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Review Article

Human Radiation-Induced Eye Diseases: A Scoping Review towards "*In-silico*" Experimental Studies

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Abstract

This article delves into how certain human tissues, as the eye's lens, are prone to damage from radiation. Notably, the eye's lens has shown a significant vulnerability to low- LET radiation through a variety of processes. There's been an effort by the International Commission on Radiological Protection (ICRP) to revise the guidelines on acceptable limits for high-LET radiation exposure. The article offers important perspectives on how radiation affects human tissues, emphasizing the necessity for correct radiation exposure guidelines. It also examines the potential impact of radiation on other eye diseases and the development of cataracts among health workers, flight personnel, and astronauts. According to this review results, more international work thought epidemiological studies is needed additionally to alternative approaches combining advanced computational modeling techniques and medical imaging data, we may be able to develop accurate computer models capable of simulating how radiation interacts with the eye. This could offer valuable insights into the root causes of radiation-induced eye diseases and aid in refining radiation protection strategies.

Keywords: Radiation; Eye; Lens; Cataract; Eye diseases.

Introduction

The International Commission on Radiological Protection (ICRP) has recognized that certain human body tissues, specifically the bone marrow, reproductive organs, and the eye's lens, have been particularly susceptible to radiation damage for over 50 years. These tissues' increased susceptibility to radiation, particularly which with low linear energy transfer (low- LET), can be linked to a number of cellular and molecular elements. For instance, the lens of the eye has demonstrated significant sensitivity to low-LET radiation through a variety of processes [1]. These include an elevated level of oxidative stress, abnormal lens epithelial cell proliferation and differentiation, and degenerative changes in the crystalline proteins of the lens. It's interesting to note that several subsets of human LECs with different radiation sensitivity have been found. One fraction responds to radiation by speeding up its rate of proliferation, whereas another subset develops a vulnerability to senescence or premature aging as a result of radiation exposure. Human cell-based *in vitro* studies and *in vivo* studies utilizing animal models like mice and rabbits has both provided evidence for the phenomenon of radiation-induced LEC growth. In contrast to other tissues, the lens of the eye exhibits an unusually high level of sensitivity to high-linear energy transfer (high-LET) radiation. The lens's reduced oxygen content, high nitrogen content, and state of cellular quiescence could all be contributing factors to this heightened sensitivity [2].

The US National Council on Radiation Protection and Measurements (NCRP), which has been pushing for a change in the guidelines for establishing acceptable limits for high-LET radiation exposure, has done so starting in 2016. In its place, they advocate using a radiation weighting factor (wR) known as relative biological effectiveness (RBE). The ICRP has also proposed a similar adjustment. The ICRP, however, has fallen behind in delivering up-to-date reports on high-LET radiation-induced cataracts in recent years. For radiation safety measures and protection tactics, it is crucial to assess and debate the potential effects of a potentially increased relative biological efficacy. The goal should be to preserve human health in areas where radiation exposure is a possibility. The lens exhibits various unique properties that make its radiobiological reaction particularly noteworthy, in addition to the previously mentioned low turnover of lens cells and their components. Notably, neither naturally nor after radiation exposure do primary malignancies develop in the lens. However, mounting data points to the potential contribution of tumor-associated variables to the initiation and progression of cataracts.

It's also interesting to take note of the one-of-a-kind reverse dosage rate effect that has been found in a very small dose rate range and affects how the lens reacts to DNA damage. These findings imply that the lens's reaction to radiation may be governed by still-unknown processes and mechanisms. These findings imply that the lens's internal processes and radiation-response mechanisms may still be under investigation. In order to further understand the biological processes and underlying mechanisms, continual efforts are required. Current programs like the LD Lens Rad, funded by the European CONCERT program, are working in this direction.

According to Shore et al. [3,4] and Blakely et al. (2010), ionizing radiation has been linked to the development of lens opacities, which can ultimately lead to cataracts. As the primary cause of significant vision loss and blindness globally, cataracts have been the subject of much research into their risk factors [5-7]. Some of these factors include infrared and ultraviolet B radiation exposure, use of corticosteroids, age, gender, genetic vulnerability, lifestyle decisions like smoking, chronic diseases like diabetes, and genetic predisposition [8-10].

Understanding these risk factors is crucial for developing effective preventative and therapeutic strategies. The level of vision impairment that a person considers bothersome varies substantially. The claimed incidence of self-diagnosed cataracts or the frequency of procedures to remove lenses, as a result, do not always correspond to the reported prevalence of observable lens opacities. Several grading systems for lens opacities have been established and used in epidemiological research in order to accurately define the diversity and severity of cataracts.

Methods

For this review article, a comprehensive search was conducted in the period of time from 01/12/2022 until 30/7/2023, on published medical literature using several electronic databases including Medline, Google Scholar & Science Direct. The research used keywords such as radiation exposure, eye, lens, cataract, eye diseases (Figure 1).

