeded 2 mmHg, a control measurement was made as described by Bengtsson (1972). In this event, the second readings were defined as the IOP for that person.

Automated perimetry

The assistant tested the visual fields of both eyes on the Competer 350 automated perimeter, using the screening test logic.

Grading of the optic discs

The optic discs were graded into three categories (see Optic disc section) by the same ophthalmologist. With the exception of patients with a known diagnosis of glaucoma, the examiner was ‘masked’ from the results of the IOP measurements and the visual field tests at the grading.

Optic disc photography

Stereo colour photographs (Carl Zeiss AG, Jena, Germany) of the optic disc in both eyes after dilatation were taken on patients with suspected OAG, optic disc haemorrhages, and on those recommended a check-up for increased IOP.

Protocol

The same standardized protocol was used for all examinations. A drawing of the optic disc of both eyes was made in the protocol, as previously described.
Identification of cases

Participants with at least one of the following criteria were classified as glaucoma suspects, and were asked to return for manual Goldmann perimetry: (1) history of treatment for glaucoma; (2) IOP >27 mmHg in either eye; (3) visual field defect in either eye, compatible with glaucoma, or of uncertain aetiology; (4) glaucomatous optic disc in either eye; (5) optic disc haemorrhage in either eye.

After manual perimetry, a definite classification (‘suspect’ or ‘non-suspect’) was applied to the following characteristics of each individual: visual field defects at manual perimetry, compatible with glaucoma; abnormal screening fields, compatible with glaucoma, or of uncertain aetiology; history of treatment for glaucoma. Those ultimately classified as glaucoma suspects underwent repeat visual field testing using Goldmann perimeter and Competer. The criteria for a diagnosis of definite OAG are presented in Table 6.

Table 6. Classification criteria for definite open-angle glaucoma in the population survey

1. A reproducible VFD on the Competer, consistent with glaucoma and not explainable on other grounds, using supraliminal or threshold test logic
2. Automated perimetry not performed owing to end-stage disease:
   Advanced VFD at manual perimetry or loss of central visual field
   Excavation of optic disc to margin at any part of the circumference
3. Automated perimetry not performed owing to dense cataract:
   A previous VFD at manual perimetry, compatible with glaucoma, is documented
   Reduced visual acuity, either to blindness or to perception of light only

VFD = visual field defect
Follow-up study (Paper II)

Participants
A total of 527 participants in the population survey were invited to attend a second examination between April 1988 and January 1991. Those excluded were 218 individuals with abnormal, unreliable or untestable visual fields in either eye, or with a history of cataract surgery. Fifteen patients receiving treatment for glaucoma were also excluded. The follow-up of patients with suspected OAG, or referred to the Eye Department in Tierp for various eye problems, started after the population survey and was not completed until December 1991. However, complementary examinations took place as late as in September 1992.

Automated perimetry
The visual fields were tested with the screening test logic of the Competer, using the same protocol as in the population survey. IOP was always measured before automated perimetry was undertaken.

End-points
The end-points of the follow-up study were a non-interpretable or abnormal visual field of any cause in either eye, initiation of pressure reducing therapy, intraocular surgery, and non-participation.

Optic disc photography
Simultaneous stereo colour photographs of the optic disc in both eyes were taken on the same category of participants as in the population survey.

Identification of cases
For a diagnosis of OAG, a reproducible visual field defect with the screening test logic in either eye was required.
Incidence study (Paper IV)

The cohort

The incidence study concerned 711 individuals, all of whom participated in the population survey. Forty-nine cases of prevalent glaucoma, and 78 individuals not attending the survey, were not included in the cohort. Follow-up started on the day of the baseline examination and stopped on the date of glaucoma diagnosis, removal, or death, or when the study ended (after 20 years), whichever occurred first. The development of definite OAG in either eye was the outcome of interest. In addition, follow-up could be concluded by the occurrence of angle closure glaucoma or secondary glaucoma. The Swedish population register was checked for information on domiciliary removals and deaths.

Identification of cases

Most cases in the cohort were found among people invited to participate in the follow-up study, described in the previous section. As a result of a second review of visual field charts, the size of the follow-up study increased from 527 to 530 individuals with normal and reliable visual fields in both eyes at the population survey. More importantly, the study was extended over time. For those who did not reach an end-point, perimetry was repeated every fourth year after the survey for the next 20 years. Ineligible for the study were 44 subjects not found in the population register, and 1 subject treated for glaucoma. Altogether 453 people, 93% of that eligible, had at least one follow-up examination.

