

EPIDEMIOLOGY AND CLINICAL BURDEN OF SKIN CANCER IN PAKISTAN: A REVIEW

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Abstract

Skin cancer is the fifth most prevalent cancer worldwide. The skin acts as a barrier against UV rays and toxins; however, skin cancer is a significant issue that has been largely overlooked in Pakistan. Data regarding skin cancer is mostly unavailable. Skin cancer is a chronic disease, with the melanoma type being particularly dangerous as it can potentially lead to death. The symptoms of skin cancer vary and may include changes in the size, shape, and color of moles or growths, as well as bleeding and oozing. Various environmental, genetic, and kidney transplants can contribute to its development. Treatment options include traditional, conventional, and advanced techniques within the field of dermato-oncology. Data suggests that Pakistan is particularly vulnerable to skin cancer, making it essential for the government to take serious action against this growing concern. This can be achieved by recruiting highly trained experts, enhancing research networks, educating the public, and adopting innovations to address skin carcinogens. Indirect risk factors include obesity and age. Preventive measures and public awareness regarding skin cancer should be prioritized to help control and reduce its incidence.

INTRODUCTION

The skin is the largest organ in the human body, serving as a hurdle against UV radiation and toxins, as well as helping to regulate temperature. It consists of three layers: the epidermis, the dermis, and the hypodermis. Skin cancer, first identified in the 1800s by Théophile Hyacinthe Laennec (who also invented the stethoscope), occurs when abnormal skin cells spread to other parts of the body. The skin also protects against microbial organisms and assists in temperature regulation [1]. Non-melanoma skin cancers account for about 99% of all skin cancer cases [2]. Skin cancer is the fifth most common cancer worldwide, consisting of about 5.8% of all cancer cases,

with melanoma representing 1.6% of those. The global mortality rate for skin cancer is between 0.6% and 0.7% [2]. It can affect anyone, regardless of skin color. Non-melanoma skin cancers (NMSC), such as basal cell carcinoma and squamous cell carcinoma, are the most common and generally treatable. However, melanoma skin cancer (MSC), though less prevalent, is significantly more dangerous. It is an aggressive kind of skin cancer that originates in melanocytes (the cells that produce pigment) and spreads rapidly, resulting in the majority of skin cancer-related deaths [3]. Skin cancer is very common and is becoming increasingly so. While deaths from non-melanoma skin cancer are decreasing, deaths from melanoma are on the rise. Both types can cause serious health problems [5].

In Pakistan, between 1994 and 2021, nearly 3,000 cases of melanoma were reported, with a higher incidence in men compared to women. Data from Shaukat Khanum Hospital indicates that melanoma ranks among the top ten cancers in Pakistan, making up 2.2% of all cancer cases, and its frequency is on the rise. Melanoma is particularly perilous due to its ability to spread easily and its generally poor prognosis [6].

According to a report from Ayoub Medical College in Abbottabad, Khyber Pakhtunkhwa, Pakistan, 94% of non-Melanoma skin cancer and 06% of Melanoma skin cancer cases were reported between 1995 and 2003 [7].

2. Types of Skin Cancer

2.1 Basal Cell Carcinoma (BCC):

This is the most common type of skin cancer, accounting for approximately 80% of all skin cancer cases. BCC is slow-growing and rarely spreads to other parts of the body. It is believed to originate from hair follicles and is mostly caused by sun exposure, specifically ultraviolet (UV) damage to DNA. BCC predominantly affects white individuals over the age of 40, with men being more affected than women [1].

2.1.2 Signs and Symptoms of Basal Cell Carcinoma (BCC)

1. Pearly pink or white bumps on the face.
2. Red, scaly patches on the upper trunk and shoulders.
3. Skin-colored, waxy, scar-like lesions on the face.
4. Brown, blue, or greyish lesions.
5. Large, slow-growing lesions (greater than 20 mm).
6. Multiple lesions.
7. Ulcerated lesions [8].

2.2 Squamous Cell Carcinoma (SCC):

This is the second most common type of skin cancer, constituting about 20% of non-melanoma skin cancers (NMSC). SCC is more likely to spread than BCC. An early, non-spreading form of SCC is known as Bowen's disease. This cancer grows in the flat cells of the outer layer of the skin and basically begins on sun-exposed areas. However, it can also develop in scars, ulcers, or the genital region [1].

