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Review Article

Cataract prevalence and prevention in Europe: a literature review

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ABSTRACT.
This literature review is aimed at the evaluation of the potential for cataract prevention in Europe. It was performed using PubMed with Mesh and free-text terms. Studies included were (i) performed on a population of Caucasian origin at an age range of 40–95 years, (ii) cataract was clinically verified, (iii) drug record of prescriptions, their indication, a record of every diagnosis, dosage and quantity of prescribed medicine were available, (iv) sample size >300 and (v) published between 1990 and 2009. The results of 29 articles were reviewed. Former [3.75 (2.26–6.21)] or current smoking [2.34 (1.07–5.15)], diabetes of duration >10 years [2.72 (1.72–4.28)], asthma or chronic bronchitis [2.04 (1.04–3.81)], and cardiovascular disease [1.96 (1.22–3.14)] increased the risk of cataract. Cataract was more common in patients taking chlorpromazine during ≥90 days with a dosage ≥300 mg [8.8 (3.1–25.1)] and corticosteroids >5 years [3.25 (1.39–7.58)] in a daily dose >1600 mg [1.69 (1.17–2.43)]. Intake of a multivitamin/mineral formulation [2.00 (1.35–2.98)] or corticosteroids [2.12 (1.93–2.33)] also increased the risk of cataract. Corticosteroids applied orally [3.25 (1.39–7.58)], parenteral [1.56 (1.34–1.82)] or inhalational [1.58 (1.46–1.71)] lead to cataract more frequently than those applied topically: nasal [1.33 (1.21–1.45)], ear [1.31 (1.19–1.45)] or skin [1.43 (1.36–1.50)]. Outpatient cataract surgery was negatively associated with total cataract surgery costs, and chlorpromazine, corticosteroids and multivitamin/mineral formation increase the risk of posterior subcapsular cataract dependent on dose, treatment application and duration. This review presented a comprehensive overview of specific and general cataract risk factors and an update on most recent experimental studies and randomized control trials directed at cataract prevention.

Key words: adverse effect – cataract – cataract surgery – costs – epidemiology – Europe – medications – prevention – risk factors

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Introduction

Cataract still is a leading cause of visual impairment worldwide (Abraham et al. 2006). Despite the fact that 90% of cataracts in the world are reported in developing countries, its social, physical and economic impact is still substantial in the developed world (Resnikoff et al. 2004; Abraham et al. 2006). Cataract is a common cause of visual impairment in the elderly that is often noticed by patients at an early stage, and surgery is often effective in restoring vision (Foster 2001). Nevertheless, cataract surgery still remains a major healthcare cost in Europe and other Western countries.

Progressive ageing of the European population is linked to the increase of incidence and prevalence of cataract. As an example, the general population of Denmark is expected to increase by 10%, the proportion of the population aged 70 or older is predicted to double from 10.5% (2009) to 20.40% (2050), and the number of cataract surgeries is projected to correspondingly increase from 46 000 in 2004 to 86 000 in 2050 (Rasanen et al. 2006). The increased demand for cataract surgery may be hard to meet in the future unless preventative actions are taken (Kessel 2011). Therefore, a review of modifiable risk factors of cataract and the evaluation of aspects that affect total costs of cataract surgeries is needed.

Cataract is a multifactorial disease associated with age, female sex, genetic predisposition, smoking, diabetes mellitus, drug intake and environmental exposure to UVB radiation (Vrensen 2009). Previous reviews were often focused on one of the aspects of cataract epidemiology, such as common risk factors (Taylor 1999; Abraham et al. 2006; Navarro Esteban et al. 2007), the cost-effectiveness of different treatment approaches (Chang 2005) and their comparison between different countries in Europe (Baltussen et al. 2004). Several epidemiological studies report on cataract as a possible adverse effect of widely used drugs (Ruigomez et al. 2000; Smeeth et al. 2003); nevertheless, this aspect of cataract aetiology was not reviewed previously. This literature review was undertaken to provide an overview of cataract epidemiology, cataract risk factors and cataract-related economic burden as well as to evaluate the potential for cataract prevention in Europe.

Search and Selection Criteria

A literature search was performed in the Medline database (PubMed) using the following controlled vocabulary (Mesh) search terms: 'Cataract' [Mesh] AND 'Epidemiology'[Mesh], 'Cataract'[Mesh] AND 'numerical data'[Subheading], 'Cataract'[Mesh] AND 'Drug Toxicity'[Mesh] and 'Cataract'[Mesh] AND 'Risk Factors'[Mesh]; and the free-text search terms 'cataract', 'prevalence', 'incidence', 'population-based', 'cross-sectional', 'cohort studies', 'epidemiology', 'statistical data', 'adverse event', 'risk factors', 'cataract surgery', 'surgical activity' and 'costs'.

Only studies that used a standardized definition of cataract were included. Cataract was detected if patients presented lens opacities, in one or both eyes, with best corrected visual acuity (VA) equal to 0.2 log minimum angle of resolution (logMAR) (or 20/30 or 0.6) or worse. Cataracts are subdivided into three types: a) nuclear cataract, b) cortical cataract and c) posterior subscapular cataract (Cedrone et al. 1999).

The abstracts of the articles identified were reviewed, and those considered of high and medium relevance were obtained. Additionally, attention was also given to papers referenced in the selected articles. Special attention was given to studies focusing on prevalence and incidence by age and gender, as cataract in the industrialized countries primarily is an age-related eye disease. Prevalence quantifies the proportion of individuals in a population who have a disease at a specific time-point. Incidence quantifies the number of new events or cases of the disease that develop in a population of individuals at risk during a specific time interval. Results are shown here via a map of Europe for crude prevalence values and a table for cataract risk factors.

