GLOBAL CLINICO-EPIDEMIOLOGIC CHARACTERISTICS OF OCULAR CANCER AND ITS IMPLICATIONS FOR GLOBAL HEALTH POLICY: A NARRATIVE REVIEW

U.A. Eze[1,2], A.A. Salami[1,3,4], K. Aminu[1], C. Norah[1], T. Akinyemiju[1], A.A. Gbadamosi[1], C. Olomo[1], E.B. Okeke[1], K.K. Kanmodi[1,5,6], H.A. Alen[7]

1. Cephas Health Research Initiative Inc, Ibadan, Nigeria.
2. Department of Ophthalmology, Federal Medical Center, Asaba, Nigeria.
3. School of Nursing, Midwifery and Public Health, University of Suffolk, Ipswich, United Kingdom.
4. Department of Oral and Maxillofacial Surgery, University College Hospital, Ibadan.
5. Department of Public Health, Thomas Adewumi University, Oke-Irese, Nigeria.
6. Department of Community Dentistry, United of Witwatersrand, Johannesburg, South Africa.
7. Department of Ophthalmology, University College Hospital, Ibadan, Nigeria.

Correspondence:
Dr. A.A. Salami
Department of Oral and Maxillofacial Surgery,
University College Hospital,
Ibadan.
Email: afeezsalami2016@gmail.com

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ABSTRACT

Introduction: **Ocular cancer refers to a group of rare but serious malignancies that affect the eye and its surrounding structures. Although ocular cancers account for less than 0.1% of all cancers globally, they represent a significant public health challenge because of their impact on vision, quality of life, and overall patient's survival. The most common forms are retinoblastoma in children and uveal melanoma in adults.**

Improving global outcomes requires integrating ocular cancer control into broader health policies, expanding research, and specialist care capacity. Stronger collaboration and equitable access to eye cancer care can reduce disparities and improve survival.

Objective: **This narrative review underlines the global epidemiology of ocular cancer and discusses its implications for global health policy.**

Methods: **This narrative review utilized secondary data sources obtained through a thorough literature search of relevant articles on multiple electronic databases including PubMed, Google Scholar, and Web of Science. All published books, journal articles, and other published materials that were written in English were reviewed for the purpose of this study.**

Results: **The global burden of ocular cancer is rising, influenced by longer life expectancy, increased ultraviolet radiation exposure, genetic mutations, and unequal access to healthcare services. Key risk factors include inherited mutations such as RB1, BAP1, and TP53, viral infections like HPV and Epstein–Barr virus, immunosuppression, fair skin pigmentation, and environmental conditions. Preventive measures include the use of UV-protective eyewear, early screening, public health education, and genetic counselling.**

Diagnosis relies on advanced imaging, histopathology, and molecular testing to guide personalized treatment. Management typically requires a multidisciplinary team involving ophthalmologists, oncologists, pathologists, and radiologists. The treatment includes surgery, chemo-radiation therapy, targeted therapy, and immunotherapy. Importantly, the role of research in limiting burden and improving care cannot be overemphasized.

Conclusion: **Although ocular cancers are rare, they are associated with significant morbidity. Therefore, modern diagnostics and therapeutic techniques are hugely required for better treatment outcome.**

Keywords: Ocular cancer; Prevention; Diagnosis; Treatment; Prognosis; Global health policy.

INTRODUCTION

Ocular cancer (OC) is a diverse group of malignancies affecting the intraocular structures, such as uvea, retina, ocular adnexa, and surrounding tissues such as the retina, eyelids, uvea conjunctiva, and lacrimal glands.[1] According to the National Cancer Institute, OC can be in the form of melanoma, carcinoma, lymphoma, or retinoblastoma. Melanoma develops in the cells that make melanin in the eye, lymphoma involves the white blood cells, primarily, the central nervous system lymphoma (PCNSL), the carcinomas form in tissues covering structures in the eye, while retinoblastoma develops in the retina due to genetic mutation.[2,3]

When Ocular cancer develops within the eye, they are referred to as intraocular cancer, while those that occur on the outer structures of the eye are called extraocular cancers.[4] They can also be primary (when the site or cell of origin is in the eye) which is rare or secondary (where the cancer starts in other parts of the body like the breast or lungs and spreads to the eye) which is more common.[5]