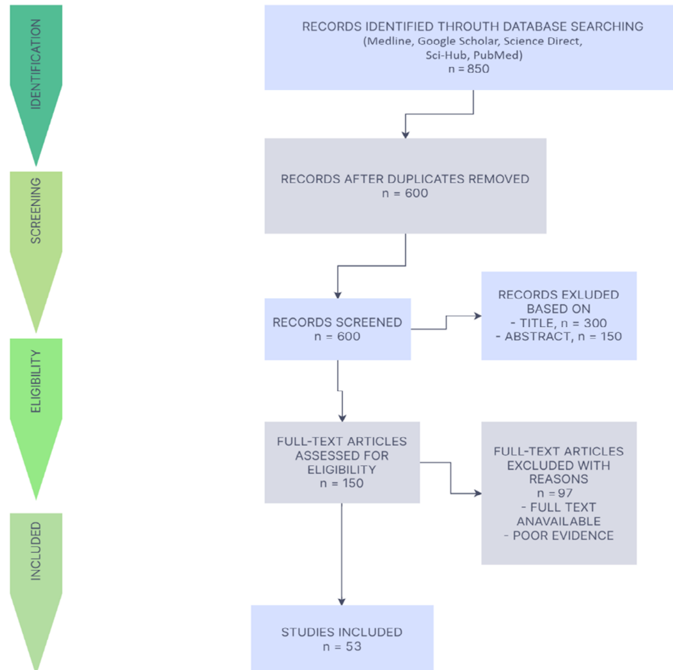

Figure 1: Research methodology flowchart.

Results

The Lens Opacities Classification System (LOCS) is one of these often-employed systems. It makes use of reference photographs to help ophthalmologists categorize nuclear cataracts, cortical cataracts, and posterior subcapsular cataracts (PSCs) into 5 to 6 degrees of severity based on their color and opalescence [11]. There are several methods in use, one of which was created by Merriam and Focht and is particularly helpful for identifying changes in the lens caused by radiation [12]. Other systems include the Oxford Clinical Cataract Classification and Grading System [13], the World Health Organization (WHO) Cataract Grading Group system [14] and the Wisconsin System [15].

It's important to understand that statistics on the prevalence of lens opacities are not directly comparable. This is due to the fact that estimates of prevalence heavily rely on the grading system used to assess opacities and the precise cutoffs or thresholds used within a given epidemiological investigation. In order to properly compare and understand data from research that use various approaches, a nuanced approach is required.

The POLA study, an innovative population-based research project from France, provides an estimation of the prevalence of "severe" cataracts associated with significant visual impairment. According to the study, "severe" cataracts are those that correspond to LOCS III stage 4 for nuclear or cortical cataracts, and stage 2 for posterior subcapsular cataracts. Men are reported to have a "severe" cataract incidence of 9.2% and women "severe" cataract incidence of 12.3% in the age group of 60-69 years. By the time a person reaches their 80th year, these percentages nonetheless substantially rise in later age groups, reaching 61.8% for males and 73.4% for women [16]. An accurately identified posterior subcapsular cataract (PSC) was present in 48% of male and 41% of female cataract cases in patients under the age of 60. Older individuals had a higher incidence of various opacities and combination types.

PSC can occur in the general population, despite the fact that it is commonly associated with exposure to ionizing radiation. According to Brown et al. [17], PSCs can develop independently or as a result of other eye disorders such as uveitis or retinal detachment. Although radiation exposure is a known risk factor for PSCs, it's important to remember that other factors may also affect how they appear. These discoveries illustrate the complexity and variety of the factors that influence cataractogenesis. For a very long time, cohort studies involving patients who received high radiation doses during radiotherapy and early studies on atomic bomb survivors were the main sources of epidemiological data regarding the effect of ionizing radiation on cataract development, which is still not entirely complete [3]. According to clinical research involving radiotherapy patients, parameters including radiation dose, dose rate, and fractionation can have an impact on the latency duration and the level of lens opacification [7,18,19].

It's crucial to keep in mind that not all radiation-induced ocular changes are clinically significant, and cataract development usually takes years following exposure [20]. The majority of posterior subcapsular cataracts (PSCs) are linked to ionizing radiation exposure, according to research by Belkacemi et al. [21] and Hall et al. [22]. Despite the fact that nuclear opacities do not seem to be related to radiation exposure [3,23,18,24], cortical opacities may be related to radiation exposure.

Numerous non-systematic review publications, each with a special concentration, have provided numerous viewpoints on the literature relating to this topic's epidemiological and experimental investigations. For instance, Cardis and Hatch [25] explore the cohort of Ukrainian Chernobyl liquidators as well as epidemiological elements of the Chernobyl event. Ainsbury et al. [7] combine epidemiological and mechanistic study results. Shore et al. [3] presents a critical analysis of the large studies that led to the modification of the ICRP guidelines. The eyes of medical professionals, a group of workers who may be exposed to high lens doses of radiation, are the focus of Rehani et al. [26]'s review, which is the last but not least.

The International Commission on Radiological Protection (ICRP), a group that provides guidance and recommendations on radiation protection, classifies cataracts as a latent deterministic radiation effect. According to this classification, cataracts are a predicted result after a specific amount of radiation exposure and develop later. The ICRP noted that detectable lens opacities might develop following a single, brief exposure between 0.5 and 2 Gy or after a series of sustained exposures between 5 and 6 Gy in their 2007 recommendations.

Animal experiments and epidemiological studies on humans also lend support to these estimations. But it's critical to be aware of any constraints that might be imposed on these data sources. Due to the wide range of diagnostic techniques used in ophthalmology and the frequently brief observational intervals used in epidemiological and clinical investigations, the amount of information these studies may sometimes provide may be constrained. As a result, the ICRP suggested that it could be essential to reevaluate current exposure criteria.

In light of this, the ICRP has announced a considerable reduction in the recommended equivalent dosage limit for the lens of the eye during planned exposure conditions. The updated recommendation establishes a limit of 20 mSv per year, averaged over a period of five years, and guarantees that exposure does not exceed 50 mSv in any individual year (ICRP, 2011). This revision was based on data from a cohort study of radiological technologists [27], survivors of atomic bomb incidents [28,29], and individuals who helped with the cleanup following the Chernobyl nuclear disaster [18]. All of these investigations revealed that the threshold model's previous presumption, which predicted a particular level of exposure beyond which the effect is noticed, needed to be reviewed and maybe altered.

