



Ocular Side-Effects of Tobacco Smoking: a literature review

Recent and past literature proves that cigarette smoking has become the most prevalent form of drug dependence and evidence of the serious damage to eye health is emerging. However, public awareness about smoking and ocular disease is sadly lacking.

Age-related macular degeneration

According to the largest study of the association of smoking and age-related macular degeneration (ARMD) in the British population, currently there are estimated to be approximately 200,000 people aged 75 years and above visually impaired due to ARMD in the United Kingdom¹ of whom approximately 28,000 may be attributable to smoking.² In the United Kingdom, ARMD is the most common cause of blind registration.³

Apart from West et al⁴ and Chan⁵ who did not find any association between tobacco smoking and ARMD, all major studies have shown a direct relationship to its development⁷ mostly the neovascular type and geographic atrophy.^{8,9} The *Macular Photocoagulation Study*¹⁰ found that 85% of patients with neovascular ARMD who smoked more than 10 cigarettes per day suffered a recurrence of neovascularisation; either contiguous with or independent of prior laser treatment, compared to 51% of



Mrs Nihal Kenawy,
Specialist Registrar,
Royal Liverpool
University Hospital,
Liverpool, UK.



Mr David Clark,
Consultant Ophthalmic
Surgeon,
Walton Hospital,
Aintree University Hospitals,
Liverpool, UK.



Dr Marcela Votruba,
MRC Clinical Scientist,
Hon. Consultant
Senior Lecturer,
School of Optometry
& Vision Sciences,
Cardiff University,
Cardiff, UK.

Correspondence:

Mrs Nihal Kenawy,
SPR Ophthalmology,
Royal Liverpool University Hospital,
Prescott Street,
Liverpool,
L7 8XP,
UK.
Email: nkenawy@yahoo.co.uk

non-smokers. Smith et al¹¹ in their report of the combined data from three major studies; the *Beaver Dam Eye Study*, the *Rotterdam Study*, and the *Blue Mountains Eye Study*, stated that apart from age, tobacco smoking was the only risk factor consistently associated with any form of ARMD.

Number-years of cigarette smoking and / or gender relationship to development of ARMD has also been investigated, Khan et al⁶ found a strong association between ARMD and pack years ($P=0.002$); with more than 40 pack years of smoking odds ratio (OR) was 2.75 (95% confidence interval [CI]: 1.22-6.20) compared with non-smok-

ers. They stated that stopping smoking was associated with reduced odds of ARMD, and the risk in those who had not smoked for over 20 years was comparable to non-smokers. This risk profile was similar for males and females. The same investigation revealed that passive smoking was associated with an increased risk of ARMD (OR: 1.87; 95% CI: 1.03-3.40). Hyman et al¹² found that cigarette smoking was significantly related to ARMD in men (relative risk [RR]: 2.6; CI: 1.15-5.75) but not in women (RR: 0.84; CI: 0.48-1.47). Seddon et al¹³ found that women smokers who smoked 25 or more cigarettes a day had a relative risk of 2.4 (CI: 1.40-4.00) com-

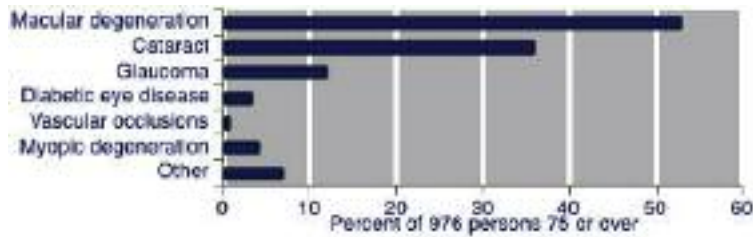


Figure 1: Cause of binocular vision impairment in 976 over-75s in UK general practice. (source: National Electronic Library For Health, August 2004).

pared to women who have never smoked. Past smokers of 25 or more cigarettes a day had almost the same relative risk (2.0) as current smokers. Smith et al.⁹ stated that compared with never smokers, ex-smokers (OR: 1.34; CI: 0.96-1.87) and current smokers (OR: 3.11; CI: 2.10-4.63) were more likely to have ARMD. The subsequent extension of those analyses by Seddon et al.¹⁴ found that current smokers had 1.9 fold increased risk (95% CI: 0.99-3.68; $P=0.06$) of ARMD while past smokers had about a 1.7-fold increased risk (95% CI: 1.2-2.6; $P=0.009$).

Different pathophysiological mechanisms were implicated in the pathogenesis of ARMD. One possible factor is the compromised choroidal blood flow (see section under ocular ischaemia) promoting ischaemia, hypoxia and microinfarcts subjecting the macula to various degenerative changes.¹⁵ Another mechanism is suggested by the findings that serum levels of antioxidant compounds, such as selenium, vitamins C, E, carotenoids, lutein, zeaxanthin and lycopene are lower in patients with ARMD than in the normal population.^{16,17} The outer retina is rich in polyunsaturated fatty acids and may be damaged by free radical formation and oxidation.¹⁸⁻²⁰

Cataract

Several reports have highlighted the tobacco-smoking associated risk of cataract formation.²¹⁻²⁵ Nuclear and posterior subcapsular cataracts are the most prevalent types in smokers.²⁶⁻²⁹

A positive dose-response relationship has been reported by many. *The City Eye Study*²⁶ found that the relative risk for nuclear cataract ranged between 1.0 for past light smokers and 2.6 for past heavy smokers, while the relative risk for current heavy smokers was 2.9. Similarly, Christen et al.²³ showed that past smokers were at increased risk of developing posterior

subcapsular opacities (RR: 1.44), whereas current light smokers had the same chance of developing any type of cataract as subjects who had never smoked. Hankinson et al.³⁰ found a strong association of posterior subcapsular cataract and smoking of 65 or more pack-years (RR: 2.59). West et al.²¹ found a staggering 18% increase in the risk of cataract progression with each pack-year. Smoking also appears to increase the risk of cataract in type 2 diabetics.³¹

The *Beaver Dam Eye Study*³² found that the odds ratio associated with 10 pack-years was 1.09 (CI: 1.04-1.16). The incidence of posterior subcapsular cataract was increased for men (OR: 1.05; CI: 1.00-1.11) and women (OR: 1.06; CI: 0.98-1.14) but cortical opacities were not found to be linked to smoking. Similarly, Krishnaiah et al.²⁴ found that compared with never smokers, heavy cigarette smokers who smoked more than 14 pack-years had a significantly higher prevalence of nuclear cataract (OR: 2.11; 95% CI: 1.38-3.24) and in cigar smokers who smoked heavily (>21 person-years of smoking; OR: 1.50; 95% CI: 1.10-1.95). In contrast to other studies, they found that heavy cigarette smokers had higher prevalence of cortical cataract (OR: 2.11; 95% CI: 1.38-3.24) than non-smokers.