Altogether 181 people with abnormal or unreliable visual fields, treated for ocular hypertension, or with a history of cataract surgery, were not invited to the follow-up study. In this part of the cohort, new cases of OAG were identified among patients seeking medical attention at the Eye Department in Tierp. Visual fields were tested on the Competer. The patients were subsequently registered in glaucoma case records. Computer files at the Department of Public Health and Caring Sciences, Uppsala University, were used to search for glaucoma patients unknown in Tierp (see Glaucoma population section). Up to 1998, purchases of drugs for the treatment of glaucoma were recorded for 41 cohort members. In addition, medical records of 104 patients, visiting the Eye Department at Uppsala University Hospital from 1999 to 2003, were reviewed.

A diagnosis of incident OAG was based on the demonstration of a visual field defect in either eye, with the screening test logic of the Competer.
Final classification of open-angle glaucoma

Participants diagnosed with OAG in the population survey or the cohort study underwent repeat visual field testing using the threshold test logic of the Competer. In 2006, threshold fields of the ‘first eye’ were sent to University Hospital, Trondheim, Norway, for grading by an ophthalmologist unconnected with the study. According to the variation of visual field loss over time, the ‘first eye’ of each individual was classified as having either progressive or non-progressive disease. Those deemed to have progressive disease were regarded as definite OAG cases.

The glaucoma case records of patients with non-progressive disease, or missing threshold fields, were reviewed by an ophthalmologist at Uppsala University Hospital. Drawings of the optic discs, made in the glaucoma case records on different occasions, were evaluated together with automated or manual visual fields of the ‘first eye’. In addition, stereo photographs of the optic discs were examined. Before the review, all information of clinical importance, with the exception of visual acuity and optic disc drawings, were masked. The reviewer classified the cases as having definite OAG (or not).

Consequently, a diagnosis of OAG was established in two steps. First, OAG cases were identified on the basis of visual field testing. Secondly, among individuals with a visual field defect, the progressive cases described above and the cases classified as OAG by the reviewer, constituted the final number of OAG.

Statistical methods

Prevalence rates were adjusted for non-response to the screening examination by applying the frequency of OAG among those who presented for the examination to those who did not, with age, sex, and screening category strata. Prevalence differences were estimated after direct standardization according to a minimum variance method suggested by Kahn & Sempos (1989). To calculate confidence intervals (CI), a normal approximation to the binomial distribution was applied.

A method described by Antón et al. (2004) was used to calculate prevalence rates of OAG. Prevalence $P$ in individuals 65–74 years of age was estimated from the prevalence of new cases detected in the population sample and patients already diagnosed with OAG:
\[ P = \frac{N' P_1 + m}{N}, \]

where
\[ N' = \text{number of glaucoma-free individuals in population (all diagnoses)} \]
\[ P_1 = \text{proportion of OAG in sample} \]
\[ m = \text{already diagnosed cases of OAG in population} \]
\[ N = \text{size of population} \]

Incidence rates were obtained by dividing the number of cases by the number of person-years at risk. Poisson distribution was used to estimate CI. Incidence rates and their differences were standardized (Rothman & Greenland 1998). When calculating incidence rates and rate ratios, the disease was believed to have started when a visual field defect was demonstrated for the first time.

Exact confidence intervals for odds ratios were calculated. Control for confounding was made according to Mantel-Haenszel (1959). In order to assess several factors affecting the risk being studied at the same time, logistic regression analysis was used.

In the follow-up study, standardized risk ratios were estimated, defined as the ratio of standardized incidence rates, using the exposed part of the cohort as a standard (Rothman 1986). Interaction between increased IOP and PEX regarding the risk of developing OAG was evaluated.

A time-weighted mean IOP was calculated, using weights proportional to the interval between two measurements:

\[ IOP-\text{mean} = \frac{\sum w_i (IOP_n + IOP_{n-1})}{2}, \]

where
\[ w_i = \frac{(t_n - t_{n-1})}{t}, \text{ and } t = \text{observation time} \]

At each visit, the higher pressure in whichever eye represented the individual. Risk ratios were calculated to examine the association between exposure time and mean IOP. The Mantel extension method was used to test for linear trend in proportions (Schlesselman 1982).

**Ethics**

The population survey and the follow-up study were approved by the Human Subjects Committee at the Faculty of Medicine, University of Uppsala. Informed consent was obtained from all participants. The Regional Human Subjects Board granted approval for the incidence study. The Tenets of the Declaration of Helsinki were observed.
Results

Chronic open-angle glaucoma in a defined population (Paper I)

Altogether 229 patients diagnosed with glaucoma on December 31, 1983 were identified. OAG with visual field defects in the 'first eye' was found in 126 patients, of whom 3 had normal tension glaucoma. Capsular glaucoma was diagnosed in two-thirds of all OAG. Two patients had visual field defect in the 'second eye'. The prevalence was therefore calculated from 128 cases with visual field loss in either eye. On December 31, 1983 there were 8,944 residents in Tierp in the age range 45 years and older, giving a prevalence of 1.43% (95% CI: 1.18 to 1.68). OAG was three times as frequent in the age group 75–94 years as in the 55–74-years old. Four patients had advanced visual field defects in both eyes and were classified as blind.