Although primary OCs are rare, the commonest type in adults is intraocular melanoma, especially uveal melanoma (UM) [6] which develops in the melanocytes of the ciliary body, choroid and iris.[6] In addition, retinoblastoma, which is the most frequent intraocular malignancy found in children under age 5, accounts for 2-4% of paediatric cancers while ocular lymphoma is seen in older adults especially those with some form of immunosuppression.[7] The commoner secondary ocular cancer is commonly found in the uveal tissues from primary growth from breast and lungs include periocular tumors (most common is basal cell carcinoma of the eyelid), Orbital tumours (Rhabdomyosarcoma, most common in childhood) etc.[8]

As a neglected public health issue, OC contributes significantly to cancer mortality and vision loss, thus making an understanding of its epidemiology crucial for strategies to reduce both visual impairment and global cancer burden.[9] Ocular cancer constitutes less than 0.1% of all new cases of cancer worldwide but are very difficult to manage due to their anatomic location, serious clinical implications and the need for specialized multidisciplinary care. [1] Hence, contributing to the global burden of non-communicable diseases. The incidence of ocular cancer surged in most countries, with the highest rise observed in the Middle East and East Africa while countries with high Socio-demographic Index (SDI), such as Austria, Japan, and France, recorded moderate increases in incidence.[1] Disparities in OC incidence and outcomes are influenced by limited knowledge, inadequate finance, genetics, skin pigmentation, exposure to ultraviolet-radiation, and healthcare access.[10] Even though survival exceeds 95% in high-income countries, it is as low as 30% in low-income settings due to delayed diagnosis.[10] In addition to physical outcomes, OCs also carry heavy psychosocial burdens. Survivors often experience partial or total vision loss, affecting daily activities and quality of life, mental health challenges such as anxiety, social isolation and depression.[10,11] Treatments such as enucleation worsen psychosocial impacts, with many patients experiencing persistent functional and psychological challenges.[12]

Overall, this evidence demonstrates that OC is a critical global health issue with varying burdens.[10] Early prevention, detection, and targeted treatments can improve outcomes, but persistent disparities driven by environmental and socioeconomic factors as well as social determinants of health continue to undermine equity.[13] Advances in clinical diagnosis and treatment, from imaging technologies to targeted therapies, have largely improved prognosis and outcome in high-income regions, while low-resource regions face high mortality due to delayed diagnosis and inadequate infrastructure. Therefore, OC control requires holistic strategies in clinical care and public health.[10,13] International research collaborations, targeted policies, and resource allocation to reduce inequalities and improve clinical response are essential to improve treatment outcomes worldwide.[10]

This review therefore assesses the comprehensive landscape of OC, including its epidemiological burden, diagnosis, therapeutic options, and prognosis, while emphasizing the need for global health policy.

Burden of ocular cancer

Epidemiology

Ocular cancers vary substantially in incidence, prevalence, survival, and mortality depending on histological subtype, geographic region, ethnicity, and socioeconomic context.[1] Among these, UM represents the most frequent primary malignant eye tumor in adults, making up about 81% of all ocular melanomas and up to 5% of melanomas overall. Among these, roughly 5% arise in the iris, around 10% in the ciliary body, and the vast majority (about 85%) originate in the choroid.[14] The worldwide incidence of iris melanoma is estimated at 1–9 cases per million people. Compared with choroidal melanoma, it generally shows a more favorable prognosis and reduced mortality. Its distribution varies by region and ethnicity, occurring most frequently in Caucasians, less often in East Asian populations, and rarely among individuals of African ancestry.[15,16]

Conjunctival melanoma, though rare, largely affects fair-skinned individuals and is characterized by marked geographic variation.[17] In the United States, approximately 130 new cases are reported annually, while Europe records around 320 cases each year.[18] The disease is relatively uncommon among individuals of Asian or African descent.[17] Although less common than UM, it has attracted increasing attention due to its association with ultraviolet radiation exposure and reports of rising incidence in certain regions.

