Spring 2020

"Skin Cancer Types and the Effectiveness of Mohs Surgery Against Them"

Andrew M. Brockman
Eastern Kentucky University, andrew_brockman52@mymail.eku.edu

Eastern Kentucky University

Skin Cancer Types and the Effectiveness of Mohs Surgery Against Them

Honors Thesis Submitted

In Partial Fulfillment

Of the Requirements of HON 420 Spring 2020

By Andrew Brockman

Faculty Mentor

Dr. Suzanne Byrd

Department of Biological Sciences

Skin Cancer Types and the Effectiveness of Mohs Surgery Against them

Andrew Brockman

Dr. Suzanne Byrd

Department of Biological Sciences

Abstract Description: Skin cancer is the number one form of cancer around the world today. It affects people of all races and discriminates no one when it comes to how deadly it can become when it metastasizes. As rates of skin cancer continue to increase year after year, research is being conducted at a very high rate on possible treatments for this disease. Understanding the three basic types of skin cancer, basal cell carcinoma, squamous cell carcinoma, and melanoma gives a wary victim of skin cancer a guide for what they are dealing with as they progress through possible treatment. There are a variety of types of treatments in modern medicine, many of them being experimental and relying on fresh research. While new research is being introduced at a high pace, the most effective type of treatment there is against non-melanoma skin cancer is Mohs surgery, a type of surgical excision developed in the 1930s. This surgery has been the foundation of effective treatment research against skin cancer for going on ninety years, and still today is more cost effective, less time consuming, and produces better results than any type of modern surgical excision for non-melanoma skin cancers.

Keywords: skin, cancer, basal, squamous, melanoma, carcinoma, Mohs, surgery, excision, treatment

Table of Contents

List of Figures

Acknowledgments Page

Acknowledgements: I would like to thank my mentor, Dr. Suzanne Byrd, for all of her help in creating this paper and presentation. I would also like to thank all Honors faculty advisors, especially Dr. Erik Liddell, Dr. David Coleman, Dr. Minh Ngyuen, and Ms. Katie Patton, and all of my Honors professors I have had in EKU Honors classes, for providing such a rewarding and unique experience over the last four years.

Introduction

Skin cancer may develop from a variety of contributing factors, such as where a person lives geographically, how much radiation from the sun or other sources they expose their skin to, and even through genetic pathways. Many people wonder about which of these factors is the most significant. Awareness of the causes of skin cancer are essential to the prevention of skin cancer. Many people know the main cause is UV radiation from the sun, but many other factors can play into the development of skin cancer as well. Smoking is well associated with lung cancer, and it also plays a major role into developing cancer in the gums, brain, and skin. It is important to make people aware of the severe consequences of ignoring the risk factors of skin cancer. Non-melanoma skin cancers, which include squamous cell carcinoma and basal cell carcinoma, are the most common malignancies in the United States, with approximately 3.5 million new cases diagnosed each year (Kimmel 2016). Melanoma, although less common, is the deadliest form of skin cancer. Nearly 60,000 people are diagnosed and about 8,600 people die from melanoma each year (Babbin 2015).

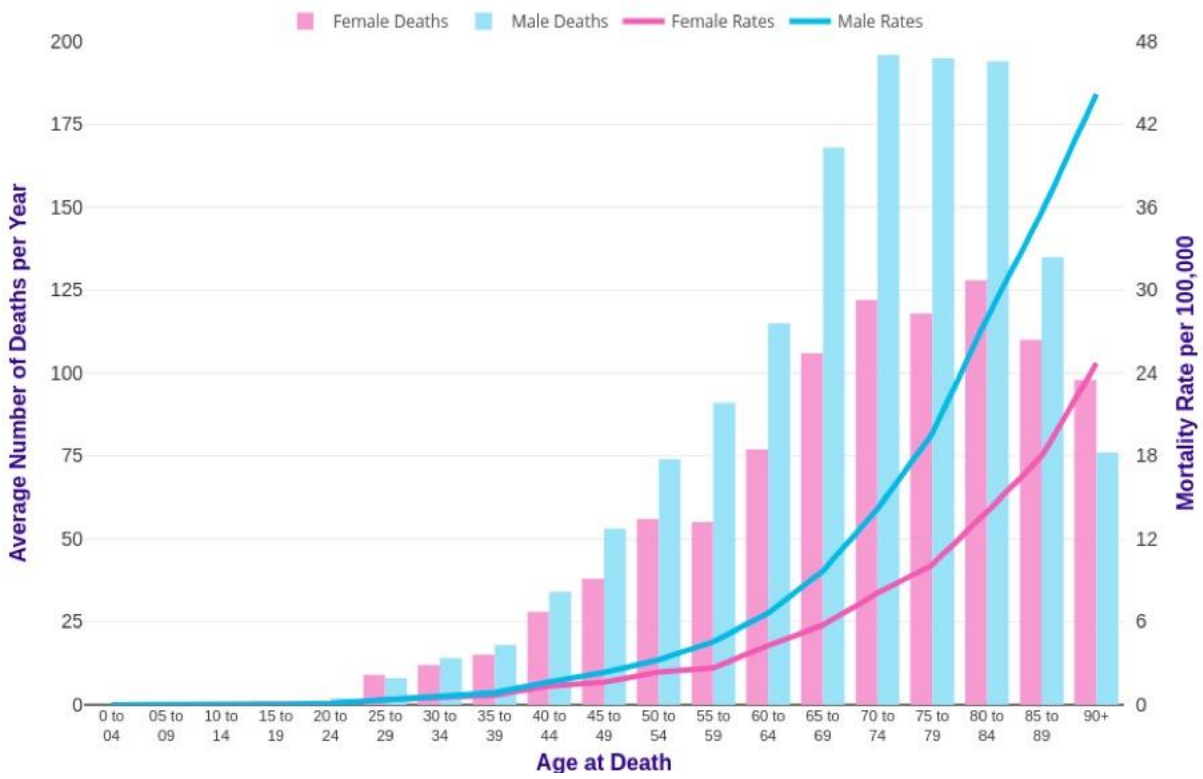

Figure 1: Average Death Rate from Advanced Melanoma in Different Age Groups from Years 2015-2017 Worldwide. There is a significant rise in average number of deaths per year with every 5-year increase in age group.

Overall, skin cancer is the most common form of cancer in the United States, and the incidence is increasing. The burden of skin cancer can be reduced through prevention efforts. Exposure to ultraviolet radiation via the sun is the most common and avoidable cause of skin cancers. Most adults in the United States do not protect themselves from the sun, and prevalence of at least one sunburn per year is over 50% (Babbin 2015).

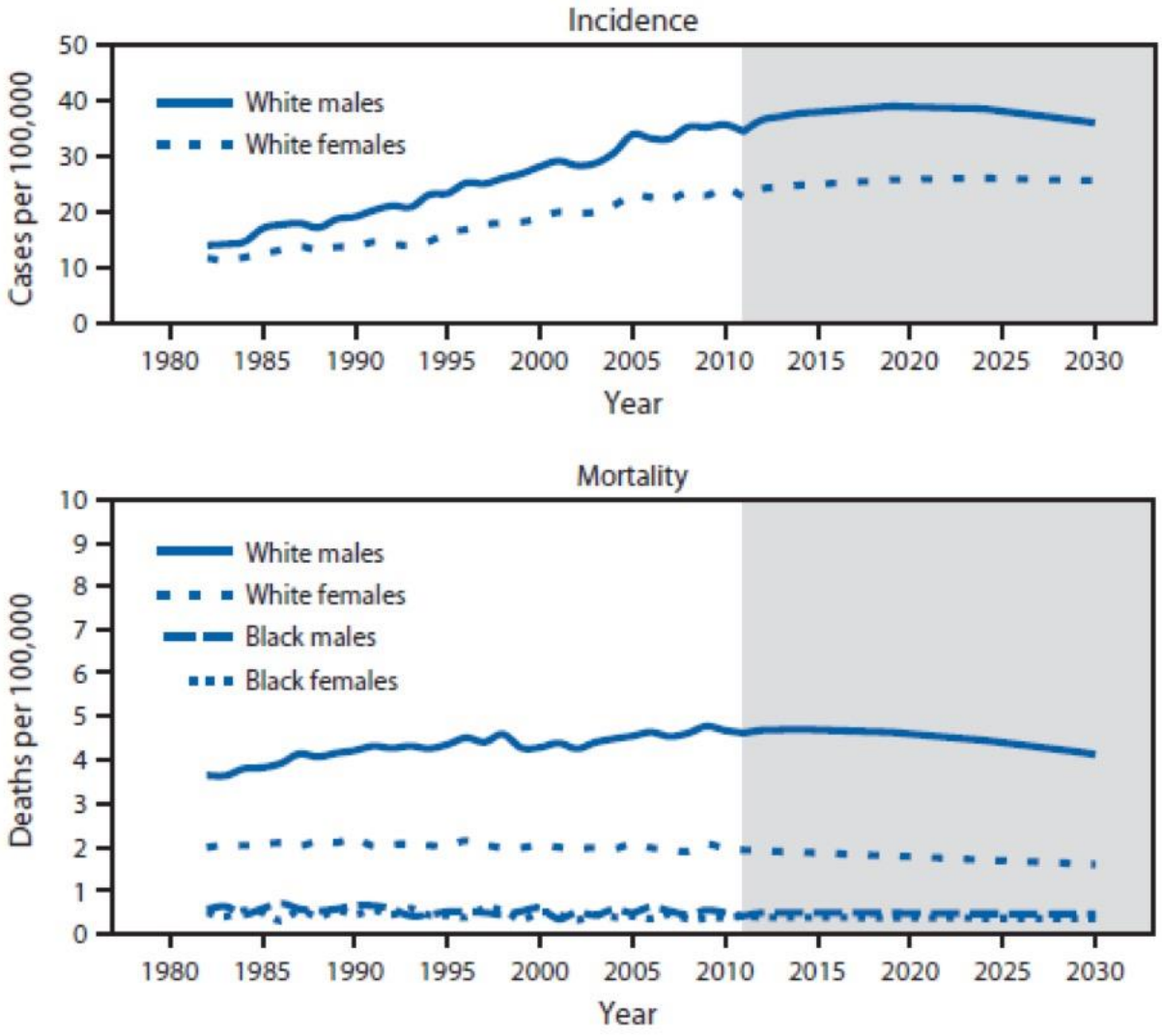

Figure 2: Experimental Overview of Skin Cancer Incidences and Mortality Rates in the United States. Observes differences in effectiveness against race and gender race over five-year increments.