'Late presentation', i.e. advanced visual field defect in at least one eye at the time of diagnosis, had occurred in 15 of the 128 patients (12%), 11 with capsular glaucoma and 4 with chronic simple glaucoma. They were older and had significantly higher IOP than the other patients (t-test, \( p = 0.0031 \)).

The visual fields of 123 patients were classified according to the stage of visual field loss at the time of diagnosis. Visual field defect stage III was assigned to 49 cases. A mean initial IOP \( \geq 35 \) mmHg at the time of diagnosis signified that the risk of having defect stage III, when age and type of glaucoma were taken into consideration, was 8.6 (2.9 – 22.8) times as great as when the IOP was <35 mmHg.

Advanced visual field defect in at least one eye was found in 49 patients with OAG on December 31, 1983. The risk of developing advanced visual field defect with respect to age, duration of disease, and stage of defect at diagnosis was estimated in 106 patients using logistic regression analysis. A significant increase in the risk was seen with both increasing age and disease duration. The risk of advanced visual field defect was 14.3 (95% CI: 3.6 to 56.1) times higher if visual field defect stage III was seen at the time of diagnosis. There was no relationship between gender or type of glaucoma and the risk of developing advanced visual field defect.
Population survey

Prevalence of open-angle glaucoma (Paper III)

A total of 760 people underwent an eye examination. The overall response rate was 91%. Of 107 people in the population sample classified as ophthalmic outpatients, 104 were examined. Since, according to medical records, non-attendees of this category were free of the disease being studied, they were all counted as non-cases.

Medical records concerning the 78 non-participants were searched for at Uppsala University Hospital. Information was also provided by private ophthalmologists. Furthermore, the register of prescribed drugs was used to look for any unknown patient being treated for glaucoma, but no additional cases were found.

Altogether 45 people were diagnosed with OAG in the population sample, 29 with capsular glaucoma and 16 with chronic simple glaucoma. Twenty-five new cases were detected. Closed-angle glaucoma was diagnosed in 1 case and secondary glaucoma in 2 cases. The prevalence of OAG was estimated to 5.70% (95% CI: 4.12 to 7.27). Capsular glaucoma accounted for 60% of previously diagnosed OAG cases, whereas 84% of newly detected OAG were of chronic simple type. Normal tension glaucoma was diagnosed in 8 cases, all of which were revealed during the survey. Optic disc haemorrhages were present in 6 individuals, of whom 4 had OAG.

Forty-five individuals with suspected OAG, detected during the survey, were referred to Uppsala University Hospital for further examinations. Of the latter, 24 were diagnosed with OAG according to the diagnostic criteria of the study. Twenty of the 24 cases received a hospital discharge diagnosis of OAG (Table 7). Two of the 20 cases, however, were not accepted as definite OAG at the review undertaken in 2006 (see Final classification of open-angle glaucoma section). On the other hand, of the remaining 4 cases without a discharge diagnosis of OAG, all were finally classified as definite OAG. One individual with OAG refused to visit the Hospital.
Table 7. Forty-five cases of suspected open-angle glaucoma (OAG) referred to Uppsala University Hospital, by study criteria of OAG and discharge diagnosis

<table>
<thead>
<tr>
<th>OAG</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>

Revised prevalence estimates (Paper V)

As a result of the review of OAG cases, the number of cases in the population sample decreased from 45 to 43; 1 case was added and 3 cases were removed. The effect on prevalence rates was minimal: the overall adjusted rate of OAG decreased from 5.70 to 5.43% (95% CI: 3.90 to 6.97).

A diagnosis of definite OAG was established in 77 cases in the target population of 65–74 years olds: 43 in the sample and 34 in the remainder of the age group. Bilateral disease was found in 24 individuals. Sixty-seven of the 77 cases fulfilled classification criterion 1 (see Table 6), and 6 criterion 2; 4 fulfilled criterion 3. Twenty-three new cases were detected, all of whom were classified according to criterion 1.

The overall unadjusted prevalence of definite OAG was 5.27% (95% CI: 4.38 to 6.16). Chronic simple glaucoma was found at a prevalence of 3.38 (95% CI: 2.66 to 4.10), and capsular glaucoma, 1.89% (95% CI: 1.35 to 2.43). The effect of adjusting for age and gender was minimal. OAG was more common in men than in women, owing to an excess of chronic simple glaucoma cases among men.