Results

Twenty-nine studies met the inclusion criteria: two multicentre global population-based studies (Foster 2001; Resnikoff et al. 2004), one case–control study from Greece (Theodoropoulou et al. 2011), five multicentre cross-sectional European population-based study (Das et al. 1994; Resnikoff et al. 2004; Simmons et al. 2007; Moshetova 2008), one Finnish nationwide population-based survey (Laitinen et al. 2009), and thirteen prevalence population-based studies: two from Rotterdam, the Netherlands (Klaver et al. 1998; Kocur & Resnikoff 2002), one from the European North of Russia (Bannikova et al. 2002), two from France (Cohen et al. 2000; Waked et al. 2007), three from Italy (Giuffre et al. 1994; Cedrone et al. 1999; Kocur & Resnikoff 2002), three from Germany (Krumpaszky et al. 1999; Trautner et al. 2003; Blum et al. 2007), one from Spain (Navarro Esteban et al. 2007), one from Bulgaria (Kocur & Resnikoff 2002) and one from Reykjavik, Iceland (Gunnlaugsdottir et al. 2010). Seven studies describing cataract as an adverse event of widely used drugs were reviewed: three case–control from the UK (Smeeth et al. 2003) and Spain (Valero et al. 2002; OECD 2005); two cohorts from the UK (Ruigomez et al. 2000) and Australia (Taylor 1999); an observational population-based study from France (Delcourt et al. 2000a,b); and one randomized, double-masked, placebo-controlled clinical trial (Maraini et al. 2008).

Early cortical lens opacities and cataract prevention

Adequate cataract extraction with implantation of an intraocular lens is recognized as the most effective approach to prevent blindness from cataract worldwide. However, it is important to consider that this treatment approach causes high economic expenditure and can lead to postoperative complications such as capsule opacification, retinal detachment, endophthalmitis, posterior capsular rupture with vitreous loss, vitreous stands to the surgical incision and iris prolapsis through the corneal/limbal incision that may result in irreversible blindness (Vrensen 2009). Therefore, nonsurgical approaches for prevention and treatment of cataract should be given priority. More knowledge on the aetiology of different types of cortical, nuclear and posterior subcapsular cataracts (PSCs) in humans is needed to formulate possible type-specific preventive strategies.

The accommodative power of the lens declines after 40–50 years of age. A constant increase in stray light because of age-related lens changes accounts for considerable glare that sometimes can lead to disabling handicaps, for example, during driving in darkness (Sasaki et al. 1997). A yellowish colour and smaller opacities in the equatorial region are common observations in older lenses (Truscott 2005). The number of opacities can vary significantly from a few scattered spots to shades, opaque segments or full opaque annular rings (Vrensen 2009). Most of these opacities are often located outside the pupillary space and are not seen during slit-lamp microscopy even in mydriasis. Early opacities can take two forms, which were first described by Obazawa (1982)): (i) circular shades running parallel to the circumference of the lens and (ii) radial shades running perpendicular to the circumference of the lens. Early or incipient opacities consist of cohorts of disorganized lens fibre cells located in the deep equatorial cortex of the lens and characterized by a high content of phospholipids, cholesterol, disulphide cross-linked proteins and free Ca^{++}

(Vrensen 2009). In a recent article, Michael et al. (2008) emphasized that the early opacities are the precursors of a common type of cataract: age-related cuneiform cortical cataract. Studies on several hundreds of donor's lenses showed that the prevalence of spots and shades and of segmental and annular opacities is already considerable between the ages of 30 and 45; at older ages, up to 75–80% of the eye lenses exhibit this form of early cataractous defect (Vrensen 2009). The detrimental effects of oxidative stress lead to local ruptures of fibre membranes in the superficial cortex at a relatively young age (second or third decade). These ruptures are repaired by internalization and lysosomal breakdown of the disordered membranes and proteins (Vrensen & Willekens 1990). In the fourth or fifth decade, local opacities occur in the deep equatorial cortex close to the cortical–nuclear barrier. These injuries are sealed by 'nonleaky' membranes that delay progression into the pupillary cortex and the nucleus of the lens (Vrensen 2009). Age-related cataracts are largely caused by lifelong accumulation of oxidative insults, which, despite the defence mechanism, eventually lead to cortical and nuclear cataracts rather late in life (Truscott 2005). Balanced nutrition, rational use of antioxidants and avoiding oxidation-enhancing lifestyle factors such as obesity, smoking, excessive drinking and excessive exposure to UV light are at the moment the best measures to be taken to delay the onset of cataract (Valero et al. 2002; Beebe et al. 2010).

Epidemiology of cataract in Europe

Cataract is a leading cause of blindness globally accounting for 33% of blindness worldwide (Pascolini & Mariotti 2011). Global prevalence of cataract in adults over 50 years of age was estimated at 47.8% (Resnikoff et al. 2004). Crude prevalence of cataract in European adults in 2007 was 19.3% (Simmons et al. 2007). The studies that are reviewed below represent the prevalence of lens opacification and do not include patients who underwent cataract surgeries. The presented prevalence rates highlight the impact cataract on the population in Europe.