Sun protection behaviors, such as avoiding the sun, wearing protective clothing, and wearing sunscreen, can be emphasized in interventions designed to increase sun protection. The skin of the head and face is habitually exposed to sunlight and there may consequently be ultraviolet (UV)-induced chronic damage such as solar elastosis, actinic keratosis and lentigo, with possible consequent development of cutaneous squamous cell carcinoma, cutaneous basal

cell carcinoma and cutaneous melanoma (Brash 2008).

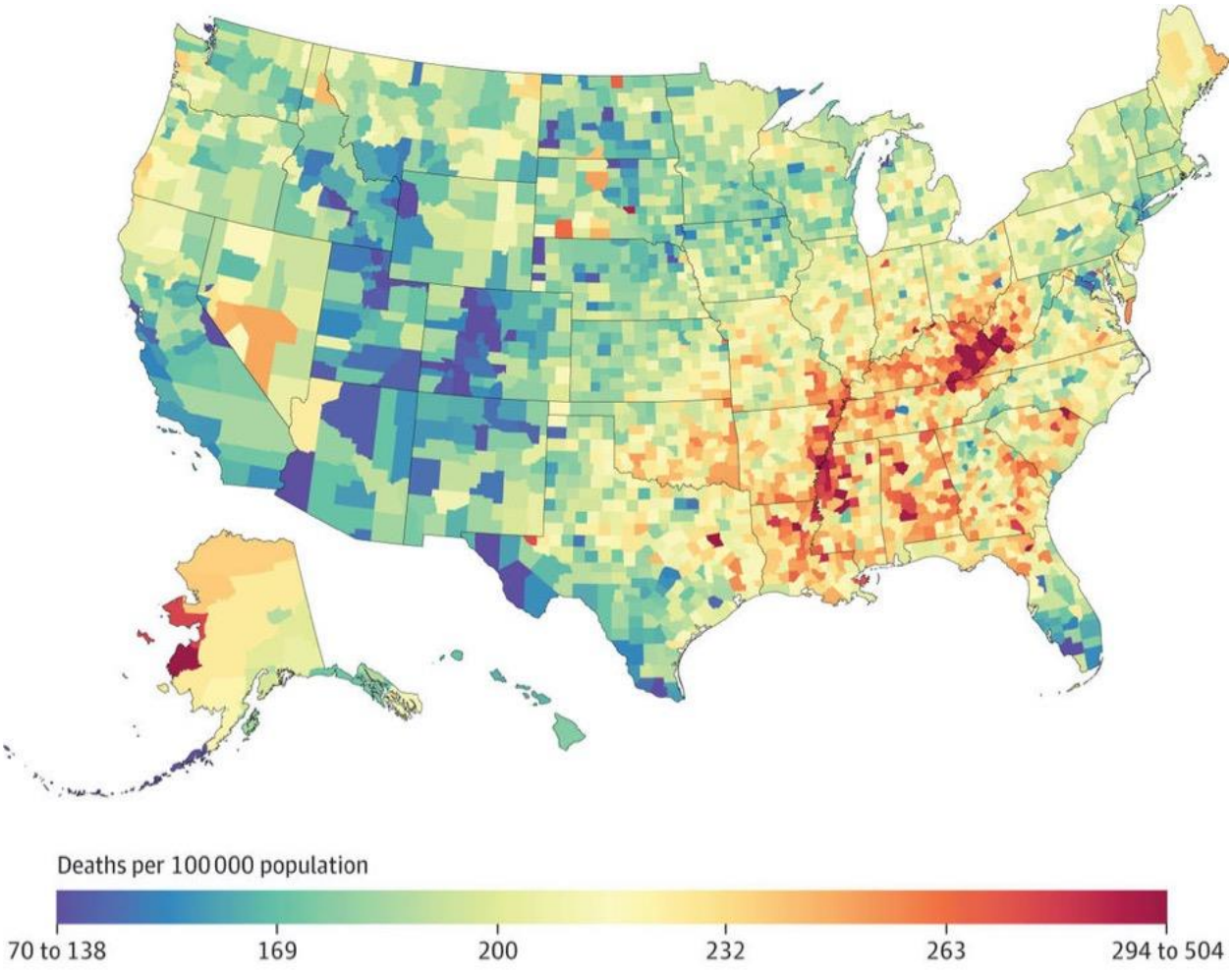

Figure 3: Geographical Map of Deaths from Advanced Melanoma in United States (2015-2017). Density significantly increases in the Southeastern region of the United States.

Cutaneous basal cell carcinoma is the most common cancer in White people. Cutaneous is used in front of the cancer type because it is the technical term for the combination of all three layers of skin, these being the epidermis, dermis, and subcutaneous layers (Feller 2016). It is named with the prefix of cutaneous because the cells of basal cell carcinoma resemble the cells of the basal cell layer of the epithelium. Cutaneous basal cell carcinoma affects mainly chronically sun-exposed skin of the head and neck of fair complexioned older people (Donovan

2009). Both intermittent acute, and long-standing continual exposure to UV are high risk factors for cutaneous basal cell carcinoma. It is a slow-growing cancer that if left untreated will invade locally, but only rarely metastasizes. Black people are rarely affected. People with cutaneous basal cell carcinoma are at increased risk for cutaneous squamous cell carcinoma and cutaneous melanoma (Tlholoe 2015).

The Hedgehog (Hh) signaling pathway was first identified in the common fruit fly. It is a highly conserved evolutionary pathway of signal transmission from the cell membrane to the nucleus. The Hh signaling pathway plays an important role in the embryonic development. It exerts its biological effects through a signaling cascade that culminates in a change of balance between activator and repressor forms of glioma-associated oncogene (Gli) transcription factors (Skoda 2018). Dysregulation in the hedgehog intracellular signaling pathway is implicated in the pathogenesis of cutaneous basal cell carcinoma and is thought to be an early genetic factor in its tumorigenesis. The hedgehog signaling pathway plays an essential role in organogenesis' development of different organs throughout the body, and later, postnatally, in regulating proliferation and differentiation of keratinocyte stem cells, and in the development of hair follicles and sebaceous glands (Skoda 2018). In the hedgehog signaling pathway, patch 1 (PTCH1) functions as a tumor suppressor gene, inhibiting the activity of the proto-oncogene, smoothened (SMO) (Wong 2014). Signaling by SMO results in activation of transcription of hedgehog target genes, eliciting mitogenic responses with increased proliferation of keratinocyte stem cells, which produce keratin, a fibral structural protein that is a key component in the makeup of hair, nails, and the outermost layer of skin (Wong 2014). Clonal expansion of dysregulated cells within the keratinocytes stem cell niche is favored by loss-of-function mutation in PTCH1 that allows upregulated activity of SMO, and by gain of function mutations

in the SMO gene that render SMO protein resistant to inhibition by PTCH1. These promote escape of cancer precursor cells from the niche to colonize other cellular compartments in the skin, ultimately giving rise to a basal cell carcinoma (Brash 2008).

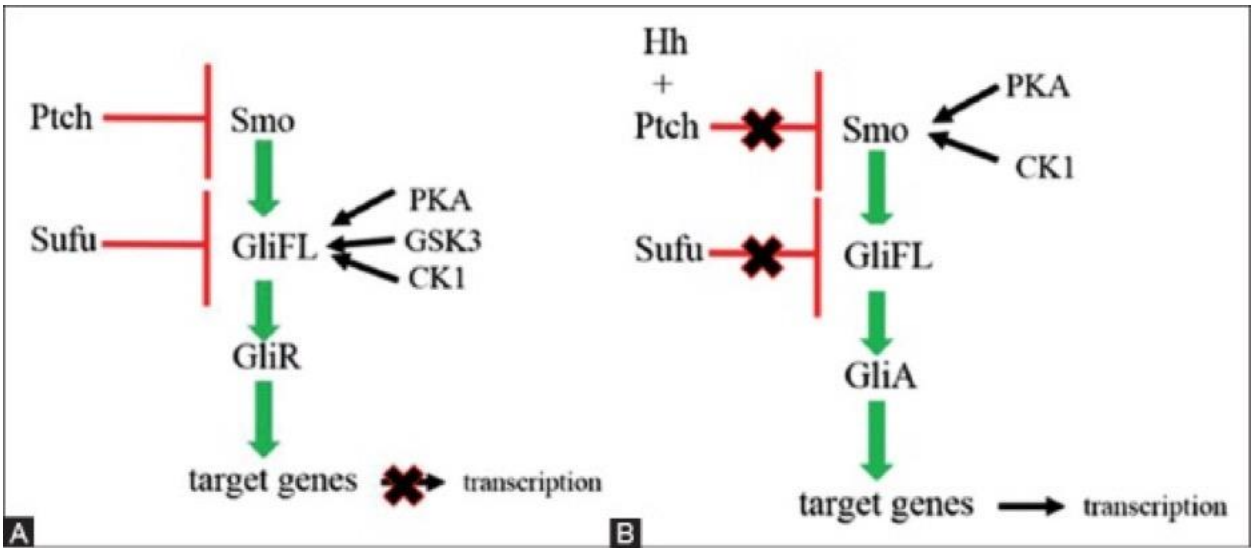

Figure 4: Summary of Hedgehog Signaling Pathway. Indicates the process that the hedgehog pathway helps conduct, leading to eventual transcription of DNA. Full ability of the pathway to lead to transcription depends on where the signal transmission is initiated.