It is unclear whether any benefit is obtained from smoking cessation. Christen et al.³³ found that compared with current smokers, multivariate rel-



ative risks of cataract in past smokers who quit smoking fewer than 10 years, 10 to fewer than 20 years, and 20 or more years before the study were 0.79 (95% CI: 0.64-0.98), 0.73 (95% CI: 0.61-0.88), and 0.74 (95% CI: 0.63-0.87), respectively after adjustment for other risk factors. The relative risks for non-smokers was 0.64 (95% CI: 0.54-0.76). Weintraub et al.³⁴ found that compared with current smokers, former smokers who had given up smoking 25 or more years previously had a 20% lower risk of cataract extraction after adjustment for other risk factors (RR: 0.80; 95% CI: 0.71, 0.91). However, risk among past smokers did not decrease to the level seen among never smokers (for never smokers, RR: 0.64, 95% CI: 0.52, 0.79).

Speculations about the role of smoking in the mechanism of cataractogenesis abound. One probable mechanism is through oxidative damage.³⁵⁻³⁷ Cadmium (a metal found naturally in soil which is taken up by green leafy plants such as tobacco) may directly interact with lens proteins and denature them, and its precipitation in human lens may also lead to precipitation of lead and copper, causing further toxicity.³⁸⁻⁴⁰

Thyroid eye disease

Smoking is a major avoidable risk factor for developing thyroid eye disease (TED) and those patients are four times more likely to be smokers or former smokers than never smokers.⁴¹⁻⁴⁴ The greater the number of cigarettes

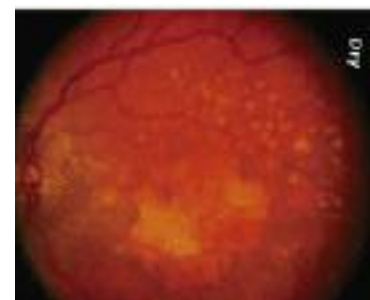


Figure 2: ARMD and cataract are the main ocular risks of tobacco smoking.

smoked per day, the greater the risk of developing TED.⁴⁵⁻⁴⁷ Tellez et al⁴⁸ confirmed the association between cigarette smoking and Graves' ophthalmopathy, but stressed the importance of genetic factors, such as ethnic origin, in the relationship. They concluded that Europeans have 2.4 times (CI: 1.12-3.18, 95%) higher risk of developing smoking-related TED than Asians. Chen et al⁴⁷ found a significantly higher prevalence of cigarette smoking in women with Graves' ophthalmopathy and non-toxic nodular goitre than for healthy female controls (OR: 8.15), while all enrolled men and women with Graves' disease without ophthalmopathy showed no significant association with cigarette smoking. Cigarette smoking was found to increase the risk for progression of ophthalmopathy after radioiodine therapy and decreases the efficacy of orbital radiation therapy and glucocorticoid therapy.⁴⁶

Tobacco smoking affects iodine metabolism in the thyroid gland.⁴⁹ Metcalfe and Weetman⁵⁰ found that tobacco-induced hypoxia could stimulate both protein synthesis and proliferation of extraocular muscle-derived fibroblasts and enhancing muscular inflammation.

Ocular circulation

Robinson et al.⁵¹ reported that macular leukocyte velocity in habitual smokers was increased by about 12% immediately after smoking. Morgado et al⁵² reported that smoking caused a 10% decrease in retinal blood flow in habitual smokers. Williamson et al⁵³ found that cigarette smoking was associated with lower ophthalmic artery velocities which may be relevant to the pathogenic mechanisms of conditions such as central retinal vein occlusion. Tamaki et al⁵⁴ found that smoking increases tissue blood velocity in the optic nerve head and possibly that in the choroid, in habitual smokers whose length of smoking history was 10 years on average.

The mechanisms by which cigarette smoking affect the ocular circulation have been studied by several investigators. Havelius and Hansen⁵⁵ found that the normal capacity for the increase in flow velocity in the central retinal artery in darkness is strongly reduced in smokers. This effect is probably explained by the combined effects of increased blood viscosity and the vasoconstrictive action of nicotine. Synchronously, the impaired release of oxygen to the tissues caused by the binding of car-

bon monoxide (CO) to haemoglobin further compromises the microenvironment of the retina, creating a state of relative tissue hypoxia. Nicotine causes increase in mean blood pressure due to stimulation of the sympathetic nervous system and adrenal medulla.⁵⁶⁻⁵⁸ Further, cigarette smoking or nicotine infusion increases plasma concentration of vasopressin or angiotensin II^{59,60} in addition to noradrenaline or adrenaline^{57,58,61} causing a larger decrease in vessel diameter and subsequently in blood flow. Both erythrocyte and leukocyte concentrations are elevated in smokers⁶²⁻⁶⁴ and platelets are activated in the blood of long-term smokers,⁶⁵ which cause hyperviscosity and increased risks of thrombosis. Elevated levels of plasma fibrinogen increase the clotting potential of the blood.⁶⁶ Carbon monoxide accumulates in the circulation and reduces the oxygen-carrying capacity of the blood. Atherosclerosis is more severe and accelerated in smokers due to raised low-density lipoproteins with greater risk of vasoocclusive disease, whereas high-density lipoproteins are decreased.^{67,68} Moreover, free fatty acids have been shown to increase following intravenous administration of nicotine,⁶⁹ which may be one of the promoting factors for atherosclerosis and hence ocular ischaemia, manifested as amaurosis fugax, retinal infarcts and retinal artery emboli.^{69,70}

The role of cigarette smoking in anterior ischaemic optic neuropathy has been controversial. While Moro et al⁷¹ and Ghung et al⁷² identified smoking to be an important risk factor, Johnson et al⁷³ did not find it to play an important role. Gonzalez et al⁷⁴ have reported that cigarette smoking has been found as an independent risk factor for giant cell arteritis (GCA) and irreversible blindness secondary to anterior ischaemic optic neuropathy occurs in 14.9% of GCA patients, whereas less severe ischaemic complications of the eye are seen in 26.1% of the patients.

