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Iris color and associated pathological ocular complications: a review of epidemiologic studies

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Abstract

• AIM: To elucidate the associations of iris color with major eye diseases.

• METHODS: A systematic search on Medline with coverage up to August 2013 was conducted. Assessment of the quality of studies based on their levels of evidence was in accordance with the Centre for Evidence-Based Medicine, Oxford, United Kingdom.

• RESULTS: A relationship between darker iris color and an increased risk of age-related cataract has been reported from cross-sectional studies and prospective cohort studies. There was no consistent evidence supporting a major role of iris color in the development or progression of age-related macular degeneration. The association of iris color with ocular uveal melanoma has been confirmed by a meta-analysis of observational studies previously. The etiologic synergism between light iris color and environmental exposure such as UV the exposure of UV radiation was found. There were no studies evaluating the refractive associations with iris color but there may be a possible link between iris color and myopia.

• CONCLUSION: Darker iris color is associated with an increased risk of cataract and a reduced risk of ocular uveal melanoma. The association of iris color with age-related macular degeneration is not confirmed. Ophthalmologists should be aware that the risk of ocular disorders appears to vary by differences in iris color.

• KEYWORDS: iris color; eye diseases; epidemiology
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INTRODUCTION

The color of iris is an important physical characteristic of human beings [1]. It is mainly determined by melanocytes, which form the double-layer posterior pigment epithelium at the back of the iris and the content of melanin in the anterior border layer of the iris stroma. Another factor determining iris color is the spectral property of the extracellular matrix components. Iris color fully develops during infancy and does not change significantly during later lifetime. Although melanocytes isolated from irises of adults show the ability to form melanin, pigment production is not normally observed during later stages of organism development [2]. Epidemiological studies suggest that the human iris becomes lighter with increasing age, which may result from a change in the melanosome granule morphology, similar to what apparently occurs in human retinal pigment epithelial cells with aging[3].

Many diseases were driven by a gene-environment interaction pattern. For example, the skin color genes determine the color of skin while environmental factor such as excessive sun exposure would lead to people with white skin at greater risk of developing skin cancer than people with other skin colors [4]. Similarly, although iris color is mainly determined by genes, but environmental factors interactive with the iris color by filtering out different color or wavelength of lights. This might have impact on eye growth or control the amount of light entering the eye through the pupil, which has a range of effects on the eye and leads to various pathological complications. Clinically, a clear understanding of the relationship between iris color and associated pathological ocular complications provides valuable insights into the pathophysiology of these complications. From a public health perspective, this may also help to understand the racial/ethnic variations observed in many eye diseases. In this review, we summarized the evidences linking iris color to various eye diseases.

SUBJECTS AND METHODS

A systematic search on Medline with coverage up to August 2013 was conducted using the following keywords: iris color or eye color or iris pigmentation in various combinations

Table 1 Studies investigating the relationship between iris color and age-related cataract

Study			Definition of cataract	Summary of main findings	Level of evidence
Year	Design	Population			
2000	PB, C	3654 adults in the baseline examination of the blue mountain eye study	Lens photographs	Eyes with dark brown irises were more likely to have nuclear (adjusted odds ratio, 1.59; 95% confidence interval [CI], 1.03-2.28) or posterior subcapsular cataract (adjusted odds ratio, 2.50; 95% CI, 1.57-3.98) than eyes with lighter-colored irises.	II
2000	PB, P	2609 black participants of the barbados eye studies	Clinical examination	Compared with persons with lighter irises, the RR of developing new nuclear opacities at persons with darker irises was about 5 times greater (RR=4.9, 95% CI: 1.10, 22.00)	I
2001	PB, CC	4477 age 60 to 80y in the age-related eye disease study	Clinical examination	Moderate cortical opacities were associated with dark iris color (OR=3.13; 95% CI: 2.16, 4.54)	II
2002	PB, C	1045 persons aged 50y and older in Reykjavik, Iceland	Lens photographs	No correlation was found between cataract and iris color	II
2002	PB, P	2335 survivors from the Blue Mountain Eye Study (75.1%) after 5y	Lens photographs	Participants with dark brown iris color had an increased incidence of nuclear cataract (OR=1.8; 95% CI: 1.2, 2.8) and cataract surgery (OR=2.5; CI 1.4, 4.2) compared with participants with blue iris color	II

