An Overview of Environmental Factors on Skin Cancer and Photodynamic Therapy

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Abstract

Cancer is one of the largest leading causes of death in the world, collectively accounting for the second leading cause of death, with 600,000 deaths in the US alone as of 2020. Cancer is the abnormal growth of skin cells that grow uncontrollably and can spread to other body parts. Lung, colorectal, stomach, prostate, female breast, cutaneous melanoma, cervical and thyroid cancers are among the most commonly diagnosed cancers among adults.[2] Nevertheless, incidence rates and the burden of cancer have continuously risen rapidly, having a significant impact on public health over the years. However, with improved technologies and new ways of detecting cancer beginning to emerge, survival rates have shown a significant increase. This research paper serves to provide a comprehensive review of one of the most common cancers worldwide—skin cancer—and focuses on its etiology, while also incorporating a review on preventions and certain treatment methods.

Introduction

Skin cancer is one of the largest global threats that has resulted in the death of millions of people, not just in the United States, but worldwide. Skin cancer involves the abnormal growth of skin cells, usually caused by ultraviolet radiation (UVR) or genetic mutations, and can be highly treatable when detected at its early stages. This type of cancer is divided into three categories—melanoma and nonmelanoma skin cancers (NMSCs). Melanoma is usually associated with the largest mortality rates while NMSCs are perceived as more benign with harmful side effects. UVR from the sun has been proven to alter our body's DNA that can lead to certain DNA mutations among our skin. [3] As of 2024, it is estimated that 400,680 cases of skin cancer will be diagnosed. Data from the American Academy of Dermatology remarks that invasive melanoma is estimated to be the fifth most commonly diagnosed cancer among Americans in 2024.[4] Nevertheless, National Cancer Institute researchers have recently discovered more advanced ways to understand and treat melanoma. To date, various treatment methods include surgery, cancer medicines, and radiotherapy.[1]

What is Skin Cancer?

Approximately 1 in 5 people suffer with skin cancer in their lifetime.[4] Early detection treatments have given rise to lower mortality rates. Skin cancer is associated with the cell proliferation of cancer cells. The most common skin cancers that are diagnosed in North America, Australia, and New Zealand are NMSCs, or non-melanoma skin cancer.[5]

One of the most commonly diagnosed skin cancers in the United States is basal cell carcinoma (BCC) which rarely results in death. Basal cell carcinoma accounts for 80-85% of all diagnosed NMSCs. It is estimated that around 4.3 million cases will arise each year, most frequently in people over the age of 50.[4, 5, 6] Due to its low mortality rate and rarity of spreading to other organs, BCC is not considered within cancer registries. Nonetheless, mortality rate being low doesn't equate to its destructive properties of tissue. Generally, keratinocytes are cells that make up the epidermis in which keratinocyte carcinomas are essentially categorized into basal cell carcinoma or squamous cell carcinoma based on the type of cells involved. In basal cell carcinoma, basal cells are keratinocytes at the bottom layer of the epidermis that are mutated

which results in complications with DNA and replication. Basal cell carcinoma tends to grow gradually and starts in areas of the body that are frequently exposed to UV light, including the face, hands, arms, and neck.[5, 8] However, if not detected early, basal cell carcinoma can continue to grow and spread to nerves or bone.

The other type of keratinocyte carcinoma is called squamous cell carcinoma. Squamous cell carcinoma accounts for 15-20% of all NMSCs and is more likely to cause death by spreading to other tissue, compared to basal cell carcinoma.[4] There are an estimated one million cases of SCC reported each year. This type of carcinoma involves keratinocytes located at the upper layer of the epidermis and are classified as squamous cells. When these cells grow out of control, they can develop into squamous cell carcinoma and appear as reddish bumpy patches of skin on anywhere of the body.[5, 7] However, people with darker complexions are more likely to obtain SCC on parts of the body that aren't exposed to direct sunlight, such as the genitals.[8]