The prevalence of cataract in Europe increased with age from 5% for the 52–62 (Moshetova et al. 2008) and 30% for 60–69 years of age to 64% for the population over 70 years (Das et al. 1994). In a population-based survey performed in Casteldaccia, Italy, lens opacities of moderate or severe grade were found at the following crude rates: nuclear opalescence in 18.5%, cortical cataract in 12.9% and PSC in 10.8% (Giuffre et al. 1994). All these types of cataract were much more frequent in the elderly population and were about 1.5 times more common in women than in men. Advanced stages of cataract were found in about 1/3 of subjects aged 60–69 years and in 2/3 of subjects aged 70 or more, but only rarely in subjects <60 years of age. Cataracts causing a reduction in VA under 0.7 in the worst eye were found in 4% of subjects 40–49 years old, 8.7% of subjects 50–59, 21.5% of subjects 60–69 and 54.4% of subjects 70 years old or over (Giuffre et al. 1994). In a study from Lebanon, it was estimated that cataract was the most frequent cause of visual impairment in the region and accounted for 38.5% of visually impaired people (Waked et al. 2007). A population-based study of blindness incidence in Germany showed that cataract accounted for 3.32 per 100 000 person-years (3.11–3.52) and was the second most frequent cause of blindness (Trautner et al. 2003). The Reykjavik Eye study indicated that cataract was a principal cause of unilateral visual impairment, accounting for 50% of cases (WHO criteria) to 65% of cases (US criteria) (Gunnlaugsdottir et al. 2010). In contrast to this, age-related cataract predominantly caused an increased prevalence of visual impairment, but was not among leading causes of blindness in Rotterdam (Klaver et al. 1998). Cataract, with a crude prevalence of 9.5% (95% CI 8.9–10.2%), was the most common chronic eye disease in the Finnish population (Laitinen et al. 2009). About 53% of the Finnish population underwent cataract surgery. This study also supports the fact that the prevalence of cataract significantly increased with age ($p < 0.001$), from 2% in persons under 65 years of age to 67% in those aged 85 or older.

The highest overall cataract prevalence for adults was seen in Germany (Blum et al. 2007) and Italy (Kocur & Resnikoff 2002). A map of cataract prevalence in Europe is shown in Fig. 1.

Sex-specific cataract prevalence in a Spanish study was higher in men over 64 years of age (69.50%) than in women (65.50%) at the same age ($p > 0.05$) (Navarro Esteban et al. 2007). The highest crude incidence of cataract in adults was estimated to be in Germany (0.20 per 100 000) (Krumpaszky et al. 1999), followed by Italy (0.065 per 100 000) (Cedrone et al. 1999) and the European North of Russia (0.039 per 100 000) (Arkhangelsk Oblast Administration et al. 2007).

Cataract risk factors

Cataract can develop because of many factors, age being a constant subliminal modifier (Vrensen 2009). Former or current smoking, diabetes of duration >10 years, asthma or chronic bronchitis, and cardiovascular disease increased the risk of cataract (Delcourt et al. 2000a,b). The recent results of the Blue Mountains Eye Study showed that baseline fasting blood glucose level was associated with the 10-year incidence of cortical cataract [1.79 (1.25–2.57) for fasting glucose ≥6.0 mm compared to fasting glucose <6.0 mm]. This study also underlined that each 1.0 mm increase in fasting glucose was associated with 5-year progression of PSC [1.25, (1.15–1.35)] and 10-year progression of cortical [1.14, (1.01–1.27)] and nuclear [1.20, (1.01–1.43)] cataract, with no thresholds identified (Kanthan et al. 2011). Cataract surgery takes place approximately 20 years earlier in patients with type 1 diabetes in comparison with patients without diabetes (Grauslund 2011). The population-based cohort study of patients with type 1 diabetes based on data from the Danish patient registry reported high 25-year cumulative incidence of cataract surgery (20.8%) (Grauslund et al. 2011). A case–control study performed in Greece also showed that current or previous smoking, a history of coronary heart disease, a family history of ophthalmologic diseases and higher sunlight exposure at the beach or at work significantly increased the risk of cataract (Theodoropoulou et al. 2011). Wearing hats and sunglasses on the beach