PB: Population-based; P: Prospective cohort; C: Cross-sectional; CC: Case-control; OR: Odds ratio; RR: Relative risk; 95% CI: 95 percent confidence interval.

with eye (8283), eye disease (4089), ocular (2109), cataract (428), lens opacity (434), glaucoma (733), myopia (184), macular degeneration (468) and retinopathy (1387). Following the reviewing of abstracts, the full text of relevant articles in English were extracted and reviewed. Relevant studies cited by all articles considered in this review were consequently followed up.

Assessment of the quality of studies based on their levels of evidence was in accordance with the Centre for Evidence-Based Medicine (CEBM), Oxford, United Kingdom (www. cebm.net). Studies with Level I evidence were high-quality prospective studies, in which all patients were enrolled at the same point in their disease, with at least 80% follow-up. Studies with Level II evidence were of a retrospective nature, or were prospective studies where patients enrolled at different stages of their disease, with less than 80% follow-up. Case-control studies provided a quality of evidence equivalent to Level III. Case series and poor quality cohort and case-control studies provided Level IV evidence, and studies based on expert opinion without explicit critical appraisal, physiology, bench research or "first principles" provided Level V evidence.

RESULTS

Age-related Cataract Age-related cataract is the leading cause of blindness in the world[5-9]. Due to the world's ageing population and longer life expectancies, visual impairment due to cataract is increasing [10,11]. The consistent risk factors of cataract include diabetes, smoking and ultraviolet (UV) exposure [12,13]. Epidemiologic studies, especially population-based, have investigated the relationship between iris color and age-related cataract (Table 1). In the Blue Mountain Eye study of whites aged over 49y, baseline cross-sectional analysis revealed that eyes with dark brown irises were more likely to have nuclear [odds ratio (OR), 1.59; 95% confidence interval (CI), 1.03-2.28] or posterior subcapsular cataract (OR=2.50; 95% CI: 1.57-3.98) than eyes with lighter-colored irises [14]. In 5-years follow-up report, participants with dark brown iris color had an increased incidence of nuclear cataract (OR=1.8, 95% CI: 1.2-2.8) compared with participants with blue iris color [15]. In the Barbados Eye Study, the 4y incidence of nuclear opacities increased greatly darker iris color [relative risk (RR)=4.9][16]. In the age-related eye disease study, darker iris color was associated with cortical cataract (OR=3.85) and mild nuclear cataract (OR=1.38)[17]. No correlation was found between cataract and iris color in 1045 persons aged 50y and older in Reykjavik, Iceland[18].

The biological mechanism behind the observed association has not been fully elucidated and could be explained either genetically or environmentally. From an environmental perspective, it is possible that heat transference from iris to lens can accelerate the senescence of the crystalline lens by increasing the rate of molecular degradation due to disruption of hydrogen and covalent bonds [19]. Raising the temperature of the lens also lowers the threshold for photochemical effects and other types of radiation-related damages[19]. The iris pigment melanin absorbs photon energy across a wide range. Therefore, higher levels of melanin are related to higher temperature in the iris and associated tissues. Brown eyes generally contain more melanin than blue eyes [20]. Animal models have shown that rats with pigmented irises are more susceptible to the induction of cataract by infrared (lens opacities originally developing directly under the pigmented iris) compared to non-pigmented rats [21,22]. Thus, greater ocular pigmentation may be causally associated with more rapid aging of the crystalline lens. The heat hypothesis, however, is supported largely by experimental data on animal models examining acute effects. Moreover, under certain conditions (*e.g.* thermal-induced cataract in welders), increases in lens temperature may be due to heat transference from corneal rather than iris tissues [23]. From an genetic perspective, iris color is a classic Mendelian trait determined by a set of major genes located on chromosome 19[24]. Cataract may also

Table 2 Studies investigating the relationship between iris color and age-related macular degeneration

