

Understanding Cataract Risk in Aerospace Flight Crew And Review of Mechanisms of Cataract Formation

Jones, J.A.^{1,2}, McCarten, M.², Manuel, K.³, Djojonegoro, B.⁴, Murray, J.⁴, Cucinotta, F.¹,
Feiversen, A.¹, Wear, M.⁴

- 1- National Aeronautics and Space Administration, Lyndon B. Johnson Space Center
- 2- United States Navy, Medical Corps
- 3- Kelsey-Seybold Clinic
- 4- Wyle Laboratories

Correspondence:

Jeffrey A. Jones, MD, MS, FACS
SD- Space Medicine and Health Care Systems
2101 Nasa Parkway
Houston, TX 77030
jajones@ems.jsc.nasa.gov

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Abstract

Induction of cataracts by occupational exposure in flight crew has been an important topic of interest in aerospace medicine in the past five years, in association with numerous reports of flight-associated disease incidences. Due to numerous confounding variables, it has been difficult to determine if there is increased cataract risk directly caused by interaction with the flight environment, specifically associated with added radiation exposure during flight. Military aviator records from the United States Air Force (USAF) and Navy (USN) and US astronauts at the National Aeronautics and Space Administration (NASA) /Lyndon B. Johnson Space Center (JSC) were evaluated for the presence, location and age of diagnosis of cataracts. Military aviators were found to have a statistically significant younger average age of onset of their cataracts compared with astronauts, however the incidence density of cataracts was found to be statistically higher in astronauts than in military aviators. USAF and USN aviator's cataracts were most commonly located in the posterior subcapsular region of the lens while astronauts' cataracts were most likely to originate generally in the cortical zone. A prospective clinical trial which controls for confounding variables in examination technique, cataract classification, diet, exposure, and pharmacological intervention is needed to determine what percentage of the risk for cataracts are due to radiation, and how to best develop countermeasures to protect flight crews from radiation bioeffects in the future.

Introduction

In the past five years, an increased scrutiny of the occupational health risks of flight crews has been observed, and the evaluation of ocular health risks has been no exception. Cataracts, if found in the visual axis can produce diminution in visual acuity, and are disqualifying for pilots. However they are usually only slowly progressive and can be detected with routine screening, usually before significant visual acuity loss. They can be surgically excised and the affected lens artificially replaced, making them usually a source of healthcare cost and morbidity in the United States, but not mortality in the flight crew population. Cataracts surgery is the most frequently reimbursed procedure by Medicare, and accounts for 12% of Medicare budget. 1.18 million lens implanted /year in the U.S. Studies of the incidence and prevalence of cataracts in the U.S. is summarized in Table 1.

[Table 1 here]

However worldwide, cataracts are a major cause of blindness. There is an increased incidence of cataracts in equatorial(45)and high altitude locations, presumably associated with increased UV exposure. (21, 28, 75, 94, 121, 122, 126, 128, 136, 138-140, 142, 153, 155) The risk of cataracts has many associated risk factors including age(104, 108, 127), diabetes, nutrition(137), genetic factors, cigarette smoking, drug use (30, 43, 103, 125), e.g. psoralen(61, 62, 141), steroids and alcohol, obesity, occupational exposures (117, 151, 152), e.g. welding(37), elevated temperatures (95, 134) or radiofrequency energy(31, 68-71, 87, 88, 102), including microwaves(32, 33, 54-57, 66, 89, 112, 120), ultraviolet (UV)(2, 5, 6, 8, 47, 96) and ionizing radiation exposure. (14, 40, 48-50, 52, 53, 64, 65, 76, 77, 82-84, 92, 109, 110, 133, 143-150). Research to date seems to indicate that multiple mechanisms may cause the lens to degenerate (29, 30) thereby making assignment of causative blame to the principle risk factors which may account for an increased rate of cataract formation in flight crew, a rather complex task.(125) Nevertheless, since 2000, there have been multiple reports of increased rates of cataract formation in specific flight populations, e.g. airline pilots (86, 97-99) and astronauts (23, 24, 100), however a comparison of the aerospace-induced cataract risk across flight populations has not previously been reported. Understanding the correlation of the degree of occupational environmental exposure and the subsequent rate and severity of biological outcome is essential to quantifying the risk to flight crews for carrying out their missions(34, 35).

Several etiologies for the increased rate of cataracts in astronauts and pilots have been discussed, however since there are potentially a number of confounders, pinpointing the precise causative agent is difficult and most likely multi-factorial. A key question still unanswered, is how much did the spaceflight-specific radiation exposure contribute to the cataracts rate and degree of formation? The methodology for the clinical detection of cataracts has also varied over the years and amongst different screening examination facilities, thereby rendering the validity of the comparisons questionable. The objectives of the current evaluation are 1) to compare the cataract formation rate across several flight and non-flight groups, to determine if any light can be shed on the etiologic factors contributing to this organ-specific disease, and 2) to review the pathogenic mechanisms

for cataract formation, in order to suggest candidates for countermeasure development for prevention of ocular diseases in flight crews.

Methods

A retrospective review of US Air Force, Navy, FAA and NASA flight crew databases was conducted to determine the incidence of cataract formation in the relevant flight populations. The information in the databases was verified by reviewing individual aviator records within each of the databases, to ensure accurate characterization of each cataract occurrence was correctly cataloged.