In children, retinoblastoma (RB) remains the commonest intraocular malignancy and represents about 6% of all cancer cases diagnosed in children under the age of five.[19] Its occurrence differs greatly

across populations, with regional variations reaching up to 50-fold. Recent evidence suggests that incidence rates are particularly high in Africa and Asia.[20] Within Asia, Jordan reports the greatest burden, while in the Asia–Pacific region, India shows the highest incidence, followed closely by China.[21] Mortality rates are estimated at less than 5% in high-income countries but may rise to nearly 70% in parts of Africa.[22]

Orbito-ocular cancers also demonstrate substantial geographic and demographic variation. Conjunctiva and orbital squamous cell carcinoma are particularly prevalent in sub-Saharan Africa with strong association with ultraviolet radiation and HIV infection.[23] Sebaceous gland carcinomas, although rare, is disproportionately reported in Asian populations, accounting for up to 30–40% of malignant eyelid tumors in India and China compared with less than 5% in Western countries. Basal cell carcinoma constitutes up 80–90% of eyelid cancers and it regarded as the commonest periocular malignancy worldwide, with a marked predominance among fair-skinned populations who are regularly exposed to sunlight.[24] In the pediatric populations, 3% of all childhood malignant tumors are orbital rhabdomyosarcoma (RMS) and are the third most prevalent pediatric extracranial solid tumours. Despite advances in diagnostics and treatment methods, children with high-risk RMS have less than 30% five-year survival rates.[25] In addition, when treating a recurrent RMS, the five-year survival is reduced to 17%. These cancers impose substantial morbidity through local invasion, disfigurement, and vision loss, with survival outcomes varying widely depending on histology, access to multidisciplinary care, and regional health resources.

Risk factors

Genetic Predisposition

Genetic predisposition is a central determinant in the pathogenesis of ocular cancers, most prominently in retinoblastoma and uveal melanoma. Childhood ocular malignancy is associated with genetic tumor predisposition syndrome which is the leading cause of retinoblastoma. Retinoblastoma arises from biallelic inactivation of the RB1 tumor suppressor gene on chromosome 13q14.[26] Approximately 40% of cases are heritable, predisposing affected children to bilateral and multifocal tumors and earlier disease onset compared with non-heritable cases. Heritable forms confer a lifelong predisposition to secondary malignancies, particularly osteosarcoma and soft tissue sarcomas, risks further amplified by exposure to external beam radiotherapy.[19] Amplification of the MYCN gene has also been associated with development of retinoblastoma, independent of the RB1 gene in nearly 3% of children with unilateral retinoblastoma.[27]

In uveal melanoma, germline mutations in BAP1 (BRCA1-associated protein 1) have emerged as a critical predisposing factor. BAP1 mutations are strongly associated with aggressive disease, characterized by larger tumor size, ciliary body involvement, and markedly elevated metastatic potential.[28]

Pigmentation-related genetic traits also modulate ocular cancer risk, particularly in populations of European descent. Variants associated with lighter iris color, such as those identified in the IrisPlex model, have been correlated with increased risk of UM.[29] The biological basis for this association lies in reduced melanin-mediated protection against ultraviolet radiation, which may facilitate DNA damage in uveal melanocytes.[29]

Rhabdomyosarcoma arises from pluripotent mesenchymal cells and is associated with mutations in the genes PAX3, PAX7 AND FOX01, leading to chromosomal translocations, malignant abnormal cellular growth.[30] Rarely, TP53 gene mutation with inhibition of p53 protein formation and subsequent uncontrolled cell division has been associated with orbital rhabdomyosarcoma.[30]

Neurofibromatosis type 1 is caused by mutations in the NF1 tumor suppressor gene, which encodes neurofibromin, a protein that inhibits the RAS-MAPK pathway. When the RAS-MAPK pathway is disrupted, there is unregulated cell growth which leads to ocular neoplasms.[31]

Pathological mechanisms associated with Ocular surface squamous neoplasia include dysfunction of the TP53 gene with abnormal cellular proliferation and ocular surface cancer development.[32] Less commonly, UV radiation-induced mutations in HGF, CREB, BRCA1, BRCA2, APC, MSH6, PDGFRA, PTCH1 genes, with abnormal cell growth regulation and uncontrollable cell differentiation with cancer formation occurs.[32]

Environmental factors

While genetic predisposition underlies susceptibility to ocular cancer, environmental and host-related factors exert powerful modifying influences, shaping geographic and demographic disease patterns. Ultraviolet (UV) radiation is the most extensively studied environmental determinant. Robust evidence links UV exposure to ocular surface squamous neoplasia (OSSN) and conjunctival melanoma[18], with incidence rates highest in equatorial regions such as sub-

Saharan Africa and South Asia, where cumulative lifetime exposure is highest. Outdoor activities, lack of use of protective eyewear, and high ambient UV indices amplify this risk.[33]