Cigarette smoking was found to play a role in ischaemic oculomotor nerve palsy,⁷⁵ idiopathic ophthalmoplegia and functional paresis⁷⁶ and ischaemic idiopathic retinal vasculitis, a rare inflammatory disorder that causes visual loss due to retinal ischaemia and cystoid macular oedema.⁷⁷

The role of smoking in diabetic retinopathy has been controversial. Some studies have correlated cigarette smoking with the development and deterioration of diabetic retinopathy⁷⁸⁻⁸⁵ while others have not.⁸⁶⁻⁹⁶

The balance of evidence suggests that a possible association between smoking and diabetic retinopathy could be due to its effect on the retinal vascular bed as part of the general circulation.

Glaucoma and field loss

Although the meta-analysis by Bonovas et al.⁹⁷ suggested that current smokers are at increased risk of developing progressive open angle glaucoma (POAG) (OR: 1.37; 95% CI: 1.00-1.87), several population-based⁹⁸⁻¹⁰⁴ and case-control studies¹⁰⁵⁻¹⁰⁸ have found no association between smoking habits and glaucoma or intraocular pressure (IOP), others have detected a causal relationship.¹⁰⁹⁻¹¹⁴ Vasoconstriction of episcleral veins leading to an inhibition of aqueous outflow from the trabecular meshwork has been postulated.^{115,116}

Ocular surface and anterior segment disease

A common complaint of passive smokers is eye irritation,¹¹⁷⁻¹²¹ sometimes due to dry eyes.^{122,123} Altinors et al.¹²⁴ found no statistically significant difference in goblet cell densities or in Schirmer 1 test values between smokers (average duration 13.1 years, range 5 to 35 years) and controls ($P > .05$), but higher grades of lipid layer changes were observed in smokers. Brown deposits in artificial corneas were found to be correlated to cigarette smoking and were difficult to remove completely which caused cosmetic inconvenience for the patients.¹²⁵ Smoking during treatment of scleritis and episcleritis was found to delay full response to therapy by a month or more due to pharmacodynamic interaction (OR: 5.4; 95% CI: 1.9-15.5), smoking scleritis patients with additional ocular complications and associated systemic diseases react even slower than non-smoking patients with similar severe disease and have a worse general outcome.¹²⁶

Optic neuropathy

Tobacco smoking was identified as early as the 19th century as a cause of bilateral optic neuropathy. There is still some controversy over whether tobacco-alcohol amblyopia (TAA) is caused by tobacco alone or whether alcohol consumption is a requirement for its development.^{127,128} Smoking is known to impair vitamin B12 absorption in patients with TAA¹²⁹ and patients treated with hydroxycobalamin may recover.¹³⁰ There is also evidence that cyanide present in cigarette smoke is poorly metabolised in

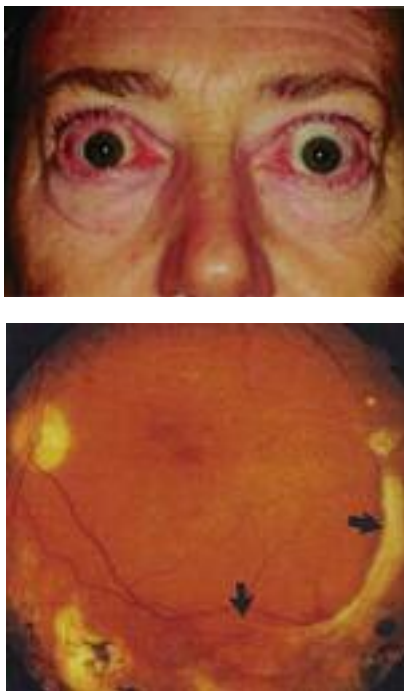


Figure 3: Worsening of thyroid and diabetic eye disease are important side-effects of smoking.

patients with TAA because of alcohol-induced hepatic dysfunction and the lack of vitamin B12 and this may play a role in the pathogenesis.^{131,132} Castagliola et al¹³³ showed that reduced erythrocyte levels of glutathione can serve as a marker of smoking-induced optic neuropathy.

The role of smoking as a possible causative factor in the expression of Leber's hereditary optic neuropathy (LHON) is still controversial. While Riordan et al¹³⁴ and Tsoa et al¹³⁵ confirmed a positive association between smoking and LHON expression, Kerrison et al¹³⁶ confirmed that tobacco and alcohol do not appear to promote vision loss in affected individuals. Berninger et al¹³⁷ concluded in his literature review that in many cases the severity of the disease is related to tobacco smoking and this hypothesis was supported by increased blood levels of cyanocobalamin and cyanide in patients with severe disease.