Description of Examination procedures for ocular examinations:

NASA: A complete ocular history and medical history was accomplished with particular emphasis on the exclusion items of active ocular disease, dilating drug sensitivity, pseudophakia, glaucoma, diabetes, use of history of use of steroids, visually significant corneal opacities or visually significant retinal/ocular pathology.

Bilateral ocular examinations were conducted annually to include standard visual acuity, color and depth perception evaluations. Intraocular pressure was measured by applanation tonometry. Gross evaluation of adnexal tissues was evaluated; to include lids, lashes, extraocular muscle function and pupillary function (size, symmetry and light response), All anterior segment tissues were evaluated by slit lamp methods to include lashes, lids, conjunctiva, cornea, iris, lens and media. Closeable angles were ruled out.

Refraction was derived by standard optometric methodologies utilizing monitor derived eye charts positioned and calibrated at a 6 meter test distance. Upon completion of the manifest refraction (non-cycloplegic) the measurement of best correctable LogMAR visual acuity was documented via Precision Vision ETDRS back-illuminated charts at 4 meters. The acuity was measured while viewing through the refractor with the derived best correction. Each eye was tested independently and both high and low contrast acuities were recorded.

Proparicaine 0.5% was utilized for the measurement of intra-ocular pressure by applanation (Goldmann). Pupillary responses were evaluated, and if normal, pupils were dilated with a combination of tropicamide 1% and neosynephrine 2.5%. Dilation allowed evaluation of the posterior segment tissues to include lens, vitreous, retina, optic nerve and associated vasculature. The lens was evaluated in great detail utilizing both subjective and objective methodologies. Subjective methods involved estimating nuclear color and opacity, area of cortical and posterior sub-capsular using the LOCS III (Lens Opacities Classification System – Version III) point system. Objective methods involved imaging the lens using a Nidek EAS1000 digital camera to capture both Scheimflug slit and retroilluminated images of each eye. The retroilluminated images were captured at two repeated anterior and posterior lens points of reference.

Each subject was requested to fill out a detailed standardized food frequency survey and smoking questionnaire annually. A standardized questionnaire regarding life-style issues such as the amount of time spent in the sun, time spent in water activities, flight

activities and locations lived for the past thirty years was administered during the first year visit only.

DOD- USAF/USN The majority of testing points and methods are the same as NASA with some significant and notable exceptions.

1. Test Distance: Testing in DOD facilities may vary in test distance in that some facilities may have 6 meter testing lanes while others are much shorter but utilize mirrors to create the 6 meter test distance.
2. Pupil Dilation: Dilation may not be accomplished each year as it is at the discretion of the examining doctor.
3. Detail of lens evaluation accomplished at NASA is far more detailed than is standard in DOD facilities. DOD facilities will evaluate lens opacities as present or absent, or possibly use a grading system, which is generally a 0 to 4 method and not standardized from facility to facility or doctor to doctor.

Data collection and Statistical methods:

Standard epidemiological methods were applied to cataract case logging and determination of follow-up for each case as well as for the entire cohort. For 206 subjects with recorded cataracts before age 65 yrs. (27 astronauts, 144 AF, 35 Navy), a Cox proportional hazards model was used to compare the distributions of age at cataract diagnosis, adjusting for time since beginning of service and age at entry. As long as the diagnosis was made before age 65 yrs., subjects were included in this analysis even if they had retired from astronaut or military service. Since this analysis was made only on recorded cases of cataracts, no censoring was involved and by definition, all three groups had 100% cataract cases by age 65. After fitting the model, the method of Grambsch and Therneau was used to see if the proportional hazards assumption was reasonable. Differences between astronauts and the military groups are reflected in estimates of hazard ratios for AF and Navy relative to astronauts.

Results

[Figure 1 here]

Figure 1 shows a graph of prevalence of cataracts comparing 4 populations: U.S. males general populace, commercial airline pilots, and previously flown astronauts who received low dose or high dose space radiation, influenced by duration, altitude and destination of the mission. (Dose rate is generally higher for missions beyond low earth orbit (LEO), although high altitude and high inclination LEO missions can also see higher dose rates due to interaction with trapped particulate radiation within the Van Allen belts). This data would suggest that space radiation is an independent and stronger risk factor than either commercial flight altitude and polar aviation route radiation, or surface UV. However most of the early spaceflight crews during Mercury, Gemini, Apollo, Skylab and Apollo-Soyuz, who are now of likely cataract age, came from a military aviation background. So it seems that the military aviator cohort is the most relevant for comparisons that would confirm if space radiation is the likely causative factor in the increased prevalence of cataracts in space crewmembers. There are several

reasons for this assertion: 1) the prior occupational exposures are similar, 2) the physical, educational, and medical screening selection processes are similar, and 3) the annual examinations are conducted in a similar standardized manner, as seen in the methods description. The latter factor is in contrast to the comparisons the authors made earlier to the LSAH control population. (24)

Review of the Department of Defense aircrew ocular health information, from USAF and USN aircrew health records revealed 13,560,303 person-years of cumulative follow-up. This is compared with 5086 person-years of follow-up obtained from review of NASA astronauts and matched controls.