The molecular alterations in the hedgehog signaling pathway may be of germline origin or may occur postnatally subsequent to UV-induced DNA damage, or rarely may arise spontaneously. Keratinocytes which show dysregulated expression of the hedgehog signaling pathway fail to undergo cell-cycle arrest in response to the p21 cell cycle inhibitor, and thus have enhanced proliferative capacity. It has been reported that most cases of cutaneous basal cell carcinomas that arise spontaneously show loss of function of PCTH1 and a minority show enhanced function of SMO (Carucci 2008). About half of all cases of sporadic basal cell carcinoma also show mutations in the p53 tumor suppressor gene, but these seem to be late genetic events in the tumorigenesis of cutaneous basal cell carcinoma, which are related to its progression. Taking advantage of the inhibition of the hedgehog signaling pathway as a mean of

treatment of cutaneous basal cell carcinoma of the skin has become possible through the use of an inhibitor, vismodegib, and other hedgehog pathway antagonists (Wong 2014).

Three Types of Skin Cancer

Cutaneous basal cell carcinoma requires a specific stromal environment to maintain its morphological characteristics. Key regulators of the biological behavior of cutaneous basal cell carcinoma appear to be stromal fibroblasts and myofibroblasts. Cutaneous basal cell carcinoma cells express bone morphogenetic protein (BMP) 2 and 4, while GREMLIN 1, a BMP antagonist, is highly expressed in the stroma of the tumor but not in the dermis underlying normal keratinocytes (Boehnke 2012). GREMLIN 1 counteracts the growth-inhibitory effect of BMPs and is therefore assumed to be an important agent supporting cutaneous basal cell carcinoma cell proliferation and survival. Matrix metalloproteinase expressed in the stroma of cutaneous basal cell carcinoma also plays an important role in regulating growth and other functions of cutaneous basal cell carcinoma cells. It is probable that cutaneous basal cell carcinoma tumorigenesis depends substantially on specific factors produced by stroma damaged by UV, but on the rare occasions when cutaneous basal cell carcinomas occur at sites that are not exposed to sunlight, other biological factors drive its initiation and progression (Boehnke 2012).

Although UV-radiation is a primary etiological factor for cutaneous basal cell carcinoma, the mechanism whereby exposure to UV triggers cutaneous basal cell carcinoma is complex and the details are as yet unknown (Epstein 2008). The development of cutaneous basal cell carcinoma at sites not exposed to UV is unexplained. Cutaneous basal cell carcinoma usually develops at sites continually exposed to UV which explains why basal cell carcinoma so frequently affects the skin of the head and face. Reduced functional activity of genes regulating

repair of DNA damaged by UV may be a modifying factor in the pathogenesis of cutaneous basal cell carcinoma (Feller 2010). In support of this, subjects with the genetic condition, xeroderma pigmentosum in whom there are high-penetrance germline mutations in genes encoding proteins involved in the mechanism of nucleotide excision-repair are at great risk of developing multiple and recurrent cutaneous basal cell carcinomas at a young age. In contrast to subjects not affected by basal cell carcinoma, those who do have basal cell carcinoma show reduced clearance of mutagenic photoproducts from UV-induced DNA lesions of sunlight exposed skin, probably owing to low-penetrance genetic polymorphisms of specific genes encoding enzymes involved in breaking down reactive oxygen species and DNA repair (Radiespiel-Troger 2009).

Cutaneous squamous cell carcinoma originates from stem/progenitor cells of the basal cell layer of the epidermis and cutaneous basal cell carcinoma from either the bulge region of a hair follicle, which is rich in keratinocyte stem cells, or from stem/progenitor cells of the basal cell layer of the epidermis. While the origin of melanoma cells is unknown, it has been proposed that cutaneous melanoma precursor cells may arise either from dedifferentiated melanocytes or from melanocyte progenitors in the bulge region of hair follicles, or from neural crest-derived Schwann cell precursors (Tlholoe 2015).

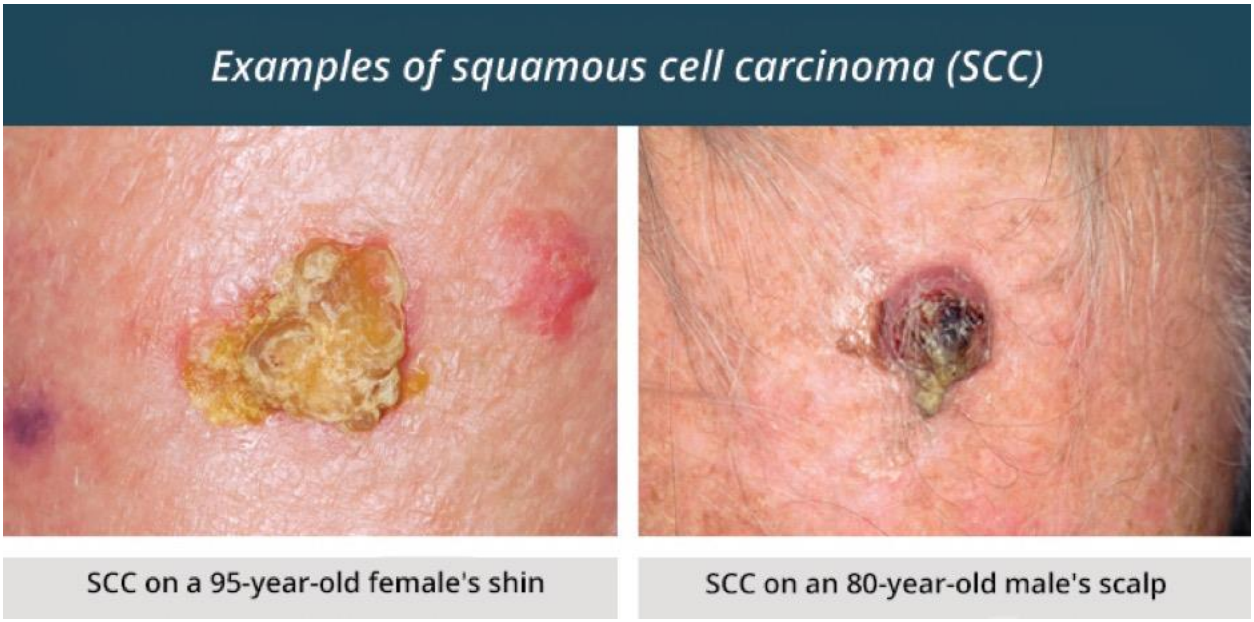

Figure 5: Examples of Squamous Cell Carcinoma. These photos represent advanced stages of squamous cell carcinoma, and this is when a person with the disease is more likely to notice the tumor.

Cutaneous squamous cell carcinoma of the skin is associated with frequent moderate chronic UV exposure, and is often preceded by premalignant actinic keratosis or by Bowen disease. On the other hand, cutaneous basal cell carcinoma is usually associated with intermittent, infrequent, intense UV exposure and almost invariably arises *de novo*, which means it is typically the first type of cancer that a patient has developed (Grossman 2008). Cutaneous melanoma can also arise *de novo* after intermittent, infrequent, intense UV exposure, but there is evidence that as many as 30 % of cases evolve from pre-existing sites of melanotic pigmentation, whether or not they have actually been exposed to UV (Grossman 2008).

Both cutaneous squamous cell carcinoma and melanoma are very likely to metastasize whereas cutaneous basal cell carcinoma very seldom does. Even in the absence of exposure to

UV, squamous cell carcinoma is occasionally associated with non-healing wounds or scarring, or with chronic lesions which are, or have been preceded by chronic immuno-inflammatory processes. This is not the case with cutaneous basal cell carcinoma or cutaneous melanoma.

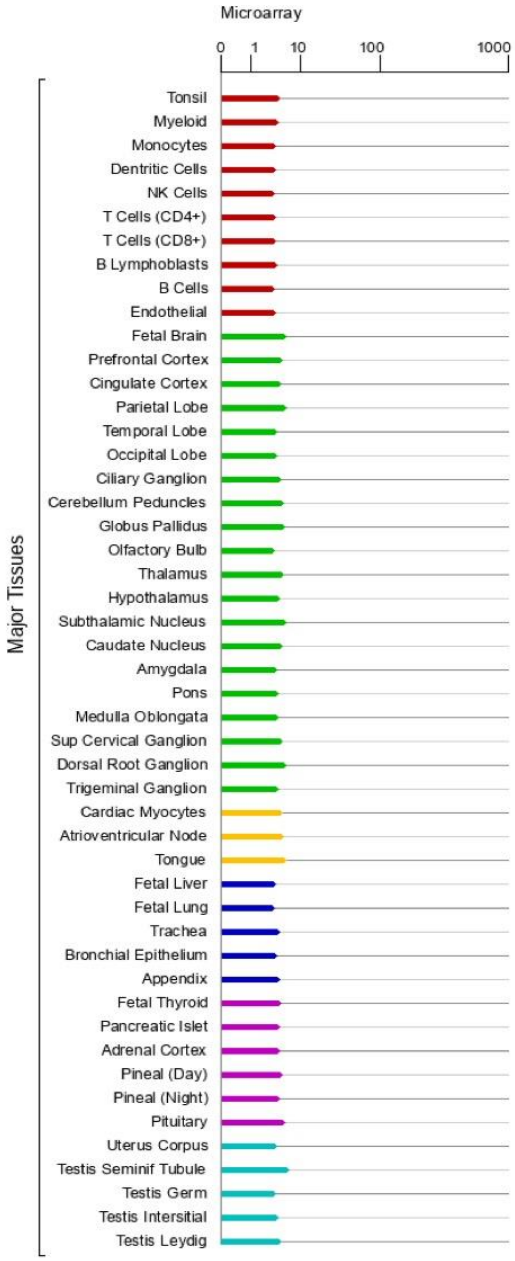

Figure 6: MC1R Receptor Effect on Different Signaling Pathways. This diagram thoroughly outlines the different chemical signaling pathways that MC1R has an effect upon.

