The association between cigarette smoking and ocular diseases

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Objective. To review the effect of smoking on common ocular disorders.
Data sources. *Medline* literature search, 1966 to 1999.
Study selection. The following key words were used: smoking; Graves' disease, age-related macular degeneration; glaucoma; cataract.
Data extraction. Epidemiological and experimental studies were reviewed.
Data synthesis. Cigarette smoking is an important risk factor for cardiovascular, respiratory, and malignant diseases. There is also a strong association between smoking and a number of common eye diseases, which include Graves' ophthalmopathy, age-related macular degeneration, glaucoma, and cataract. Despite the multifactorial aetiology of these ocular syndromes, smoking is an independent risk factor that has dose-response effects. It causes morphological and functional changes to the lens and retina due to its atherosclerotic and thrombotic effects on the ocular capillaries. Smoking also enhances the generation of free radicals and decreases the levels of antioxidants in the blood circulation, aqueous humour, and ocular tissue. Thus, the eyes are more at risk of having free-radical and oxidation attacks in smokers.
Conclusion. Smoking, if continued, may perpetuate further ocular damage and lead to permanent blindness. Cessation of smoking and avoidance of passive smoking is advised to minimise the harmful effects of smoking on the eyes.

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Key words: Eye diseases/epidemiology; Eye diseases/prevention & control; Risk factors; Smoking/adverse effects

Introduction

Cigarette or tobacco smoking is a well-recognised major risk factor for a wide range of diseases, such as cardiovascular, respiratory, and malignant diseases, in both men and women.[1] A study has shown that men who never smoke have a 78% chance of reaching an age of 73 years, while this chance is reduced to 42% in those who start smoking by the age of 20 years and never stop.[2] The association between cigarette smoking and dyslipidaemia is also well established.[3] Smoking causes an increase in the levels of total cholesterol, low-density lipoprotein (LDL)–cholesterol and triglycerides, but a decrease in the level of high-density lipoprotein (HDL)–cholesterol in the blood circulation. The dyslipidaemic, atherosclerotic, and thrombotic effects of smoking greatly increase the incidence of cardiovascular diseases, and there is an apparent dose-response effect from smoking on cardiovascular mortality.[4-6] Smoking is also an independent risk factor for stroke in a dose-response manner.[7] The risk of stroke is decreased with cessation of cigarette smoking, as is the risk for myocardial infarction.[8,9] While most cancers are the result of interactive effects of genetic and environmental factors, smoking is a direct cause of lung cancer and is associated with cancers of the bladder, breast, and colon.[1,10]

Smoking also has adverse ocular effects. It has been shown to be a risk factor for many common and severe eye diseases, such as Graves' ophthalmopathy, age-related macular degeneration, glaucoma, and cataract. Many of these diseases lead to irreversible blindness. There is also evidence for a dose-response effect of smoking on eye morbidity.[11] Various hypotheses have been advanced to explain this causal relationship; some

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of these hypotheses are substantiated with solid evidence, while others require further investigation. The multifactorial nature of common eye diseases poses difficulties when researchers design studies to elucidate the effect of a single factor. Large sample sizes are required to minimise the effects of factors that are unaccounted for. Discrepancies in the results of various studies are hard to avoid because of the complexity of the aetiologies of these diseases, which involve many interactive genetic and external factors. This article reviews the evidence and controversies involving the link between smoking and eye diseases, and attempts to explore the pathogenetic mechanisms.

Graves' ophthalmopathy

As with most autoimmune diseases, Graves' disease (exophthalmic goitre) is multifactorial in origin. While the exact aetiology remains unknown, interactive genetic and environmental factors are involved in the pathogenetic mechanism.[12] A large proportion of patients with Graves' disease have subclinical eye disorders.[13] Smoking has been extensively investigated in relation to Graves' ophthalmopathy. Increased serum levels of thyroxine and thyroid-stimulating hormone (TSH) receptor autoantibodies in smokers with Graves' ophthalmopathy are not consistently reported. Chronic smokers, however, tend to have mildly lower TSH levels and elevated thyroglobulin levels.[14,15] There are also more goitres in people who smoke.[16]