The prevalence of cataracts in astronauts by age is shown in Figure 2. When grouped together, the shape of the curve does not look dissimilar to what would be expected in an aging predominantly male population, and from what was previously reported in Table 1.

[Figure 2 here]

Figure 3 depicts the cumulative prevalence of cataract cases according to age amongst the analogous flight groups. Inspection of this data reveals an earlier age of onset of cataracts in the military aviator populations compared to astronauts, especially astronauts with higher grade cataracts. It should be noted here that follow-up data for USN aviators was not complete beyond age 65 and is therefore not shown in this graph.

[Figure 3 here]

The finding of earlier age of onset for cataracts in USAF and USN aviators compared to astronauts is reinforced in figure 4 which shows the average age of onset of cataract per eye, including those that developed cataracts in both eyes. Since follow-up was not complete in the USN aviators, the means were not compared statistically with the other groups, although the trend would suggest at earlier age of onset in that cohort as well.

[Figure 4 here]

The most telling information in comparing these 3 cohorts may come from evaluating incidence density of cataracts, as shown in figure 5. The total number of cataracts in astronauts is almost an order of magnitude greater incidence density than in military aviators, especially those occurring in both eyes. Even the number of grade 3 and 4 cataracts has a higher incidence density than total cataracts in aviators.

[Figure 5 here]

Finally, figure 6 shows the incidence of cataracts by anatomic location, comparing the 3 groups. Prior studies have found that UV and other sources of ionizing radiation-induced cataracts are commonly found in the subcapsular location.(11, 13, 16, 17, 19, 22, 26, 27, 42, 75, 124) The most common anatomic location for military aviator cataracts in this study was in the posterior subcapsular location, as is commonly observed in ionizing radiation induction, however the astronaut cataracts were mostly found in the lens cortical region, as previously reported.(24)

[Figure 6 here]

The Grambsch and Therneau test showed no significant departure from the proportional hazards assumption ($P = 0.63$). Estimates of hazard ratios (AF/astronauts and Navy/astronauts) were 2.6 (1.5, 4.8) and 4.1 (2.1, 8.0) respectively, where numbers in parentheses are 95% confidence limits. In other words, AF and Navy pilots had significantly higher hazards than astronauts ($P < 0.005$, $P < 0.001$, respectively), thus given that they had a cataract, the distribution of age of occurrence for the military pilots tended to be shifted significantly towards younger ages than for astronauts, even after adjusting for age of entry and time since beginning of service. Within the two military groups, Navy pilots had a significantly higher hazard ($P = 0.018$), hence an earlier adjusted age distribution at cataract diagnosis than did Air Force pilots.

[Figure 7 here]

Discussion

Pathophysiology of Cataracts Formation:

The formation of cataract in the ocular lens is a complex, multi-factorial, and incompletely understood set of processes. (123) Cataracts may form due to genetic and other dietary and disease-associated factors, which are independent of the environmental exposures of the individual. (12) Yet it is the environmental exposure risk associated with the flight crew occupation that is under scrutiny in this study. Possible mechanisms for observed changes in the lens associated with external factors can be classified into the following categories: biophysical(59, 115, 116), biochemical(8, 15, 59, 60, 106, 127), physiological(5, 115, 116), and cellular(25, 36, 79, 81, 106, 114, 118, 123, 143).

- Some important biophysical considerations include: 90% of UV which hits lens is UVA (315-400 nm), tryptophan absorbs 95% of photon energy absorbed by amino acids in the lens, tryptophan + UV produces 3-HKG (hydroxykynurenine) and other products, 3-HKG- attaches to proteins and turns from clear to brown in color (46, 78, 118).
- Some key biochemical considerations related to lenticular cataracts, are tied to potential oxidative injury with aging: defense enzymes' G-3-PD, G-6-PD, aldolase, enolase, and PG kinase activity decrease with age. Aging is associated with decreased antioxidant concentration which leads to increased vulnerability to oxidative damage, and lipid peroxidation, e.g. decreased glutathione, ascorbate, Aging is also associated with decreased protein solubility and number of soluble proteins (protein denaturation by free radicals), increased disulfide bonds in proteins, oxidation of protein thiols, and changes in membrane permeability, all of which can lead to dehydration of the lenticular cells (osmotic change) especially with radiation exposure. In addition, formation of crystallins, which are high molecular weight aggregates that accumulate with aging, along with degraded polypeptides and amino acid changes e.g., loss of sulfhydryl groups,

deamination of glutamine and asparagine, are commonly observed with typical senile cataracts.

Typical physiological changes observed in the lens over time include: loss of gap junction proteins(15, 20, 22 kDa) with age, loss of cellular membrane potential, increased intracellular sodium concentration (25 mEq/l to 40 mEq/l), as well as changes in Na⁺, K⁺-ATPase activity, secondary to loss of the γ -isoform of ATPase with advancing age.