Cutaneous squamous cell carcinoma, basal cell carcinoma and melanoma more frequently affect elderly, red haired, blue eyed and fair complexioned persons, and it has been consistently demonstrated that variants of the highly polymorphic melanocortin 1 receptor (MC1R) gene are associated with increased risk of these malignancies (Scherer 2010). The pathogenesis of cutaneous squamous cell carcinoma is associated with multiple local genetic alterations that may bring about dysregulation of the cell cycle, of apoptosis, of DNA repair, of cellular differentiation, of telomerase activity with evasion of cellular senescence, and of expression of the enzyme cyclo-oxygenase 2 (COX-2) (Hoban 2002). In contrast, cutaneous basal cell carcinoma is primarily driven by genetic mutations causing uncontrolled activation of the hedgehog intracellular pathway leading to enhanced proliferative capacity of basal cells, and by molecular alterations in the p53 tumor-suppressor gene. Most cases of cutaneous basal cell carcinoma occur sporadically, but they may also occur as a manifestation of the rare heritable basal cell nevus syndrome in association with germline molecular aberrations of the hedgehog intracellular signaling pathway (Epstein 2008).

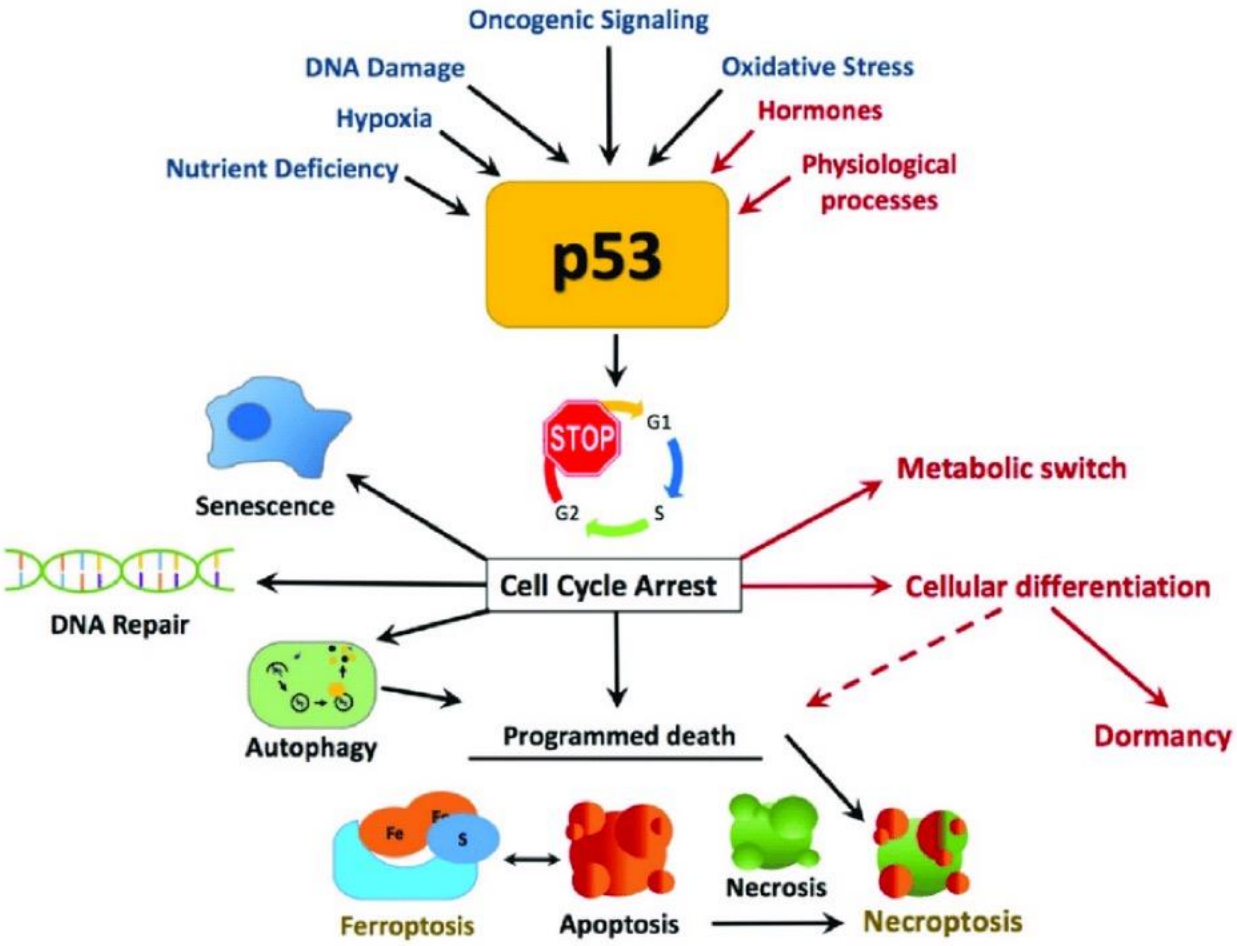

Figure 7: Outline of p-53 Tumor Suppressor Gene Pathway. This diagram shows the importance that p53 can have on different cellular pathways throughout the human body.

Melanomas of the skin of the head and face are usually of the lentigo maligna type, which is commonly associated with frequent, moderate chronic UV exposure. This is in contrast to melanomas of the trunk, for example, which are associated with intermittent, acute UV exposure. Skin melanoma cells show molecular alterations of the RAS-BRAF-MEK-ERK mitogen activated protein kinase (MAPK) signaling pathway, mediating uncontrolled proliferation of the affected malignant melanocytes, genetic alterations in the CDKN2A gene encoding the p16INK4A tumor suppressor protein, and MC1R genetic polymorphism (Riker

2010). In 10-30% of cases, cutaneous melanoma arises from pre-existing melanotic hyperpigmentation such as lentigo, freckles or pigmented naevi, or moles (Feller 2016). Despite an established cause-and-effect relationship between the development of melanoma and exposure to UV, genes with UV-induced 'signature mutations' are not common in melanoma. Thus, it is evident that the etiopathogenesis of melanoma is complex, with UV playing a critical role, but UV by itself does not necessarily cause melanoma. Indeed, in Black people, melanomas mainly affect body sites that are not exposed to UV such as the soles of the feet and the palms of the hands, or more commonly known as acral melanoma (Jhappan 2003).

Cutaneous melanoma is an aggressive skin tumor that can be classified into 4 main subtypes: superficial spreading, nodular, lentigo maligna and acral melanoma. Lentigo maligna melanoma typically affects long-term chronically UV-exposed skin of the head and face, where other subtypes are relatively rare. The frequency of lentigo maligna melanoma increases with age and peaks in the seventh to eighth decades of life. Lentigo maligna is an epithelial field of atypical melanocytes which takes the form as an ill-defined brown macule which slowly expands centrifugally (Andreassi 2011). When these atypical epithelial melanocytes breach the basement membrane and invade the connective tissue, the lesion is referred to as lentigo maligna melanoma. Cutaneous melanomas of the head and neck are less likely to arise in association with pre-existing pigmented nevi than cutaneous melanomas of the trunk.

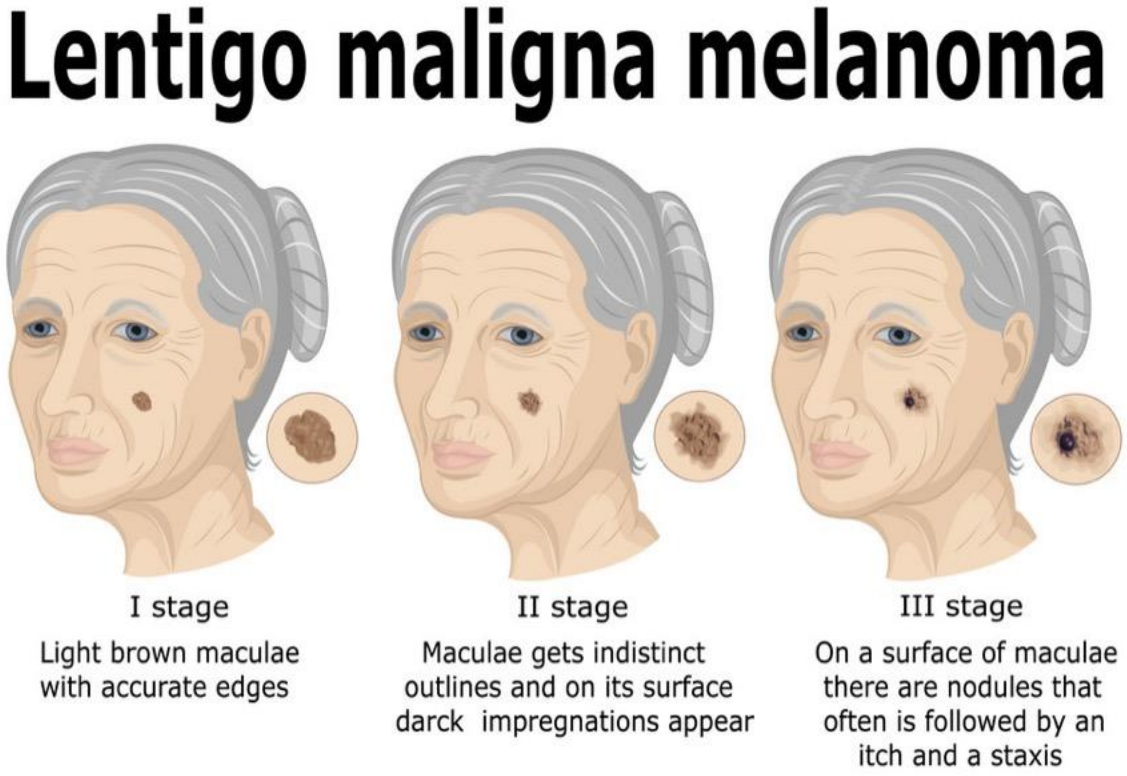

Figure 8: Examples of Lentigo Maligna Melanoma. As stages of the skin cancer progress, the melanoma typically gets darker as it seeps deeper into the dermis.