2.2.1 Signs and Symptoms of Squamous Cell Carcinoma (SCC)

1. Firm, nodular, crusted lesion (abnormal skin tissue).
2. An open sore (ulcer) with no crusting.
3. Lesion larger than 1 cm.
4. Non-healing lesion.
5. Keratinized (rough, scaly) or crusted lesion.
6. Erythematous (red), scaly plaques with defined margins (Bowen's disease).
7. Pigmented, flat lesions with poorly defined margins (Bowen's disease).
8. Rounded, fast-growing nodules with a central hyperkeratotic (scaly) region (keratoacanthoma) [8].

2.3 Melanoma

Melanoma arises from pigment cells called melanocytes and can develop from moles in about 25% of cases. Signs of melanoma include changes in the size, color, shape, or itchiness of a mole (pigmented growth on skin). This type of skin cancer is more commonly found on the legs in women and on the backs of men [1]. Research consistently shows that people of color are more likely to die from melanoma, a treatable disease, compared to white individuals [9].

2.3.1 Symptoms of Different Types of Melanoma Skin Cancer

1. A changing mole (is a small, pigmented spot) in size, shape, or color.
2. A new growth bump (A bump is a raised area on the skin).
3. Ulceration (inflammation of the skin).
4. A new spot.
5. Growth of a mole or spot [8].

Skin cancer can develop on any part of the skin, but it is most commonly found on areas exposed to the sun. The skin consists of various layers, and skin cancer typically originates in the outermost layers known as the epidermis [10]. This type of cancer arises from damaged DNA that undergoes mutations, ultimately leading to skin cancer [11]. Early detection of skin cancer is crucial, as it can significantly reduce risk factors for patients. Research indicates that if skin cancer is diagnosed at an early stage, the mortality ratio can be reduced by up to 90%. Therefore, timely diagnosis is critically important [12]. The areas that are closer to the equator, such as Karachi, are more susceptible to skin cancer due to solar radiation directly reaching them compared to those areas that are farther from the equator [3].

3. Skin cancer cells stages

Skin cancer, like other cancers, is classified into stages. The World Health Organization (WHO) has established criteria for the classification of skin cancer, which ranges from stage 1 to stage 4. Grade 1 resemble normal cells and tissues, categorizing them as low-grade tumors known as well differentiated (specific function), Grade 2 characterize as relatively normal appearance and are

classified as moderately differentiated, Grade 3 tissues appear large, abnormal, and poorly differentiated. Whereas, Grade 4 cells appear more abnormal compared to other cells and tissues. They have a higher grade and spread faster than lower-grade cells [1].

4. Causes of skin cancers

4.1. UV ray's exposure

Ultraviolet (UV) rays from the sun are the leading cause of skin cancer [4] [13]. Historically, occupational exposure to sunlight was a significant risk factor, but in recent years, increased outdoor activities and tanning have also contributed to this risk. UV rays are classified into three types: Ultraviolet type A (UVA), Ultraviolet type B (UVB) and Ultraviolet type C (UVC) based on their wavelength. UVC absorbs by atmospheric ozone layer. However, only UVA and UVB rays reach the Earth's surface. UVA rays penetrate deeper into the skin, causing indirect DNA damage, while UVB rays primarily affect the skin's outer layer and directly damage DNA. Both types of DNA damage can lead to mutations and raise the risk of developing skin cancer [13].

4.2. Air pollution

Air pollution is a significant and growing global health issue that affects not only our lungs and heart but also our skin. It is considered the world's largest environmental health risk, and researchers around the globe are investigating its effects. Air pollutants originate from both natural and human-made sources. Key pollutants include polycyclic aromatic compounds [14]. Which are characterized by strong carbon-to-carbon bonds, which contribute to their stability. They are referred to as 'polycyclic aromatic hydrocarbons' (PAHs) and consist of several benzene rings interconnected. PAHs occur naturally in substances such as bright pigments found in plants and animals [15]. Volatile organic compounds (VOCs); are substances that, when exposed to air, can quickly and easily transform into gases. They impact the air we breathe, both inside and outside [16]. Nitrogen oxides (Nox); Nitrogen oxides are gases made of nitrogen and oxygen. Examples include NO, NO₂, N₂O, and N₂O₅. Most are poisonous, especially NO and NO₂. People cause a lot of these gases to be released into the air [17]. Cigarette smoke; is full of harmful

chemicals. Burning a cigarette creates even more harmful chemicals. Examples of these chemicals include tar, nicotine, and carbon monoxide etc. These chemicals are very injurious to your health [18]. Ozone; is a special form of oxygen. Instead of two oxygen atoms (O₂), it has three atoms (O₃). It's not very stable, which means it breaks down quickly back into regular oxygen. Because it breaks down quickly, we have to make it when we need it. It's a powerful oxidizer, meaning it readily reacts with other substances [19]. Particulate matter (PM); is tiny stuff floating in the air. It's a mix of solids and liquids. It includes things like acids, chemicals, metals, and dust. Basically, it's all the little bits of pollution in the air [20].