Changes in lenticular cells depend on the mechanism and location of the cataract process. Anterior subcapsular cataracts most commonly associated with UV light exposure, show lenticular metaplasia, i.e. the cells become spindle-shaped, (myofibroblast-like) in the central lens epithelium. Posterior subcapsular cataracts, which are commonly associated with ionizing radiation and also with UV, show germinal epithelium dysplasia and posterior migration along suture lines.(38, 154) Whereas nuclear cataracts, most commonly associated with aging (senile) show few cellular changes, as it seems the light scatter is produced by high molecular weight proteins in the cytoplasm. (135)

The observations regarding radiation induction of cataracts are not uniform, mainly due to the differences in cellular and biophysical and biochemical effects of various forms of radiation. There is not a universal bioeffect and cellular response across the spectrum of electromagnetic and particulate radiation energy. Prior common thinking on radiation-induced cataracts was posterior subcapsular (11, 13, 26) as the most common location, however they had potential to progress to full cortical, and even nuclear (mixed) cataracts with time(16, 19, 27, 42, 75, 103, 124, 126).

Energy deposition from cosmic, gamma rays, and neutrons causes ionization of lens constituents (mainly water) producing free radicals (primarily hydroxyl radicals) which can easily react and alter function of DNA and cell membranes.(83, 91, 98, 101) Cells with higher mitotic rate, such as the lens equatorial fibers, are differentially affected by these processes.

Typically a 9-12 month latent period from time of exposure to onset of lenticular opacity has been observed. The radiation-induced cataract has been typified by multiple vacuoles, feathery appearance, and even web-like fringes. Glare is a common initial complaint from patients with PSC cataracts.

Although it was the first clinical study to quantify cataracts in astronauts in association with their specific spaceflight radiation exposures(24), there were some issues with the authors previous study in trying to determine if the incidence of cataracts was higher than would be expected in the aging cohort evaluated. These issues include:

- Inequality in screening examination between the LSAH controls and astronauts, in that the controls typically had indirect, non-dilated ophthalmoscopy and no slit lamp examination vs. direct dilated ophthalmoscopy and slit-lamp in the astronaut exams.
- The influence of non-space flight radiation- UV, blue light exposure during high altitude flights; LASER, toxin (e.g. metals, anticholinesterases, antimalarials) exposure was not controlled in the astronauts

- The influence of space-acquired UV and blue light, independent of the cosmic and trapped particulate radiation, determined by the number of spacewalks (EVA-extravehicular activity) time spent with spacesuit visor up, amount of time looking through space windows with sun in the field of view, etc. was not controlled in astronauts.
- There was a lack of photographic documentation for post-hoc review of categorization/stage of cataracts, Instead there was subjective assignment of each diagnosed cataract by a single examiner, resulting in a clinical grading.
- Other risk factors for cataracts were not controlled in either group.

Although the data was highly suggestive of a dose-dependent increase in cataracts in the astronauts relative to age-matched controls, it is still difficult to attribute the risk specifically to the spaceflight radiation exposure, without controlling for the confounders.

In striving to answer the question, does spaceflight radiation produce an independent risk of cataracts in astronauts, we compared the incidence of astronaut cataracts to a population with a background similar to the typical astronaut between 1962 and 1985 – the military aviator. That comparison reveals some important findings: 1) astronauts do not acquire lenticular opacities at a younger age versus their military aviator counterparts, 2) the incidence density of cataracts is much higher in astronauts than in military aviators, 3) the location of cataracts in astronauts is not typical of either what is observed in aviators or what is commonly associated with ionizing radiation exposure.

Perhaps the first two findings can be explained by the fact that while the aviation flight exposure to radiation is common to both groups and occurs relatively early in their career, the exposure to space radiation usually occurs later in the astronaut career. However, given the above fact, the latency from age of exposure, as cited in Cucinotta et al(24), to the age of diagnosis, is longer than would be commonly observed with radiation-induction. This finding may be due to the reduced rate and total dose of exposure than is typically given during research studies on radiation bioeffects. However, the location of the cataracts in astronauts may be the most difficult to explain, if our current mechanistic understanding is correct.(38, 39, 46, 47) Perhaps space radiation, both cosmic and trapped particulate, produce cataract-like changes in the lens via a different mechanism than does ultraviolet, gamma and other ionizing radiation sources. Clearly the location of cataracts in the lens cortex in astronauts is not typical of the nuclear cataracts seen with aging alone.

What is needed:

A prospective study is underway, being led by one of the nation's experts in the field, Dr. Leo Chylack. This study may go a long way to determining if astronauts are truly at increased risk associated with their occupational exposures, although the numbers of individuals with significant space radiation exposure is quite small and the numerous confounders discussed above will still be at play. The study by Chylack, et al employs lenticular imaging with photographic records that will allow independent assessment of the classification/grade of the cataract in both astronauts and controls thereby eliminating the bias in grading of opacities, potentially affecting the earlier reported results.

Since the majority of cataracts detected in astronauts did not result in visual axis impairment thereby limiting the usefulness of acuity as an outcomes measure, the current prospective study would benefit from a more sensitive means of detecting cataract formation prior to the development of clinical sequelae. This would facilitate reducing the length of follow-up required to determine if a statistical and clinical difference exists between the study groups. Such a device has been recently developed at the NASA, John Glen Research Center, under a NASA-NEI interagency agreement and employs a dynamic light scattering device. It appears to be the most sensitive method of detecting early lens abnormalities, currently available for clinical use (3).