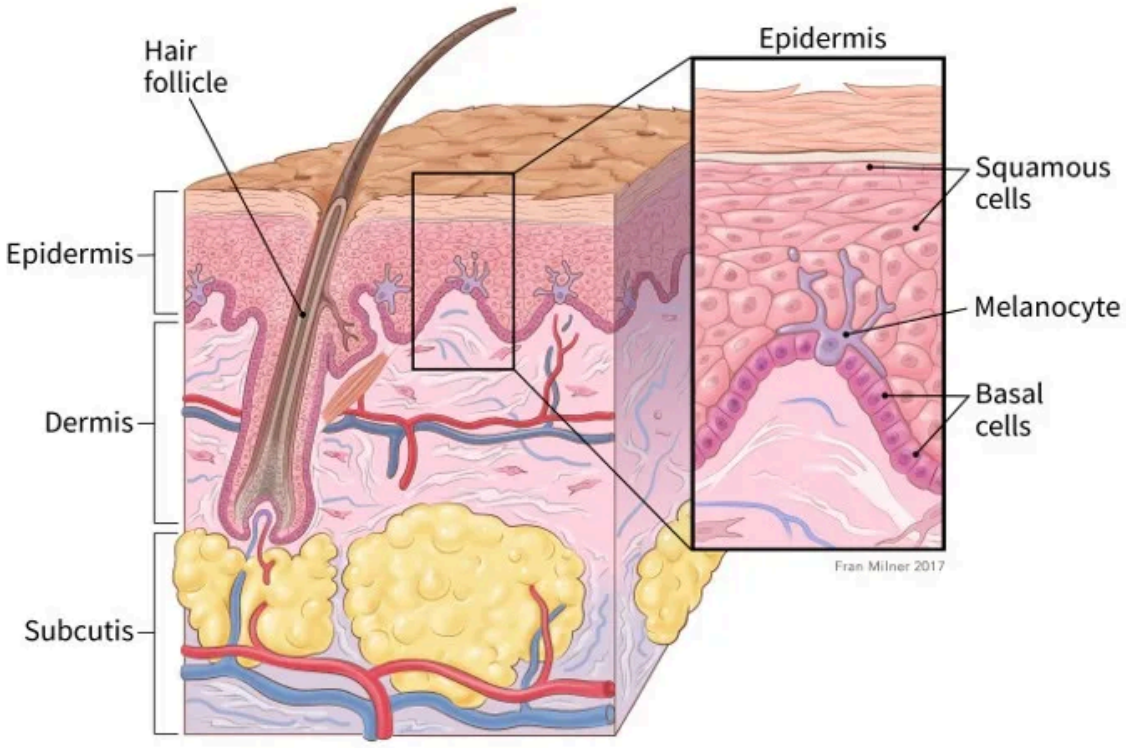

Fig. 1. Different layers of the epidermis [8]

Lastly, melanoma is the most aggressive malignant tumor in which incidence rates are rapidly increasing. From being a rare cancer just decades ago, melanoma mortality rates have been on the rise, resulting in thousands of Americans suffering with melanoma. Melanoma accounts for 1.7% of global cancer-related deaths and is the fifth most commonly diagnosed cancer in the United States. Predominantly affecting fair-skinned individuals, melanoma rates increased 320% from 1975. Currently, it is estimated that 1 in 63 Americans will develop melanoma throughout their lifetime, resulting in record high numbers since then.[9, 10] Melanoma starts in the skin's melanocytes (cells that make the pigment melanin) which are located in the basal layer of the epidermis, or the bottom layer. A buildup of genetic mutations within melanocytes deactivate

tumor suppressor genes that work to stop harmful cells from forming and spreading, especially when exposed to UVR. These cells can form a mole on one's skin or alter a pre-existing mole, thus altering our DNA makeup and leading to the development of melanoma. Early detection of melanoma remains the most important factor in treating it and lowering mortality rates. Melanoma is often pictured as a pink or red lesion on the skin but can also be present as other subtypes and can appear on the eyes, soles of the feet, palms, fingernails, etc.[5, 9, 10]