Granulomatous inflammation

Ocular sarcoidosis may be aggravated by cigarette smoking because of incomplete phagocytic clearance of non-biodegradable foreign bodies present within the tobacco dust. These particles might become antigenic to the immunologically susceptible host and evoke an immune response.¹³⁸

Passive smoking and children

Maternal smoking during pregnancy has

been found to increase the risk of strabismus. Hakim and Tielsch¹³⁹ found this resulted in offspring esotropia but not exotropia (OR: 1.8; CI: 1.10-2.80). There was no evidence of a dose-response relationship, and babies of mothers who have quit smoking during pregnancy were not at higher risk than the overall population. The association of maternal smoking and esotropia was strongest for children whose birth weight was less than 2,500g (OR: 8.2) or more than 3500g (OR: 5.6). Stone et al¹⁴⁰ found that if one or both parents had ever smoked, their children had a lower myopia prevalence (12.4% vs. 25.4%; $P=0.004$) and more hyperopic (1.83 ± 0.24 vs. 0.96 ± 0.27 dioptres; $P=0.02$) than those whose parents never smoked and similar results were found if either parent smoked during the mother's pregnancy. By contrast, no relationship was found between parental smoking and refractive errors^{141,142} or congenital / infantile cataract.¹⁴³

Ocular tumours

Egan et al¹⁴⁴ did not find smoking to be a risk factor of metastasis of choroidal and ciliary body melanomas following proton beam therapy. Metastasis-free survival rates three years after irradiation were 86%, 89%, and 90% for never, past, and current smokers respectively. Wojno¹⁴⁵ found that patients with basal cell carcinoma of the eyelid were no more likely to be smokers than controls (OR: 1.78, not statistically significant at 95% CI); however, there was increased incidence in smoking women (OR: 2.87, statistically significant at the 95% CI).

Visual function

It has not been proven whether tobacco smoking had adverse effects on colour perception, visual acuity or contrast sensitivity.¹⁴⁶

Conclusion

There is strong epidemiological and cellular evidence that tobacco smoking is a major cause of eye morbidity and blindness particularly in age-related macular degeneration, cataract, aggravation of thyroid and diabetic eye disease as well as tobacco amblyopia. Foetal ocular disorders, mainly strabismus, may also be related to smoking, caused by passive transmission of toxins through the placenta. Evidence of the direct harmful effect of both primary and passive smoking is accumulating prompting a need for increased awareness from

the general public and health care professionals. **EN**

References

- Owen CG, Fletcher AE, Donoghue M, Rudnicka AR. How big is the burden of visual loss caused by age-related macular degeneration in the United Kingdom? *Br J Ophthalmol* 2003;**87**:312-7.
- Evans JR, Fletcher AE, Wormald RPL. 28,000 cases of age-related macular degeneration causing visual loss in people aged 75 years and above in the United Kingdom may be attributable to smoking. *Br J Ophthalmol* 2005;**89**:550-3.
- Evans J, Rooney C, Ashwood F, Dattani N, Wormald R. Blindness and partial sight in England and Wales: April 1990 - March 1991. *Health Trends* 1996;**28**:5-12.
- West S, Munoz B, Emmett EA, Taylor HR. Cigarette smoking and risk of nuclear cataracts. *Arch Ophthalmol* 1989;**107**:1166-9.
- Chan D. Cigarette smoking and age-related macular degeneration. *Optom Vis Sci* 1998;**75**:476-84.
- Khan JC, Thurlby DA, Shahid H, Clayton DG, Yates JR, Bradley M, Moore AT, Bird AC. Smoking and age-related macular degeneration: the number of pack years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularisation. *Br J Ophthalmol* 2006;**90**:75-80.
- Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. *Eye* 2005;**19**:935-44.
- Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: age-related eye disease study report no.3. *Ophthalmology* 2000;**107**:2224-32.
- Clemmons TE, Milton RC, Klein R, Seddon J, Ferris FL III. Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no.19. *Ophthalmology* 2005;**112**:533-9.
- Macular Photocoagulation Study Group. Argon laser photocoagulation for neovascular maculopathy. Five-year results from randomized clinical trials. *Arch Ophthalmol* 1991;**109**:1109-14.
- Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, et al. Risk factors for age-related macular degeneration. Pooled findings from three continents. *Ophthalmology* 2001;**108**:697-704.
- Hyman L, Lilienfeld A, Ferris FL, Fine S. Senile macular degeneration: a case control study. *Am J Epidemiol* 1983;**118**:213-27.
- Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. *JAMA* 1996;**276**:1141-6.
- Seddon JM, George S, Rosner B. Cigarette smoking, fish consumption, omega 3 fatty acids and associations with age-related macular degeneration. The US Twin study of ARMD. *Arch Ophthalmol* 2006;**124**:995-1001.
- Bettman JW, Fellows V, Chao P. The effect of cigarette smoking on the intraocular circulation. *Arch Ophthalmol* 1958;**59**:481-8.
- Tsang NC, Penfold PL, Snitch PJ, Billson F. Serum levels of antioxidants and age-related macular degeneration. *Doc Ophthalmol* 1992;**81**:387-400.
- The Eye Disease Case-Control Study Group. Antioxidant status and neovascular age-related macular degeneration. *Arch Ophthalmol* 1993;**111**:104-9.
- Pryor WA, Hales BJ, Premovic PJ, Church DF. The radicals in cigarette tar: their nature and suggested physiological implications. *Science* 1983;**220**:425-7.
- Blackman BC, White P, Tsou W, Finkel D. Peroxidation of plasma and platelet lipids in chronic smokers and insulin-dependent diabetics. *Ann N Y Acad Sci* 1984;**435**:385-7.

Take Home Message

- Strong evidence of major hazardous effects of tobacco smoking on the eye exists but public awareness is sadly lacking.
- ARMD, cataract, thyroid and diabetic eye disease and foetal ocular disorders are the main risks.
- Ocular complications strain NHS resources; hence there is a great need to increase awareness of the general public and health care professionals.
- Past and present history of tobacco smoking should not be ignored whilst managing ocular conditions.