For future space missions, taking astronauts again beyond low earth orbit (LEO) and onto other planetary bodies within the solar system, an effective countermeasure to reduce the risk of biological effects in the crew needs to be developed. Countermeasures for exploration spaceflight should protect not only ocular tissue (18, 73, 119, 129, 132): such as the cornea, lens, retina, but also other tissues vulnerable to ionizing radiation-induced direct cellular injury and secondary oxidative damage. Understanding the mechanism of the cataract formation in space radiation-induced forms of the disease, may be pivotal in producing an effective countermeasure.(9, 129) Recent studies suggest that agents which limit the propagation of peroxidation and the interaction of reactive oxygen species(72) with cellular organelles (1, 107) and membranes(44, 73, 93, 131) may protect the lens(105) and retina(85, 90, 111) from damage. (4, 7, 10, 41, 74, 103, 105, 113, 125, 129, 137) Measuring the state of oxidative damage in the 2 study groups may improve characterization of the contributing factors. While understanding the role of spaceflight shielding(20, 67, 130), dietary and pharmacological interventions which may augment the inherent cellular repair mechanisms; (80) are likely to be helpful in developing an effective defense for exploration-class spaceflight.

Tables and Figures

Tables

Table 1: U.S. study data on cataracts prevalence and incidence- (51, 58, 63)

Framingham	n=2477	
Age group	% with lens changes (opacities prevalence)	% with visually significant cataracts
52-64	42	5
65-74	73	18
75-85	91	46
NHANES	n=10,000	
65-74	60	18
	5-year Incidence	
55	10	
60	16	
65	23	
70	31	
75	37	

Table 2: Incidence; Incidence Density and Age at Diagnosis for military pilots and astronauts

	Number of Cases (Number of Individuals)			Number of Person-years (Time of Observation)	Incidence Density /100 Person-years	Average Age at Diagnosis		
	Right Eye Only	Left Eye Only	Both Eyes	Both Eyes	Both Eyes	Right Eye	Left Eye	Both Eyes
Astronaut Corps	51	51	102 (54)	5,103 (1971 - June 2003)	1.999	61.2	60.8	61.0
Astronaut Corps (Grades 3 & 4 only)	4	4	8 (5)	5,103 (1971 - June 2003)	0.1568	65.8	68.5	67.1
U.S. Air Force Aviators	133	137	270 (179)	1,356,303 (1955 - 2000)*	0.0199	44.1	44.7	44.4
U.S. Navy Aviators	20	29	49 (37)	446,130 (1973 - 1999)	0.0110	41.0	39.5	40.1

(*The year 1999 was used twice to serve as a proxy for year 2000, which was not included in the data provided by the USAF. The difference in incidence density for 1955-1999 as compared with 1955-2000 with the year 1999 used twice as a proxy is less than 0.001cases/100 person years.)

Figures

Figure 1

Prevalence of cataracts as a function of age in astronauts, pilots and healthy U.S. males.

Prevalence of Cataracts amongst Astronauts, Pilots, and US Males as a function of Age

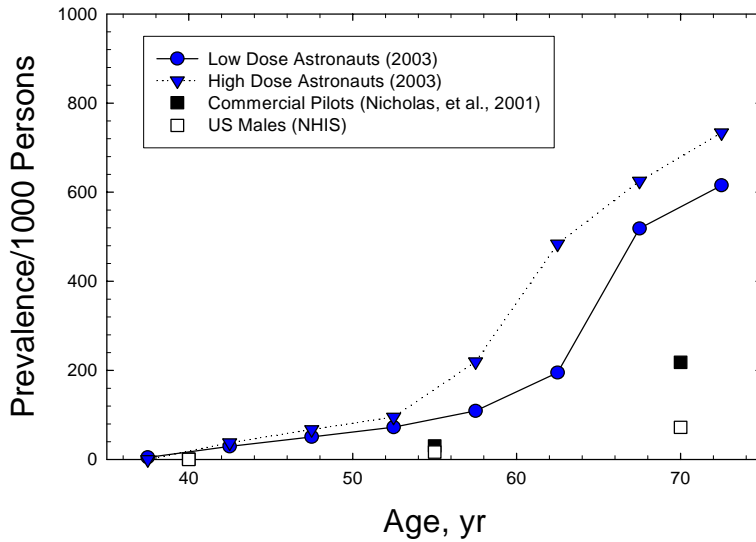


Figure 2

Cataract prevalence by age in U.S. astronauts

Prevalence of Cataracts among NASA Astronauts



Figure 3: Cumulative Prevalence of Cataract Cases by Age Category among Analogous Populations: Astronaut Corps, Air Force Aviators, Naval Aviators