Epidemiological studies provide evidence for the adverse effects of cigarette smoking on Graves' ophthalmopathy. Hagg and Asplund[17] were among the first to describe an association between smoking and Graves' disease. This relationship has since been confirmed by other studies.[16,18] More smokers than non-smokers develop Graves' ophthalmopathy.[19] The amount of smoking also correlates with the severity of the ocular disorder, and patients with Graves' disease who smoke more cigarettes per day have more serious eye disease. While smoking is an independent risk factor for Graves' disease, its association with smoking in Graves' ophthalmopathy is even stronger and statistically more significant.[14,15] A case-control study involving 400 subjects showed that smoking significantly increased the risk for Graves' ophthalmopathy with hyperthyroidism, after adjusting for confounders such as sex and age (odds ratio [OR]=6.5; 95% confidence interval [CI], 3.8-11.2).[20] The risk of the development of Graves' hyperthyroidism alone was also increased (OR=1.8; 95% CI, 1.1-2.9), but no such associations were found in sporadic non-toxic goitre, primary autoimmune hypothyroidism, or toxic nodular goitre. Smokers with active, moderate to severe Graves' ophthalmopathy had less favourable therapeutic outcome from orbital radiotherapy than non-smokers.[21,22] Although the risk imposed by cigarette smoking on Graves' ophthalmopathy is panethnic, there is genetic predisposition to the development of the disease. In one study, European smokers were found to have a much higher chance of developing Graves' ophthalmopathy than Asian smokers, who were mainly subjects of Indian and Pakistani origin (OR=6.4; 95% CI, 1.78-22.7).[23]

Many hypotheses have been proposed to explain the association between smoking and Graves' disease. One hypothesis is that smoking may cause disturbances in the immune system. Smokers have a lower T-suppressor lymphocyte activity and a lower level of immunosupression than non-smokers.[24,25] It has been postulated that smoking may affect immune surveillance, thus resulting in decreased control of naturally occurring clones of T-helper cells that are directed against thyroidal or orbital antigens. This lowered control is an important factor in the pathogenesis of autoimmune thyroid disorder.[26] The immunological effect of smoking might also be medicated by the increased release of a thyroid auto-antigen that cross-reacts with eye muscle, thereby affecting the elasticity of muscle fibre.[27] A piece of indirect evidence that smoking affects the immune system was the induction of autoimmune thyroiditis in rats by 3-methylcholanthrene, which is an anthracene derivative found in cigarette smoke.[28]

Smoking also enhances the formation of superoxide radicals and decreases the formation of antioxidants. In cultures of fibroblasts from retro-ocular connective tissue obtained from patients with Graves' ophthalmopathy, cell proliferation was induced by superoxide in a dose-response pattern.[29] The proliferation of retro-ocular fibroblasts and secretion of glycosaminoglycans into the extracellular matrix cause orbital oedema. Such volume expansion is a feature of Graves' ophthalmopathy.[30,31] Contributing to the volume increase is interleukin 1 (IL-1), which has pro-inflammatory and fibrogenic effects. The naturally occurring IL-1 receptor antagonist inhibits the effects of IL-1, and the increase in the serum level of the antagonist is significantly less in patients with Graves' ophthalmopathy who show a much poorer response to orbital radiotherapy. Most of these patients have been found to be smokers.[32] It has also been found that antibodies to heat shock protein 72 are present in normal healthy individuals who smoke, as well as in patients with Graves' disease.[33]

Evidence from experimental and epidemiological studies support the association between smoking and Graves' ophthalmopathy. Cigarette smoking increases the risk of Graves' ophthalmopathy and adversely affects the clinical course and response to treatment.[22,34] Although the actual mechanism of the adverse effects is still unknown and perhaps more than one mechanism is involved, patients—particularly those at risk—should be recommended to give up smoking.

Age-related macular degeneration

Early age-related macular degeneration (ARMD) may be defined as the presence of either soft drusen or any type of drusen if associated with changes in retinal pigment epithelium or increase in retinal pigmentation in the macular area. It is a major cause of blindness in the West and the leading cause of severe visual loss in the elderly. The prevalence of advanced ARMD in most Caucasian populations is estimated to be 1.5%.[35] The incidence also increases with age. A recent study in Hong Kong showed that among 355 adults older than 40 years who were randomly recruited for visual examination, 19% had ARMD and 19% had both ARMD and cataract.[36] Blindness in ARMD is caused by the degeneration of the retinal pigment epithelium.[37] Secondary causes include damage to the photoreceptors. Age-related macular degeneration characteristically takes the form of localised degeneration and leads to death of the associated rods and cones, with (exudative ARMD) or without (non-exudative ARMD) the complications of vascular invasion. Although only 10% of ARMD patients have the exudative form of the disease, more than 85% of legal blindness attributable to ARMD is the result of this form of disease (American Academy of Ophthalmology, written communication, 1999). Risk factors that are attributed to ARMD include age, smoking, diet, sunlight exposure, and hypercholesterolaemia.[38]