Study			Definition of AMD	Summary of main findings	Level of evidence
Year	Design	Population			
1985	CB, CC	650 white patients with senile macular degeneration and a control group of 363 patients from New England states and Florida	Retinal photography	494 patients with senile macular degeneration (76%) had light-colored irides compared with 145 of the controls (40%)	III
2005	PB, P	946 volunteers aged between 60 and 80y living in Copenhagen were examined at baseline. 359 subjects were re-examined 14y later	Retinal photography	Brown iris color did not have significant effect on AMD (OR=1.1; 95% CI: 0.6, 2.0)	II
2000	CB, C	306 sequential patients 60y of age or older from retina clinics	Retinal photography	In white patients, AMD was significantly more prevalent in individuals with blue or hazel irides than in those with brown irides (χ^2=15.04, P=0.02).	IV
2010	PB, C	6357 self-identified Latinos aged 40y and older	Retinal photography	Lighter-colored irises were associated with GA (OR=5.0; 95% CI, 1.0, 25.3)	II
2003	PB, P	171 participants aged between 52 and 93y who were identified as having early AMD features at their baseline examination (1992–1995) were followed for an average of 6.8y (until 2001)	Retinal photography	Participants with light iris colour had two-fold the risk of AMD progression of those with dark or intermediate iris colours, although the age-adjusted and multivariate-adjusted associations were not significant (both P=0.13).	II
1990	PB, C	1000 Danes 60-80y of age	Clinical examination	No significant differences in prevalence rates of AMD were found between dark and light ocular pigmented Danes	II
2006	CB, CC	446 cases with end stage AMD were compared with 283 spouse controls.	Retinal photography	No significant association between AMD and iris color or change in iris color was demonstrated.	III
1998	CB, CC	1844 controls were compared with 1844 patients with AMD aged 50–85y	Clinical examination	Lighter-colored irises were associated with increase OR of AMD (OR=1.22; 95% CI, 1.05, 1.42)	III
1983	CB, CC	228 cases and 237 controls matched by age and sex	Retinal photography	Statistically significant associations were demonstrated between senile macular degeneration and blue or medium pigmented eyes (OR=3.5)	III
2003	PB, P	A population of 4926 adults (range, 43–86y of age at baseline) living in Beaver Dam, Wisconsin, was studied at baseline (1988–1990); of these, 2764 subjects participated in 10y follow-up examinations	Retinal photography	People with brown eyes were significantly more likely to develop soft indistinct drusen (RR=1.53; 95% CI, 1.19-1.97) than were people with blue eyes. However, people with brown eyes were significantly less likely to develop retinal pigment epithelial depigmentation (RR=0.58; 95% CI, 0.41-0.82) than were people with blue eyes.	I
1998	PB, P	3684 adults living in Beaver Dam were studied baseline and 5y later	Retinal photography	There was no relationship between iris color and incident or progression of AMD	I
2001	PB, C	14,752 participants with gradable photographs from the Beaver Dam eye study (n=4756), Rotterdam study (n=6411), and blue mountains eye study (n=3585)	Retinal photography	There was no relationship between iris color and prevalence of AMD in the pooled analysis	II
2004	PB, P	9523 adults (age range, 43-95y at baseline) living in Australia, the Netherlands, and the United States who participated in a baseline examination and a follow-up examination on average 5 or 6y later	Retinal photography	There was no relationship between iris color and incidence of AMD in the pooled analysis	I

PB: Population-based; P: Prospective cohort; C: Cross-sectional; CC: Case-control; CB: Clinic-based; OR: Odds ratio; RR: Relative risk; 95% CI: 95 percent confidence interval.

be influenced by Mendelian inheritance and determined by a major set of genes, although the chromosomal locus for these genes has yet to be determined. The hypothesis that there is genetic linkage between these two traits (cataract and iris color) would predict that chromosome 19 is a possible locus for genes that predispose individuals to age-related cataract. No data are available to support the hypothesis of a genetic linkage between iris color and age-related cataract.