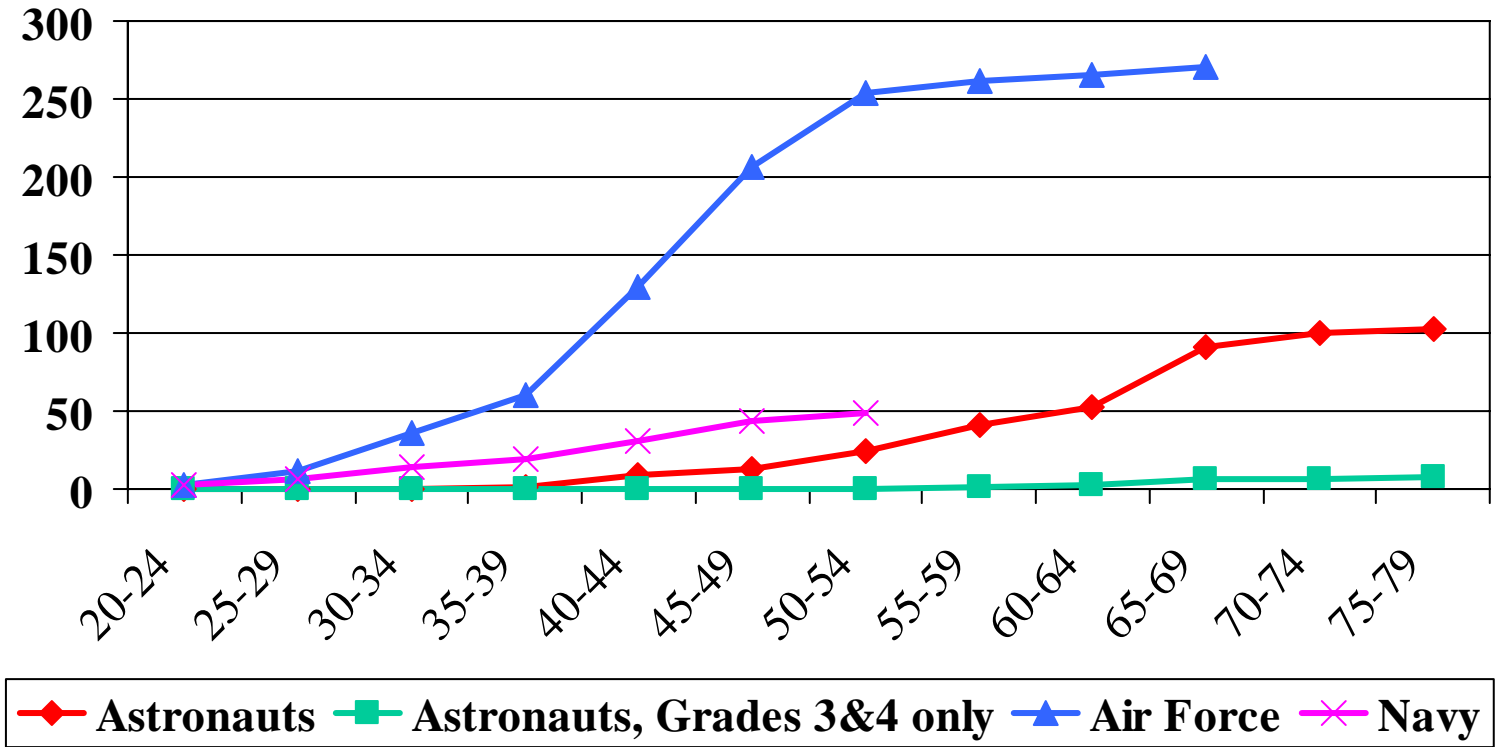


Figure 4; Average Age at Diagnosis of Cataracts among Analogous Populations:
Astronaut Corps, Air Force Aviators, Naval Aviators