Prevalence of pseudoexfoliation (Paper V)

PEX was observed in at least one eye of 133 people, 84 women and 49 men, in the population sample. One of the 3 non-participants in the ophthalmic outpatient category had PEX according to medical records, while the others had not. Therefore, the prevalence was calculated from 134 cases, resulting in an adjusted rate of 17.2% (95% CI: 14.6 to 19.9). PEX was significantly more common in females, with a female to male ratio of 1.6:1.
Risk factors for prevalent open-angle glaucoma (Paper V)

PEX as a risk factor for OAG was estimated in 744 individuals in the population sample. After stratification for gender, PEX was associated with a 4.7-fold (95% CI: 2.2 to 9.4) increased risk of OAG. Exclusion of 23 cases detected at the survey strengthened the effect of PEX. The odds for having OAG was 16-fold greater (95% CI: 4.8 – 56) in individuals with PEX, compared with those without PEX.

In the analysis of associations between increased IOP, PEX and definite OAG, individuals with a known diagnosis of glaucoma were excluded. An IOP of ≥20 mmHg at the population survey signified that the risk of having OAG, when PEX was taken into consideration, was 9.7-fold greater (95% CI: 3.7 to 27) than when the IOP was <20 mmHg. PEX alone was not associated with OAG (OR = 0.96, adjusted for IOP). There was no indication of interaction between PEX and increased IOP.

Follow-up study (Paper II)

Eleven of the 527 cohort members were excluded before the first follow-up examination, 43 could not be identified in the population register and 32 did not attend (6.8% of those invited). Interpretable visual fields from both eyes were not available from 28 subjects. The remaining 413 people constituted the study population.

Thirteen participants fulfilled the study criteria of incident OAG, 10 of whom had capsular glaucoma. Twelve of the cases were referred to the University Hospital for further examinations; a hospital discharge diagnosis of OAG was assigned to 9 of them. One patient refused to visit the Hospital. In the review undertaken in 2006, all 13 subjects were deemed to have definite OAG.

The cohort comprised more than 1,900 person-years at risk. The mean follow-up time was 4.6 years. Twenty per cent of the cohort was exposed to increased IOP, defined as an IOP ≥21 mmHg, 17% to PEX, and 6.1% to both increased IOP and PEX. The risk of OAG associated with increased IOP was estimated on the assumption of an equal distribution of PEX in exposed and non-exposed people. The standardized risk ratio was 3.4-fold higher (95% CI: 1.1 to 11) in exposed individuals. PEX was associated with a 16-fold increased risk of OAG. Assuming an equal distribution of increased IOP, the standardized risk ratio was estimated to be 9.8-fold higher (95% CI: 2.5 to 38) in those exposed to PEX.

There was indication of interaction between increased IOP and PEX; i.e. the joint effect of IOP and PEX was greater than the sum of their individual effects. Increased IOP and PEX increased the risk ratio for OAG 67-fold compared with the reference (no exposure) group.
Incidence study (Paper IV)

By the end of the study in May 2006, 51 cases of OAG had been identified, 31 with capsular glaucoma and 20 with chronic simple glaucoma, all of whom were classified as definite cases. Forty-six cases were detected in the follow-up study, corresponding to an incidence of 7.11 (95% CI: 5.06 to 9.17) per 1,000 person-years. This part of the cohort comprised nearly 6,500 person-years at risk. There was a marked increase in incidence between those 65–74 years old and the 75–84-year-olds. In the oldest age category, however, the incidence decreased. Four of the capsular and eight of the chronic simple glaucomas were classified as normal tension glaucoma.

While controlling for gender, incidence of definite OAG was significantly higher among participants in the follow-up study, than among those who were not invited. The difference was estimated to 4.49 (95% CI: 1.40 to 7.58) per 1,000. All cases of normal tension glaucoma were found in the follow-up study.

The overall incidence of OAG was higher in females than in males, owing to an excess of chronic simple glaucoma cases among females. The difference in incidence of capsular glaucoma was small. There was a predominance of normal tension glaucoma in females, accounting for 9 of the 12 cases. No cases of OAG were found among men in the oldest age category, the part of the cohort with the lowest number of person-years.

In OAG, the data indicated an association between mean IOP and time from the baseline examination to the end-point. This finding was evident in the follow-up study. The risk of having a mean IOP ≥23 mmHg was reduced by 70% in cases detected 14 years or more after the population survey, compared with cases detected during the first 7 years. A test of linear trend in proportions, adjusted to age at baseline, revealed a p-value of 0.00721.
Information on consumption of anti-glaucoma drugs and consultations at Uppsala University Hospital was used to identify patients diagnosed with glaucoma, unknown at the Eye Department in Tierp. Purchases of prescribed drugs outside the small township of Tierp were not registered. Dispensing of drugs to Tierp residents from the pharmacies in Uppsala was estimated to be about 5% of the total amount in the 1980s (Isacson 1987). This figure is not negligible, but it is important to remember that a single purchase from the pharmacies in Tierp is sufficient for the registration of a patient, treated for glaucoma. Thus, it is reasonable to assume that data collection in the present studies is complete and encompasses practically all patients diagnosed with glaucoma in the population.