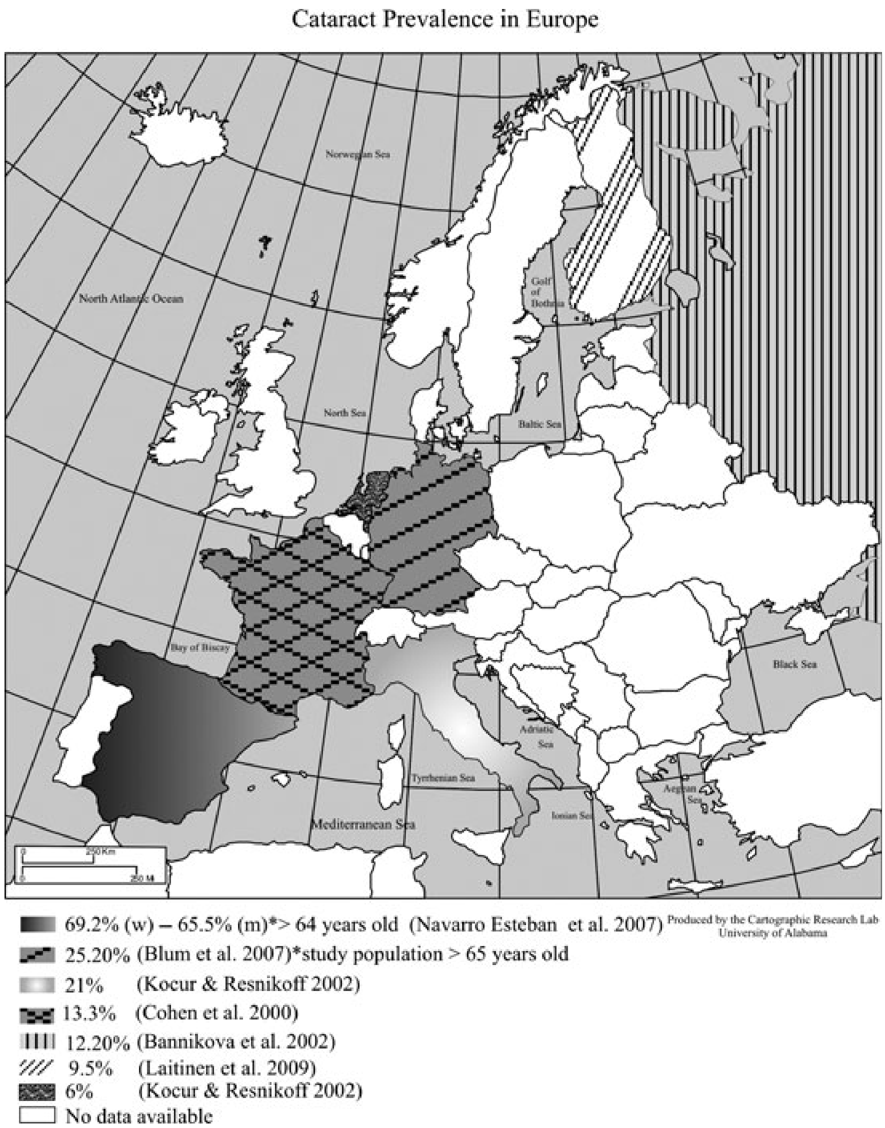

Fig. 1. A map of cataract prevalence in Europe.

had a protective effect (Theodoropoulou et al. 2011). The link between female gender and cataract remains unclear. A nationwide Finnish survey showed that cataract was more common in women than in men [1.55 (1.26–1.91)] (Laitinen et al. 2009), whereas in a case–control study from Greece, only borderline significance of female gender was found for cortical cataract (p = 0.06) (Theodoropoulou et al. 2011). Interestingly, a prospective population-based study found no significant longitudinal associations between exogenous oestrogen exposure, female reproductive factors and the long-term incidence of cataract in this older population-based cohort (Kanthan et al. 2010). Modifiable risk factors of cataract with adjusted odds ratios are summarized in Table 1.

Cataract as an adverse event of widely used drugs

Cataract appeared to be one of the most frequent adverse events for widely used drugs. Patients with schizophrenia had the highest relative cataract risk (Ruigomez et al. 2000). Cataract was more common in patients taking chlorpromazine during ≥90 days with a dosage ≥300 mg (Ruigomez et al. 2000), a multivitamin/mineral formulation (PSC) (Maraini et al. 2008) or corticosteroids (Smeeth et al. 2003). The highest risk of cataract was detected for corticosteroids use > 5 years in a daily dose > 1600 mg (Smeeth et al. 2003). Corticosteroids applied orally, parenteral or inhalational lead to cataract more frequently than those applied topically: nose, ear or skin (Smeeth et al. 2003). Detailed data on cataract as an adverse effect of widely used drugs are presented in Table 1.

Type-specific cataract risk factors

Knowledge of type-specific risk factors of cataract is important for the investigation of possible type-specific approaches to cataract prevention.

Nuclear cataract risk factors. Nuclear cataracts are associated with poorer diet, lower socio-economic status, nonprofessional status and lower educational achievement. The Age-Related Eye Disease Study (AREDS) showed that increasing age (hazard ratio (HR), 1.07; 95% CI, 1.06–1.09) is significantly associated with increased nuclear cataract, whereas female sex was of borderline significance (HR,

Table 1. Modifiable risk factors of cataract.

Risk factor	Study location	Year of study	Age group	Sample size	Study design	Adjusted odds ratio, 95% CI	References
Cardiovascular disease	France	1995–1997	60–95	2584	Population-based study	1.96 (1.22–3.14)	Delcourt et al. (2000a,b)
Asthma or chronic bronchitis						2.04 (1.04–3.81)	
Smoking (current smokers)						2.34 (1.07–5.15)	
Diabetes ≥10 years duration						2.72 (1.72–4.28)	
Female sex						3.03 (1.83–5.00)	
Smoking (former smokers)						3.75 (2.26–6.21)	
Smoking (current smokers)	Greece, Athens	2007–2008	45–85	314 patients/314 controls	Case–control study	1.99 (1.23–3.23)	Theodoropoulou et al. (2011)
Smoking (former smokers)						1.64 (1.02–2.70)	
History of coronary heart disease						2.25 (1.43–3.55)	
Family history of ophthalmologic diseases						1.51 (1.03–2.20)	
Higher sunlight exposure at the beach						2.26 (1.37–3.72)	
Use of cortisone drops						2.59 (0.93–7.21)	
Higher sunlight exposure at work						2.03 (1.32–3.12)	
Wearing hat at the beach						0.58 (0.39–0.85)	
Sunglasses						0.44 (0.30–0.65)	
Inhaled corticosteroids, current use	UK	2003	Over 40	15 476	Population-based case–control	1.15 (1.03–1.27)	Smeeth et al. (2003)
Topical steroids, ear						1.31 (1.19–1.45)	
Topical steroids, nasal						1.33 (1.21–1.45)	
Topical steroids, other						1.35 (1.25–1.46)	
Topical steroids, skin						1.43 (1.36–1.50)	
Systemic steroids, parenteral						1.56 (1.34–1.82)	
Inhaled corticosteroids						1.58 (1.46–1.71)	
Systemic steroids, oral						1.59 (1.47–1.71)	
Daily dose of inhaled corticosteroids > 1600 mg						1.69 (1.17–2.43)	
Ocular corticosteroids						2.12 (1.93–2.33)	
Use of oral corticosteroids at least 5 years	France	1995–1997	60–95	2584	Population-based study	3.25 (1.39–7.58)	Delcourt et al. (2000b)
Lycopene, > 0.30 mm	Spain	2002	55–74	347	Case–control	1.43 (1.02- 2.06)	Valero et al. (2002)
Retinol, 7.99 mm						1.52 (1.02–2.35)	
Posterior subcapsular cataract/multivitamin/ mineral formulation	Multicentre	2008	55–75	1020	Randomized controlled trial	2.00 (1.35–2.98)	Maraini et al. (2008)
Chlorpromazine/current use ≥90 day duration, dosage ≥300 mg	UK	1992	30–85	4209	Cohort study	8.8 (3.1–25.1)	Ruigomez et al. (2000)
Relative risk in cohort of patients with schizophrenia			60–69			10.6 (3.2–35.7)	