20. Beatty S, Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. *Surv Ophthalmol* 2000;**45**:115-34.
21. West S, Munoz B, Emmett EA, Taylor HR. Cigarette smoking and risk of nuclear cataracts. *Arch Ophthalmol* 1989;**107**:1166-9.
22. Leske MC, Chylack LT Jr, Wu SY. The Lens Opacities Case-Control Study. Risk factors for cataract. *Arch Ophthalmol* 1991;**109**:244-51.
23. Christen WG, Manson JE, Seddon JM, Glynn RJ, Buring JE, Rosner B, Hennekens CH. A prospective study of cigarette smoking and risk of cataract in men. *JAMA* 1992;**268**:989-93.
24. Krishnaiah S, Vilas K, Shamanna BR, Rao GN, Thomas R, Balasubramanian D. Smoking and its association with cataract: results of the Andhra Pradesh eye disease study from India. *Invest Ophthalmol Vis Sci* 2005;**46**(1):58-65.
25. Mukesh BN, Le A, Dimitrov PN, Ahmed S, Taylor HR, McCarty CA. Development of cataract and associated risk factors: the Visual Impairment Project. *Arch Ophthalmol* 2006;**124**:79-85.
26. Flay DE, Sullivan KN, Cullinan TR, Silver JH, Whitelocke RA. Cataracts and cigarette smoking. *The City Eye Study*. *Eye* 1989;**3**:379-84.
27. Mitchell P, Cumming RG, Attebo K, Blanchapakesan J. Prevalence of cataract in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1997;**104**:581-8.
28. McCarty CA. Cataract in the 21st Century: lessons from previous epidemiological research. *Clin Exp Optom* 2002;**85**:91-6.
29. Tsai SY, Hsu WM, Cheng CY, Liu JH, Chou P. Epidemiologic study of age-related cataracts among an elderly Chinese population in Shih-Pai, Taiwan. *Ophthalmology* 2003;**110**:1089-95.
30. Hankinson SE, Willett WC, Colditz GA, Seddon JM, Rosner B, Speizer FE, Stampfer MJ. A prospective study of cigarette smoking and risk of cataract surgery in women. *JAMA* 1992;**268**:994-8.
31. Klein BEK, Klein R, Moss SE. Prevalence of cataracts in a population-based study of persons with diabetes mellitus. *Ophthalmology* 1985;**92**:1191-6.
32. Klein R, Klein BE, Linton KL, Demets DL. The Beaver Dam Eye Study: the relation of age-related maculopathy to smoking. *Am J Epidemiol* 1993;**137**:190-200.
33. Christen WG, Glynn RJ, Ajani UA, Schaumberg DA, Buring JE, Hennekens CH, Manson JE. Smoking cessation and risk of age-related cataract in men. *JAMA* 2000;**284**:713-6.
34. Weintraub JM, Willett WC, Rosner B, Colditz GA, Seddon JM, Hankinson SE. Smoking cessation and risk of cataract extraction among US women and men. *Am J Epidemiol* 2000;**155**:72-9.
35. Kallner AB, Hartmann D, Hornig DH. On the requirements of ascorbic acid in man: steady-state turnover and body pool in smokers. *Am J Clin Nutr* 1981;**34**:1347-55.
36. Teramoto S, Fukuchi Y, Uejima Y, Teramoto K, Orimo H. Influences of chronic tobacco smoke inhalation on aging and oxidant-antioxidant balance in the senescence-accelerated mouse (SAM)-P/2. *Exp Gerontol* 1993;**28**:87-95.
37. Taylor A, Jacques PF, Epstein EM. Relations among aging, antioxidant status, and cataract. *Am J Clin Nutr* 1995;**62**:1439-47.
38. Marklund SL. Superoxide dismutase in human tissue cells and extracellular fluids, clinical implication. Free radicals aging and degenerative disease. New York: *Alan R Liss* 1986:509.
39. Cecik O. Effect of cigarette smoking on copper, lead, and cadmium accumulation in human lens. *Br J Ophthalmol* 1988;**82**:186-8.
40. Racz P, Erdohelyi A. Cadmium, lead and copper concentrations in normal and senile cataractous human lenses. *Ophthalmic Res* 1998;**20**:10-3.
41. Vestergaard P. Smoking and thyroid disorders—a meta-analysis. *Eur J Endocrinol* 2002;**146**:153-61.
42. Nunery WR, Martin RT, Heinz GW, Gavin TJ. The association of cigarette smoking with clinical subtypes of ophthalmic Graves' disease. *Ophthalm Plast Reconstr Surg* 1993;**9**:77-82.
43. Winsa B, Mandahl A, Karlsson FA. Graves' disease, endocrine ophthalmopathy and smoking. *Acta Endocrinol* 1993;**128**:156-60.
44. Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. *JAMA* 1993;**269**:479-82.
45. Bartalena L, Marzocchi C, Tanda ML, Manetti L, Dell'Unto E, Martino E. Cigarette smoking and treatment outcomes in Graves Ophthalmopathy. *Ann Intern Med* 1998;**129**:632-5.
46. Pfeilschifter J, Ziegler R. Smoking and endocrine ophthalmopathy: impact of smoking severity and current vs lifetime cigarette consumption. *Clin Endocrinol* 1996;**45**:477-81.
47. Chen YL, Chang TC, Chen CJ. Influence of smoking on Graves' disease with or without ophthalmopathy and non-toxic nodular goitre in Taiwan. *J Formos Med Assoc* 1994;**93**:40-4.
48. Tellez M, Cooper J, Edmonds C. Graves' ophthalmopathy in relation to cigarette smoking and ethnic origin. *Clin Endocrinol* 1992;**36**:291-4.
49. Bertelsen JB, Hegedus L. Cigarette smoking and the thyroid. *Ugesk Laeger* 1995;**157**:4019-22.