Many complex factors are implicated in the pathogenesis of cutaneous melanoma including family history, phenotypic characteristics such as pale skin and red hair with propensity to sunburn, many episodes of sunburn especially in youth, the presence of numerous melanotic nevi or freckles, and pre-existing dysplastic nevi. Further factors are MC1R genetic polymorphism, and perhaps other yet ill-defined environmental factors, but some MC1R variants are associated with increased risk of cutaneous melanoma regardless of skin type and hair color (Kennedy 2001).

Like cutaneous squamous cell carcinoma, lentigo maligna melanoma typically affects chronically UV-exposed skin of the head and face, but the risk of other subtypes of melanoma is

more related to intermittent, intense UV exposures. In contrast to malignant keratinocytes of cutaneous squamous cell carcinoma that show UV-induced signature-mutations, these are rare in cutaneous melanoma cells, and while mutations to tumor-suppressor gene p53 are frequent in UV-induced squamous cell carcinoma, in UV-induced cutaneous melanoma they are not (Feller 2016). Cutaneous melanoma cells but not malignant keratinocytes show oncogenic mutations in either NRAS or BRAF, which are specified genes in the body that deal with cell signaling and cell growth (Feller 2016). Except for acral and mucosal melanomas, BRAF mutations are an early genetic event of melanoma tumorigenesis and can be found in up to 60 % of frank melanomas (Situm 2010). In contrast, in mucosal and acral melanomas there are gain-of-function mutations in the cKit receptor thyrosine kinase. Inactivating mutations in the CDKN2A gene, which encodes for p16INK4a tumor suppressor protein, poses a high risk for development of cutaneous melanoma. Both BRAF and CDKN2A mutations in cutaneous melanoma cells are characteristic of indirect UV-induced oxidative damage (Abdel-Malek 2009).

Cutaneous melanoma arising from melanocytes residing in the basal cell layer of the epidermis usually shows one of two histopathological patterns. In one pattern there is a radial growth phase characterized by proliferation of atypical melanocytes within the epidermis and by small breaches of the basement membrane. In the other pattern there is a phase of ‘vertical’ growth which occurs once the basement membrane is breached and the melanoma starts to invade the dermis in a nodular pattern without any significant preceding phase of radial growth (Tlholoe 2015). A further third pattern of growth occurs when the cutaneous melanoma originates from melanocyte precursors that reside in the dermis as a result of arrest in their migration from the neural crest. In this case, epidermal melanocytes do not contribute to the cutaneous melanoma and there is no evidence of invasive breaching of the basement membrane.

Cutaneous melanoma is rare in Black persons, and when it occurs, it preferentially affects body sites not habitually exposed to UV such as the sole of the foot, the palm of the hand and the nail bed (acral melanomas). Although the dorsum of the hand is usually constantly exposed to UV-radiation, for some obscure reasons it is only rarely affected by cutaneous melanoma. Curiously, while the frequency of cutaneous basal cell carcinoma and cutaneous squamous cell carcinoma is high in albino Blacks, cutaneous melanoma is rare in this population group. There is evidence of loss of integrity of membranes of the melanosomes in melanoma cells with consequent leakage of reactive oxygen species (ROS) and metabolic by-products of melanogenesis that may be cytotoxic, genotoxic or mutagenic into the cytoplasm of melanoma cells contributing to progressive DNA damage (Terenziani 2003). It is possible that the primary alterations to DNA, favoring initial transformation of normal melanocytes and later promoting malignant transformation of the initially transformed melanocytes may result from a similar loss of integrity of the membranes of melanosomes within normal melanocytes (Gidanian 2008).

Potential Treatment Types

The Self-Efficacy Scale for Sun Protection was designed to assess an individual's confidence to protect oneself from sun exposure (Babbin 2015). Variations of this measure have been utilized in multiple population-based interventions that have demonstrated effectiveness. Assessments of factorial invariance and internal consistency suggest that the Self-Efficacy Scale for Sun Protection is a reliable and valid instrument. It can be used across a full range of adult participants varying by age, educational level, skin tone, gender, ethnicity, race, and stage attributes. This measure is used to determine a person's susceptibility to skin cancer.

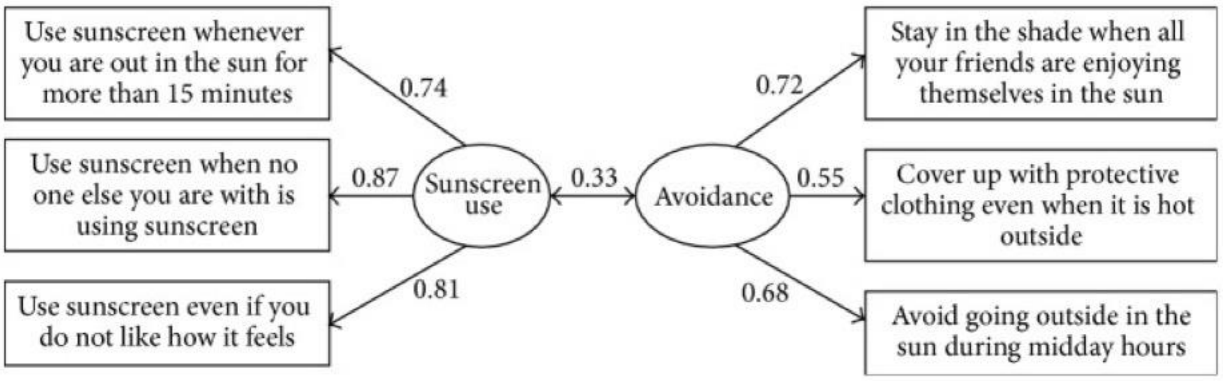

Figure 9: Self-Efficacy Effectiveness Ratios of Different Treatments. These ratios represent the effectiveness ratio of these preventative measures on a 1.00 scale.

Skin is the largest human organ, our protection against various environmental assaults and noxious agents. Accumulation of damage to this organ may lead to the formation of skin cancers, including both melanoma and non-melanoma skin cancers. A safer, affordable, and more effective strategy for chemoprevention and treatment is clearly needed for the improvement of skin cancer care. Phytochemicals have the potential to play a role in skin cancer treatment. First, pre-cancerous and cancerous skin lesions are readily accessible to topical agents that can be applied only to the suspicious lesions with minimal damage to normal skin. This contrasts with the use of phytochemical for internal organ tumors, which may require oral ingestion of the phytochemical resulting in a systemic effect. Secondly, skin lesions and treatment efficacy can easily be evaluated by physicians. Skin biopsies are relatively non-intrusive unlike biopsies of tumors in internal organs. Thus, future trials evaluating the effectiveness of phytochemicals in skin cancer could produce encouraging results.

Several promising phytochemicals have been found in a variety of fresh fruits, vegetables, roots, and herbs, such as epigallocatechin-3-gallate, resveratrol, curcumin, proanthocyanidins, silymarin, apigenin, capsaicin, genistein, indole-3-carbinol, and luteolin. These compounds may contribute to cancer chemoprevention and treatment via multiple

mechanisms (Chau Yee Ng 2018). While these different treatments are promising, they are still in an experimental phase, and should be regarded as such. There has been research conducted to show they decrease susceptibility to, but no proven evidence for curing skin cancer.

Colorful Fruits, Vegetables, and Phytochemicals

Color	Phytochemicals	Fruits and Vegetables
White and green	Allyl sulphides	Onions, garlic, chives, leeks
Green	Sulforaphanes, indoles	Broccoli, Brussels sprouts, cabbage, cauliflower
Yellow and green	Lutein, zeaxanthin	Asparagus, collard greens, spinach, winter squash
Orange and yellow	Cryptoxanthin, flavonoids	Cantaloupe, nectarines, oranges, papaya, peaches
Orange	Alpha and beta carotenes	Carrots, mangos, pumpkin
Red and purple	Anthocyanins, polyphenols	Berries, grapes, plums
Red	Lycopene	Tomatoes, pink grapefruit, watermelon

Figure 10: Table of Different Fruits and Vegetables Producing Phytochemicals. Research has been developed about the chemical pathways that can be inhibited or enhanced by these chemicals and helps to develop treatments for cancers.

The need for new research into treatment development for later stage skin cancer is pressing, as in recent years, the elderly population affected by skin cancer has rapidly increased. Aging is a risk factor for most cancers. In general, two different mechanisms have been suggested to explain the increase of cancer risk with aging. The first explanation is the exposure to occupational carcinogens. The second mechanism is the physical changes in the body due to aging. Vulnerability to cancer with multiple effects of age such as disturbance of hormonal balance, an increase of chronic proliferation and the decline in immune response with age. Skin cancer is the most common cancer worldwide. In fact, the incidence of skin cancers is rising each year along with the increase of an aging population. The longer life expectancy is considered among main risk factors as well as the increased sun exposure and the ozone layer depletion. Exposure to some chemicals such as solvents, polycyclic aromatic hydrocarbons (PAHs), arsenics are considered risk factors for skin cancer (Atis 2015).