1.12; 95% CI, 0.99–1.28) (Chang et al. 2011). A recent study reported an increased incidence of cataract surgery in subjects taking vitamin C supplements (but not those taking multivitamin supplements or diets high in vitamin C) (Rautiainen et al. 2010). The risk of nuclear cataracts also increases with the amount and duration of smoking. Several studies identified larger lens size as a risk factor for nuclear cataracts (Klein et al. 1998; Praveen et al. 2009). Longitudinal studies confirmed that having a larger lens is correlated with increased risk of developing nuclear opacities over a 5-year follow-up period (Klein et al. 2000). Epidemiological studies have also shown that living in a region with increased ambient temperature leads to the increased lens hardening and risk of developing nuclear cataract (Sasaki et al. 2002). Recent laboratory investigations have supported this hypothesis (Heys et al. 2007). Genetic factors also play an important role in the aetiology of nuclear cataract. Studies on twins and examination of familial associations have suggested that about one-third of the risk of nuclear cataracts is hereditary (Heiba et al. 1993; Hammond et al. 2000).

Cortical cataract risk factors. High sunlight exposure has been consistently associated with an increased risk of cortical cataracts, although its contribution to aetiology of other cataract types is modest. Exposure to sunlight can be effectively eliminated by wearing a brimmed hat or plastic glasses, making it a preventable risk (Taylor et al. 1988). Females of African heritage and those who have a family member with cortical cataract have more significant risk of developing cortical cataracts (Leske et al. 1991, 1997; The Italian-American Cataract Study Group 1991; McCarty et al. 2000; Hammond et al. 2001; Congdon et al. 2005). Fifty to 60% of the risk of developing cortical cataracts is hereditary. Lens size was also identified as a significant risk factor for cortical cataracts, but in contrast to nuclear cataract, the increased prevalence and incidence of cortical opacities were linked to having a smaller lens (Klein et al. 1998, 2000; Praveen et al. 2009). The AREDS indicated that increasing age (HR, 1.05; 95% CI, 1.03–1.06), diabetes (HR, 1.31; 95% CI, 1.04–1.66), weight change of middle quintiles (HR, 1.20; 95% CI, 1.00–1.43) and top quintile (HR, 1.35; 95% CI, 1.09–1.67) in comparison with lowest quintile, smoking status (current versus never) (HR, 1.41; 95% CI, 1.09–1.83) and mild cortical cataract at baseline (HR, 5.17; 95% CI, 4.29–6.22) are associated with an increased risk of cortical cataract, whereas male gender (HR, 0.83; 95% CI, 0.72–0.95), white ethnicity (HR, 0.56; 95% CI, 0.42–0.75) and college education (HR, 0.77; 95% CI, 0.66–0.91) were associated with decreased risk of cortical cataract (Chang et al. 2011).

Posterior subcapsular cataract. Several studies have shown that patients with diabetes have an increased risk of developing cortical cataracts and PSCs, although diabetes patients with well-controlled blood sugar develop a similar risk of age-related cataracts as nondiabetics (Bron et al. 1993; Oishi et al. 2006). Persons with uncontrolled diabetes often rapidly develop cataracts. These opacities are associated with osmotic damage to the superficial lens cortex that may also involve oxidative damage (Obrosova et al. 1999; Hegde & Varma 2005). Other risk factors of PSCs are high myopia, diabetes and exposure to therapeutic doses of steroids and ionizing radiation. Increasing age (HR, 1.06; 95% CI, 1.04–1.08), male gender (HR, 1.32; 95% CI, 1.11–1.58), diabetes (HR, 1.71; 95% CI, 1.29–2.27), increased weight change (highest quintile versus lowest quintile: HR, 1.48; 95% CI, 1.10–1.97) and thyroid hormone use (HR, 1.37; 95% CI, 1.00–1.87) were associated with increased risk of PSC, whereas hyperopia was associated with a decreased risk of PSC (HR, 0.78; 95% CI, 0.61–0.99) (Chang et al. 2011).

Common aetiology for all cataract types. Oxidative damage is an important aetiological factor for nuclear and cortical cataracts. Substantial research data suggest that, with increasing age, the lens nucleus becomes more susceptible to oxidation and less able to repair oxidative damage (Truscott 2005). Absorption of UV light can generate free radicals, leading to increased oxidative damage (Wood & Truscott 1993; Truscott 2003). Interestingly, cortical cataracts first appear at the lens equator, the region of the lens that is best protected from exposure to sunlight. This can be explained by the absorption of UV light by other eye tissues, the iris, for example, which might produce toxic metabolites that damage cortical fibre cells. Higher sunlight exposure increases the stiffness of the lens nucleus, and this increased stiffness contributes to the formation of cortical cataracts through mechanical stress.

Potential sources of oxidative stress. Potential sources of oxidative stress to the lens include UV light, oxidants in the ocular fluids, endogenous oxidants produced in lens cells and smoke constituents. The increase in UV-absorbing compounds in older lenses (‘UV filters’) may increasingly sensitize the lens to UV exposure (Mizdrak et al. 2008). Smoking is one of the most reliable risk factors for nuclear cataracts in epidemiology studies throughout the world (Hodge et al. 1995; Cumming & Mitchell 1997; McCarty et al. 2000; Age-Related Eye Disease Study Research Group 2001). Exposure to cooking fuel smoke has also been linked to nuclear cataract (Pokhrel et al. 2005). The exact components of smoke that cause oxidative stress, however, are unknown.