The effects of cigarette smoking on the development of ARMD have been investigated by epidemiological, case-control, and surveillance studies. Patients with exudative ARMD are more likely to be smokers than non-smokers.[39] The Eye Disease Case-Control Study Group in the United States (US) examined environmental risk factors for advanced ARMD. The study involved 421 patients who had neovascular ARMD and who were older than 55 years, as well as 615 sex- and age-matched controls.[38] Current smokers (risk ratio [RR]=2.2; 95% CI, 1.4-3.5) and past smokers (RR=1.5; 95% CI, 1.2-2.1) had a statistically increased risk of ARMD compared with 'never smokers' after adjusting for other risk factors, including serum levels of carotenoids and cholesterol. Similar pan-ethnic results have also been obtained by the cross-sectional Beaver Dam Eye Study of subjects aged 43 to 86 years in the US[40] and a Japanese study on subjects aged 50 to 69 years.[41] Some smoking habits lead to more serious adverse effects than others. In Japan, smokers have been shown to have an increased risk for ARMD if their smoking involves deep inhalation, they smoke without a filter, they started smoking at an age younger than 20 years, and if they have smoked for more than 40 years.[39]

The effect of cigarette smoking on the risk of ARMD is dose-dependent. In a prospective study involving 21 157 male physicians in the US, current smokers of more than 20 cigarettes a day had a two- to three-fold increased risk of ARMD with visual loss.[42] The risk among former smokers also remained elevated several years after the cessation of smoking. Heavy smokers in the past, who had quit less than 20 years prior to the start of the study, had relative risk of ARMD with visual loss of 1.76 (95% CI, 1.23-2.53). Former past heavy smokers who had quit 20 years or more before the study had a mild but significantly (40%; P=0.07) increased risk of ARMD with visual loss (OR=1.40; 95% CI, 0.97-2.03). This statistically significant difference was obtained after adjusting for other risk factors such as age, diabetes, hypertension, obesity, and alcohol consumption. In a parallel study of 31 843 female nurses, the duration of smoking years was also found to affect risk.[43] According to these reports, cigarette smoking is an independent but avoidable risk factor for both dry and exudative types of ARMD.

In 162 ARMD patients and 175 controls, Hyman et al[44] found a statistically significant increased risk of ARMD in males (OR=2.6; 95% CI, 1.15-5.75) but not in females (OR=0.84; 95% CI, 0.48-1.47), thus suggesting a sex difference. However, the large confidence interval in the female study participants represented inconclusive results and indicated a type II error due to the small sample size. In a follow-up report of the Beaver Dam Eye Study, a dose-response effect, after controlling for age, sex, vitamin supplementation and beer consumption, was observed in men but not in women.[45] A subsequent prospective study[43] of 31 843 female nurses showed that women who currently smoked 25 or more cigarettes per day had a relative risk for ARMD of 2.4 (95% CI, 1.4-4.0) compared with women who never smoked. Former smokers of approximately[25] or more cigarettes daily also had a

two-fold increased risk (RR=2.0; 95% CI, 1.2-3.4). In these studies, the statistical significance of the results was obtained after adjusting for the use of postmenopausal oestrogen, which is a potential risk factor for the development of ARMD in women.

There are discrepancies among different reports regarding the effects of smoking on the non-exudative form of ARMD. In the cross-sectional Blue Mountains Eye Study[46] from Australia, which involved 3654 subjects, geographic atrophy or dry ARMD showed a significant increased risk of ARMD among current smokers when compared with the 'never smoked' individuals (OR=4.46; 95% CI, 2.20-9.30). Similar but more moderate results were obtained for neovascular (exudative) and late ARMD, with odds ratios being 3.20 and 1.75, respectively. On the contrary, the Rotterdam Study from the Netherlands showed no association between cigarette smoking and atrophic (non-exudative) ARMD.[11] However, this study involved a relatively small number of patients (n=36).

