A.2 Lens Opacities and cataract

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A.2.1 Introduction

The lens of the human eye changes with increasing age: it looses its clearness, it turns yellowish to brownish, its fluorescence increases [Van Best et al., 1998], and its internal scattering of light increases [Sasaki et al., 1999]. In addition to these general changes in the bulk of the lens, localised changes may occur: opaque spots which can grow in size and ultimately hamper vision. Such an advanced stage of lens opacity forms a cataract, and as it appears to be related to age, it is referred to as 'senile cataract'. Cataract is world-wide a major cause of blindness. In developed countries cataract is adequately treated by an operation, but in developing countries it often leads to permanent blindness with grave social/economic consequences. Three main types of cataract can be distinguished: cortical cataract (CC) involving the surficial part at the front, nuclear (sclerotic) cataract (NC) at the centre of the lens, and posterior subcapsular cataract (PSCC) at the inwardly turned surface of the lens.

Among 297 subjects with cataracts from a US health survey of 1971-72 104 (35%) had pure NC, 55 (18.5%) pure CC, 18 (6%) pure PSCC and 120 (40%) mixed forms of cataracts [Hiller et al. 1986]. Percentages from a hospital-based study (1008 cataract patients) in the region of Parma, Italy, are 49% CC, 11% NC, 3% PSCC and 38% mixed [Italian-American Cataract Study Group, 1991], with - according to the authors - an unexpectedly low number of NC. CC appears to be more abundant in populations living in temperate climates and NC in populations in more tropical climates, e.g. Iceland and Noto versus Singapore and Amami [Sasaki et al. 1999]. Of people older than 40 years in Victoria, Australia, 12% were found to have CC, 13% NC and 5% PSCC [McCarty et al 1999].

A.2.2 UV radiation and the etiology of cataracts

A.2.2.1 Literature survey

The mechanisms underlying all of these 'senile' changes are not fully established, but a general contention on ageing is that it is caused by (endogenous) oxidative processes (see for example [Berry and Truscott 2001, Fu et al. 1998]). As UV radiation can generate reactive oxygen species, it is also suspected to contribute to the deterioration of the lens [Eaton JW 1994, Dillon 1994, Sommerburg et al. 1998, Lee et al. 1999]. By comparing Portuguese and Dutch males, evidence was found that autofluorescence of the lens may indeed be related to sun (UV) exposure, and Van Best et al. (1998) reported that after a 15-year followup of a cohort of 15 people, the individual with the highest initial lentigular fluorescence developed a cataract.

Epidemiology shows that the etiology of cataract is complicated and involves many risk factors, among which some very prominent ones like alcohol abuse, heavy smoking, severe diarrhoea (dehydration), diabetics and chronic steroiud use (odd ratios 2-6) [Harding and Van Heyningen, 1987, Clayton et al., 1984, Hodge et al. 1995]. In considering all risk factors Taylor (1999) concludes that the only effective preventive interventions seem to be to stop smoking and to reduce ocular UVB exposure.

In a thorough review of epidemiological studies Dolin (1994) concluded that there is limited evidence that UV exposure causes cortical and posterior subcapsular opacities in humans, but no evidence that UV-exposure causes NC. In a more recent review [West 1999] the conclusion is drawn that there is sufficient evidence of an increase in cortical opacities with
increasing UV exposure to warrant advising the public on measures to decrease their ocular exposure.

The reported risks from sun (UV) exposure in population-based studies are generally quite moderate, mostly odd ratios < 2 (e.g. 1.12, 95% CI 1.06-1.18, for women in [Hayashi et al. 1998]), and often not significantly different from 1 (e.g. 1.05, 95%CI 0.97-1.14, for men in [Hayashi et al. 1998]). However, the poor quality of retrospective assessments of exposure will inevitably lead to large errors and consequently to underestimation of the relative risk. Importantly, the potential impact of solar UV radiation is population-wide, and not - like the most prominent risk factors - limited to certain high risk groups. A majority of ecological studies show an increase in cataracts in geographical locations with high UV insolation [West 1999, Javitt and Taylor 1994, Hiller et al. 1986, Hollows and Moran 1981]. Despite the 'ecological fallacy' (i.e., importance of factors not considered), these studies are superior in assessing UV exposure, albeit an ambient instead of a true personal exposure, and they have an obvious direct relevance to assessments of the impact of increases in ambient UV radiation (on the merits of ecological studies for assessments of health impacts see [Soskolne et al. 2000]).