Experimental evidence. Increased exposure of the lens to oxygen is considered to be a major cause of age-related nuclear cataracts. This is supported by several studies on patients undergoing hyperbaric oxygen therapy that confirms the occurrence of a myopic shift, even after relatively short-term therapy (Fledelius et al. 2002; Evanger et al. 2004). Furthermore, this fact is supported by many studies on patients undergoing vitrectomy. These studies have documented very high rates of nuclear cataract formation (60–95%) within 2 years after vitrectomy surgery (de Bustros et al. 1988; Cherfan et al. 1991; Van Effenterre et al. 1992; Thompson et al. 1995). Studies during which the vitreous gel was intentionally preserved or destroyed highlighted that vitreous gel protects the lens from oxygen and from nuclear cataract. Loss of the gel state of the vitreous is likely to increase the exposure of the lens to oxygen and increase the risk of nuclear cataract (Shui et al. 2009). Vitrectomy surgery is a frequently performed procedure; therefore, patients undergoing this operation can be a promising model to test this hypothesis.

Cataract prevention

Although in the majority of cataract patients vision can be restored to a satisfactory level by surgically removing the natural lens and substituting it with a lens made of synthetic polymers, the incidence of cataract is so large that surgery alone has been found ineffective in solving this problem. Cataract remains a consistent public health problem because of a shortage of surgical facilities especially in developing countries as well as the continuous replacement of old cases with new ones because of ageing and population growth. Cataract extraction can lead to surgical and postsurgical complications, such as vitreous loss, macular oedema and retinal detachment, which are known to occur in 5% of patients undergoing cataract surgeries (Clayman 1982; Stark et al. 1984; Smith et al. 1987). Therefore, development of pharmacological means of cataract prevention should be one of the main priorities for future cataract research.

Randomized controlled trials for cataract prevention

The preventive effects of vitamins E and C on age-related cataract were studied in a randomized, double-masked, placebo-controlled trial

(RCT) in a large population of male physicians (Christen et al. 2010). This study also included longitudinal data regarding influence of treatment with vitamins E and C on cataract incidence and cataract extraction. Treatment with vitamin E showed no significant influence on incidence of nuclear (HR, 0.99; 95% CI, 0.88–1.11), cortical (HR, 0.96; 95% CI 0.80–1.15) and posterior subcapsular (HR, 0.95; 95% CI 0.77–1.18) cataract and cataract extraction. There were no apparent benefit of vitamin E at any point during the trial and no significant effects of vitamin C on the incidence of nuclear (HR, 1.01; 95% CI, 0.89–1.14), cortical (HR, 1.10; 95% CI 0.92–1.31) or posterior subcapsular (HR, 0.94; 95% CI 0.76–1.17) cataract and cataract extraction. Overall, results of this RCT from a large population of middle-aged and older, generally well-nourished men exclude any large effect of long-term dietary supplementation with vitamins E and C on diagnosed cataract extraction. AREDS, a double-masked clinical trial, showed no statistically significant effect of the antioxidant formulation on the development or progression of age-related lens opacities (OR = 0.97, p = 0.55), as well as no statistically significant effect of treatment in reducing the risk of progression for any of the three lens opacity types or for cataract surgery (AREDS 2001). The Roche European American Cataract Trial (REACT) demonstrated a small but statistically significant deceleration of cataract progression because of the antioxidant micronutrients, vitamins C and E and the carotenoids (Schalch & Chylack 2003). It was noted that the techniques for following the course of a cataract in the REACT study were more sensitive to subtle changes than those used in the AREDS; furthermore, the REACT study intervention started earlier in the disease process, with higher doses of vitamins C and E and beta-carotene (Schalch & Chylack 2003). The REACT results support the early complementation of a diversified diet with supplements containing vitamins C and E and beta-carotene as well as other carotenoids as a preventive measure as well as during the early stages of cataract.

The information on nonsteroidal anti-inflammatory drugs (NSAID) and cataract risk is conflicting. Earlier studies suggest preventive effect of NSAIDs or aspirin on prevalence of cataract and cataract surgery (van Heyningen & Harding 1986; Harding & van Heyningen 1988; Klein et al. 2001), whereas others do not indicate any association (Chew et al. 1992; Hankinson et al. 1993). Most recent analysis of data from the AREDS reports the association between NSAID intake and increased risk of cataract surgery and no influence on prevalence of three major types of cataract (Chang et al. 2011). The effect of NSAID should be further studied in order to clarify its effect on the risk of cataract.

In vitro *studies for cataract prevention*

In vitro studies showed that tempol is an effective radioprotective agent (Sasaki et al. 1998). It also has a capability of inhibiting many of the processes implicated in generating the oxidative stress thought to be central to cataractogenesis. It is cell permeable and has been shown to penetrate the blood/brain and blood/aqueous barriers. A reduced form of tempol (tempol-H) has been found to have antioxidant effects on cells exposed to H_2O_2. The study on rat lenses supported the hypnosis that tempol-H protects the lenses from loss of transparency and from deterioration of crucial biochemical parameters including glutathione concentration and membrane transport capacity (Zigler et al. 2003).

A study of possible inhibition of oxidative stress and cataract formation by caffeine in mice with selenite-induced cataracts (Varma et al. 2010) showed that lenses of the pups isolated from the caffeine-untreated group developed highly advanced opacities by day 20, whereas in the group treated with caffeine, cataractogenesis was highly attenuated in a majority of the lenses. Cataract development was significantly inhibited in the majority of pups treated with caffeine. No advanced cataract developed at least in the majority (64%) of this group. The effectiveness of caffeine was related to its ability to prevent oxidative stress to the tissue and consequent maintenance of tissue metabolism. Current observation showed that caffeine could have a generalized anti-cataractogenic effect when used pharmacologically. This effect can be achieved by its topical application, which avoids potential systemic side-effects. There are no clinical trials in humans that investigated the association between caffeine intake and risk of cataract; therefore, further randomized control studies with application of appropriate cataract identification techniques such as photography of the anterior eye segment according to Scheimpflug's principle (Wegener & Laser-Junga 2009) are required to investigate potential preventive effects of caffeine in humans.