The degeneration of retinal pigment epithelium in AMD is believed to be a consequence of abnormal cellular metabolism due to defective intracellular degradation and clearance of biomolecules. This abnormal metabolism results in the accumulation of unwanted biochemical by-products within the epithelium. Various theories have been proposed to explain the causal relationship between cigarette smoking and ARMD.[39] Firstly, smoking may promote the development and progression of new subretinal vessels, which leads to the formation of a tubular capillary network from choriocapillaries. Choroidal neovascularisation is invasive to the retinal pigment epithelium and causes disciform macular degeneration.[47,48] Secondly, smoking may exert atherosclerotic and hypoxic damage to the choroidal vasculature. Smoking decreases the plasma level of HDL-cholesterol but increases total cholesterol and LDL-cholesterol levels, platelet adhesiveness, and the fibrinogen level. These effects promote hypoxia, ischaemia, and microinfarction in the macula.[49-51] Increased carboxyhaemoglobin concentrations reduce choroidal blood flow, further accelerate degenerative changes in the macula, and stimulate neovascular growth.[52,53] Thirdly, oxidants that are present in cigarette smoke or generated by the activation of phagocytic cells can increase oxidative stress in the retina.[21,54] The increased oxidative stress enhances the peroxidation of polyunsaturated fatty acids in photoreceptor outer segments, which is an early precipitating event in ARMD.[55] Fourthly, smoking reduces the plasma concentration of antioxidants and consequently decreases retinal levels of antioxidants.[56-59] Smoking also decreases carotenoid concentrations in the blood and retina.[60] The ability to accommodate oxidative stress and maintain retinal structures against free radicals formed during light exposure is thus adversely affected.

In general, there seems to be more positive than negative evidence to show that smoking is an independent risk factor for ARMD (the exudative form in particular) with a dose-response relationship. Discrepancies in results exist largely between prospective studies and retrospective cross-sectional studies.[11,42,53,61] Studies taking the latter approach reveal a less significant association between smoking and ARMD. In contrast, cross-sectional studies with large sample sizes tend to agree with prospective studies on a positive association in a dose-response manner.

Glaucoma

Glaucoma is an optic neuropathy associated with characteristic visual field changes for which high intra-ocular pressure is a major risk factor. Glaucoma is a common and serious ocular disorder in most populations. In particular, primary open-angle glaucoma is associated with an asymptomatic but irreversible loss of vision due to damage to the optic nerve.

There is a weak correlation between smoking and intra-ocular pressure.[49,62,63] A recent population-based study of 3752 non-glaucoma subjects aged 40 to 84 years in the West Indies has shown that smoking is associated with a slightly higher intra-ocular pressure ($P<0.05$); however, other risk factors such as hypertension, and diabetes have stronger associations ($P<0.01$).[64] Since the elevation of intra-ocular pressure is a major risk factor for open-angle glaucoma, cigarette smoking may be a secondary causative factor. A case-control study has shown that cigarette smokers are more prone to glaucoma than are non-smokers (OR=2.9; 95% CI, 1.3-6.6).[65] On the contrary, another population-based study of 4926 subjects has revealed no difference in the frequency of glaucoma, based on cigarette-smoking status.[40]

As in macular degeneration, there are strong putative environmental determinants for glaucoma, such as diet, alcohol consumption, and smoking. Cigarette smoking may be one of the environmental factors that affects the optic nerve and increases the risk of glaucoma. There is experimental data for a physiological basis of the association between smoking and glaucoma. A study of the dynamics of aqueous humour showed a 5-mm Hg rise in intra-ocular pressure immediately

after smoking.[66] Selective vasoconstriction might lead to a rise in the episcleral venous pressure, thereby impeding the outflow tract. There is a positive correlation between intra-ocular pressure and progressive glaucomatous damage in primary open-angle glaucoma.[67] Various anomalies of the anterior chamber of the eyes can increase the intra-ocular pressure. Environmental factors, such as hypertension, diabetes, age, family history, smoking, and alcohol consumption, account for about 10% of the variation in intra-ocular pressure.[67]

Smoking may be an avoidable risk factor for glaucoma, but the conflicting results obtained from different investigations of the effect of smoking on the intra-ocular pressure have not established a causal relationship between the two. More studies are required to confirm such a relationship, which are likely to be subject to interaction with other factors.

Cataract

Cataract refers to the opacification of the lens. Anatomically, there are nuclear, cortical, and posterior subcapsular types of cataract. Nuclear cataracts, usually seen in elderly patients, are caused by the exaggeration of the sclerosis of the nucleus. Because of the central location, vision is significantly affected. Cortical cataracts affect the peripheral cortical layers of the lens away from the visual axis. Posterior subcapsular cataracts affect the 'onion skin' of the lens at the posterior pole. They are related to metabolic disorders including hypoparathyroidism, diabetes mellitus, galactosaemia, and homocystinuria.