50. Metcalfe RA, Weetman AP. Stimulation of extraocular muscle fibroblasts by cytokines and hypoxia: possible role in thyroid-associated ophthalmopathy. *Clin Endocrinol* 1994;**40**:67-72.
51. Robinson F, Petrig BL, Riva CE. The acute effect of cigarette smoking on macular capillary blood flow in humans. *Invest Ophthalmol Vis Sci* 1985;**26**:609-13.
52. Morgado PB, Chen HC, Patel V, Herbert L, Kohner EM. The acute effect of smoking on retinal blood flow in subjects with and without diabetes. *Ophthalmology* 1994;**101**:220-6.
53. Williamson TH, Lowe GD, Baxter GM. Influence of age, systemic blood pressure, smoking, and blood viscosity on orbital blood velocities. *Br J Ophthalmol* 1995;**79**:17-22.
54. Tamaki Y, Araie M, Nagahara M, Tomita K, Matsubara M. The acute effects of cigarette smoking on human optic nerve head and posterior fundus circulation in light smokers. *Eye* 2000;**14**:67-72.
55. Havelius U, Hansen F. Ocular vasodynamic changes in light and darkness in smokers. *Invest Ophthalmol Vis Sci* 2005;**46**:1698-705.
56. Ball K, Turner R. Smoking and the heart: the basis for action. *Lancet* 1974;**11**:822-6.
57. Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. *N Engl J Med* 1976;**295**:573-7.
58. Rooney MW, Hirsch LJ. Skeletal muscle blood flow and O₂ uptake during intravenous nicotine with and without hypertension. *J Cardiovasc Pharmacol* 1991;**18**:535-41.
59. Hayward JN, Pavasuthipaisit K. Vasopressin released by nicotine in the monkey. *Neuroendocrinology* 1976;**21**:120-9.
60. Hock CE, Passmore JC. Mechanisms mediating canine renal vasoconstriction induced by nicotine infusion. *Life Sci* 2003;**73**:1997-2003.
61. Benowitz NL. Clinical pharmacology of nicotine. *Ann Rev Med* 1986;**37**:21-32.
62. Howell RW. Smoking habits and laboratory tests. *Lancet* 1970;**2**:152.
63. Corre F, Lellouch J, Schwartz D. Smoking and leukocyte count. Results of an epidemiological survey. *Lancet* 1971;**2**:642-4.
64. Fisch IR, Freedman SH. Smoking, oral contraceptives, and obesity. Effect on white blood cell count. *JAMA* 1976;**234**:500-6.
65. Fitzgerald GA, Oates JA, Nowak J. Cigarette smoking and homeostatic function. *Am Heart J* 1988;**115**:267-71.
66. Bertelsen JB, Hegedus L. Cigarette smoking and the thyroid. *Ugesk Laeger* 1995;**157**:4019-22.
67. Garrison RJ, Kannel WB, Feinleib M, Castelli WP, McNamara PM, Padgett SJ. Cigarette smoking and HDL cholesterol: the Framingham offspring study. *Atherosclerosis* 1978;**30**:17-25.
68. Mjos OD. Lipid effects of smoking. *Am Heart J* 1988;**115**:272-5.
69. Tippin J, Corbett JJ, Kerber RE, Schroeder E, Thompson HS. Amaurosis fugax and ocular infarction in adolescents and young adults. *Ann Neurol* 1989;**26**:69-77.
70. Levine SR, Deegan MJ, Futrell N, Welch KM. Cerebrovascular and neurologic disease associated with antiphospholipid antibodies: 48 cases. *Neurology* 1990;**40**:1181-9.
71. Moro F, Doro D, Mantovani E. Anterior ischemic optic neuropathy and aging. *Metab Pediatr Syst Ophthalmol* 1989;**12**:46-57.
72. Chung SM, Gay CA, McCrary JA III. Non-arteritic ischemic optic neuropathy: The impact of tobacco use. *Ophthalmology* 1994;**101**:779-82.
73. Johnson LN, Botelho PJ, Kuo HC. Is smoking a risk factor for NAION (nonarteritic anterior ischemic optic neuropathy)? *Ophthalmology* 1994;**101**:1322-4.
74. Gonzalez-Gay MA, Garcia-Porrúa C, Llorca J, Hajeer AH, Branas F, Dababneh A, Gonzalez-Louza C, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. *Medicine* 2000;**79**:283-92.
75. Teuscher AU, Meienberg O. Ischaemic oculomotor nerve palsy. Clinical features and vascular risk factors in 23 patients. *J Neurol* 1985;**232**:144-9.
76. Hoffmann A, Barth A, Perthel U, Steffen HM, Brunner R, Alolio B. Vascular risk factors in patients with ophthalmoplegia. *Med Klin* 1990;**85**:459-62.
77. Palmer HE, Jurd KM, Hunt BJ, Zaman AG, Stanford MR, Sanders MD, Graham EM. Thrombophilic factors in ischaemic and non-ischaemic idiopathic retinal vasculitis. *Eye* 1995;**9**:507-12.
78. Paetkau ME, Boyd TAS, Winslip B, Grace M. Cigarette smoking and diabetic retinopathy. *Diabetes* 1997;**26**:46-9.
79. Sjolte AK. Ocular complications in insulin treated diabetes mellitus. An epidemiological study. *Acta Ophthalmol* 1985;**1**:172.
80. Walker JM, Cove DH, Bevers DG, Dodson PM, Leatherdale BA, Fletcher RF, Wright AD. Cigarette smoking, blood pressure and the control of blood glucose in the development of diabetic retinopathy. *Diabetes Res* 1985;**2**:183-6.
81. Muhlhauser L, Sawicki P, Berger M. Cigarette-smoking as a risk factor for macroproteinuria and proliferative retinopathy in type 1 (insulin-dependent) diabetes. *Diabetologica* 1986;**29**:500-2.