The 1.4% prevalence of OAG, diagnosed in health-care services in the Tierp population aged 45 years and older, is in agreement with results from the Nordic countries (Lindblom & Thorburn 1982; Viggósson et al. 1986). The small proportion of normal tension glaucoma, 2.4%, has been reported in other studies (Lindblom & Thorburn 1984b).

Glaucoma blindness was a rare finding; only 4 OAG patients in a population of 20,000 inhabitants (0.02%) had advanced visual field defect in both eyes. In addition, 2 patients were blind as a consequence of secondary glaucoma. The number of blind subjects did not increase if the definition was changed to a visual acuity of 0.1 or less. The prevalence in Tierp was higher than the estimate of 0.007% reported in a Swedish study, based on a search for glaucoma patients attending low vision clinics (Blomdahl et al. 1997). In the American ‘Model Reporting Area’, 0.016% of the population was blind from OAG or closed-angle glaucoma (US Department of Health, Education and Welfare 1973).

In Tierp, advanced visual field defect in at least one eye was present in 40% of all OAG cases. As might be expected, the risk of developing advanced visual field defect was dependent on the age of the patient, the duration of the disease, and the severity of glaucoma damage at the time of diagnosis.

The demonstration of a relationship between mean initial IOP and the stage when visual field defects become evident tallies with the result of a study by Vogel et al. (1990). A major problem in the struggle against glaucoma blindness is that many patients refrain from seeking medical attention.
until they have severe visual field loss (Miller & Karseras 1974; Grant & Burke 1982). In Tierp, 'late presentation' had occurred in 15 of 49 patients with advanced visual field defect in at least one eye.

Compared with many other studies, the population survey conducted in Tierp, covering those aged 65–74 years, was a small study. In a target population of 2,429 residents, a sample of 760 people was examined. The prevalence of OAG was estimated from the prevalence in the sample and data of patients already diagnosed with OAG. This method allows an estimation of OAG prevalence with a tolerably small standard error, compared with estimation based entirely on the sample.

The prevalence of definite OAG in the target population, 5.3%, was higher than that reported for other comparable studies conducted on Caucasian populations, with the exception of the study in Reykjavik (Table 8). The prevalence in Reykjavik was identical to that in Tierp, both populations having a high a frequency of PEX. In Norway, a prevalence of 5.3% was reported for South-Trøndelag (Ringvold et al. 1991). The case definition in the latter study, however, was more liberal than that of the other studies.

Table 8. Prevalence of definite OAG in people 65–74 years old in the Framingham Eye Study, the Beaver Dam Eye Study, the Rotterdam Study, the Reykjavik Eye Study, and the Thessaloniki Eye Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham, USA ¹</td>
<td>Kahn &amp; Milton 1980</td>
<td>1.6%</td>
</tr>
<tr>
<td>Beaver Dam, USA</td>
<td>Klein et al. 1992</td>
<td>2.3%</td>
</tr>
<tr>
<td>Rotterdam, The Netherlands</td>
<td>Dielemans et al. 1994</td>
<td>1.4%</td>
</tr>
<tr>
<td>Reykjavik, Iceland ²</td>
<td>Jonasson et al. 2003</td>
<td>5.4%</td>
</tr>
<tr>
<td>Thessaloniki, Greece ²</td>
<td>Topouzis et al. 2007</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

¹ Adjusted for non-response to definite examination
² Including capsular glaucoma
Approximately one-half of those affected in the Tierp survey were previously undiagnosed, which tallies with other surveys carried out in industrialized countries. In particular, normal tension glaucoma was an undiagnosed condition, accounting for one-fifth of all OAG. This is consistent with results from the Baltimore Eye Survey (Sommer et al. 1991). One of the 8 cases of normal tension glaucoma had utilised the eye care services during the 8 years preceding the survey, and none within the last 4 years. Thus, 1 case may have been ‘missed’.

There are conflicting reports on the relationship of OAG to gender in Caucasian populations. In the Tierp study, OAG was significantly more common in males than in females. All the variation, however, was accounted for by chronic simple glaucoma. Capsular glaucoma was equally common in males and females.

Practically all population surveys that have investigated the association between IOP and OAG have reported an effect of increased IOP on the risk of having OAG. The population survey in Tierp was no exception. Excluding patients previously diagnosed with glaucoma, an IOP ≥20 mmHg was associated with a 9.7-fold increased risk of OAG, adjusted for exposure to PEX.