In a study on Chesapeake Bay watermen a special effort was made to assess retrospectively the individual solar UV exposures, and a relative risk of 3.3 (95% CI 0.9-10) was found for CC between the top and bottom quartiles of exposure [Taylor et al. 1988]. The lifetime exposure of individuals with CC was significantly higher than that of cataract-free controls, no association between UV exposure and NC was found (exposures before the age of 15 years were not included in the assessment). Using the same methodology of exposure assessment in a hospital-based study, Bochow et al. (1989) found a significant risk of PSCC associated with annual and cumulative ocular UV exposure. Most of the other studies found either no significant increase in risk [Collman et al. 1988, Dolezal et al. 1989] in relation to sun/UV exposure, or solely a significant increase in the risk of CC [Hiller et al. 1986, Italian-American Cataract Study Group 1991]. The latter result was also obtained in the 'Beaver Dam Study' of the various types of lens opacities in male patients with eye diseases, however, no association between sun exposure and lens opacities was found in female patients [Cruickshanks et al. 1992]. Cortical, nuclear and posterior subcapsular opacities were observed at similar frequencies in this population of patients, but the average age of the women was higher and they showed a significantly higher incidence of cortical and nuclear opacities than the men. The authors stress the point that despite the higher frequency of cortical opacities in females, these opacities do not show an increased risk with increases in UV exposure, like in the males. However, the percentages and numbers of persons that spend most of their professional and/or leisure time outdoors are dramatically smaller for females than for males. Thus, the numerical strength of testing any relation with UV exposure may be lost in the female population. The relation between CC and UV exposure was more broadly confirmed in a more recent population-based study in Salisbury, Maryland, by West et al. (1998). They found odd ratios just over 1 (1.10 , 95%CI 1.02-1.20, for males and 1.14, 95%CI 1.00-1.30, for females and 1.18, 95%CI 1.04-1.33, for African Americans). In a recent study in Iceland on people (n = 1045) older than 50 years odd ratios of 2.80 (1.01-7.80) and 2.91 (1.13-9.62) were found for grades II and III, respectively, of cortical opacification in people who spend more than 4 hours per day outside on weekdays [Katoh et al., 2001]. Although they found a substantial association with the time spend outdoors (a surrogate for UV exposure), these investigators stress - what has been found time and again - that 'age' appears to the main independent risk factor. Interestingly, cortical opacities appear to develop mainly in the lower (inferior) half of the lens [Mohan et al. 1989, Berliner 1949] or the nasal-inferior quadrant [Duke-Ehler 1926, Schein et al. 1994] which is taken as
evidence of the causal role of sun exposure (consider the convergence of oblique incoming UV light toward the equatorial region at the opposite side of the lens [Coroneo 1993]).

Although NC is commonly not found to be associated with UV exposure (mostly evaluated over the adult life), Wojno et al. (1983) intriguingly found a significant reduction in the risk of NC in people that wore (glass) spectacles for most of their lives. This would indicate a possible effect of blocking UVB radiation, perhaps most importantly, early in life before the onset of substantial brunescence of the lens. Such a significant reduction in risk was also found in the Beaver Dam Eye Study for men - but not for women - wearing glasses for distance before the age of 21 years when compared to those who started wearing glasses at ages over 40 years; a similar reduction in risk of CC was observed, but it did not reach statistical significance [Cruickshanks et al. 1992]. Myopia -short sightedness - has also been reported to be associated with a reduction in cataracts [Dolezal et al. 1989, Belkin et al. 1982], but other studies found myopia to be associated with an increase in cataract [Van Heyningen and Harding 1988, McCarty et al. 1999]. The reason for this discrepancy is unclear, and no dedicated study has yet been done to test the hypothesis that early-in-life solar UV exposure carries a risk of NC later in life.