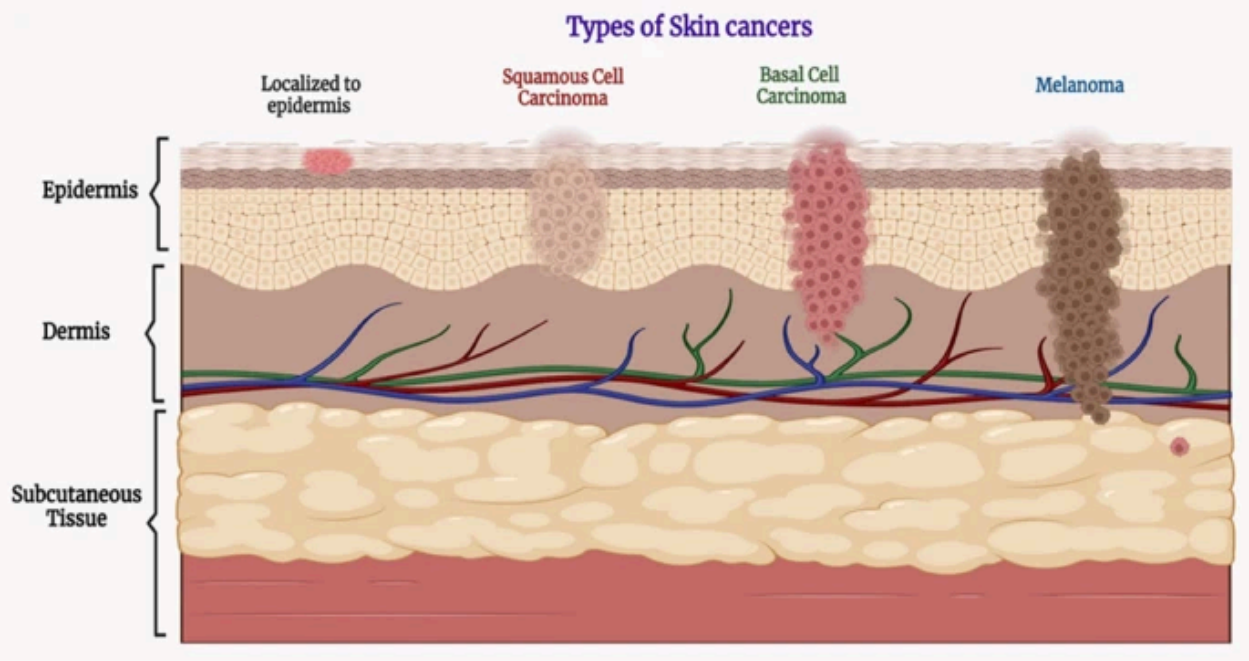

Fig. 2. Three types of skin cancer and their level of penetration to the epidermis [5]

Etiology and Environmental Factors

Skin cancer progression is largely due to a complex interplay of genetic and environmental factors that alter normal, healthy skin cells to cancerous ones.

Perhaps the most prevalent and preventable environmental risk factor is that of ultraviolet radiation due to its genotoxic effect. UVR is responsible for more than 80% of skin cancer cases and exposure to UVR in one's adolescent years is associated with future skin cancer development later on.[4, 5] This radiation is known to have damaging effects to one's DNA, subsequently causing DNA mutations among cells. Ultraviolet radiation comes in the form of 3 ways—UVA, UVB, and UVC. UVA is perhaps the most harmful, as it has the longest wavelength of 320-400 mm, yet, all of those contribute to the breaking down of collagen and elasticity in the skin. In addition, UVR contributes to the activation of p53, a protein that acts as a tumor suppressor gene that inhibits the growth of cancerous cells. When UVR damages p53, the nitrogenous base cytosine in the DNA sequence changes into thymine, in which cytosine is only supposed to pair with guanine. Thus, this causes a mutation in p53 and a mutation in DNA. The epidermis will usually be scattered with "sunburn cells" as a normal response to exposure to UVR. However, sunburn cells in the epidermis that lacked p53—which is supposed to program

cell death (apoptosis) in order to eliminate potentially dangerous cancerous cells from progressing—were unable to mediate healthy apoptosis, allowing damaged cells to survive and potentially grow into skin cancer.[11, 12]