The limit for increased IOP was set at ≥20 mmHg rather than at ≥21 mmHg, used in most studies. Evidently, any cut-off value is arbitrary. In the present study, an IOP ≥20 mmHg provided a better separation between the pressure categories on the risk of having OAG, than an IOP ≥21 mmHg.

The presence of PEX was related to an adjusted 4.7-fold increased risk of OAG among all participants in the sample. This estimate is close to the finding in other cross-sectional studies (Mitchell et al. 1997b; McCarty et al. 2000; Krishnadas et al. 2003; Rotchford et al. 2003b). In contrast, PEX was not recognized as a risk factor in the Reykjavik Eye Study (Jonasson et al. 2003). When analysing people with a history of pressure-reducing therapy, however, PEX was found to be associated with OAG. The finding in the population survey in Tierp corroborates this tendency. The odds for being diagnosed with OAG before the survey was 16-fold greater among sample participants with PEX, compared with those without PEX. Moreover, when excluding patients previously diagnosed with the disease, the impact of PEX disappeared.

The odds for having the capsular disease was 8.8-fold greater in already diagnosed cases in the sample, than in cases detected during the population survey. All of the 8 cases of normal tension glaucoma, previously undiagnosed, were classified as chronic simple glaucoma; PEX was observed in the ‘second’ eye in one case.

The follow-up study in Tierp was a small study, generating 13 incident cases over a 5-year period. However, it was the first population based cohort study, using automated perimetry, to demonstrate an effect of increased IOP
on the risk of developing OAG. Exposure to increased IOP was associated with a 3.4-fold increased standardized risk ratio for OAG in individuals 65–74 years of age. Moreover, exposure to PEX was identified, for the first time, as an independent risk factor for OAG. The joint effect of an IOP ≥21 mmHg and PEX in the population survey increased the risk of OAG 67-fold. The combination of PEX and increased IOP probably accounts for the high morbidity of OAG in Tierp.

Before results of the Tierp study were published, Lundberg et al. (1987) had carried out a 20-year follow-up of individuals examined in a mass survey in the Swedish town of Skövde (Strömberg 1962). Subjects with an IOP ≥22 mmHg in the population survey ran a higher risk of developing OAG, than did a sample of those with IOP <22 mmHg. Follow-up of the large-scale population surveys in Barbados (Leske et al. 2007), Australia (Mukesh et al. 2002), and Rotterdam (de Voogd et al. 2005) has revealed an association between increased IOP and incident OAG.

Information on the joint effect of increased IOP and PEX in follow-up studies is sparse. Increased IOP and PEX were recognized as independent risk factors for the progression of OAG in the Early Manifest Glaucoma Trial (Leske et al. 2003). Hazard ratios associated with an IOP ≥21 mmHg and PEX were 1.70 and 2.22, respectively. Grødum et al. (2005) conducted a follow-up study composed of matched pairs, participating in the Early Manifest Glaucoma Trial. PEX increased the risk of developing OAG 2.0-fold. The analysis, however, based on individuals rather than pairs may be misleading.

It is important to remember that the conception of PEX as an independent risk factor for the development of OAG, demonstrated in Tierp, refers to a single point in time, the baseline examination. The impact of increased IOP over time modifies the effect of PEX. In a 16-year follow-up study of participants in the population survey, enlarged by the addition of ophthalmic outpatients, the effect of PEX was eliminated when IOP at the follow-up examinations was taken into account (Ekström 2000). The conclusion was that the effect of PEX was mediated by increased IOP.

Spanning over 20 years, the incidence study in Tierp is the longest follow-up study on OAG, based on automated perimetry, presented so far. It is the first study of its kind conducted in a population with a high exposure to PEX. The overall incidence of definite OAG, 7.11 per 1,000 person-years in the age range 65–94 years, based on those who participated in the follow-up study, was higher than that reported for other studies conducted on Caucasian populations.

As a consequence of the design of the follow-up study, participants who reached a study end-point were not invited to the next examination. Altogether 131 subjects had a specific end-point, unrelated to OAG, and 66 subjects did not comply with the visual field testing. Forty patients with normal
visual fields had received cataract surgery. Although an undefined number of cohort members had consultations at the Eye Department in Tierp during the coming years, incident cases of OAG may have been overlooked. The bias expected to arise from this study limitation is an underestimate of the incidence rate.

Incidence rates of definite OAG were reported from the Rotterdam Study (de Voogd et al. 2005). In the age range 65–74 years, the incidence may be estimated to 1.24 per 1,000 person-years (own calculation), which is lower than the rate of 3.76 for the Tierp population. None of the cases had capsular glaucoma.