The epidemiological research investigating the relationship between low doses of ionizing radiation and the development of cataracts are reviewed in-depth and methodically in the current work. It describes the requirements for starting new research projects and identifies demographics that would be the best candidates for upcoming investigations. The study analyzes the unique concerns relevant to such a situation when examining the relationship between radiation exposure and cataract development, with a focus on Germany as a sample example of an industrialized country.

Radiation Exposure and Cataract Development in Healthcare Professionals

This inquiry focused on a group of U.S. radiologic technicians who were initially cataract-free in order to go into more depth about the specifics of the largest known cohort study addressing prolonged exposure. The technologists had received X-ray exposure over a 19.2- year period on average, with a median estimated dose of 28.1 mSv to the lens [27].

There was observed a consistent, linear increase in the excess relative risk (ERR) of being diagnosed after making the necessary adjustments to account for various factors such as gender, birth year, marital status at the time of initial data collection, body mass index, status of diabetes, smoking behavior, presence of hypercholesterolemia (high cholesterol), hypertension, alcohol consumption levels, arthritis, exposure to diagnostic X-rays, and head- targeted radiotherapy. This indicates that when these risk variables change, so do the probabilities that a person will be diagnosed with a cataract. The rise was quantified as 1.98 per Sievert (Sv), with a 95% confidence interval spanning from 0.69 to 4.65 per Sv, even though it was not deemed to be statistically significant. This shows that the results revealed a potential increase in cataract risk with each Sievert of exposure, despite the absence of statistical significance. Further study would be necessary to establish this potential trend, though, given the large range of the confidence interval.

Advanced statistical approaches, notably multivariate Cox regression models, were used in the study's primary analysis. With a 95% confidence interval of 0.99-1.40, these models showed that the hazard ratio (HR), a measurement of the probability of acquiring cataracts, was predicted to be 1.18. This comparison was done between subjects in the categories with the highest exposure (60.1 mSv on average for the lens dose) and the categories with the lowest exposure (5.1 mSv on average for the lens dose). This estimate took into account a number of the previously listed parameters.

Because such high exposure levels were thought to be highly implausible and hence potentially bias the results, participants with occupational exposure estimates exceeding 80 mSv were omitted from this particular phase of the research. This suggests that those who have had more X-ray exams and people who have had head and neck radiation treatments are more likely to acquire cataracts.

Information about 647 documented cases of cataract extraction added to the study's richness. With the use of this information, the study was able to clarify the subject. For instance, the research showed that people with 25 or more X-ray exams had an adjusted HR of 1.50 (with a 95% confidence interval of 1.09-2.06) compared to subjects with fewer than five extractions. In a similar vein, the study found that individuals with head and neck cancer who had received radiation therapy had an HR of 1.71 (with a 95% confidence interval of 1.09-2.68).

Large cohort size and a broad range of clinical data, which include a range of risk variables and potential confounding factors, are the study's key advantages. However, its findings might be somewhat limited due to the lack of clinical confirmation and the lack of a particular ophthalmological classification of the lens opacities. The results are somewhat questionable because the study's cataracts were self-reported, which raises the chance that the diagnosis may have been influenced by the participants' subjective judgments.

The International Atomic Energy Agency (IAEA) launched the global investigation Retrospective Evaluation of Lens Injuries and Dose (RELID) in 2008. This multidisciplinary, international research project sought to learn more about the effects of radiation exposure on the eye through a series of ocular assessments. The preliminary results from these tests have already been reported in a number of journals. 93 non-exposed people served as the control group in the initial RELID trial, which included a cohort of 116 interventional cardiology practitioners. The topics came from two conferences that were held in Montevideo and Bogota, respectively [30]. The prevalence of posterior lens opacities linked to radiation exposure was assessed using a slit lamp examination performed by two different examiners. They used a modified Merriam-Focht scoring system to conduct their evaluations.

In order to estimate lens exposures, the researchers used data from tests assessing scattered radiation doses in catheterization laboratories along with workload-specific factors and staff safety precautions. Interventional cardiologists' cumulative lens dose from work exposure ranged from 0.1 to 27 Sievert (Sv), with a mean value of 6.0 Sv. The standard deviation, which gauges the data's variability, was 6.6 Sv. The total occupational lens exposure for the nursing and technical staff ranged from 0.2 to 4.5 Sv, averaging 1.5 Sv, with a standard deviation of 1.4 Sv.

The prevalence of posterior lens opacities, which are signs of cataract formation, was also investigated by the researchers across a range of professional categories. They discovered that the incidence was lowest in the control group who had no radiation exposure, with a frequency of 12%, and that it was highest among interventional cardiologists (38%), followed by nurses and technicians (21%). The relative risks for developing lens opacities were noticeably higher for the exposed professional groups in comparison to this unexposed control group. For interventional cardiologists, the relative risk was 3.3 (with a 95% confidence interval of 1.7-6.1) while for nurses and technicians, it was 1.7 (with a 95% confidence interval of 0.8- 3.7). This shows that radiation exposure at work considerably raises the likelihood of cataract development.

The study has some limitations, despite the contributions it made. Combining data from two distinct conferences helped to somewhat offset the low number of attendees. However, the study did not assess the high likelihood of self-selection among the study participants, which could result in some selection bias. Furthermore, despite the fact that the cardiologists were on average 5 years older than the control group, no adjustments were performed for the age factor when comparing the prevalence of lens opacity. Despite these drawbacks, the study does give some more evidence in favor of the theory suggesting a higher risk for interventional radiology workers.