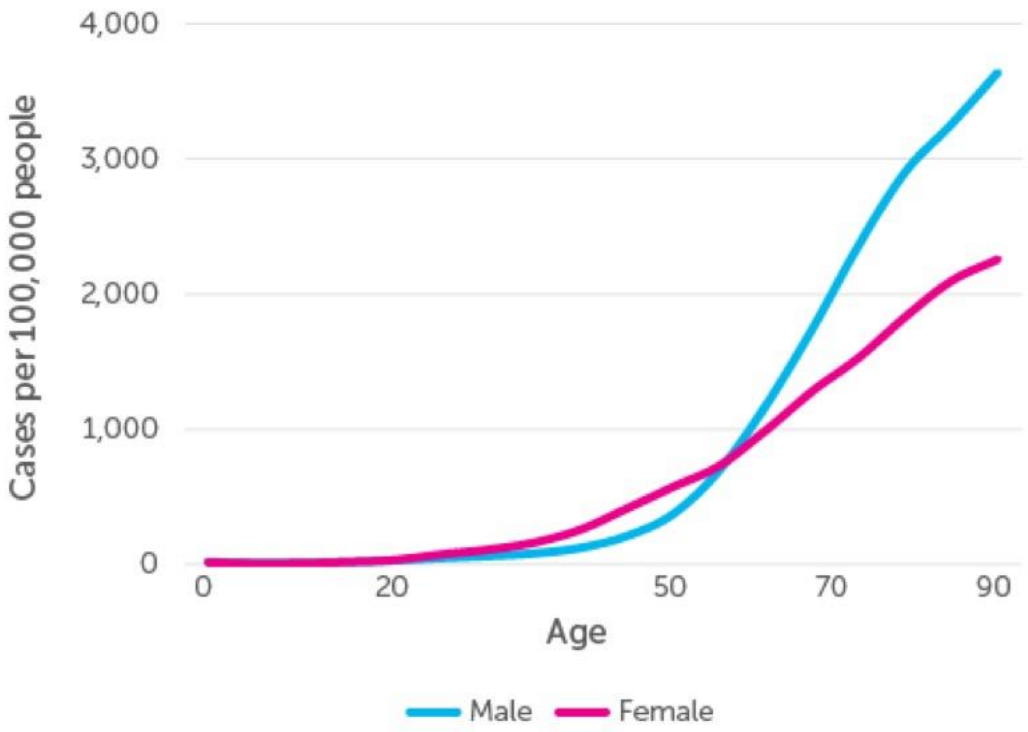

Figure 11: Graph Showing Rapid Increase in Number of Skin Cancer Patients in Older Populations Worldwide (2015-2017). Male rates almost double female rates.

The extensive background knowledge of the current understanding of skin cancer types, as well as knowing many different risk factors leads to conclusions upon current preventative measures. While there is no definitive cure for skin cancer, and to a further extent malignant cancer in general, there are preventative measures people can take that are widely available to the general public. Most people know of sunscreen, which acts as a preemptive course of action against UV-radiation and can lessen or even prevent future risk of skin cancer. Below, more procedural routines are discussed to prevent skin cancer, which are also widely available, but most people may not know about.

Retinol and vitamin A derivatives play a role in cell development and differentiation, therefore most cancers such as skin, lung, prostate, breast and ovarian appear to be suppressed by

retinoic acids. This study (Atis 2015) closely were geriatric patients, or the elderly population, who make up 70% of all dermatological expenditures through Medicaid and Medicare. They are a huge group of the overall population of skin cancer patients, so knowing their symptoms is essential to keep current with types of skin cancers and who they affect most. This is critical in the research for how people become susceptible to skin cancer, in showing that it is not an immediate effect, but rather an accumulation over time that generally affects an average person in the elderly stages of life.

Skin pigmentation is a phenotype evolved and retained over generations, primarily as protection against harmful Ultraviolet (UV) radiations. Melanin, a light-absorbing polymer with photochemical properties imparts color to human skin and other tissues such as hair and iris and provides protection against UV induced damage (Gómez 2016). Variations in skin pigmentation depend on the level and the type of melanin expressed. The two major forms of melanin expressed in humans are eumelanin, imparting black or brown skin and hair color, and pheomelanin, found in red hair and freckled skin. Melanin is synthesized in melanocytes in specialized organelles called melanosomes. Transfer of the pigment to keratinocytes that constitute the upper layers of the epidermis is essential for phenotypic manifestation of skin pigmentation. The dendrites on melanocytes aid in the transfer of melanosomes to keratinocytes where melanosome uptake occurs through phagocytosis (Gómez 2016).

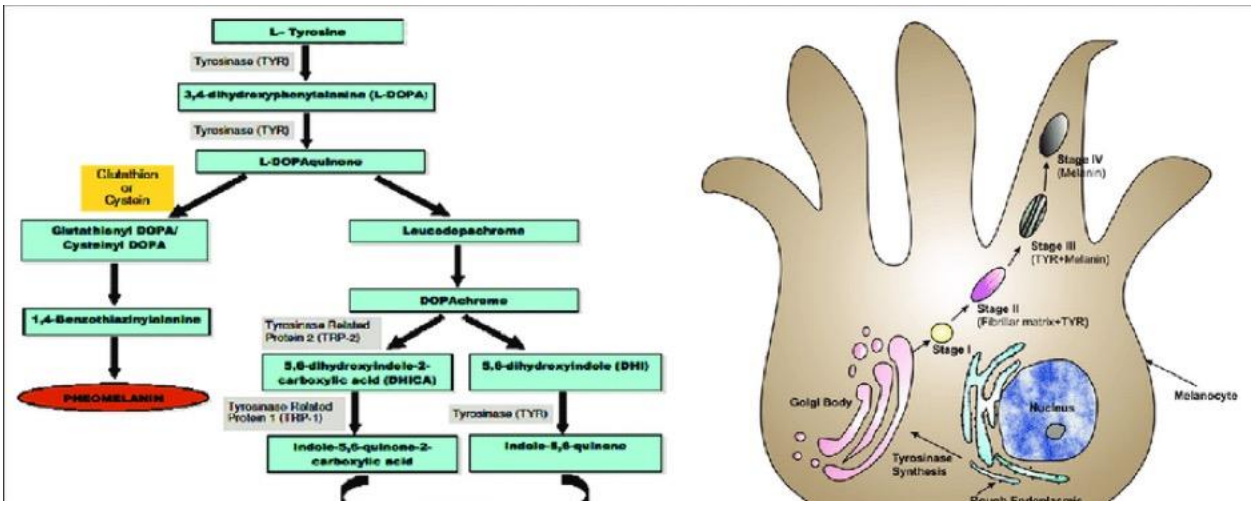

Figure 12: Melanin Transport System Outline. Tyrosine is taken from its initial starting point and transport into many different cellular processes to initiate the release and creation of melanin from the melanocyte.

Human skin responds to UV radiation exposure by increasing the expression of melanin in skin, a pigment that protects it from UV induced damage. Melanin has a role to play in various pigmentation disorders such as albinism, vitiligo as well as in melanoma and non-melanoma skin cancers. A detailed understanding of the process of skin pigmentation is thus vital for understanding the molecular pathology of these disease conditions (Terenziani 2003). Melanin synthesis takes place in response to UV induced cues from neighboring cells such keratinocytes and dermal fibroblasts, and exerts its protective effects when transported and expressed in keratinocytes. Multiple roles are suggested for the protective effect of melanin in UV induced damage. Melanin can filter UV radiation and scavenge reactive oxygen species produced as a result of UV exposure (Raghunath 2015). The supra-nuclear cap of melanin protects cells from DNA damage. It is reported to inhibit production of cyclobutane pyrimidine dimers and 6,4-photoproducts, both of which are mutagenic. Patients with albinism have been shown to be more susceptible to various skin cancers (Raghunath 2015).

Overview of Mohs Surgery

Simply using sunscreen when it is sunny outside does not always keep a person from getting skin cancer, and that is the point to make people aware of. Physicians have been developing techniques for years to combat skin cancer, and to date, the most effective type of treatment is still surgical excision (SE) of the entire tumor itself. A specific technique called Mohs surgery is discussed as the most beneficial technique to combat non-melanoma basal cell carcinomas and leave the least amount of damage in its wake as well. One study conducted in 2016 (Nassiripour 2016) totals the vulnerable populations that were studied and compares the cost effectiveness of Mohs surgery to the typical surgical excision used in the region. One possible explanation for the higher cost of surgical excision compared to the Mohs surgery method in the current study can be the fact that since the Mohs surgery has an outpatient procedure, the costs of anesthetics, the operating room, the para clinical tests, and medical advices before the surgery were not considered.

This difference between the costs of the Mohs and standard Surgical Excision (SE) group can be because of the difference between physicians' visits of the two groups. The patients of the Mohs surgery group were visited by a fellowship physician, and the patient visits of the SE group were performed by a specialist physician, both specializing in dermatological practices. A fellowship physician is a physician going through their residency to complete specialization, while a specialist physician has already completed this training at an expert level (Nassiripour 2015). Typically, the fellowship visit costs are more expensive than the specialist visit costs. Another reason for the difference between the costs of the two groups is the medication used by the patients after their discharge. The medication given to patients by a dermatologist using

Mohs surgery is designed to speed skin recovery after surgery which may be more expensive than drugs prescribed by a general surgeon (Nassiripour 2015).