The follow-up of the Dalby population in southern Sweden was the first incidence study based on automated perimetry to be published (Bengtsson 1989a). Use of the Lexis diagram presented by Bengtsson gives an incidence rate of 2.4 per 1,000 person-years in people 65–80 years of age. This estimate is lower than the unadjusted rate of 6.4 per 1,000 calculated for participants of the same age in the follow-up study in Tierp. Three of 27 cases in Dalby had the capsular disease, compared with 18 of 31 in Tierp.

The 9-year cumulative incidence of definite OAG in people 60–69 years of age in the black population of Barbados was 6.6% (Leske et al. 2007), substantially higher than the estimated 2.4% for the Tierp population in the age range 65–74 years.

The incidence of chronic simple glaucoma was higher in females than in males. This finding contradicts the results of the population survey, but agrees with the finding of the Dalby study. In view of the paucity of cases, the data should be interpreted with caution.

Ocular hypertensive patients with increasing IOP are usually followed-up more frequently than patients with stable IOP, producing an accumulation of pressure readings within a short period of time. When a patient with increasing IOP develops OAG, a time-weighted mean IOP provides an unbiased estimate of the pressure during the follow-up period, compared with an ordinary average of pressure readings. In the incidence study, OAG with a mean IOP ≥23 mmHg, calculated as a time-weighted average of all pressure readings during clinic hours, had a tendency to occur nearer to the population survey than OAG with an IOP <23 mmHg. Associations between mean IOP and exposure time concur with the pressure theory of optic nerve damage in glaucoma.

Individuals who participated in the follow-up study had a 2.7-fold increased incidence of OAG, compared with those who were not invited. Normal tension glaucoma was an exclusive phenomenon at the follow-up examinations. OAG cases detected in the rest of the cohort, however, were all of the high-tension type, following exposure to PEX. This finding tallies with the results of the population survey. An interesting question is how many of the normal tension glaucoma cases would have been diagnosed in subsequent years, had not the disease been detected in the study?
There are two likely explanations to the disparity between cases detected in health care services and those detected in studies of ‘normal’ populations. First, patients with capsular glaucoma may be more likely to seek medical attention due to the emergence of symptoms. A number of studies have documented a higher IOP at first presentation in capsular glaucomas than in chronic simple glaucomas (Lindblom & Thorburn 1984b; Berggren & Widengård 1993). Some studies have demonstrated a possible association between cataract and PEX (Hiller et al. 1982; Hirvelä et al. 1995; Krishnadas et al. 2003), though others have not (McCarty & Taylor 2000).

Second, there may be an inability to detect normal tension glaucoma in clinical practice. Grødum et al. (2002) found a 4-fold increased proportion of normal tension glaucoma in cases identified in a population survey in southern Sweden, compared with self-selected patients diagnosed at the Eye Department in Malmö.

The strengths of the present studies include the community-based approach, the long follow-up time, and the use of computerised perimetry to identify cases. In the population survey, data on patients already diagnosed with OAG were used to improve prevalence estimates. Participation rates were high, both in the population survey and in the follow-up study. The final classification of OAG was based on the decision of independent observers, ‘masked’ to information on IOP and PEX. Only definite cases of OAG were included. Eye examinations were conducted by the same ophthalmologist throughout the studies.

The limitations are the tolerably small size of the population survey and the follow-up study, and the lack of optic disc photography of all participants. Only people in the age range 65–74 years were invited. A large number of participants, reaching a study end-point, were excluded from the follow-up study for reasons other than glaucoma. The potential impact of these losses on the study results is an underestimate of the incidence rate.

Information on the purchases of prescription drugs at the pharmacies in Tierp was used to identify OAG cases, unknown at the Tierp Eye Department. Unfortunately, this registration ceased in 1998. Furthermore, purchases at the pharmacies in Uppsala were not registered. It is not impossible that occasional cases of OAG might have been overlooked, but any effect on the estimates in the present studies would be minimal.
Conclusions

A significant proportion of the population in the age range 65–74 years in Tierp was exposed to PEX. In this part of Sweden, OAG is a common disease. The prevalence of OAG in Tierp was higher than that reported for comparable studies carried out on Caucasian populations, with the exception of studies in Norway and Iceland, all populations with a high prevalence of PEX. Similarly, incidence of OAG in Tierp was higher than in other studies on Caucasians. Glaucoma blindness was a rare finding, however.

Approximately half of all individuals with OAG in the age range 65–74 years were unaware that they had the disease. Already diagnosed glaucoma was mainly of the capsular type, whereas the vast majority of unknown cases detected in the population were of the chronic simple type. Normal tension glaucoma was an undiagnosed condition. Consequently, PEX was a risk factor for OAG only in people previously diagnosed with the disease. A possible explanation for this finding is that patients with capsular glaucoma are more likely to seek medical attention due to the emergence of symptoms.