These pollutants are particularly harmful to the skin because their particles are smaller than skin pores, allowing them to penetrate deeply. This can lead to inflammation, dehydration, and cellular changes, resulting in a loss of elasticity and firmness.

Different pollutants have varying toxic effects on the skin, operating through different mechanisms. They can contribute to; Advanced aging (early aging), Inflammatory skin conditions such as acne, atopic dermatitis (long time inflammation of skin), eczema (dry, itchy and inflamed skin) and psoriasis (autoimmune disease characterized by patches on the skin), Skin cancer [14].

4.3. Genetic Disorders

90% of melanoma cases are caused by solar radiation. Spending time in the sun without protection increases the risk of developing melanoma. About 10% of melanoma cases are attributed to inherited genetic predispositions, which can increase the likelihood of developing melanoma and other cancers. Specific genes, such as CDKN2A (Cyclin-Dependent Kinase Inhibitor 2A), CDK4 (Cyclin-Dependent Kinase 4), TERT (Telomerase Reverse Transcriptase), POT1 (Protection of Telomeres 1), ACD (Adrenocortical Dysplasia (also known as TP53BP1)), TERF2IP (Telomeric Repeat Binding Factor 2 Interacting Protein), MITF (Microphthalmia-Associated Transcription Factor), and BAP1 (BRCA1-Associated Protein 1), are associated with hereditary melanoma. A mutation in one of the genes associated with melanoma does not guarantee that an individual will develop melanoma. Having a mutation in a single gene associated with melanoma does not

guarantee that an individual will develop melanoma. Multiple genetic and environmental factors contribute to development.

UV radiation and NMSC particularly UVB, is a significant cause of non-melanoma skin cancer (NMSC), as it causes DNA damage in skin cells [21].

4.4 Kidney Transplantation

Skin cancer is the most common malignancy observed after kidney transplantation, accounting for 90% of cases, with basal and squamous cell carcinomas being the most prevalent types. Kaposi's sarcoma (lesions or patches on skin) is also more frequently seen in these patients. This increased risk of skin cancer is driven by several factors, including UV exposure, weakened immune surveillance due to immunosuppression, and the possible impact of certain immunosuppressant medication. While chimerism and immunosuppressant contribute to the overall cancer risk following kidney transplantation and increase susceptibility to virus-related cancers, skin cancer remains the most commonly diagnosed malignancy. This heightened risk is specifically linked to impaired DNA repair mechanisms resulting from immunosuppression, which particularly affects the skin's ability to manage UV radiation damage [22]. In Pakistan, the initial ordinance regarding kidney transplants was introduced in 2007, and the law became operational in 2010. Pakistani healthcare professionals involved in organ transplantation must adhere to the national transplant law, which prioritizes the safety and well-being of living donors. Donation decisions should be made freely, without any coercion. Since the implementation of this law, 28 out of 42 authorized hospitals have performed over 1,721 kidney transplants between September 5, 2007, and December 31, 2009. Further research is required to assess the long-term impact of this legislation and its effectiveness in addressing the country's organ donation needs [23].

4.5 Human Pappilloma viruses

HPV is a virus. It's made of DNA. It belongs to the Papillomaviridae family. It causes growths and cancers, mostly on the skin and mucous membranes (like inside the mouth or genitals) [24].

Human Papillomaviruses (HPV) are known to cause certain cancers, particularly anogenital cancers. Researchers are now exploring whether HPV also contributes to non-melanoma skin cancer, the most common malignancy in fair-skinned populations. HPV DNA is often detected in non-melanoma skin cancer samples. HPV is also commonly found in normal skin, hair follicles, and benign skin disorders. Functional studies suggest that HPV interacts with ultraviolet radiation, host cytokines, and cellular proteins, which could contribute to skin cancer development. While these findings are intriguing, more research is needed to confirm a causal link between HPV and skin cancer. HPV is a known cause of anogenital cancers [25].

5. Advance treatment of skin cancer

5.1 Nanotechnology

Nanotechnology works with things that are super, super tiny. (Think atoms and molecules.) It involves things measured in nanometers (1-100 nm). At this tiny size, things act differently [26]. Various nanomaterials, such as nanofibers and nanoclays, are utilized in addressing skin cancer, but nanoparticles (NPs) have proven particularly effective. Phospholipid-based oil emulsions (POEs) can act as anticancer agents themselves, deliver both water-soluble and lipid-soluble drugs, target tumors, combat drug resistance, control drug release, and enhance skin penetration for improved administration of anticancer medications. These capabilities make nanoparticles a vital tool in the fight against skin cancer [27].