A.2.2 Conclusions
Overall, the prudent conclusion on the potential impact of UV radiation appears to be that all types of cataract may be affected, albeit perhaps at different stages of life (early versus continuously) and to different degrees: CC appears to be most clearly related to UV exposure (especially in chronically exposed male outdoor workers), and NC the least clearly (perhaps related to early in life UVB exposure). This prudent conclusion is somewhat at odds with more rigorous epidemiological analyses that require consistent results over several studies, preferably 'proper' case-control studies; in that case, UV would only be considered a weak risk factor for CC. The impact of UV exposure on the relative risks in most case-control studies appears to be generally very moderate, but there is a general problem with assessments of lifetime personal exposures (mostly based on surrogates or crude estimates from recall). The inherent large errors are bound to yield underestimates of relative risks. Ecological studies appear to show a more substantial increase in prevalence of cataract with increasing ambient UV exposure (see below).

A.2.3 Cataract and UV: a Model

A.2.3.1 Dose-response relationship
A proper quantitative risk assessment needs to be based on a dose-response relationship. Such a relationship is not available for UV-induced cataracts in humans, and because of obvious ethical reasons, it cannot be determined directly by experimentation. Animal experiments on UV-induced lenticular opacification are not fully adequate in modelling senile cataracts observed in humans [Hockwin et al. 1999]. Because of the aforementioned inaccuracies in assessments of UV exposures, case-control studies and most other retrospective epidemiological studies are totally unsuitable to base a dose-response relationship on. Here, we will attempt to piece together a dose-response relationship from a combination of other epidemiological studies (ecological data and registries), animal and in vitro studies.

Burch and Chesters (1985) found that the age-dependency of the prevalences, P, of lenticular opacities and cataracts (from the Farmingham study [Podgor et al. 1983]) could be described
with a simple formula - similarly to incidences of skin cancer in accordance with Weibull statistics -

\[
P(a) = 1 - \exp \left[-k(a - d)^6\right] \tag{1}\]

where 'a' stands for age, 'k' a rate constant, and 'd' a delay time which equals 3.4 \(\pm\) 2.5 year for 'senile lens changes' and 22.2 \(\pm\) 1.9 year for 'senile cataract'. They interpret this formula in the framework of their theory on 'auto-aggressive diseases', among which they consider cancers. In case of cancers, a simple multiple (=6) interpretation would equate 'k' with 'm^6', where 'm' is an average mutation rate.

This analogy to the age-dependence of cancers invites the idea that the underlying process for cataracts may also involve a series of discrete (molecular) events, maybe even mutations in certain genes. This conjecture is not without substance: it is well known that certain inherited genetic defects cause cataract, e.g., specifically mutations in genes coding for crystallins. These proteins show homology to heatshock proteins and they serve as molecular 'chaperones' to prevent the aggregation of other proteins which could cause turbidity in the lens [Kumar et al. 1999]. Moreover, it would provide a natural explanation for the increasing risk with age, and why an opacity would increase in size: a clonal expansion of cells with a dysfunctional crystallin. As the proliferative cells are located in the equatorial region of the lens and the differentiating cells move inward, one would expect a similar course of development in expanding lens opacities; this appears to be particularly true for cortical opacities developing into cataracts. In connection with this, it is noteworthy that Burch and Chester (1985) already drew attention to the fact that cataract was "the first late effect to be recognised unequivocally among the survivors of the nuclear-bomb explosions at Hiroshima and Nagasaki". This clearly illustrates that a single exposure causes cataracts with a substantial delay, which calls for a mechanism of autonomous development and expansion of the opacity - analogous to the development of a cancer, but involving benign instead of malignant cells.

In this description according to eq. 1 it would appear that any effect from UV exposure will be expressed in the rate constant 'k' (in skin cancer, UV radiation would increase the rate of at least one of the mutations). Presently, the best way of establishing an appropriate dose dependency seems by considering latitudinal gradients in cataract as being caused by gradients in ambient UV exposure. Thus, we can look at published data on the latitudinal gradient in the Aboriginal population in Australia [Hollow and Moran 1981] or the registered cataract operations in the USA [Hiller et al. 1983]. Both of these data sets are related to the ambient UV in units from a Robertson-Berger meter with a spectral sensitivity that approximates the erythemal (sunburn) sensitivity of human skin. The first data set stretches from 1000 to 3000 UV units, and shows a corresponding 3 fold rise in prevalence in the age group of 40-59 years. The second data set goes from 2600 to 6000 UV units and shows a 1.58 fold rise in risk for people that have spent at least half of their life’s at the location investigated, and with an increase in UV from 3000 to 4800 units a 1.28 fold rise in risk is observed. For prevalences <30% we can take the prevalence to equal the yield, i.e. k(a-d)^6. This in turn implies that these increases in risk are approximately equal to the increases in k. These data can be described by k (UV dose)^p - in analogy with skin cancers - and we find that p = 1 for the first data set and p = 0.55 for the second. Thus, we find for the overall yield, Y, of cataract that