In people without a previous diagnosis of OAG, increased IOP was a serious risk factor for having the disease. Increased IOP and PEX were both recognized as independent risk factors for the development of OAG. Interaction between increased IOP and PEX was demonstrated. Increased IOP, in the presence of PEX, may account for the large number of OAG cases in Tierp and the Nordic countries.
Gluukom är en vanlig sjukdom hos äldre personer i de flesta befolkningarna. Sjukdomen kännetecknas av typiska förändringar av synnervspapillen och bortfall i synfältet, som kan leda till blindhet.


De flesta glaukom som upptäcks i den svenska sjukvården kännetecknas av ett markant förhöjt ögontryck och förekomsten av pseudoexfoliationer. I befolkningsundersökningar har man däremot i regel upptäckt glaukom av simplextyp med ögontryck inom det övre normalområdet. Målsättningen med avhandlingen var att studera öppenvinkelglaukomets epidemiologi i Tierps kommun, som har en befolkning med hög exponering för pseudoexfoliationer.

I en sjukvårdsbaserad studie av personer med känd glaukomdiagnos upptäcktes 128 fall av öppenvinkelglaukom. Prevalensen uppgick till 1,4% hos personer i åldern 45 år och äldre. Dataregister över konsumtionen av glaukomläkemedel och besök vid Akademiska sjukhuset användes för att identifiera fall som inte var kända i Tierp. Kapsulareglaukom svarade för 63% av alla öppenvinkelglaukom. Patienter med uttalade glaukomskador var äldre, hade haft sjukdomen längre, hade högre initialt ögontryck och hade större synfältsdefekter när sjukdomen upptäcktes än övriga patienter. Endast fyra personer i en befolkningen på över 20.000 individer var blinda till följd av öppenvinkelglaukom.

Prevalensen av öppenvinkelglaukom skattades till 5,3%. Pseudoexfoliationer påträffades hos 17% och var vanligare hos kvinnor. Kapsulareglaukom utgjorde 36% av alla öppenvinkelglaukom och var i de flesta fall kända. Alla fall av normaltrycksglaukom upptäcktes i undersökningen. Efter att ha uteslutit patienter med känd glaukomdiagnos var ett förhöjt ögontryck för- enad med 9,7 gånger högre risk för sjukdom. Pseudoexfoliationer var en riskfaktor för öppenvinkelglaukom endast hos personer med tidigare känd diagnos.


Insjuknande i öppenvinkelglaukom över tiden studerades hos individer som deltog i den uppföljande undersökningen. I maj 2006 hade 46 nya fall upptäckts. Incidensen av öppenvinkelglaukom skattades till 7,1 per 1.000 personår i åldern 65–94 år. Incidensen av kapsulareglaukom var högre än incidensen av simplexglaukom.

Sammanfattningsvis visade avhandlingen att prevalensen och incidensen av öppenvinkelglaukom var högre än i andra studier genomförda på befolkningar av europeiskt ursprung, med undantag för några studier i de nordiska länderna. Exponering för pseudoexfoliationer är den troligaste förklaringen till den höga sjukligheten.
Acknowledgements

I wish to express my appreciation to everyone who helped me to complete this thesis, especially those residents in Tierp who participated in the follow-up study over the years, and to Albert Alm, my co-author and supervisor, for valuable support and review of OAG cases.

Lennart Berggren, my first supervisor, gave valuable support and introduced me to the field of glaucoma epidemiology. Björn Smedby made it possible for me to make use of resources connected with The Tierp Project, and assisted in planning the population survey.

Ann-Marie Elebjörk and Börje Nordh conducted the automated perimetry, and Inger Fällman Hedberg the manual perimetry. Börje Nordh took the optic disc photographs.

Bengt Haglund, my co-author in the first article, performed the multivariate analysis. Lennart Berggren and Ingmar Widengård graded the manual visual fields and Dordi Austeng the threshold fields. Ingmar Widengård compiled the program for calculating time-weighted mean IOP.

Birgit Andersson dealt with the economic matters, and Olav Mäepea assisted in technical questions. Mirja Korpela assisted in the administration of the population survey and the follow-up study, and Håkan Jansson provided lists of Tierp residents.

Ann-Marie Elebjörk, Inger Fällman Hedberg, Eva Nuja and Rolf Rudelflod re-created Goldmann perimetrics from microfilm.

The Swedish Medical Research Council, Crown Princess Margareta’s Foundation for Visually Impaired and the Glaucoma Research Fund at the Department of Ophthalmology, Uppsala University Hospital, provided financial support for the present studies. The thesis could not have been carried out without additional time for research provided by the Department of Ophthalmology at Uppsala University Hospital.
References


Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 294

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.

Distribution: publications.uu.se
urn:nbn:se:uu:diva-8323