As part of the larger RELID research, a complementary study was conducted with a specific focus on medical professionals who went to a national conference in Malaysia. This study's sample size was lower, and it was carried out in 2010 by Ciraj-Bjelac and associates. The presence of posterior subcapsular cataracts (PSC), a particular form of cataract, was evaluated in three groups. 56 interventional cardiologists, 11 nurses, and 22 people who were not exposed to occupational radiation made up the groups. These people served as the control group.

The results of the study showed that there were substantial differences in the prevalence of PSC between the groups. It was discovered that interventional cardiologists had the greatest rate, at 52%, closely followed by nurses, at 45%. The prevalence was just 9% in the non- exposed control group, which was noticeably lower.

The cardiologists' cumulative lens doses from work exposure ranged from 0.02 to 43 Sv, with an average dose of 3.7 Sv and a standard deviation of 7.5 Sv, showing a wide range of values. With an average dose of 1.8 Sv and a standard deviation of 3.1 Sv, the nurses' range was less variable, ranging from 0.01 to 8.5 Sv. Both interventional cardiologists and nurses showed a statistically significant elevated risk of getting PSC as compared to the control group. Cardiologists' and nurses' respective relative risk ratios were 5.7 (with a 95% confidence interval of 1.5-22) and 5.0 (with a 95% confidence interval of 1.2-21). This demonstrates that radiation exposure at work is associated with a higher risk of PSC in healthcare workers.

Milacic [31] conducted a cohort analysis on 3,240 healthcare workers in Serbia who had worked between 1992 and 2002 as part of a different study. The aim was to examine the cataract risk between 1,680 people who were not exposed to ionizing radiation and 1,560 people who were. However, neither the term "cataract" nor the procedure for calculating cataract incidence rates were made explicit. Although they identified 115 (7.3%) and 26 (1.5%) occurrences in the exposed and non-exposed groups, respectively, they also documented an incidence rate ratio of 4.6.

A preliminary investigation by Mrena et al. [32] in Finland focused on 57 physicians with at least 15 years of experience and who had been exposed to an effective dose of at least 10 mSv, as recorded in the national dosage registry. This study's primary goal was to determine how common cataracts are among these medical practitioners.

The researchers' logistic regression analysis used the presence or absence of lens opacities, namely those graded 1 or above, as the binary outcome variable. For this, the LOCS II method—a well-known methodology for categorizing and grading lens opacities-was used. They discovered that 5%, or three study participants, had posterior subcapsular opacities and 7%, or four participants, had cortical opacities. The computed odds ratio per 10 mSv of effective dosage for non-nuclear cataract after adjusting for age, sex, and smoking behavior was 1.04 (with a 95% confidence interval of 0.80-1.28). This indicated a small but not statistically significant increase in the risk of cataract development with each additional dose of 10 mSv.

The lack of a non-exposed reference group to compare against and the relatively small size of the study group, however, limit how interpretable these data can be. Because of this, even while the data gives experienced doctors some preliminary understanding of the potential risk of cataract formation owing to radiation exposure, the results should be interpreted cautiously and would benefit from additional investigation in larger, more thorough research.

The Effects of Cosmic Radiation on Flight Personnel and Astronauts

The effects of cosmic radiation exposure on flight crew members, especially astronauts, and its connection to the development of cataracts have been the subject of a variety of scientific studies over the past ten years [33-36,23].

The NASA Longitudinal Study of Astronaut Health (LSAH) investigation is one noteworthy study from this collection of studies. This extensive study [33] examined the likelihood of lens opacities, a precursor to cataracts, in a cohort of 295 astronauts. For analysis, the research participants were divided into two separate groups: one group was made up of astronauts who only participated in missions with lens radiation exposure below 8 mSv (averaging about 3.6 mSv), and the other group was made up of astronauts who participated in missions with an average lens radiation dose of 45 mSv.

Slit-lamp biomicroscopy was used to conduct investigations and analyze participants' eyes. Furthermore, using thermos-luminescent dosimeter (TLD) badges and complex calculations, mission-specific lens dosages were rebuilt. According to the risk analysis, astronauts exposed to 8 mSv of space radiation had a 65-year-old cataract hazard ratio of 2.44 (95% CI 1.20–4.98). Comparable hazard ratios for nuclear cataracts and posterior subcapsular cataracts (PSC) were 3.44 (95% CI 1.07-11.1) and 5.76 (95% CI 0.97-34.2), respectively.

These studies suggest that the lens may respond differently to high-linear energy transfer (LET) radiation than to low-LET radiation, which constitutes a significant percentage of the cosmic radiation to which astronauts are exposed. Despite the small sample size, the study's high value is due in part to the detailed lens radiation exposure data with cumulative dose reconstruction, routine eye exams, the lengthy follow-up period, and the careful assessment of potential confounding factors. An important limitation of the study is the absence of a universally recognized classification system for cataracts, which can lead to differences in the way lens opacities are identified.

The relationship between cosmic radiation exposure and lens opacities in-flight crew members has been further explored in a number of research. A more extensive research that included 95 military aircrew members greatly enlarged the NASA Longitudinal Study of Astronaut Health (LSAH). The LOCS III system was used in this expanded research to grade lens opacities using advanced digital Scheimpflug camera imaging techniques [23]. By analyzing various potential confounding factors, such as dietary practices, exposure to ultraviolet radiation, a history of asthma, and past diagnoses of hypertension, this larger study significantly improved upon its predecessor.