Photography of the Anterior Eye Segment According to Scheimpflug's Principle for RCTs

During ageing, the layers of the lens become more pronounced, so that light scattering does not increase homogeneously but specific layers scatter more light than others. As a result, there are typical lens light scattering profiles for every decade of human life expectancy. Further increase in light scattering in the lens leads to cataract development. Scheimpflug photography and densitometric image analysis are very precise techniques for light scattering measurement and biometry in the anterior segment of the eye. They provide reproducible data on the characteristics of the anterior eye segment in clinical and experimental studies, and the set of data obtained allows discrimination of light scattering changes because of ageing. Major epidemiological studies dealing with ocular pathologies in the anterior eye segment use either simple cataract classifications systems (LOCS III) or the Scheimpflug technique (Leibowitz et al. 1980; Mitchell et al. 1997; Arnarsson et al. 2002). Scheimpflug photography is more objective and less dependent on the skills of the person performing the examination. Scheimpflug photography is more precise and objective than LOCS III or other classification systems because it relies on the densitometric features of cataract development rather than morphological features. Another field of its application is the monitoring of therapeutic (side-) effects; therefore, this method should be used as a preferred technique for cataract diagnosis and follow-up procedure for RCT on cataract prevention. A detailed overview of photography of the anterior eye segment according to Scheimpflug's principle was published by Wegener & Laser-Junga (2009).

Cataract Surgery and Socio-Economic Impact

Cataract surgery

Cataract substantially decreases patients' quality of life because of a significant decrease in VA (Heijl & Leske 2007). Surgery to remove the opacified lens is considered to be the only appropriate treatment for cataract (Baltussen et al. 2004). Other methods such as medications or diet have not been shown to stop cataract progression (Chang 2005). As cataract has a high impact on quality of life of patients, there were a number of attempts to introduce qualitative measures of assessment in patients awaiting cataract surgery in order to identify patients with potentially better prospective surgery outcomes. During the Pyhajarvi Cataract Study II, it was proposed to formulate selection criteria for cataract surgery that will lead to the best possible outcomes (Kuoppala et al. 2010). In addition to objective signs such as the presence of VA decrease and the opacification of the lens, the authors of this study proposed to add two global questions: one on the subjective view on disability and one on a more neutral view on visual function (Kuoppala et al. 2010). Another study at the Flinders Medical Centre, Adelaide, South Australia, evaluated the Impact of Cataract Surgery (ICS) questionnaire using Rasch analysis and concluded that in its present form, it is unsuitable for visual disability assessment in patients before cataract surgery (Gothwal et al. 2011).

There are two types of surgical intervention that can be used to treat cataract. Intracapsular cataract extraction is a technique where the whole lens is removed from the eye, and special eyeglasses are necessary after the operation to restore vision. During extracapsular cataract extraction, the lens and the front portion of the capsule are removed and then replaced by an artificial lens (Baltussen et al. 2004).

Cost-effectiveness analysis of cataract surgery in Europe

Cataract surgery is estimated to be the most common operative procedure performed in developed countries because of the growing volume of outpatient surgeries (OECD 2005). It was estimated that extra-capsular surgery used with 95% coverage of the population would avert more than 3.5 millions disability-adjusted life years (DALY) per year globally (Baltussen et al. 2004). A recent Finnish study estimated that cataract surgery costs €5128 per quality-adjusted life year (QALY) gained in patients with both eyes operated (Rasanen et al. 2006). The number of cataract surgeries performed in European countries varies significantly, ranging from 265 per 100 000 people in Portugal to almost 1400 per 100 000 in Belgium in 2003 (Fattore & Torbica 2008). This variation can be probably explained by the differences between demand side (older population) and supply side (capacities to perform cataract surgery) across the countries. One of the most recent studies of the cost of cataract surgery in nine countries, including 43 providers, showed that the average length of stay at the hospital ranged from 0.5 days in the Netherlands and England to 2.9 days in Germany. On average, 90% of interventions used soft lenses. Each patient required approximately 199 min of direct care by healthcare professionals, ranging from 130 min in England and Germany to 321 min in the Netherlands. The mean total cost of the operation per patient was €714 (SD = €57) and ranged from €437 in Denmark to €1087 in Italy. The mean cost of the lens was €157 (SD = €57), ranging from €135 in England to €217 in Spain. The variation in lens cost was quite modest between countries. The cost of direct healthcare labour ranged from €82 in Hungary to €406 in France, and overheads ranged from €20 in Hungary to €362 in Italy (Fattore & Torbica 2008). In other studies, the average cost of cataract surgery was €1267 per eye operated in Finland (Rasanen et al. 2006), €760 in Sweden (Kobelt et al. 2002) and US$2525 in the United States (Busbee et al. 2002).

Determinants of the cost of cataract surgery between European countries

The explanatory regression model in the study by Fattore and Torbica showed that the type of technology used (soft lenses), the amount of labour time and the length of stay were positively associated with total costs (Fattore & Torbica 2008). Each day of hospitalization increased the total costs by 62%. Using soft lenses rather than rigid ones for all patients was associated with an increase in total costs by 56%. Each additional hour of labour time was associated with a 10% increase. Therefore, performing the intervention in an outpatient hospital setting was associated with a 60% reduction in the total cost (Fattore & Torbica 2008).

The results of a global and regional cost-effectiveness analysis of cataract surgery showed that extra-capsular cataract surgery dominates intracapsular cataract surgery and is considered therefore to be the most cost-effective intervention for cataract control according to the Commission on Macroeconomics and Health (Health WCoMa 2001).