Artificial sources of UVR such as tanning beds have also grown in trend and penetrate deep and directly damage DNA, subsequently leading to melanoma. Non-melanoma skin cancers are more commonly related to chronic UV exposure, whereas melanoma can occur under intermittent intense UV exposure, even in childhood. For instance, severe sunburns in children and adolescents have been connected to a higher risk of contracting melanoma in their adult years.[11] People who are ages 18-29 and use tanning beds have a greater chance at developing melanoma compared to people ages 30-39.[13]

Although there are many factors we can limit, there are environmental things that are unavoidable for some. Arsenic is a natural element that can be found in soil, water, food, and air. This element has been associated with an increase in skin cancer rates, with majority being non-melanoma skin cancers.[11] When arsenic accumulates in the skin, hyperpigmentation and hyperkeratosis are likely to occur and prolonged exposure has been associated with p53 dysfunction, cytotoxicity, and mutagenicity in cells. Ultimately, individuals exposed to arsenic as well as UVR, have higher risks of developing melanoma unlike people who aren't exposed to arsenic and just exposed to UVR.[11, 14]

Photodynamic Therapy

With more cases of melanoma rising for the past few years, it's important to take measures to detect skin cancer early. More specifically, photodynamic therapy (PDT) is a growing treatment method that many dermatologists use to treat skin cancers. Photodynamic therapy uses a drug which is activated by a light-inducing agent, called a photosensitizer to kill cancerous cells and often treats a specific part of the body. The photosensitizer is usually taken orally, spread on the skin, given through an IV, or any place that the tumor is present. Otherwise, after 24-72 hours the tumors will be exposed to the light source. This activation of light on the affected area destroys abnormal white blood cells and also minimizes damage to nearby tissue, serving as an efficient treatment method for skin cancer.[15]

Preventions

Although most skin cancers appear in adults, it's not impossible for young children to develop skin cancer. For one, educational status is crucial in peoples likelihood of getting skin cancer screenings. As an example, a collection of data from more than 1000 men and women indicated that only 44% of them were aware of their entitlement to skin cancer screenings. Therefore, making it necessary to increase awareness of regular skin cancer screenings is imperative to early recognition of skin cancer.[16] Nevertheless, the most important factor in preventing skin cancer is reducing one's exposure to UV radiation. Seeking shade, wearing sun-protective clothing, avoiding going outdoors at the sun's peak, and using sunscreen regularly remain important factors in preventing skin cancer. When possible, wearing long clothing and darker colors prove to be more effective than shorter clothing and lighter colors. Additionally, umbrellas, trees, or other sources of shade can provide minor UV protection. However, shade doesn't block all UV rays and it is important to integrate shade with other preventative measures. Moreover, using sunscreen is one of the most effective prevention methods when used alongside other

sun protection behaviors. It is best to apply sunscreen every 2 hours and after swimming, sweating, or toweling off. When not used properly, this leads to misconceptions on sunscreen's protection and worsened exposure to UV radiation. Broad spectrum sunscreens (protects against UVA and UVB) with a SPF of 15 or higher are effective at preventing skin cancer if used properly. In addition to protecting ourselves from the sun's harmful rays, it is important to note that artificial sources of UV radiation for tanning are also a significant cause of skin cancer. Similar to excessive sun exposure, tanning beds have been correlated to increased rates of BCC, SCC, and melanoma as well as more fine lines and wrinkles. Indoor tanning is one of the easiest and most avoidable ways of preventing skin cancer.[17] Therefore, taking these measures is absolutely crucial to preventing one from developing skin cancer.

Conclusion

Skin cancer is one of the most preventable cancers, yet has the deadliest mortality rates. BCC, SCC, and melanoma are among the most commonly diagnosed skin cancers for most. Factors that are associated with skin cancer are exposure to UV rays, tanning beds, and other environmental factors. Chemotherapy, surgery, immunotherapy, and radiation therapy are some of the most common and efficient treatment methods, yet, new technologies are slowly emerging as more effective approaches to combat the disease such as photodynamic therapy. In other words, it is important that people remain aware of the implications of skin cancer and take preventative measures. Skin cancer is one of the most prevalent cancers globally and this review addresses the specificities, its etiology, and a number of prevention methods.