Comparing astronauts whose cumulative career lens dosage exceeded 10 mSv to others, the odds ratio for "high" posterior subcapsular cataracts (PSC) opacities (defined as 0.1% opaque) was found to be 2.23 (95% CI 1.16-4.26). This study did have some drawbacks, one of which being the possibility of selection bias as a result of the exclusion of astronauts who had undergone lens implant procedures and the high rate of non-participation (about 45%) among retired people.

Another insightful study by Jones et al. in 2007 [36] looked at the prevalence of lens opacities in a group of astronauts and pilots. They gathered employment data from the US Air Force, US Navy, and 5,086 years from NASA astronauts, totaling over 13.5 million person- years in employment.

Lens opacities were assessed in this investigation using a self-reported approach. However, the lack of precise definitions for the term "cataract" or information on the precise radiation dosage in the study may have caused some uncertainty in the findings. By the time they turned 50, about 8% of astronauts reported having cataracts, based on the data that was gathered. By the time they were 70 years old, this percentage had significantly climbed to about 60%.

The risk ratios for getting cataracts were determined to be 2.6 (with a 95% confidence interval of 1.5-4.8) and 4.1 (with a 95% confidence interval of 2.1-8.0) when comparing US Air Force and Navy pilots to astronauts, respectively. According to these data, astronauts appear to have a considerably higher risk of developing cataracts than their military counterparts.

The study was limited, however, by the lack of follow-up information for the Air Force and Navy soldiers who were first examined but did not have cataracts. Due to the absence of information, it was challenging to compare the chance of cataract development over time across the various groups. Therefore, while the results offer valuable preliminary insights, more studies would be helpful to confirm these findings and offer more in-depth analysis.

In a different study, a Scheimpflug camera system was used to analyze the lens opacities of a sample of 21 astronauts in comparison to 395 control subjects [35]. This comparison showed that the astronauts' lenses' posterior cortex and capsule had much higher levels of opacities. This study's main goal was to compare the state of astronauts' eye lenses to that of controls to assess their condition. Apart from the time spent in space, the study did not contain any estimates of radiation exposure. This experiment did not demonstrate a dose-response connection, but it did confirm the effectiveness of the Scheimpflug system in determining lens opacities.

The study carried out by Rafnsson and colleagues in 2005 primarily focused on commercial aircraft pilots, in contrast to research involving astronauts. The researchers sought to determine the prevalence of lens opacities specifically in Icelandic airline pilots using slit lamp microscopy in conjunction with the WHO's streamlined cataract grading system.

The information gathered from these pilots was then compared to data obtained from a sample of male Icelandic citizens who were chosen at random. It is important to note that the study took age, smoking history (ever *vs*. never), and frequency of sunbathing into account. When compared to the control group, which consisted of 374 people, it was discovered that the odds ratio for the development of nuclear cataracts among those who had ever pursued a career as a pilot (a total of 71 people) was 3.02 (with a 95% Confidence Interval ranging from 1.44 to 6.35).

It's interesting that no distinct pattern could be found despite an increase in occupational effective radiation exposure. Despite these results, there are a number of study- related constraints that make it difficult to evaluate the data. First off, the tiny sample size can reduce the results' statistical significance.

Secondly, ionizing radiation exposure, a factor that may have a big impact on cataract development, was not measured in the study. The study also ignored other significant risk factors for the development of cataracts. Finally, concerns about the choice of control groups raise concerns about the validity of the study's comparative components. The problems arising from the selection of the control groups may unintentionally have impacted the validity of the comparison study, making it more difficult to understand the results.

Beyond Cataracts: Radiation's Effects on Other Ocular Diseases

A report providing a thorough evaluation of the effects of radiation on ocular health was published in 2016 by the National Council on Radiation Protection and Measurements (NCRP) of the United States. Based on evidence collected before the early 1980s, the International Commission on Radiological Protection (ICRP) stated in 1984 that ocular tissues, with the exception of the lens, were generally resistant to radiation. However, since making this assertion, the ICRP hasn't offered any fresh findings or evaluations on the matter. The ICRP acknowledged in a 2012 statement that ocular problems other than lens opacification could manifest after acute or fractionated doses of between 5 and 20 Gy, however, earlier research suggested that this assertion was mostly connected to edema, atrophy, and telangiectasia. As a result, the radiation sensitivity of additional ocular structures at low to moderate dosage and dose rate levels is still completely unknown.

Furthermore, beyond cataracts, neither the ICRP nor the NCRP has had in-depth talks about the potential associations between radiation exposure and the emergence of a variety of ocular disorders. These include glaucoma, macular degeneration, and the common eye consequence of diabetes known as diabetic retinopathy. The effects of radiation on various ocular structures and the possibility of related disease, therefore, clearly call for a more thorough investigation and updated guidelines. The subset of atomic bomb survivors had a much higher risk of normal-tension glaucoma, a specific kind of primary open-angle glaucoma, according to research. On the other hand, there was no statistically significant decline in the risk for retinal degeneration and primary high-tension glaucoma. In these same survivors, the radiation dosage also correlated positively with retinal degeneration and retinal arteriolosclerosis, but negatively with the diameter of the central retinal vein equivalent. The risks for self-reported primary glaucoma, macular degeneration, and aggregate glaucoma in the USRT cohort of radiologic technologists and the Mayak employee cohort, however, were not statistically significant. Despite the small number of cases, there was a discernible rise in the risk of diabetic retinopathy among numerous sub cohorts of atomic bomb survivors. However, unless the prevalence of diabetic retinopathy among the cohort's diabetic individuals is evaluated in relation to radiation dose, the true link between radiation exposure and diabetic retinopathy remains unclear. Considerations like the length of the diabetes diagnosis should be included in this analysis. Currently, normal-tension glaucoma is the only serious eye condition associated with a noticeably elevated risk from radiation exposure, aside from cataracts. This increased risk, meanwhile, has only been identified among atomic bomb survivors thus far. It should be noted that normal-tension glaucoma is the most prevalent kind of glaucoma in the Japanese population, in contrast to other global populations. More testing of these results in other radiation-exposed populations, such as Mayak employees, is also necessary.