Discussion

The overall prevalence of cataract was higher in Germany and Italy. It was shown to increase with age in 2/3 of cases being diagnosed at an age over 70 years. Sex-specific cataract prevalence was higher in women than in men, although not all of the reviewed studies were consistent in this aspect. Sex-specific cataract prevalence in a Spanish study was higher in men over 64 years of age than in women at the same age (Navarro Esteban et al. 2007), and a case–control study from Athens, Greece, found only borderline significance of female sex to the risk of cortical cataract (Theodoropoulou et al. 2011). Several European epidemiological studies showed that former and current smoking, a history of cardiovascular disease, family history of ophthalmic disease, and higher exposure to sunlight at the beach or at work lead to increased risk of cataract, whereas only one study showed an association of increased cataract risk with diabetes duration of 10 years or longer, or with asthma and chronic bronchitis. Importantly, this literature review showed that chlorpromazine, corticosteroids and multivitamin/mineral formulation (PSC only) intake increases the cataract risk depending on dose, treatment application and duration and therefore should be taken into account together with patients' morbidities and lifestyle factors, when prescribing medications and testing new drugs.

The only effective treatment for cataract at the moment is surgical intervention. The healthcare costs for cataract surgery varied significantly between European countries, from €318 in Hungary to €1267 in Finland. Total costs of cataract surgery were positively associated with the type of technology used, the amount of labour time, and the length of stay. Performing the intervention in an outpatient hospital setting was associated with a 60% reduction in the total cost.

This review was mostly focused on the Caucasian population and therefore does not extensively discuss ethnic differences in prevalence and incidence of cataract. Furthermore, a comparison of prevalence and incidence of cataract between different countries in Europe should be made with caution, because of different diagnostic criteria or different age group definitions used. Specifically, for measuring the presence of cataracts, the studies utilized different classification systems such as the Lens Opacity Classification System II in Casteldaccia eye study (Giuffre et al. 1994), and simplified cataract grading system of the WHO cataract group was used in study from Cuenca, Spain (Navarro Esteban et al. 2007). Overall, reviewed studies used three types of measurements for cataract: the presence of VA deficit, the opacification of the lens and its combination. Cataract incidence is often hard to estimate, as cataract onset is not always possible to define. Nevertheless, strict inclusion criteria were used to increase comparability between reviewed studies. We have tried to clarify where differences remain.

Previous literature reviews summarized the impact of cataract on visual impairment and blindness (Pascolini et al. 2004; Resnikoff et al. 2004; Pascolini & Mariotti 2011). Data on prevalence and incidence were not presented, and they failed to make a comparison between different countries in Europe. Studies on cataract surgery and its costs in Europe (Busbee et al. 2002; Baltussen et al. 2004; Rasanen et al. 2006) did not contain a review of epidemiological data and risk factors, whereas studies on risk factors (Delcourt et al. 2000a,b; OECD 2005) did not properly evaluate the socio-economic importance of cataract. The latest systematic review on cataract prevalence was published by Acosta et al. 2006 and reviewed ten epidemiological studies, only three of which were performed in Europe. The systematic literature review mostly focused on the prevalence of cataract and its correlation with age and sex, as well as on the comparison of clinical definitions of cataract used in different studies (Acosta et al. 2006). Despite the overall high importance of this review, many important aspects of cataract epidemiology have not been discussed.

Our review of experimental and *in vivo* studies showed that cataract is a result of oxidative stress induced by light penetrating into the intraocular space and consequent photochemical reactions. A number of reviewed studies proposed that this process can be inhibited by many nutritional and metabolic oxyradical scavengers, such as ascorbate, vitamin E, pyruvate, caffeine, NSAID and tempol. These associations were extensively investigated in rat and mouse lens organ culture studies. *In vivo* studies on the possible prevention of oxidative stress and cataract formation have been conducted by administering pyruvate and caffeine orally and by their topical application using diabetic and galactosemic animal models. Photosensitized damage to lens caused by exposure to visible light and UVA has been found to be significantly prevented by ascorbate and pyruvate. Caffeine has been found be effective against UVA and UVB, whereas pyruvate was show to be effective in prevention of cataract induced by diabetes and galactosemia. Tempol-H, with its strong antioxidant activity, has been shown to be a promising candidate for development as an anti-cataract agent (Zigler et al. 2003). Results of our literature review are in agreement with the recent overview of experimental studies on cataract aetiology and cataract prevention undertaken by Varma et al. (2011).

This review presented a comprehensive overview of specific and general cataract risk factors as well as an update on most recent *in vivo*, experimental studies and randomized control trials directed at investigating pharmacological methods of cataract prevention. Overall, this systematic review showed that despite the high effectiveness of cataract surgery for cataract treatment, it still remains a suboptimal alternative because of high costs, potential side-effects and increase in cataract incidence because of population ageing and growth. Our literature overview showed that there are a number of comprehensive *in vivo* and *in vitro* experimental studies on cataract prevention, but only few RCTs to prove similar effects on humans were undertaken. No RCT used adequate technique for early cataract identification, which makes results unreliable. More RCTs using adequate early cataract detection methodology such as photography of the anterior eye segment according to Scheimpflug's principle are required.

The present meta-analysis presented a comprehensive, concise and up-to-date overview of the important questions related to cataract such as general and type-specific cataract risk factors, epidemiology of cataract, cataract treatment and its socio-economic importance. Furthermore, we present an overview of *in vivo* and *in vitro* experimental studies and RCTs on cataract prevention, as well as a short overview of sensitive techniques for cataract identification. Its authors hope that the results of this literature review will lead to increased awareness in medical doctors, researchers and the general population about cataract risk factors and will lead to the development of effective cataract preventive strategies.

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