Age-related Macular Degeneration Age-related macular degeneration (AMD) is a major cause of irreversible vision loss that affects significant number of elderly people [25-27]. Smoking is a consistent risk factor of AMD in all epidemiological studies [28-31]. In addition, hypertension [32-35], body mass index (BMI) [36,37], refractive errors [26] and lipid levels [38] were all reported to be associated with AMD. The effect of iris color on AMD has been investigated in numerous epidemiological studies with inconsistent results (Table 2). An early case-control study of 228 cases and 237 controls matched by age and gender found that age-related macular degeneration was positively associated with blue or medium pigmented eyes (OR=3.5)[39]. Another case-control study of 650 cases and 363 controls found that 494 patients with senile macular degeneration (76%) had light-colored irises compared with 145 of the controls (40%) ($P<0.01$)[41]. Similar trends were reported elsewhere [41-44]. However, other studies have been relatively inconclusive or fail to demonstrate that iris color is a risk factor for AMD [45-52]. In population-based studies, the Beaver Dam Eye Study (BDES) found non-significant associations [47] between iris color and incidence and progression of AMD in the 5-year follow-up but there was significant association in the 10-year follow-up report[53]. Low incidence of AMD and short period of follow-up in the 5y follow-up of BDES may lead to the inability to detect a significant relationship. The Visual Impairment Project (VIP) reported that individuals with light iris color had a strong tendency to greater progression of AMD[54]. There are few studies evaluating the changes in iris color associated with the risk of AMD. One study showed that an increased risk of AMD in those who reported having had light irises in youth and who reported have dark irises in youth that changed to a lighter color by adulthood compared with persons with darker iris that did not change [48]. The inconsistent findings were mainly be explained by methodological issues among different studies including disparities in study populations, sampling strategies, methods for iris color and AMD grading and statistical analyses. In the pooled analysis from the Beaver Dam Eye Study, Rotterdam Study and Blue Mountains Eye Study, iris color was not associated with either prevalent or incident AMD[38,55]. Despite the inconsistent findings, there are plausible hypotheses supporting iris color as a risk factor for AMD. Ocular pigmentation would alter the amount of light entering

or being absorbed in the eye, which may lead to differing amounts of oxidative damage to the retina. Darkly pigmented individuals may have had increased amount of melanin tissue in their eyes, which protected the retina from excessive sunlight exposure, reducing oxidative damage, and consequently lowering the risk of AMD [56]. It may also be plausible that ocular pigmentation would simply reflect underlying genotypes, which confer different risk of AMD[56-58].

Glaucoma Glaucoma is a group of diseases, which have a final common pathway of progressive nerve fiber layer thinning and concomitant ganglion cell loss. There are few studies investigating the associations of iris color with glaucoma. One hospital-based study on 1973 eyes of 1012 Caucasian subjects found no significant association of iris color with the risk for progression of glaucomatous visual field defects[59].

Uveal Melanoma Despite a rare disease, uveal melanoma of the eye is the most common primary intraocular malignancy in adults, with an age-standardized incidence rate from 2 to 8 per 1000 000 person-years in Europe [60]. Uveal melanoma is approximately 20 to 30 times more common in whites than in blacks and Asians [61]. Light iris color has been shown to be the most consistent risk factor for uveal melanoma. This review does not tend to list all the studies assessing the effect of iris color on uveal melanoma as this has been done in a previous meta-analysis paper[62]. In the meta-analysis, all but 2 published studies showed an association between light iris color and increased risks of uveal melanoma. However, it is of great interest to understand the etiologic synergism between light iris color and environmental exposure such as UV the exposure of UV radiation. A case-control study in Germany found that people with light iris color may have an especially increased risk for uveal melanoma if they are exposed to UV radiation[63]. This finding of joint effects between light iris color and UV radiation exposure support the hypothesis of gene-environmental interaction in the causation of uveal melanoma. This interaction effect has also been supported by some other indirect evidences. For example, Guenel *et al* [64], who found an increased uveal melanoma risk for people with blue or grey iris color, suggested that the increased risk for these people may be due to the smaller amount of melanin in choroidal melanocytes, which may mean less protection of the nuclei of choroidal melanocytes against solar radiation. Menon *et al* [20] found that retinal pigment epithelium from brown eyes had more melanin than corresponding tissues from blue eyes, which may protect against the development of uveal melanoma. The different iris colors are characterized by differences in the density of pigment in the iris, resulting in a greater light transmission to the uvea. Although blue eyes have similar numbers of melanocytes as dark-colored eyes, they contain less pigment and fewer melanosomes. Green-hazel eyes are the product of moderate pigment levels, melanin intensity, and melanosome number, and brown eyes are the result of high melanin levels and high melanosomal particle numbers[65,66]. Wakamatsu *et al* [67] studied the association between the quantity of eumelanin and pheomelanin in cultured human iris and choroidal melanocytes in 61 patients. They found that the quantity and type of melanin in iris and choroidal melanocytes was similar in the same eye color group. Furthermore, the amount of eumelanin, the ratio of eumelanin/pheomelanin, and total melanin were greater among dark-colored irides than light-colored ones. They concluded that melanin in light-colored irises rather than dark-colored irises, is expected to behave as pheomelanin, a pro-oxidant. De Leeuw *et al* [68] showed that cultured skin melanocytes with a high level of melanin have a better survival after ultraviolet B light radiation than melanocytes with a low level of melanin, indicating synergistic effects between a low concentration of melanin and ultraviolet B light radiation. The best survival was found in populations with high total melanin and low pheomelanin content.