Predicting Radiation-Related Eye Diseases with Artificial Intelligence

Particularly in the timely and precise prognosis of radiation-related eye diseases, artificial intelligence has demonstrated significant potential for improving the accuracy and efficiency of ocular medical imaging analysis. Healthcare professionals can gain insightful knowledge of the pathologies underlying eye diseases by utilizing deep learning and machine learning algorithms, which will help them choose the best treatments and improve patient well- being [37].

The development of automated grading systems for nuclear cataracts is one instance of artificial intelligence being used in ocular medical imaging. These algorithms can learn disease indicators directly from the data by training computational models on annotated datasets, offering important insights into the underlying pathologies. The mean absolute error and processing time were dramatically reduced after testing on a clinical dataset of slit-lamp images. This automated method could improve nuclear cataract grading and automate cataract diagnosis.

Another illustration is the classification of diabetic retinopathy using deep convolutional neural networks. Researchers have improved segmentations by using these algorithms to produce accurate and effective segmentations that outperform current methods. The proposed method represents a significant advancement in the field and has the potential for clinical application because it accurately and efficiently segments data using entropy sampling, boosting-based learning, and the SoftMax logistic classifier.

As a result, the timely and precise prognosis of radiation-related eye diseases holds great promise for the integration of modeling "in-silico" with artificial intelligence combined with ocular medical imaging. Improved diagnosis and treatment of eye diseases have resulted from the use of deep learning and machine learning algorithms in the analysis of ocular medical images [38]. These ground-breaking ideas have the power to transform the industry and improve patient well-being [39].

Conclusions

The long-held belief that the eye's lens is one of the body's most radiosensitive tissues— indeed, the most sensitive within the ocular region-remains accurate. Notably, it is no longer generally recognized that radiation-induced cataracts are a deterministic consequence with a clearly defined, rather high-dose threshold. The International Commission on Radiological Protection (ICRP) bases its operations on the tenet that the rate of radiation exposure has no bearing on the incidence of cataracts and that mild lens opacities can gradually advance to visually significant cataracts. The present data broadly supports the idea of dose rate insensitivity, but it is unclear whether mild opacities or severe cataracts advance with lower doses and dosage rates. Regarding the presence of a threshold for radiation-induced cataracts and whether or not cataracts should in fact be categorized as tissue reactions, there are still unanswered problems. These topics demand further investigation. It is crucial to include and regularly evaluate new biological and epidemiological data to create the most expert judgments that are based on the best available evidence for radioprotection objectives.

Research into cataracts and other ocular side effects of radiation exposure is important for both radiation protection and radiotherapy since cataracts are a common side effect in healthy tissue. Furthermore, the only serious health consequence of radiation exposure in astronauts that has been consistently related is cataract development. However, since 2012, the US National Aeronautics and Space Administration has not performed any additional study in this field. Therefore, it will be crucial to conduct epidemiological studies in terrestrial cohorts in order to provide a strong scientific foundation for predicting the risk of radiation-induced cataracts in astronauts and other space travelers.

There have only been a few epidemiological studies that have looked at the connection between low-dose ionizing radiation exposure and the development of cataracts. Only six research studies out of a small number have been able to quantify the risk per Sievert (Sv), a unit of ionizing radiation. Only three of these articles have also found a reasonable dosage threshold. There has historically been a speculative belief in the existence of a dose threshold at which the likelihood of cataract onset increases. However, as observed by Shore and colleagues in their 2010 research, the specific empirical evidence needed to prove this concept is still absent. To clarify the relationship between ionizing radiation exposure and cataract formation, additional comprehensive investigations are required due to the ambiguity and inconsistency in the existing body of data.

Numerous people in Germany and elsewhere are exposed to ionizing radiation every year, whether for work-related or medical reasons. Due to the nature of their profession, interventional cardiologists are frequently a notable group exposed to such radiation. Given the size of the cohort and the quantity of exposure they experience, this makes them an excellent cohort for examining the association between radiation exposure and cataract development in the German population. Additionally, if these studies use a similar methodology, this particular cohort presents a chance for a combined study with comparable populations from other nations. It's critical to keep in mind that there are more study groups accessible on a global scale that have experienced various levels of radiation exposure. People who were exposed to radiation in the wake of the Chernobyl tragedy, such as cleanup workers or residents of radiation-affected areas, present suitable research subjects, according to studies by Worgul et al. in 2007 [18] and Day et al. in 1995 [40]. Residents of the Techa River area and employees of the Mayak facility are two more noteworthy study populations that were addressed in studies by Kreisheimer et al. in 2003 and Azizova et al. in 2011 [41,42].