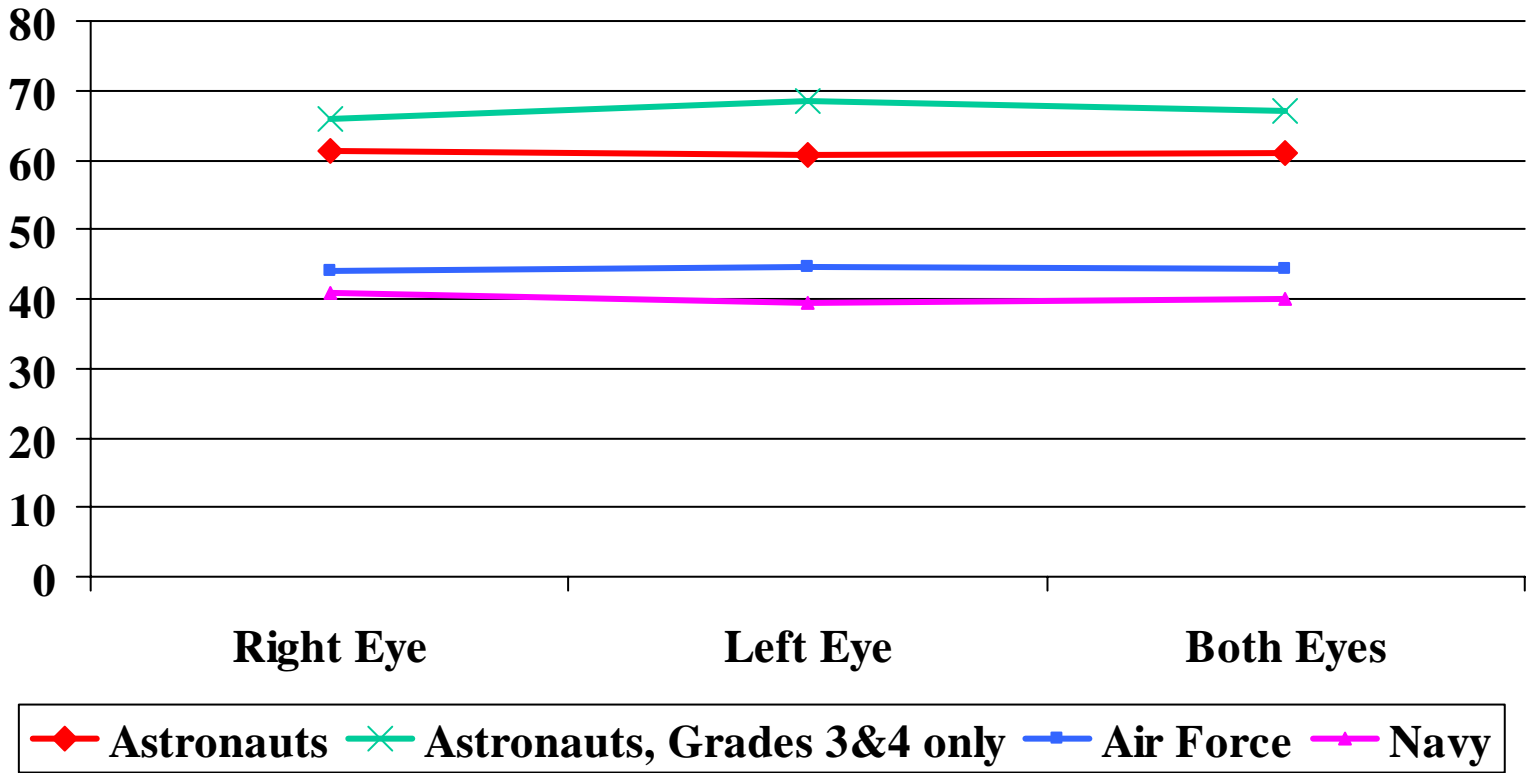
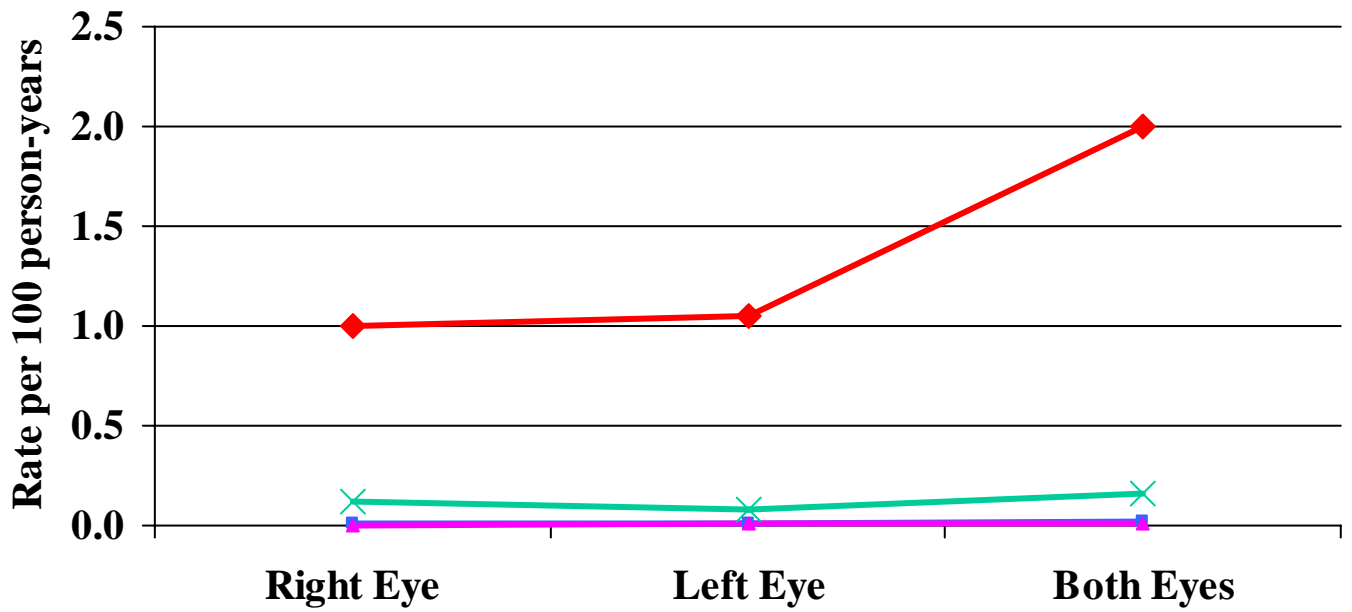
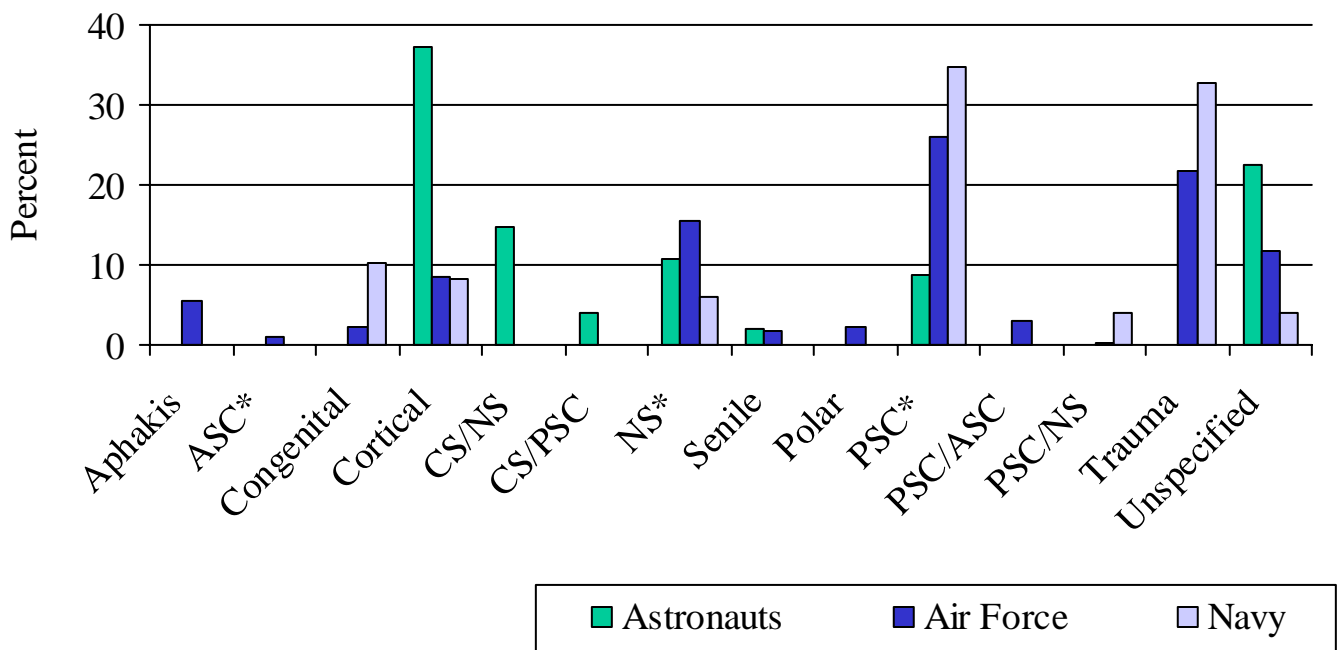