5.3 Botanical Agents

5.3.1 Red clover

A common herb that is grown all over Europe and Asia contains isoflavones that have shown promise in laboratory studies (using hairless mice) for protecting against sun-induced skin cancer when applied topically. Extracts from red clover may also help skin cells mature and function properly without increasing the risk of cancer [28].

5.3.2 Ginger

Ginger, also known as *Zingiber officinale*, has been used for centuries for its health benefits. It contains over 400 biological compounds, including 6-gingerol, which has been shown to have anti-inflammatory properties, anti-bacterial properties, and anti-cancer properties. Ginger has been found to be effective against various types of cancer, including skin cancer. It inhibits the growth of skin cancer cells and reduces nausea and vomiting caused by chemotherapy. Ginger is a natural and safe way to help prevent and treat skin cancer [29].

5.3.3 Tea Extract

The effects of tea on humans remain inconclusive. However, some studies focused on human skin suggest that components of tea may inhibit markers of cancer and inflammation. For example, green tea extract has been shown to protect against UVB-induced skin damage and Langerhans cell depletion, as well as to reduce UVB-induced inflammation. Both black and green tea extracts have also demonstrated the ability to reduce skin inflammation caused by UVB and PUVA (Psoralen ultraviolet type A), separately [30].

5.3.4 Rosemary

Rosemary, a herb whose extract has been found to have numerous health benefits, including antioxidant properties and anti-cancer effects, which can help protect against cell damage and skin cancer. Rosemary extracts have been shown to inhibit skin cancer growth and tumorigenesis. Studies have found that rosemary extracts can: inhibit skin cancer cell growth, reduce tumor incidence and burden, induce apoptosis (cell death), and reduce inflammation and oxidative stress in cancer cells [31].

5.3.5 Turmeric plants

Curcuma longa (turmeric), which consists of a compound called curcumin that is a polyphenol [32]. Its antioxidant properties protect the skin from damage caused by free radicals. Its anti-aging properties repair UV-damaged skin, reduce wrinkles, and hyperpigmentation. As a natural UV protector, it absorbs UV radiation, preventing skin damage, and its anti-inflammatory properties

reduce inflammation, promoting healthy skin. It works by activating the Nrf2 (Nuclear factors erythroid factor 2) protein, which enhances cellular antioxidant defense mechanisms, inhibits TNF (tumor necrosis factor) mRNA expression that reduces inflammation, and reduces MMP-1 (Matrix metalloproteinase 1) expression, which prevents skin damage and promotes skin elasticity [33].

5.3.6 Dandelion plant

Dandelion (*Taraxacum* genus) is a plant that lives for many years, comprising more than 300 species [34]. Dandelion Root Extract (DRE) kills skin cancer cells. DRE induces apoptosis (cell death) in human melanoma cells. DRE doesn't harm non-cancerous cells. DRE activates the extrinsic apoptotic pathway, which triggers caspase-8 activation, leading to cell death by targeting mitochondria. DRE generates reactive oxygen species (ROS), which kill mitochondria and ultimately lead to cancerous cell death [35].

5.3.7 Essential oils

Essential oils are liquid mixtures of plant compounds responsible for a plant's unique smell and part of a plant's defense system against herbivores (plant-eating animals), pests, and diseases [36]. Some essential oils may help prevent or treat skin cancer. These oils can: - Stop cancer cells from growing - Kill cancer cells - Prevent cancer from spreading. Examples of helpful essential oils include: - Turmeric essential oil - Rosewood oil. However, essential oils can also cause: - Skin irritation - Allergic reactions - Sensitivity to light. More research is needed to understand how essential oils can be used safely and effectively to fight skin cancer [37].

5.4 Antioxidants derived from Plants and Animals

Antioxidants

Antioxidants are substances that help prevent or slow down damage to cells, proteins, and other molecules caused by oxidation. Examples of antioxidants include Vitamins (C, E), Carotenoids (beta-carotene), and Phenolic compounds (flavonoids), as well as proteins and enzymes. These antioxidants help protect against cell damage, inflammation, and diseases [38]. Melanin, natural antioxidants, and dietary antioxidants (like vitamins A, C, and E) act as the primary defense for our

skin against UV rays. These dietary antioxidants are vital for maintaining a healthy balance against oxidative damage. Research has shown that UV exposure depletes these antioxidants (including ascorbate, glutathione (GSH), superoxide dismutase (SOD), catalase, and ubiquinol) in both the dermis and epidermis, leading to an increase in harmful free radicals. Studies have demonstrated that the damage caused by UV means the generation of reactive oxygen species and a reduction in antioxidants. Numerous studies have investigated the use of antioxidants to mitigate this damage, with varying degrees of success [39].