The current corpus of research on this subject could be greatly enhanced by these diversified cohorts from various geographic areas and exposure scenarios, which could offer a larger and more thorough understanding of the impacts of radiation exposure. There is a wide range of ionizing radiation exposure to the eye lens in modern occupational settings, with the overall dose potentially reaching several Sieverts (Sv). Medical professionals, particularly those doing minimally invasive interventional procedures, have made the most thorough attempts to measure this dosage. It is crucial to delve deeper into the complex chemical pathways and hereditary predispositions causing cataracts. As recommended by the Strahlenschutzkomission in 2009 [43-47], this should be explored in conjunction with epidemiological research that concentrates on the dose-response connection.

Therefore, gathering biological samples may offer a novel strategy that adds a new level of complexity to upcoming research projects. Blood and other bodily fluid samples, for example, are extremely simple to collect and may include important information. As described in the 2010 study by Shore et al., [3] the Radiation Effects Research Foundation (RERF) has developed a tissue bank that contains lens cells that were taken from the cataracts of atomic bomb survivors. Furthering our understanding of this complex problem, this method may provide essential insights into the intricate interplay between hereditary variables, cellular mechanisms, and radiation exposure in the development of cataracts.

Additional epidemiological research will be required to precisely determine the dose- response relationship between ionizing radiation exposure and the development of cataracts. These studies will face a number of difficulties, such as the difficult issue of accurately gauging health results. Several effective instruments have been created through prior research initiatives. It is advised to start with pilot research due to the considerable cost involved in carrying out these studies. Designing the study's instruments with the intention of doing combination analyses and boosting statistical power can yield significant benefits. A coordinated project including Europe is currently being planned to carry out this crucial job. Finally the results on tissue normal functioning and radiation consequence prediction in terms of temperature elevation for example the widely used the non-ionizing band could be studied with "in-silico" tissue damage calculations [39,47]. Recent integrated tissue models or body phantoms could enable the modeling and analysis of physiological processes and pathophysiological consequences of organs under external beam radiation.

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References

1. ICRP (1991) Recommendations of the International Commission on radiological protection. ICRP publication 60 Ann ICRP 21: 1-201.
2. ICRP (2007) Recommendations of the International Commission on radiological protection. ICRP publication 103. Ann ICRP 37: 1-332.
3. Shore RE, Neriishi K, Nakashima E (2010) Epidemiological studies of cataract risk at low to moderate radiation doses: (not) seeing is believing. Radiat Res 174: 889-894.
4. Blakely EA, Kleiman NJ, Neriishi K, Chodick G, Chylack LT, et al. (2010) Radiation cataractogenesis: epidemiology and biology. Radiat Res 173: 709-717.
5. Seddon J, Fong D, West SK, Valmadrid CT (1995) Epidemiology of risk factors for age-related cataract. Surv Ophthalmol 39: 323-334.
6. Asbell PA, Dualan I, Mindel J, Brocks D, Ahmad M, et al. (2005) Age-related cataract. The Lancet 365: 599-609.
7. Ainsbury EA, Bouffler SD, Dörr W, Graw J, Muirhead CR, et al. (2009) Radiation cataractogenesis: a review of recent studies. Radiat Res 172: 1-9.
8. West S (2007) Epidemiology of cataract: accomplishments over 25 years and future directions. Ophthalmic Epidemiol 14: 173-178.
9. Otake M, Schull WJ (1991) Radiation Cataract A Review of Forty-Five Years Study of Hiroshima and Nagasaki Atomic Bomb Survivors II. J Radiat Res 32: 283-293.
10. Robman L, Taylor H (2005) External factors in the development of cataract. Eye 19: 1074-1082.
11. Chylack LT, Wolfe JK, Singer DM, Leske MC, Bullimore MA, et al. (1993) The lens opacities classification system III. Arch Ophthalmol 111: 831-836.
12. MerriamJr GR, Focht EF (1962) A clinical and experimental study of the effect of single and divided doses of radiation on cataract production. Trans Am Ophthalmol Soc 60: 35-52
13. Sparrow JM, Bron AJ, Brown NAP, Ayliffe W, Hill AR (1986) The Oxford clinical cataract classification and grading system. Int Ophthalmol 9: 207-225.
14. Thylefors B, Chylack LT, Konyama K, Sasaki K, Sperduto R, et al. (2002) A simplified cataract grading system The WHO Cataract Grading Group. Ophthalmic Epidemiol 9: 83-95.
15. Klein BEK, Klein R, Linton KLP, Magli YL, Neider MW (1990)

Assessment of cataracts from photographs in the Beaver Dam Eye Study. Ophthalmology 97: 1428-1433.