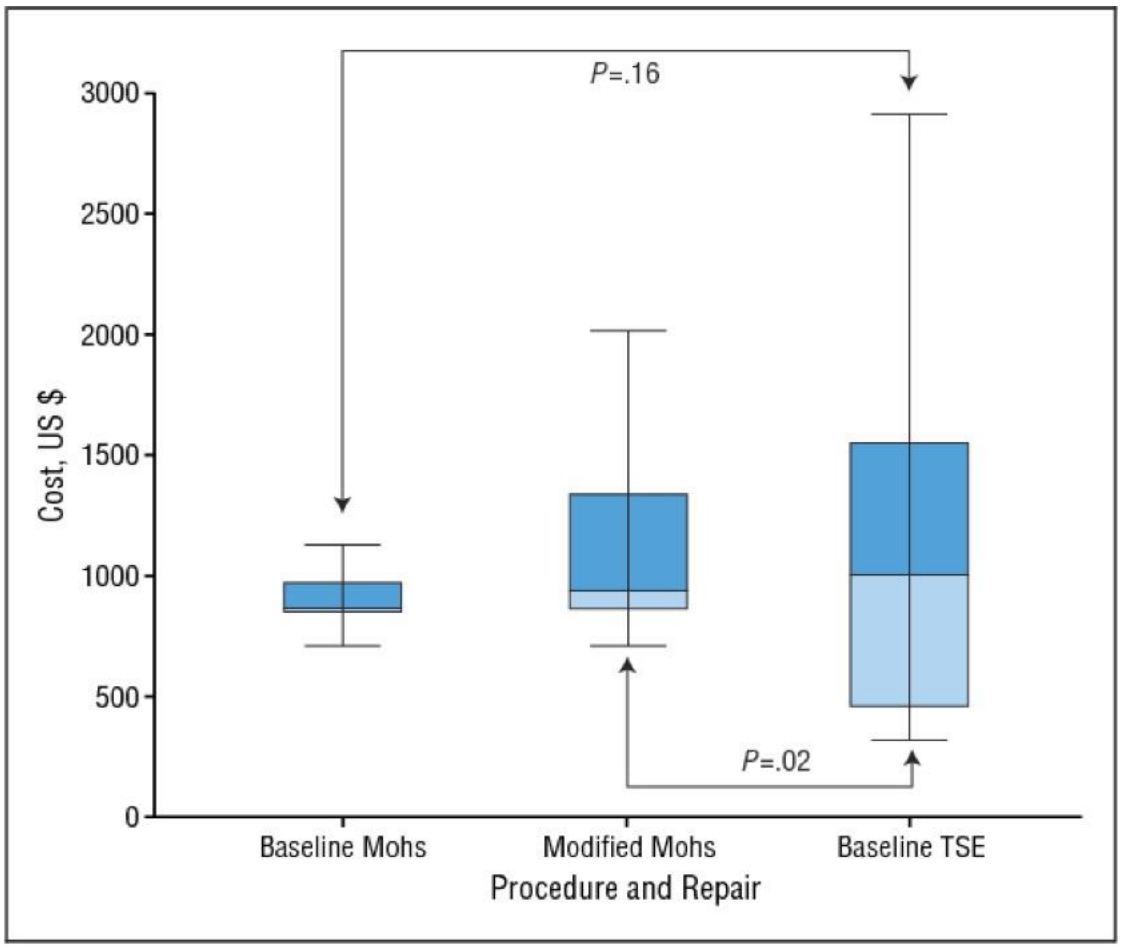

Figure 13: Cost-Effectiveness and Success Ratios of Mohs Surgery vs. Other Types of Surgical Excision. Defines Mohs as the statistically most advantageous type of SE.

One study conducted in 2018 (Chen 2018) shows how Mohs Micrographic Surgery (MMS), or Mohs surgery, is a technique used to treat skin malignancies that offers the highest cure rates, maximally spares normal skin, and allows for the best cosmetic and functional results. This technique consists of sequential steps that are performed on the same day in an outpatient setting. In MMS, the Mohs surgeon also functions as the pathologist, resulting in greater accuracy of the clinicopathology. The high cure rates in MMS are achieved through accurate

evaluation of 100% of the tissue margins. Thus, the Mohs surgeon's knowledge of dermatopathology and frozen section interpretation is essential to ensure the success of this technique.

Mohs Micrographic Surgery, a tissue-sparing technique, also produces excellent cosmetic and functional results by allowing the surgeon to obtain adequate surgical margins to clear the cancer prior to reconstruction. Of note, the success of MMS relies on tumor contiguity. Noncontiguous or “skip” lesions might not be detected by MMS, thus resulting in higher recurrence rates. Noncontinuity of lesions may occur as a result of previous treatments that failed to completely eradicate the tumor. MMS can also be more cost effective than standard surgical excisions. For melanoma treatment, the primary goal is complete removal with histologically negative margins. Mohs Micrographic Surgery has been extensively used and studied for the treatment of nonmelanoma skin cancer, particularly at sites where tissue conservation is vital (Chen 2016).

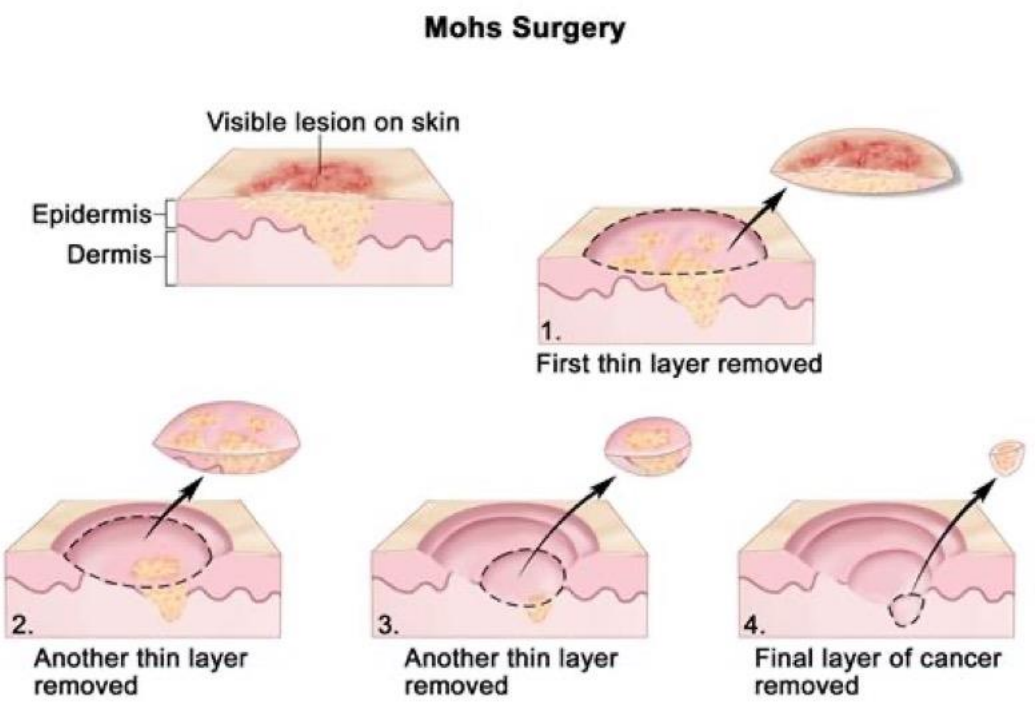

Figure 14: Overview of Mohs Micrographic Surgery. Summarizes the seemingly simple process through Specialization is required for this surgery to be performed properly.

The use of MMS for melanoma treatment has yet to become widely accepted owing to difficulties in histologic interpretation, among other factors. MMS may offer lower recurrence rates and improved survival when compared with historical controls for standard excision. Continued advances in MMS technique and immunohistochemical staining have allowed the technique to gain further support.

Mohs Micrographic Surgery was originally developed in the 1930s by a general surgeon, Dr. Frederic E. Mohs. While experimenting on skin cancer treatments as a research assistant at the University of Wisconsin, he discovered that injecting 20% zinc chloride solution to tumors caused tissue necrosis but preserved its microscopic architecture. He later formulated and patented a 20% zinc chloride paste that can be applied topically on human skin (Chen 2018). He also developed the fixed-tissue technique wherein this paste was applied on the skin cancer *in*

vivo for 24 hours prior to taking the first excision specimen. The first layer was then taken the following day, and the specimen was processed using standard paraffin sections. If further stages were necessary, zinc chloride was again applied overnight before the subsequent stage was taken. Thus, it often took several days of surgery and multiple stages to achieve clear margins for large skin cancers.

Figure 15: Image of Dr. Frederic Mohs. Developed Micrographic Mohs Surgery, which led to great advancements in surgical precision and effectiveness against skin cancers.

Mohs surgery has been found to be highly effective against these larger cancers, with the range for verification of size being measured anywhere from 6mm to 20mm. The cure rates procured in this study (Del Bino 2018) are shown to be in the range of 95% to 99% for non-melanoma basal and squamous cell carcinomas. Based on the included guidelines, MMS is recommended as a first-line option for high-risk primary or recurrent basal cell carcinoma. For high-risk primary or recurrent squamous cell carcinoma, MMS may be considered as one of the options, especially where tissue preservation or margin controls are challenging, or when the tumor is at a critical anatomical site. For squamous cell carcinoma, MMS may be indicated for digital and penile tumor, or in recurrent or incompletely excised lesions. MMS may also be considered for melanoma and Merkel cell carcinoma especially when the tumor is in a sensitive area and there are concerns of functional impairment from an excision that is too radical (Del Bino 2018).

MMS is preferable to conventional surgery in the treatment of high-risk, recurrent, or at critical site skin cancer. Even though the size of the lesion should be analyzed together with its location and histological pattern, MMS could be a better treatment option for tumors larger than 2 cm which present a higher chance of incomplete removal with conventional surgery. The review also found that MMS leads to a smaller recurrence rate than conventional surgery for dermatofibrosarcoma protuberans, a very rare type of skin cancer that begins in the middle layer of connective skin tissue called the dermis (Del Bino 2018).