82. Kingsley LA, Dorman JS, Doft BH, Orchard TJ, LaPorte RE, Kuller LH, Drash AL. An epidemiologic approach to the study of retinopathy: the Pittsburgh diabetic morbidity and retinopathies studies. *Diabetes Res Clin Pract* 1988;**4**:99-109.
83. Mouton DP, Gill AJ. Prevalence of diabetic retinopathy and evaluation of risk factors: A review of 1,005 diabetic clinic patients. *S Afr Med J* 1988;**74**:399-402.
84. Marshall G, Garg SK, Jackson WE, Holmes DL, Chase HP. Factors influencing the onset and progression of diabetic retinopathy in subjects with insulin-dependent diabetes mellitus. *Ophthalmology* 1993;**100**:1133-9.
85. Sparrow JM, McLeod BK, Smith TD, Birch MK, Rosenthal AR. The prevalence of diabetic retinopathy and maculopathy and their risk factors in the non-insulin-treated diabetic patients of an English town. *Eye* 1993;**7**:158-63.
86. West KM, Erdreich LS, Stober JA. Absence of a relationship between smoking and diabetic microangiopathy. *Diabetes Care* 1980;**3**:250-2.
87. Yanko L, Goldbourt U, Michaelson IC, Shapiro A, Yaari S. Prevalence and 15-year incidence of retinopathy and associated characteristics in middle-aged and elderly diabetic men. *Br J Ophthalmol* 1983;**67**:759-65.
88. Telmer S, Christiansen JS, Andersen AR, Nerup J, Deckert T. Smoking habits and prevalence of clinical diabetic microangiopathy in insulin-dependent diabetics. *Acta Med Scand* 1984;**215**:63-8.
89. Rand U, Krolewski AS, Aiello LM, Warram JH, Baker RS, Maki T. Multiple factors in the prediction of risk of proliferative diabetic retinopathy. *N Engl J Med* 1985;**313**:1433-8.
90. Ballard DJ, Melton LJ, Dwyer MS, Trautmann JC, Chua cp, O'Fallen WM, Palumbo PJ. Risk factors for diabetic retinopathy: a population-based study in Rochester, Minnesota. *Diabetes* 1986;**9**:334-42.
91. Segato T, Midena E, Grigoletto F, Zucchetto M, Fedele D, Piermarocchi S, Crepaldi G. The epidemiology and prevalence of diabetic retinopathy in the Veneto region of north east Italy. Veneto Group for Diabetic Retinopathy. *Diabet Med* 1991;**8**:11-6.
92. Chen MS, Kao CS, Chang CJ, Wu TJ, Fu CC, Chen CJ, Tai TY. Prevalence and risk factors of diabetic retinopathy among non-insulin-dependent diabetic subjects. *Am J Ophthalmol* 1992;**114**:723-30.
93. Li LX. Correlation of diabetic retinopathy with systemic factors. *Zhonghua Yan Ke Za Zhi* 1992;**28**:228-30.
94. Falkenberg M, Finnstrom K. Associations with retinopathy in type 2 diabetes: a population-based study in a Swedish rural area. *Diabet Med* 1994;**11**:843-9.
95. Moss SE, Klein R, Klein BE. Cigarette smoking and 10 year progression of diabetic retinopathy. *Ophthalmology* 1996;**103**:1438-42.
96. Johnson KH, Bazargan M, Cheripal CJ. Alcohol, tobacco, and drug use and the onset of type 2 diabetes among inner-city minority patients. *J Am Board Fam Pract* 2001;**14**:430-6.
97. Bonovas S, Filioussi K, Tsantes A, Peponis V. Epidemiological association between cigarette smoking and primary open angle glaucoma: a meta-analysis. *Public Health* 2004;**118**:256-61.
98. Bahna SL, Bjerkedal T. Smoking and intraocular pressure. *Acta Ophthalmol Scand* 1975;**53**:328-34.
99. Shephard RJ, Ponsford E, Basu PK, LaBarre R. Effects of cigarette smoking on intraocular pressure and vision. *Br J Ophthalmol* 1978;**62**:682-7.
100. Carel RS, Korezyn AD, Rock M, Goya I. Association between ocular pressure and certain health parameters. *Ophthalmology* 1984;**91**:311-4.
101. Klein BE, Klein R, Ritter LL. Relationship of drinking alcohol and smoking to prevalence of open angle glaucoma. The Beaver Dam Eye Study. *Ophthalmology* 1993;**100**:1609-13.
102. Leske MC, Warheit R, Wu SY. Open angle glaucoma and ocular hypertension: the Long Island glaucoma case-control study. *Ophthalmic Epidemiol* 1996;**3**:85-96.
103. Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. *Arch Ophthalmol* 2001;**119**:1819-26.
104. Kang JH, Pasquale LR, Rosner BA, Willett WC, Egan KM, Faberowski N, Hankinson SE. Prospective study of cigarette smoking and the risk of primary open angle glaucoma. *Arch Ophthalmol* 2003;**121**:1762-8.
105. Morgan RW, Drance SM. Chronic open angle glaucoma and ocular hypertension. An epidemiologic study. *Br J Ophthalmol* 1975;**59**:211-5.
106. Zheng YZ, Wang SH, Sun W. The case-control study of risk factors in primary angle-closure glaucoma. *Zhonghua Liu Xing Bing Xue Za Zhi* 1995;**16**:8-10.
107. Reynolds DC. Relative risk factors in chronic open angle glaucoma: an epidemiological study. *Am J Optom Physiol Opt* 1977;**54**:116-20.
108. Stewart WC, Crinkley CM, Murrell HP. Cigarette-smoking in normal subjects, ocular hypertensive, and chronic open-angle glaucoma patients. *Am J Ophthalmol* 1994;**117**:267-8.
109. Wilson MR, Hertzmark E, Walker AM, Childs-Shaw, Epstein DL. A case-control study of risk factors in open angle glaucoma. *Arch Ophthalmol* 1987;**105**:1066-71.