5.5 Radiation therapy

Radiation therapy is a common way to treat cancer, using high-energy rays like X-rays and gamma rays. It targets and kills cancer cells in tumors and some blood cancers. It's often used alongside surgery and chemotherapy to make treatments more effective [40]. RT was first used for skin cancer in the early 1900s. As surgery improved, RT became less common for skin cancer. However, RT is still a very viable option for many patients. Modern RT techniques have improved, making treatments more accurate and effective. Radiation therapy is a useful treatment for BCC, especially when surgery isn't the best choice. It uses high-energy radiation to kill cancer cells while protecting healthy tissue [41].

Radiation therapy is becoming more important in melanoma treatment. Early radiation therapy for melanoma was done with less advanced equipment, and melanoma was thought to be resistant to radiation because it was used for advanced melanoma (palliative care). The modern role of radiation therapy is seen as the best non-surgical treatment for melanoma in specific areas. It is part of a team approach to melanoma treatment. Approximately 23% of melanoma patients benefit from radiation therapy because it is effective at a particular stage of melanoma [42].

Radiation therapy (RT) for squamous cell carcinoma (SCC) is a good option. RT is safe and effective for SCC patients who can't have surgery or who have a high risk of the cancer returning. It's a primary treatment for those who can't have surgery [43].

6. Indirect Risk Factors contributing to skin cancer

6.1 Age factors

The chance of developing skin cancer increases as people age, particularly after 50, peaking after 75 years. However, 25% of melanomas occur in people aged 50 and younger. The primary risk factor is UV exposure, which is linked to over 80% of melanomas. This comprises of both long-term sun exposure and short, intense periods, such as sunburns—especially during childhood or from tanning beds (lying in natural sun light). cumulative UV exposure (total sun exposure throughout an individual's life) is the main risk factor for squamous cell carcinomas (SCCs), while intermittent UV exposure (short periods of intense exposure) is the main risk factor for basal cell carcinomas (BCCs) [44].

6.2 The Role of Obesity in Melanoma Progression

Recent research indicates that fat cells (adipocytes) located in the skin's lower layer (hypodermis) release tiny particles known as exosomes. These exosomes contain proteins that are involved in fat breakdown, specifically fatty acid oxidation (FAO). When melanoma cancer cells absorb these exosomes, their FAO increases, which enhances their ability to migrate and invade surrounding tissues. This effect is particularly pronounced in obese individuals, potentially explaining why melanoma patients with obesity often experience worse outcomes. Essentially, the fat cells are contributing to the spread of melanoma through these exosome deliveries [45].

7. Preventive measures

7.1 Ketogenic Diet and Skin cancer

A ketogenic diet is a high-fat, low-carb diet that may help with cancer treatment by reducing inflammation, slowing tumor growth, and protecting healthy cells. ketogenic diet contains high-fat, low-carbohydrate and moderate-protein. Ratio is 3:1 or 4:1 (fat:carbohydrate + protein). It benefits cancer treatment by lowering inflammation, limiting tumor growth, and protecting healthy cells from chemo and radiation damage [46]. Unlike healthy cells, cancer cells need a steady glucose supply for energy. High insulin levels promote cancer growth. Insulin and insulin-

like growth factor-1 (IGF-1) can stimulate tumor cell proliferation. Ketone bodies inhibit cancer growth. When insulin and blood glucose levels are low, ketone bodies can negatively affect cancer cell proliferation. Reduced carbohydrate intake may help slow down skin cancer growth. Increased protein and fat intake may benefit patients with altered glucose metabolism [47].

8. Precautions for preventing Skin cancer

Skin cancer is highly preventable by using sunscreen daily, even in moisturizers. This is important for everyone, especially children. Avoid sunburns and tanning beds, as indoor tanning greatly increases skin cancer risk. Three Levels of Prevention exist.

Primary Prevention (best) includes sunscreen use and skin checks.

Secondary Prevention involves treating precancerous cells (cryotherapy, laser therapy).

Tertiary Prevention involves treating diagnosed cancer (surgery, radiation). Education programs, especially for children, are very effective. Understanding the causes of skin cancer is crucial [48].

Conclusion

Pakistan is more vulnerable with the skin cancer due to lack of public awareness and less attention from official community. It is a dire need that the government may allocate a sufficient amount of budget not only for modernizing its cancer treatment hospitals by selecting the world's best cancers professional for therapeutic approaches but the common populace also be groomed for avoiding the menace of skin cancer.

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