Environmental influences are equally relevant in orbito-ocular cancers. Chronic UV radiation contributes significantly to eyelid squamous cell carcinoma and basal cell carcinoma, the most common malignant eyelid tumors worldwide.[41] Research from several epidemiological studies indicates that the development of basal cell carcinoma is not primarily driven by cumulative sun exposure throughout life, but rather by sporadic (recreational) sun exposure and exposure during childhood. Host-related factors such as immunosuppression further exacerbate risk, especially in settings with high HIV prevalence, where OSSN incidence is markedly elevated.[34]

The impact of viral cofactors is amplified in immuno-compromised populations. For example, HIV-positive individuals in sub-Saharan Africa have up to a ten-fold increased risk of OSSN compared with the general population.[34] Immunosuppression drives abnormalities in the TP53 gene, initiating tumour development. This systemic interaction between viral infections and impaired immune surveillance exemplifies the multifactorial nature of ocular cancer etiology in resource-limited settings.

Other risk factors

Age, sex, and ethnicity also constitute important host-related determinants of ocular cancer risk. Uveal melanoma demonstrates a clear age-related pattern, with incidence rising steadily through middle age and peaking between 65 and 75 years before plateauing.[35] Retinoblastoma, by contrast, is a disease of early childhood, reflecting the developmental biology of the retina and the role of RB1 mutations in tumor initiation.[35] Orbital rhabdomyosarcoma is similarly a predominantly pediatric malignancy, most commonly presenting in children under ten years of age, being the most common orbital malignancy at this age. These age distributions underscore the role of developmental and age-related biological processes in shaping cancer risk and clinical presentation.

Sex-based differences have also been reported. Uveal melanomas have a modest male predominance, whereas sebaceous gland carcinoma of the eyelid appears more frequently in female.[36] For ocular surface squamous neoplasia, male predominance is well documented in regions with high UV exposure, likely related to greater occupational risk among men working outdoors.[36]

Ethnic background further modulates susceptibility. The incidence of uveal melanoma is highest among populations of European descent, while sebaceous gland carcinoma is more reported in Asian populations.[36] This demonstrates complex interplay of genetic ancestry, environmental exposure, and cultural determinants in shaping the global epidemiology of ocular cancers.

Prevention & diagnosis of ocular cancer

Although the eye is a small organ, its complexity and the presence of various anatomical and physiological barriers make it a particularly challenging target for drug delivery. These challenges highlight the urgent need to encourage preventive strategies through innovative approaches to improve existing treatments. Strategies for primary and secondary prevention of ocular cancer include.

Primary prevention of ocular cancer

Ocular cancers can severely damage sight and threaten life, therefore, primary preventive measures, including reducing ultraviolet (UV) radiation exposure and avoiding genetic mutations are ideal, as the eye is mostly susceptible to ultraviolet radiation-induced damage. Exposure to ultraviolet radiation results in gene mutations, DNA damage, oxidative stress and inflammatory responses in tissues, and immunosuppression.

Scholars have established that the most effective method to primarily prevent ocular cancer is avoiding sunlight (The main source of ultraviolet radiation). This is crucial as human exposure to UV radiation is on the rise due to depletion of the ozone layer and climate changes influencing levels of surface radiation. The eyes are naturally protected against damage induced by UV radiation and the photochemical reactions through chromophores, superoxide dismutase, heme oxygenase antioxidants, melanin and glutathione (GSH) peroxidase.[37] Others include vitamin E, vitamin C, beta carotene, and ubiquinone which prevent changes in enzymatic activity after UV-B radiation. Wearing UV radiation blocking sunglasses can also offer sufficient protection against UV radiation.

Secondary prevention of ocular cancer

Researchers have documented that prompt identification and treatment are vital for best results. Treatment choices for ocular cancer may vary, depending on the type and stage of the disease The choices may include chemotherapy, surgery, targeted therapy and immunotherapy, and radiation therapy.[38]

Diagnosis of ocular cancer

Ocular cancers are uncommon, comprising only about 0.2% of all cancer diagnoses in the Western world. Sight and Life are a threat and thus, early diagnosis is imperative. Delayed diagnosis of ocular cancer is a significant challenge in low-and middle-income countries due to lack of facilities.[39] Different forms of ocular cancer diagnosis are discussed below:

Imaging techniques including ultrasound and magnetic resonance imaging

Modern imaging techniques have significantly improved how ophthalmic diseases in both anterior and posterior segments of the eyes are diagnosed and treated.[40] The combination of fundus photography and ultrasound with advanced forms of ocular coherence tomography (OCT) and OCT angiography (OCTA) has enhanced imaging diagnostics.[40]

Magnetic Resonance Imaging (MRI) on the other hand facilitates tumour localisation, evaluating the dimension of tumours, and the involvement of adjacent tissues. The MRI technique is not without drawbacks. One of the drawbacks includes formation of artifacts from involuntary eye movement, uneven distribution of melanin leading to inhomogeneous intensities, and the inability to differentiate between amelanotic and melanotic melanomas. Nonetheless, MRI aids in detecting metastasis and determines treatment options.[40]

Biopsy and histopathology in confirming diagnosis of ocular cancer

Disease entities can be diagnosed through etiological features, tissue-excision, or molecular basis. A definitive diagnosis is usually achieved through biopsy, which is the histopathological and/or cytopathological analysis of a surgically excised tissue, removed either partially or completely.[41] Biopsy is obtained to provide a specimen for further histological diagnosis and determine prognosis.[41] Ocular cancer biopsy is usually indicated when clinical examinations and other investigations to establish accurate diagnosis fail.

Clinical examination techniques for diagnosing ocular cancer

In contrast to other pathological conditions, assessment of eye disorders could be very challenging to assess based on its peculiar and typical examination.[42] Therefore, a systematic clinical examination of the eyes and its surrounding structures is required to diagnose any eye abnormalities. For example, the anterior eye examination could be conducted by using the slit-lamp biomicroscope. However, the slit-lamp biomicroscope can sometimes be used for conducting posterior eye examinations and certain ocular therapeutic procedures as it offers brilliant magnification, along with exceptional and variable illumination compared to other ocular equipment, including penlight, loupe, direct ophthalmoscopy, or Burton lamp.[42]

Funduscopic examination on the other hand comprises exclusively of inspection. The ophthalmoscope illuminates the retina via the normal iris defect that is the pupil. During the procedure, the structure lying in the inner part of the globe (collectively known as the eyegrounds, including the retina, retinal blood vessels, optic nerve head, and subjacent choroid) is observed.[43] To optimize visualisation of the retina, and foster examination of the macula, the pupil is frequently dilated pharmacologically.

Treatment of ocular cance

Ocular cancers are unique life-threatening, and their diagnosis relies strongly on imaging techniques like ultrasound, fluorescein angiography, anterior and posterior segment optical coherence tomography, computed tomography (CT), and magnetic resonance imaging (MRI). Treatment decisions usually depend on the anatomic site and extent, size, local invasion, histological type, and associated complications of the tumours. Treatment options vary from conservative management to local resection with safety margin, chemotherapy, immunotherapy and radiation and management is usually multidisciplinary and multimodal.[44]

The conservative treatment modalities which include laser photocoagulation, cryotherapy, local chemotherapy and transpupillary thermotherapy may be employed for treatment of retinoblastoma especially for tumours which are 3mm or lower and confined to the retina with no vitreous or subretinal seeding. This is usually classified as group A or very low risk retinoblastoma according to the international classification for intraocular retinoblastoma.[45] The adoption of wide local excision with safety margin in management of ocular cancers may be indicated in eyelid malignancies such as basal cell carcinomas, sebaceous gland carcinomas, squamous cell carcinoma and melanomas or following treatment failure.[46] Radiotherapy such as plaque brachytherapy or external beam radiotherapy is the standard care for most localized melanomas, and are also one of the first treatment modalities for retinoblastomas.[47,48] The use of chemotherapy to facilitate tumour regression in retinoblastoma has also been documented especially during globe salvage.[48]

Overall, the five-year survival rate following surgery of ocular cancers ranges from 17 to 53%.[49]

Implications of ocular cancer for global health policy

According to Hou *et al.*, ocular cancers are rare diseases with devastating consequences, especially when metastatic, they also pose a significant threat to global health systems.[50] Among the known eye diseases, ocular cancers cause the most significant threat to vision and quality of life (QOL). The quality of life is a multifaceted construct that encompasses physical, emotional, social and family well-being of an individual. Thus, the management of ocular cancers requires the expertise of highly trained medical professionals and multidisciplinary teams to enhance the QOL.[41] However, this is not always achievable in many regions of the globe.[52]