110. Kaimbo Wa, Kaimbo D, Missotten L. Risk factors for open angle glaucoma in 260 black subjects in Congo. *Bull Soc Belge Ophthalmol* 1997;**267**:29-34.
111. Wu SY, Leske MC. Associations with intraocular pressure in the Barbados Eye Study. *Arch Ophthalmol* 1997;**115**:1572-6.
112. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open angle glaucoma. *Arch Ophthalmol* 2002;**120**:714-20.
113. Lee AJ, Rochtchina E, Wang JJ, Healey PR, Mitchell P. Does smoking affect intraocular pressure? Findings from the Blue Mountains Eye Study. *J of Glaucoma* 2003;**12**:209-12.
114. Fan BJ, Leung YF, Wang N, Lam SC, Liu Y, Tam OS, Pang CP. Genetic and environmental risk factors for primary open angle glaucoma. *Chin Med J* 2004;**117**:706-10.
115. Mehra KS, Roy PN, Khare BB. Tobacco smoking and glaucoma. *Ann Ophthalmol* 1976;**8**:462-4.
116. Tamaki Y, Araie M, Nagahara M, Tomita K, Matsubara M. The acute effects of cigarette smoking on human optic nerve head and posterior fundus circulation in light smokers. *Eye* 2000;**14**:67-72.
117. Marumatsu S, Marumatsu A, Weber A. A survey on attitudes toward passive smoking among school children and students in Switzerland. *Soz Praventivmed* 1983;**28**:82-4.
118. Eriksen MP, LeMaistre CA, Newell GR. Health hazards of passive smoking. *Ann Rev Public Health* 1988;**9**:47-70.
119. Kjaergaard SK, Pedersen OF. Dust exposure, eye redness, eye cytology and mucous membrane irritation in a tobacco industry. *Int Arch Occup Environ Health* 1989;**61**:519-25.
120. White JR, Froeb HF, Kulik JA. Respiratory illness in non-smokers chronically exposed to tobacco smoke in the work place. *Chest* 1991;**100**:39-43.
121. Cometto-Muniz JE, Cain WS. Sensory irritation. Relation to indoor air pollution. *Ann NY Acad Sci* 1992;**641**:137-51.
122. Moss SE, Klein R, Klein BEK. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol* 2000;**118**:1264-8.
123. Yoon KC, Song BY, Seo MS. Effects of smoking on tear film and ocular surface. *Korean J Ophthalmol* 2005;**19**:18-22.
124. Altinors DD, Acra S, Akova YA, Bilezikci B, Goto E, Dogru M, Tsubota K. Smoking associated with damage to the lipid layer of the ocular surface. *Am J Ophthalmol* 2006;**141**:1016-21.
125. Hicks CR, Chirila TV, Werner L, Crawford GJ, Apple DJ, Constable II. Deposits in artificial corneas: risk factors and prevention. *Clin Exp Ophthalmol* 2004;**32**:185-91.
126. Boonman ZF, Keizer RJ, Watson PG. Smoking delays the response to treatment in episcleritis and scleritis. *Eye* 2005;**19**:949-55.
127. Victor M, Adams RD. On the aetiology of the alcoholic neurologic diseases. With a special reference to the role of nutrition. *Am J Clin Nutr* 1961;**9**:379-97.
128. Samples JR, Younge BR. Tobacco-alcohol amblyopia. *J Clin Neuroophthalmol* 1981;**1**:213-8.
129. Watson-Williams EJ, Bottomley AC, Ainley RG, Phillips CI. Absorption of vitamin B12 in tobacco amblyopia. *Br J Ophthalmol* 1969;**53**:549-52.
130. Krumsiek J, Kruger C, Patzold U. Tobacco-alcohol amblyopia neuro-ophthalmological findings and clinical course. *Acta Neurol Scand* 1985;**72**:180-7.
131. Potts AM. Tobacco amblyopia. *Surv Ophthalmol* 1973;**17**:313-39.
132. Wilson J. Cyanide in human disease: a review of clinical and laboratory evidence. *Fundam Appl Toxicol* 1983;**3**:397-9.
133. Costagliola C, Cotticelli L, Menzione M, Rinaldi M, Russo S, Rinaldi E. Red cell reduced glutathione and tobacco smoke-induced optic neuropathy. *Metab Pediatr Syst Ophthalmol* 1990;**13**:96-8.
134. Riordan-Eva P, Sanders MD, Govan GG, Sweeney MG, Da Costa J, Harding AE. The clinical features of Leber's hereditary optic neuropathy defined by the presence of a pathogenic mitochondrial DNA mutation. *Brain* 1995;**118**:319-37.
135. Tsao K, Aitkin PA, Johns DR. Smoking as a possible etiologic factor in the disease expression of Leber's hereditary optic neuropathy. *Invest Ophthalmol Vis Sci* 1996;**37**:709.
136. Kerrison JB, Miller NR, Hsu FC, Beaty TH, Maumenee IH, Smith KH, Savino PJ, et al. A case-control study of tobacco and alcohol consumption in Leber's hereditary optic neuropathy. *Am J Ophthalmol* 2000;**130**:803-12.
137. Berninger TA, Bird AC, Arden GB. Leber's hereditary optic atrophy. *Ophthalmic Paediatr Genet* 1989;**10**:211-27.
138. Merritt JC, Ballard DJ, Checkoway H, Mower P, Grimson R. Ocular sarcoidosis. A case-control study among black patients. *Ann NY Acad Sci* 1986;**465**:619-24.
139. Hakim RB, Tielsch JM. Maternal cigarette smoking during pregnancy. A risk factor for childhood strabismus. *Arch Ophthalmol* 1992;**110**:1459-62.
140. Stone RA, Wilson LB, Ying GS, Liu C, Criss JS, Orlow J, Lindstrom JM, Quinn GE. Associations between childhood refraction and parental smoking. *Invest Ophthalmol Vis Sci* 2006;**47**:4277-87.
141. Saw SM, Chia KS, Lindstrom JM, Tan DT, Stone RA. Childhood myopia and parental smoking. *Br J Ophthalmol* 2004;**88**:934-7.
142. Hajnal BL, Ferriero DM, Partridge JC, Dempsey D, Good WV. Is exposure to cocaine or cigarette smoke during pregnancy associated with infant visual abnormalities? *Dev Med Child Neurol* 2004;**46**:520-5.
144. Egan KM, Gragoudas ES, Seddon JM, Walsh SM. Smoking and the risk of early metastasis from uveal melanoma. *Ophthalmology* 1992;**99**:537-41.
145. Wojno TH. The association between cigarette smoking and basal cell carcinoma of the eyelids in women. *Ophthalm Plast Reconstr Surg* 1999;**23**:390-2.
146. Bimler D, Kirkland J. Multidimensional scaling of D15 caps: Color-vision defects among tobacco smokers? *Vis Neurosci* 2004;**21**:445-8.