Myopia Myopia is a significant global public health concern with a rapid increase in prevalence in recent decades worldwide [69-71]. It is estimated that globally 153 million people over 5y of age are visually impaired as a result of uncorrected myopia and other refractive errors, and of these 8 million are blind [72]. At current stage, no studies have evaluated if iris is an independent risk factor for myopia. Meng hypothesized that there may be possible mechanisms linking iris color to myopia [73]. Myopia is a complex multi-factorial trait driven by both genetic and environmental factors [70,74-76]. Myopia was related with decreased use of sunglasses [77]. Sunglasses are analogous to artificial dark iris and would not only reduce the amount of the light entering eyes but also decrease high-energy visible light such as blue light which is reflected back by blue iris but possibly penetrates in other color iris. Therefore, to elucidate the association between iris color and myopia would have important implications for myopia prevention.

DISCUSSION

This review demonstrates that many existing studies investigating a possible effect of iris color on different eye diseases have significant limitations, and interpretation of results should be within the context of these limitations. These limitations also highlight areas of future research.

First, there is no widely recognized classification system for iris color. Different observers may categorize a person's iris color differently. Therefore, establishing a precise and objective grading system may have important implications for further research and treatment of some eye diseases and ocular characteristics. In addition, current studies mainly focused eyes of the whites while other ethnic groups such as

Asians' iris color are difficult to grade as it is quite different from the whites. In this regard, a computer-assisted grading software may be helpful to grade the iris color in all ethnic groups automatically and objectively.

Moreover, most of the existing assessing iris color and ocular complication are cross-sectional or clinic-based. Therefore, currently available evidence is insufficient to warrant the conduct of clinical trials which purely focus on iris color and its effects on the eye. Well-designed population-based cohort studies are ideal to address this research question. Furthermore, conducting randomized trials of changing the iris color would not be feasible, due to ethical and practical difficulties.

Finally, if iris color is related to other ocular conditions and how it could affect visual functioning remains unknown. For example, iris color was reported to affect intra ocular pressure, but whether it is associated with glaucoma remains unclear [78]. If a true relationship between iris color and various ocular complications exists, it should affect visual functioning and health-related quality of life, which needs to be investigated in the future.

In summary, epidemiological data suggest the following. First, dark iris color is consistently associated with a higher risk of age-related cataract. Second, the association between iris color and AMD is inconsistent among different studies. Third, there may be a synergistic effect between light iris color and UV radiation exposure on the risk of ocular uveal melanoma. Fourth, iris color may be associated with myopia but there is no evidence at current stage. Therefore, if opportunity exists among cohort studies investigating many other ocular conditions, researchers are encouraged to provide further evidence about the possible causal relationship between iris color and myopia or AMD. In addition, considering that the current studies assessing the relationship of iris color with associated ocular complications were primarily based on non-Asians, further studies on Asians are warranted. The iris color in Asians is completely different from that in non-Asians and there is a lack of standardized grading scheme of iris color in Asians eye. Thus, a standardized grading system of iris color in Asians should be established to facilitate the comparison of data from different racial groups.

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