\[
Y(a) = k_0 D^p (a-d)^6 \tag{2}
\]
where \( D \) is the annual ambient UV dose, \( k_0 \) is the rate constant independent of UV, and \( p \) varies from 0.55 to 1.0. In a later study Hiller et al. (1986) studied CC and NC separately, and found the risk of the first to increase 3.6 fold going from 2600 to 6000 UV units while the risk of latter did not change. This means that \( p = 1.5 \) for CC and \( p = 0 \) for NC. With \( p = 0.55 \) for all cataracts together and \( p = 1.5 \) for CC, it could be inferred that about \( 1/3 \) of the total cataracts are UV-sensitive CC, and the remaining \( 2/3 \) are independent of UV (if the overall yield, \( Y_{\text{all}} = Y_{\text{cc}} + Y_{0} D^{0.5} \), and the yield of CC, \( Y_{\text{cc}} D^{1.5} \), while the yield of other cataracts, \( Y_{0} \), is constant, we find that \( 0.5 = (d \ln Y_{\text{all}} / d \ln D) = 1.5 Y_{\text{cc}} / Y_{\text{all}} \) and hence \( Y_{\text{cc}} / Y_{\text{all}} = 0.5/1.5 = 1/3 \)). Previously, Van der Leun and De Gruijl (1993) made a rough estimate of \( p = 0.7 \) for CC, based on the data from the watermen study [Taylor et al. 1988] in which it was reported that a doubling in UV exposure (assessed in retrospect form a person's professional history) increased the risk 1.6 fold. However, the UV exposure in this study was not as accurate as measurements of the ambient UV radiation.

**A.2.3.2 Action spectrum**

The remaining issue is whether an erythemally weighted UV dose is the appropriate dose for cataract formation. Much like erythema, the wavelength dependence of cataract formation in animals is found to peak in the UVB [Merriam et al. 2000, Pitts et al. 1977]. If genetical damage is really involved, like in skin cancer formation, then the carcinogenic or erythemal doses appear to be good approximations [De Gruijl and Van der Leun 1994, Young et al. 1998]. Even if next to direct dimer formation in the DNA, oxidation of DNA plays an important role the action spectrum will show a dominant peak in the UVB [Kielbassa et al. 1997]. Moreover, damage to the epithelial cells at the frontal surface and their release of prostaglandins appear to cause cortical cataract in underlying lens tissue [Li et al. 1995, Andley et al. 1996], and UVB radiation is particularly effective in inducing these cellular responses. If the oxidation of proteins is important in UV cataractogenesis [McCarty and Taylor 1996, Sommerberg et al. 1998], UVA could be relatively more important [Dillon et al. 1999] - depending on the endogeneous UV sensitizer - [Lee et al. 1999, Dillon 1994] and an erythemal spectral weighting may then underestimate the contribution from the UVA band. This would imply that the gradient in cataracts would be steeper with ambient UVA (as the latitudinal gradient in UVA is less than that in UVB), and that a change in UVB (such as with a thinning of the ozone layer) would affect the cataractogenic dose to a lesser extent.

Considering the experimental results and the good correlation between UVB and CC in the study Chesapeake Bay watermen (better than with UVA) [Taylor et al. 1988], the balance of evidence would presently favour that the main cataractogenic action in sunlight resides in the UVB, and the erythemal or carcinogenic dose would therefore be a good first approximation. Hence eq. 2 with \( p = 0.55 \) would appear an appropriate choice for the European population, and if the statistics for CC, NC and PSCC are known separately, \( p = 1.5 \) can be used for CC and \( p = 0 \) for the remaining cataracts (i.e. the latter would not respond to increases in ambient UVB radiation). With a 1% increase in ambient cataractogenic UV radiation for every 1% decrease in ozone, we find that the incidence of cataract would increase by 0.55% and that of CC by 1.5%. For a scenario study of the time course of changes in cataract incidences following a decline and a rise in ozone levels we could reasonably assume that UV radiation affects CC development continuously throughout life, similar to squamous cell carcinomas.
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