References

1. Organization, W. H. (n.d.). *Cancer*. World Health Organization. https://www.who.int/health-topics/cancer#tab=tab_1
2. Schwartz S. M. (2024). Epidemiology of Cancer. *Clinical chemistry*, *70*(1), 140–149. https://doi.org/10.1093/clinchem/hvad202
3. Narayanan, D. L., Saladi, R. N., & Fox, J. L. (2010). Review: Ultraviolet radiation and skin cancer. *International Journal of Dermatology*, *49*(9), 978–986. https://doi.org/10.1111/j.1365-4632.2010.04474.x
4. *Skin cancer*. (n.d.). https://www.aad.org/media/stats-skin-cancer
5. Hasan, N., Nadaf, A., Imran, M., Jiba, U., Sheikh, A., Almalki, W. H., Almujri, S. S., Mohammed, Y. H., Kesharwani, P., & Ahmad, F. J. (2023). Skin cancer: understanding the journey of transformation from conventional to advanced treatment approaches. *Molecular cancer*, *22*(1), 168. https://doi.org/10.1186/s12943-023-01854-3
6. Basset-Seguin, N., & Herms, F. (2020). Update in the Management of Basal Cell Carcinoma. *Acta dermato-venereologica*, *100*(11), adv00140. https://doi.org/10.2340/00015555-3495
7. Society, A. C. (2024, November 15). *What are basal and squamous cell skin cancers?: Types of skin cancer*. Types of Skin Cancer | American Cancer Society. https://www.cancer.org/cancer/types/basal-and-squamous-cell-skin-cancer/about/what-is-basal-and-squamous-cell.html#:~:text=Basal%20cell%20carcinoma,-Basal%20cell%20carcinoma&text=These%20cancers%20start%20in%20the,other%20parts%20of%20the%20body.

8. Staff, M. C. (2023, August 11). *Squamous cell carcinoma of the skin*. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/squamous-cell-carcinoma/symptoms-causes/syc-20352480
9. Rastrelli, M., Tropea, S., Rossi, C. R., & Alaibac, M. (2014). Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification. *In vivo (Athens, Greece)*, *28*(6), 1005–1011. https://pubmed.ncbi.nlm.nih.gov/25398793/
10. Saginala, K., Barsouk, A., Aluru, J. S., Rawla, P., & Barsouk, A. (2021). Epidemiology of Melanoma. *Medical Sciences*, *9*(4), 63. https://doi.org/10.3390/medsci9040063
11. Cooper, B. R. (2024, May 2). *Overview of environmental skin cancer risks*. StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK603721/#:~:text=Exposure%20to%20ultraviolet%20(UV)%20radiation,DNA%20present%20within%20skin%20cells.
12. Leffell, D. J. (2000). The scientific basis of skin cancer. *Journal of the American Academy of Dermatology*, *42*(1), S18–S22. https://doi.org/10.1067/mjd.2000.103340
13. Cust, A. E., Armstrong, B. K., Goumas, C., Jenkins, M. A., Schmid, H., Hopper, J. L., Kefford, R. F., Giles, G. G., Aitken, J. F., & Mann, G. J. (2010). Sunbed use during adolescence and early adulthood is associated with increased risk of early-onset melanoma. *International Journal of Cancer*, *128*(10), 2425–2435. https://doi.org/10.1002/ijc.25576
14. Yu, H. S., Liao, W. T., & Chai, C. Y. (2006). Arsenic carcinogenesis in the skin. *Journal of biomedical science*, *13*(5), 657–666. https://doi.org/10.1007/s11373-006-9092-8
15. National Cancer Institute. (2011, September 6). *Photodynamic Therapy for Cancer - National Cancer Institute*. Www.cancer.gov. https://www.cancer.gov/about-cancer/treatment/types/photodynamic-therapy
16. Kornek, T., & Augustin, M. (2013). Skin cancer prevention. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*, *11*(4), 283–298. https://doi.org/10.1111/ddg.12066
17. Linos, E., Katz, K. A., & Colditz, G. A. (2016). Skin Cancer-The Importance of Prevention. *JAMA internal medicine*, *176*(10), 1435–1436. https://doi.org/10.1001/jamainternmed.2016.5008