Figure 5: Incidence Density of Cataract Cases among Analogous Populations: Astronaut Corps, Air Force Aviators, Naval Aviators



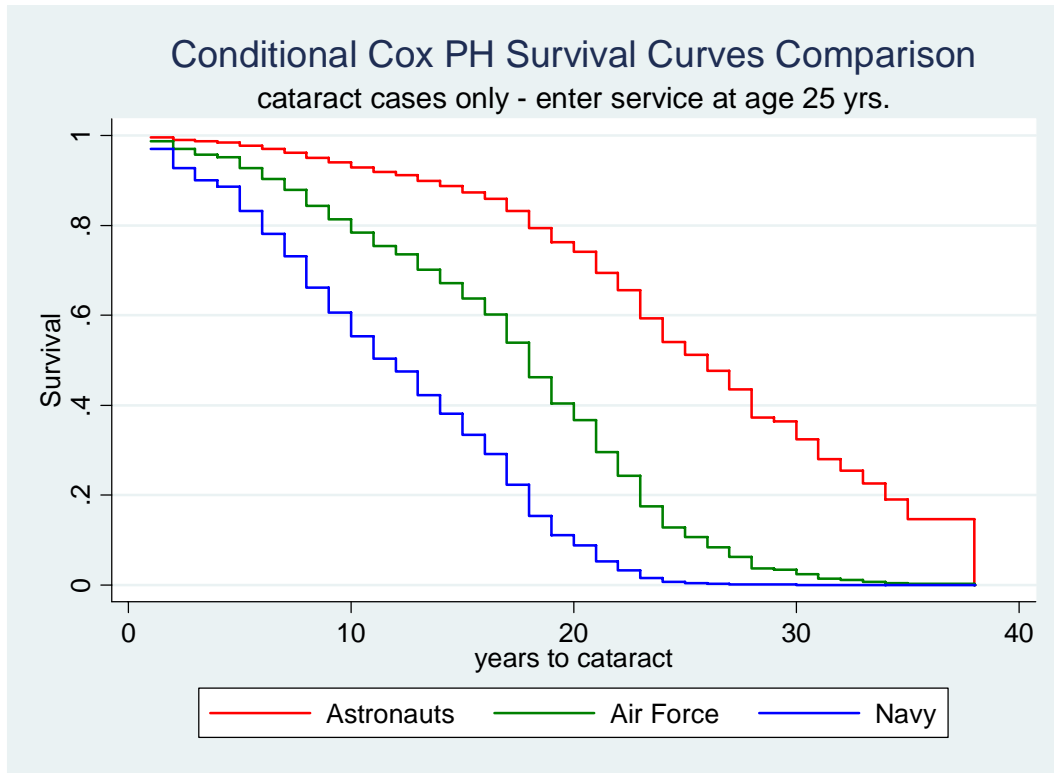
—◆— Astronauts —×— Astronauts, Grades 3&4 only —■— Air Force —▲— Navy

Figure 6: Ratio of Cataract Cases by anatomic location among Analogous Populations: Astronaut Corps, Air Force Aviators, Naval Aviators



* ASC = Anterior Subcapsular Cataract
 NS = Nuclear Sclerosis
 PSC = Posterior Subcapsular Cataract

Figure 7: Cox Porportional Hazards comparison of cataract cases in DOD pilots to astronauts, by years since entry into occupation.



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