The global burden is significantly higher in low- and middle-income countries (LMIC) due to delay in diagnoses and treatments.[1] In addition, the rarity of the disease has led to its neglect from global health cancer priorities, however, to mitigate the burden of this disease, it is important to address them within global health policy structures.[1]

Access to care

Early detection and treatment of ocular cancer can help mitigate the risk of vision loss, metastasis and death.[53] The prognosis of eye cancer treatment is better in Europe and Asia because of increased awareness of the disease, prompt access to care and advancements in eye cancer treatments.[10] Contrarily, in low resource settings, the public knowledge and awareness of ocular cancer is low, and this accounts for the delay in detecting this disease early enough as patients usually present late for treatment.[50] Advanced stage disease with poor health outcomes is often the consequence of the delay in presentation and treatment.[1] Therefore, it is important for global health policies on ocular cancers to focus on improving the awareness of the disease and prompt presentation of patients to hospitals to improve on the disease prognosis. This can be achieved through regular health education and advocacy to improve awareness among stakeholders with the aim of providing resources and environment needed for the care of this major eye condition.[54]

Healthcare infrastructure

To effectively manage ocular cancers, a multi-disciplinary team of highly specialized doctors such as ophthalmologists, oncologists, pathologists and radiation specialists are usually required.[42] However, this is not easily achievable in LMIC.[18] Thus, it becomes imperative to formulate policies that will support and help to invest in funding effective specialist programs and healthcare facilities. By doing so, the treatment outcomes will be improved, and overall survival of ocular cancer patients will become better.

Economic protection and rehabilitation

The economic impact of ocular cancer such as vision loss, cost of treatment and rehabilitation are substantial, and vulnerable individuals are the most hit. For example, retinoblastoma can have long-term effects on children psychosocial wellbeing. Therefore, it is important that Universal Health Coverage (UHC) policies should be extended to offer financial support to ocular oncology services as well as rehabilitation and psychosocial support to mitigate long-term disability and improve the overall quality of life. Khanna *et al.*, recommended the use of health insurance financing to cover the rising cost of comprehensive ocular care.[54]

Research and development

Ocular health is of global health concern as it is important to achieve many of the sustainable development goals (SDG) as well as to transform the lives of people from low- and high-income countries.[9] Studies have shown that this can be impacted by rare ocular cancers.[9,10] At present, the treatments for these cancers involve enucleation, radiation, laser, cryotherapy, immunotherapy and chemotherapy.[52] However, these treatments pose a significant burden of loss of vision and some side effects to patients.[5,53] It is important for more research work to be conducted in this area to find better treatment options that will pose little or no burden to patients. It was suggested that intercepting the signaling pathways using natural occurring phytochemicals could be a way to achieve this and possibly prevent the occurrence of the disease.[52] Nanotheranostic approach has also been put forward for efficient eye cancer diagnosis and treatment.[55] Recent developments have shown that the use of precision medicine that puts together molecular diagnostics, artificial intelligence-enhanced liquid biopsy and new systemic therapies are majorly improving the management of uveal melanoma and improving the survival rate and patients' quality of life.[56]

Global response and collaboration.

The World Health Organization (WHO) recently launched the Global Initiative for Childhood Cancers (GICC) with the aim of improving the survival rate of paediatric malignancies to over 60% by 2030. [57] Retinoblastoma has been identified under the GICC initiative to be highly curable if detected or diagnosed early.[58] However, this is significantly impacted by limited resources and technologies in resource limited countries.[59]

Partnerships with health organizations can help to reduce the global burden of ocular cancer by sharing expertise, technologies and resources. For example, organizations such as the WHO and non-governmental organizations (NGOs) can collaborate to coordinate efforts, set guidelines and provide support to nations with limited resources.

CONCLUSION

This review detailed the burden, risk factors, prevention, diagnosis, treatment, and prognosis of orbito-ocular cancer and its implications for global health policy. Though ocular cancers are, they cause significant morbidity (visual impairment, blindness, cosmetic blemish) and mortality. The global burden is on the increase with obvious regional disparities. The risk of developing orbito-ocular cancer is multifactorial including genetic mutations, environmental and host factors. Modern diagnostics and therapeutic techniques are hugely required for better outcome and treatment is evolving, especially due to its psychological impact though variable by region and cancer type. Therefore, research remains critical for improving survival and quality of life globally.

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