16. Delcourt C, Carrière I, Ponton-Sanchez A, Lacroux A, Covacho M J, Papoz L, et al. (2000) Light exposure and the risk of cortical, nuclear, and posterior subcapsular cataracts: the Pathologies OculairesLiees a l'Age (POLA) study. Arch Ophthalmol 118: 385-392.
17. Brown NA, Shun-Shin GA, Lewis P, Cramp WA, Arlett C, et al. (1989) Relationship of cataract to radiation sensitivity. Br J Ophthalmol 73: 955-959.
18. Worgul BV, Kundiyev YI, Sergiyenko NM, Chumak VV, Vitte PM, et al. (2007) Cataracts among Chernobyl clean- up workers: implications regarding permissible eye exposures. Radiat Res 167: 233-43.
19. Lipman RM, Tripathi BJ, Tripathi RC (1988) Cataracts induced by microwave and ionizing radiation. Surv Ophthalmol 33: 200-210.
20. Wilde G, Sjöstrand J (1997) A clinical study of radiation cataract formation in adult life following γ irradiation of the lens in early childhood. Br J Ophthalmol 81: 261-266.
21. Belkacémi Y, Ozsahin M, Pène F, Rio B, Laporte J P, et al. (1996) Cataractogenesis after total body irradiation. Int J Radiat Oncol Biol Phys 35: 53-60.
22. Hall P, Granath F, Lundell M, Olsson K, Holm L E (1999) Lenticular opacities in individuals exposed to ionizing radiation in infancy. Radiat Res 152: 190-195.
23. Chylack LT, Peterson LE, Feiveson AH, Wear ML, Manuel FK, et al. (2009) NASA study of cataract in astronauts (NASCA). Report 1: Cross-sectional study of the relationship of exposure to space radiation and risk of lens opacity. Radiat Res 172: 10-20.
24. Minamoto A, Taniguchi H, Yoshitani N, Mukai S, Yokoyama T, et al. (2004) Cataract in atomic bomb survivors. Int J Radiat Biol 80: 339-345.
25. Cardis E, Hatch M (2011) The Chernobyl accident—an epidemiological perspective. Clin Oncol 23: 251-260.
26. Rehani MM, Vano E, Ciraj-Bjelac O, Kleiman NJ (2011) Radiation and cataract. Radiat Prot Dosimetry 147: 300-304.
27. Chodick G, Bekiroglu N, Hauptmann M, Alexander BH, Freedman DM, et al. (2008) Risk of cataract after exposure to low doses of ionizing radiation: a 20-year prospective cohort study among US radiologic technologists. Am J Epidemiol 168: 620-631.
28. Neriishi K, Nakashima E, Minamoto A, Fujiwara S, Akahoshi M, et al. (2007) Postoperative cataract cases among atomic bomb survivors: radiation dose response and threshold. Radiat Res 168: 404-408.
29. Nakashima E, Neriishi K, Minamoto A (2006) A reanalysis of atomic-bomb cataract data, 2000–2002: a threshold analysis. Health phys 90: 154-160.
30. Ciraj□Bjelac O, Rehani MM, Sim KH, Liew HB, Vano E, Kleiman NJ (2010) Risk for radiation□induced cataract for staff in interventional cardiology: Is there reason for concern?. Catheterization and Catheter Cardiovasc Interv 76: 826-834.
31. Milacic S (2009) Risk of occupational radiation-induced cataract in medical worker. Medicina del Lavoro 100: 178-186.
32. Mrena S, Kivelä T, Kurttio P, Auvinen A (2011) Lens opacities among physicians occupationally exposed to ionizing radiation-a pilot study in Finland. Scand J Work Environ Health 37: 237-243.
33. Cucinotta FA, Manuel FK, Jones J, Iszard G, Murrey J, et al. (2001) Space radiation and cataracts in astronauts. Radiat Res 156: 460-466.
34. Rafnsson V, Olafsdottir E, Hrafnkelsson J, Sasak H, et al. (2005) Cosmic radiation increases the risk of nuclear cataract in airline pilots: a population-based case-control study. Arch Ophthalmol 123: 1102-1105.
35. Rastegar Z, Eckart P, Mertz M (2002) Radiation-induced cataract in astronauts and cosmonauts. Graefes Arch Clin Exp Ophthalmol 240: 543-547.
36. Jones JA, McCarten M, Manuel K, Djojonegoro B, Murray J, et al.(2007) Cataract formation mechanisms and risk in aviation and space crews. Aviat Space Environ Med 78: A56-A66.
37. Adamopoulou M, Makrynioti D, Gklistis G, Koutsojannis C (2023) Revolutionizing eye disease diagnosis with deep learning and machine learning. World J Advanced Research and Reviews 18: 741-763
38. Iacono MI, Neufeld E, Akinnagbe E, Bower K, Wolf J, et al. (2015) MIDA:A Multimodal Imaging-Based Detailed Anatomical Model of the Human Head and Neck. PLoS ONE 10: e0124126.
39. Kamel Boulos MN, Zhang P (2021) Digital twins: from personalised medicine to precision public health. J Pers Med 11: 745
40. Day R, Gorin MB, Eller AW (1995) Prevalence of lens changes in Ukrainian children residing around Chernobyl. Health Phys 68: 632-642.
41. Kreisheimer M, Koshurnikova NA, Nekolla E, Khokhryakov VF, Romanow SA, et al. (2000) Lung cancer mortality among male nuclear workers of the Mayak facilities in the former Soviet Union. Radiat Res 154: 3-11
42. Azizova TV, Muirhead CR, Moseeva M B, Grigoryeva ES, Sumina MV, et al. (2011) Cerebrovascular diseases in nuclear workers first employed at the Mayak PA in 1948–1972. Radiation and environmental biophysics 50: 539-552.
43. Strahlenschutzkommission (2009) Radiation-induced cataracts. Strahlenschutzkommission, Bonn
44. Armeni P, Polat I, De Rossi LM, Diaferia L, Meregalli S, et al. (2022) Digital Twins in Healthcare: Is It the Beginning of a New Era of Evidence-Based Medicine? A Critical Review. J Pers Med 12: 1255
45. Khokhryakov VV, Khokhryakov VF, Suslova KG, Vostrotin VV, Vvedensky VE, et al. (2013) Mayak Worker Dosimetry System 2008 (MWDS-2008): assessment of internal dose from measurement results of plutonium activity in urine. Health Phys 10: 4366-4378
46. Popa EO, van Hilten M, Oosterkamp E, Bogaardt M J (2021) The use of digital twins in healthcare: socio-ethical benefits and socio-ethical risks. Life Sci Soc Policy 17: 1-25.
47. WHO (2002) Blindness and visual impairment.