Cataract is the leading cause of blindness worldwide and accounts for visual loss in more than half of the 23 million people who have a best-corrected visual acuity of 3/60 or less.[68] With the growing elderly population in Hong Kong, cataract will present a serious health hazard in the future. While surgery is the only effective treatment option available, identifying risk factors may help to establish preventive measures.

The epidemiological relationship between smoking and cataracts has been well studied by case-controlled,[69,70] cross-sectional,[71-73] and prospective studies.[74-76] There is a dose-response relationship between the cumulative amount of smoking and the risk of nuclear cataract developing.[34,37,62,64] Heavy smokers are more at risk than other groups. However, the effects of smoking on non-nuclear opacity remain controversial. Some studies have shown positive results while others have been inconclusive.[58,62-64,77] A prospective 30-year study has shown that people who smoke 20 or more cigarettes per day at the time of their first eye examination have a substantially higher risk of developing nuclear opacity than non-smokers (OR=2.84; 95% CI, 1.46-5.51).[78] Those who smoke more than 20 cigarettes per day have an even higher risk than those smoking less than 20 (test for trend, $P<0.002$). A long duration of smoking poses a further threat. The risk for nuclear opacity has been shown to decrease in subjects who stop smoking for 10 years or more (OR=0.67; 95% CI, 0.49-0.92).[71] In the Blue Mountains Eye Study, questionnaires were used to obtain smoking history and lens photographs were taken to grade cortical, nuclear, and posterior subcapsular cataracts.[77] The results showed that among the 3654 participants, the smokers had a higher prevalence of both nuclear and posterior subcapsular cataracts.

Nuclear cataract is more strongly associated with pipe smoking (OR=3.1; 95% CI, 1.5-8.2) than it is with cigarette smoking (OR=1.5; 95% CI, 1.1-2.1).[58] This findings may be explained by the differences in smoking habits, rather than a genuine difference between pipe and cigarette smoking.[75] Pipe smokers are less likely to inhale than are cigarette smokers, and pipes probably produce more side-stream smoke.[79] It is possible that this excess smoke causes more harm to the lens, either by direct entry of the combustion and condensation products of tobacco into the eyes, or by continually raising the temperature of the lens.

The aetiology of cataracts is multifactorial and the mechanisms of cataract formation are complex.[80] Smoking is just one of many established or putative risk factors for cataracts, which also include advanced age, trauma, persistent intra-ocular inflammation, ultraviolet radiation, diabetes mellitus, hypoparathyroidism, prolonged corticosteroid administration, and high body mass index.[81,82] Smoking may indirectly impose additional oxidative stress on the lens by reducing the levels of nutrients with antioxidative capabilities, such as ascorbic acid and nicotinamide.[71,72,83] Furthermore, direct and structural lens injury may be caused by components in cigarette smoke[84] or its by-products, such as cadmium[85] or isocyanate.[86] In organ-cultured rat lenses, condensation products of wood smoke have been shown to accumulate in the lens and lead to morphological complications such as hyperplasia, hypertrophy, and the multilayering of epithelial cells.[87] Similar histopathological defects and elevated calcium concentrations have been detected in the lenses excised from rats that had been exposed to cigarette smoke for 2 hours daily for 60 days.[88] These studies provide direct evidence for

lens damage by in vivo exposure to cigarette smoke. Nevertheless, further intensive and large-scale investigation that is not affected by other factors is required to obtain objective evidence that smoking participates in cataract pathogenesis.

Conclusion

Experimental and circumstantial data support a causal relationship between smoking and some chronic eye diseases, principally Graves' ophthalmopathy, aged-related macular degeneration, glaucoma, and cataract. But there are also inconclusive results and conflicting evidence from different studies. Discrepancies in results may be due to various reasons. Firstly, the adverse effects of smoking may have been exaggerated or suppressed by other interactive susceptibility factors, both genetic and environmental. Secondly, the small sample sizes in some studies have led to statistically insignificant and therefore inconclusive findings. Thirdly, cross-sectional and case-control studies have been extensively used in assessing smoking as a risk factor. The nature of these studies means that the temporal relationship is difficult to assess. Fourthly, recall bias is a significant problem. Prospective studies with large sample sizes have eliminated some of these limitations, but in cohort studies, selection bias remains a problem to be addressed. Selection bias can arise owing to some of the severely harmful effects of smoking: those who are more susceptible to the adverse effects of smoking may die before the study is completed. Although the eye diseases discussed in this review have multifactorial aetiologies, it would be a good preventive measure to advise the cessation of smoking and avoidance of passive smoking.[89]

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