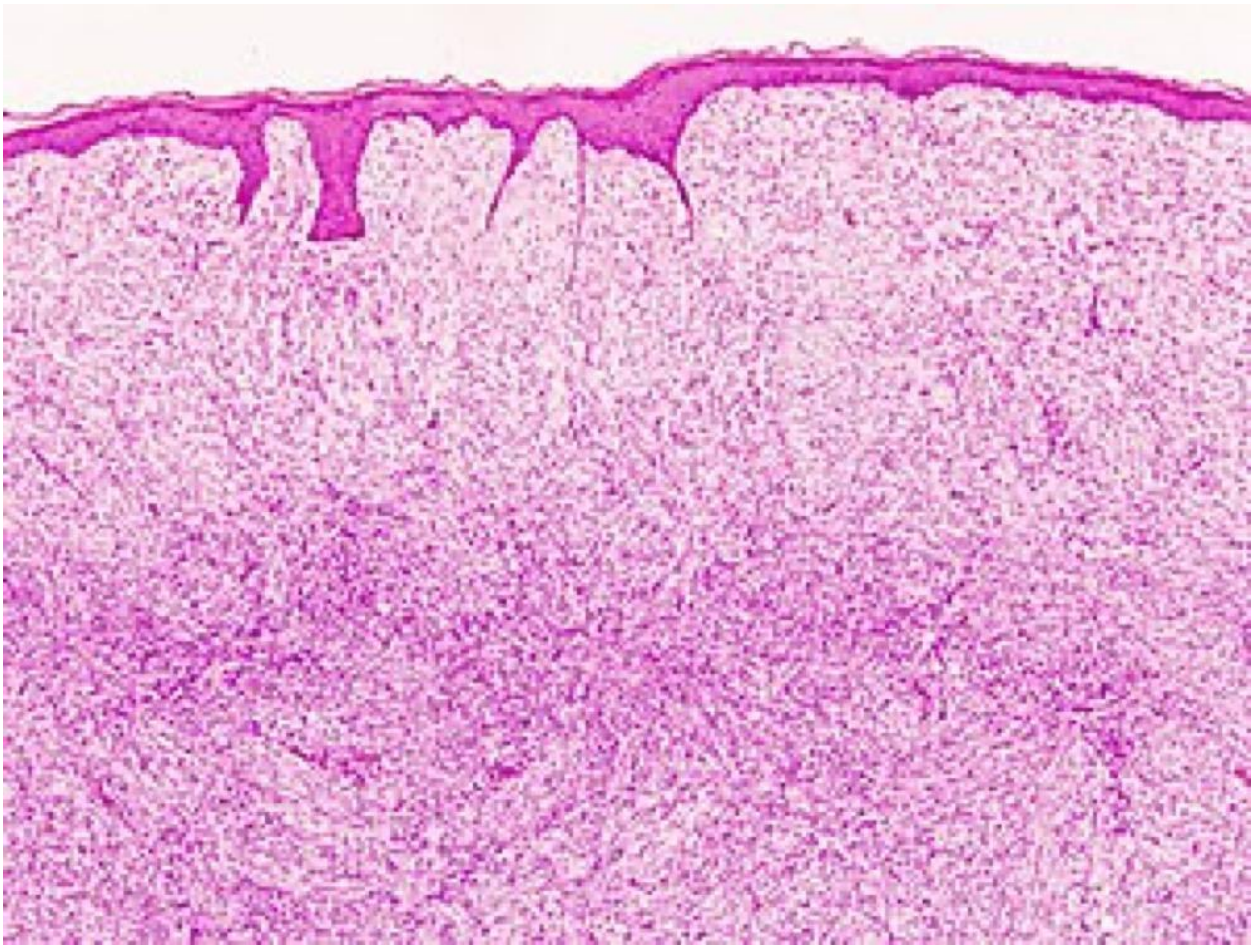

Figure 16: Immunostain of Dermatofibrosarcoma Protuberans. Dark band at top of stain represents invasion of tumor into deeper layer of skin.

There are specific reasons why Mohs Micrographic Surgery is only recommended for use on non-melanoma skin cancers. The primary concern of critics of MMS for melanoma is the perceived inferiority of frozen sections to permanent paraffin sections in evaluating melanocytic lesions. Part of the reason permanent sections are considered the gold standard in evaluating melanocytic lesions is that melanocytes retain their pericytoplasmic vacuolization with this method, allowing them to be more readily identified. In comparison, frozen sections can be plagued by numerous artifacts caused by the freezing process, tissue folding, and keratinocyte vacuolization resembling melanocytes which can lead to false positives. There are a variety of

strategies to address these concerns discussed in the research literature for this matter. One strategy to help with slide interpretation is the use of control biopsies taken from the patient's skin adjacent to the lesion, which serve as a measure of the patient's background melanocytic density. One research article (Gómez 2016) favors shallow shave biopsies harvested from both perilesional and distant skin and also describes the use of a mapping technique which matches subtle pigmented lesions clinically and histologically. With this mapping technique, the authors report a reduction in the removal of Mohs layers in their clinical practice.

Another conservative strategy is to use staged excisions with rush permanent sections. In this approach, each Mohs layer is sent for permanent paraffin sectioning, and a pathologist reads the slides. Due to the tissue processing and evaluation time involved with this method, the surgery is substantially prolonged and may even require several days to weeks to achieve clear margins, hence the nickname of "slow Mohs". Recently, one research group (Mallipeddi 2008) described a novel 2-hour method for preparing permanent sections of MIS for MMS through microwave tissue processing with comparable results. Despite its time-consuming nature, permanent sectioning has long been considered the gold standard for melanocytic lesion evaluation for the reasons previously described. However, fast and reliable immunohistochemical stains are now increasingly being used as an adjunct to H&E-stained frozen sections and can provide identical information to permanent sections.

Over the past few decades, the expansion in the number of immunohistochemical stains available and the development of expedited staining protocols have led to increased utilization of immunostaining in Mohs surgery. In addition to its use for the challenging situations previously described, immunostaining for various tumors is useful in a variety of situations such as when the tumor is poorly differentiated, exhibits single cell spread, tracks along nerves or vessels, or

when pagetoid distribution is present (Albertini 2002). Regardless of the immunostain or staining protocol used, 4-µm thin tissue sections are preferred as they provide the best staining results without masking cellular detail (Feller 2016). Immunostaining can be applied to both permanent and frozen sections and is performed concurrently with H&E staining. The amount of literature regarding immunostains and staining protocols used in MMS for melanoma is so extensive that entire review articles have been dedicated to the topic.

Discussion

The knowledge to understand each of the three main types of skin cancer can greatly improve a patient's outlook on their prognosis once diagnosed with skin cancer. Here, the three main types of skin cancer are talked about in depth, specifically dealing with pathways that they effect and what types of treatments are effective against them. Experimental treatments, such as phytochemicals and different types of UV blockers, have shown promising results in preventing the development of skin cancer in the most susceptible populations. While these methods can be perfected for full effectiveness one day, there is a treatment specifically aimed at non-melanoma skin cancers that is effective against these early stage tumors almost 100% of the time. This method is known as Mohs Micrographic Surgery, and it provides a baseline context for how methods in treatment against skin cancer have already been developed, as well as what is being expanded upon for the future. Most dermatological doctors and experts today recommend this out-patient, cost-effective surgery to anyone who wants to effectively nullify the long-term effects a simple basal or squamous cell carcinoma can evolve when metastasizing throughout the body.

Bibliography

Format: Scientific Style and Format: the CBE Manual (CBE= Council of Biology Editors)

Abdel-Malek ZA, Ruwe A, Kavanagh-Starner R, Kadekaro AL, Swope V, Haskell-Luevano C, et al. 2009. alpha-MSH tripeptide analogs activate the melanocortin 1 receptor and reduce UV-induced DNA damage in human melanocytes. Pigment Cell Melanoma Res. 22(5):635–644.

Albertini JG, Elston DM, Libow LF, Smith SB, Farley MF. 2002. Mohs micrographic surgery for melanoma: a case series, a comparative study of immunostains, an informative case report, and a unique mapping technique. Dermatol Surg. 28(8):656–665.

Andreassi L. 2011. UV exposure as a risk factor for skin cancer. Expert Review of Dermatology. 6(5):445–454.

Atis G, Altunay IK, Demirci GT, Aydin E, Mammadov D, Karsidag S. 2015. The most common skin cancers and the risk factors in geriatric patients: A hospital based-controlled study. Journal of Experimental & Clinical Medicine. 32(4):165-170.

Babbin SF, Yin H-Q, Rossi JS, Redding CA, Paiva AL, Velicer WF. 2015. Reducing Sun Exposure for Prevention of Skin Cancers: Factorial Invariance and Reliability of the Self-Efficacy Scale for Sun Protection. Journal of Skin Cancer. 2015:1-7.

Boehnke K, Falkowska-Hansen B, Stark HJ, Boukamp P. 2012. Stem cells of the human epidermis and their niche: composition and function in epidermal regeneration and carcinogenesis. Carcinogenesis. 33(7):1247–1258.

Brash DE, Heffernan T, Ngheim P. 2008. Carcinogenesis: Ultravoilet radiation. Fitzpatrick's Dermatology in General Medicine. New York: McGraw-Hill 999–1006.

Cancer Research UK. 2017. Cancer Research UK. Average Death Rate from Advanced Melanoma in Different Age Groups from Years 2015-2017. Figure 1 and 11. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer/mortality

Carucci JA, Lefell DJ. 2008. Basal cell carcinoma. Fitzpatrick's Dermatology in General Medicine. New York: McGraw-Hill. pp. 1036–1042.

Chau YN, Hsi Y, Hui-Yi H, Shih-Chi S. 2018. Phytochemicals in Skin Cancer Prevention and Treatment: An Updated Review. International Journal of Molecular Sciences. 19(4):941.

Chen ELA, Srivastava D, Nijhawan RI. 2018. Mohs Micrographic Surgery: Development, Technique, and Applications in Cutaneous Malignancies. Semin Plast Surg. 32(2):60–68.

Del Bino S, Duval C, Bernerd F. 2018. Clinical and Biological Characterization of Skin Pigmentation Diversity and Its Consequences on UV Impact. International Journal of Molecular Sciences. 19(9):2668.

Donovan J. 2009. Review of the hair follicle origin hypothesis for basal cell carcinoma. Dermatol Surg. 35(9):1311–1323.

Epstein EH. 2008. Basal cell carcinomas: attack of the hedgehog. Nat Rev Cancer. 8(10):743–754.

Feller L, Wood NH, Motswaledi MH, Khammissa RA, Meyer M, Lemmer J. 2010. Xeroderma pigmentosum: a case report and review of the literature. J Prev Med Hygiene. 51(2):87–91.

Feller L, Khammissa R, Kramer B, Altini M, & Lemmer J. 2016. Basal cell carcinoma, squamous cell carcinoma and melanoma of the head and face. *Head & face medicine*, *12*, 11.

Gidanian S, Mentelle M, Meyskens FL, Jr, Farmer PJ. 2008. Melanosomal damage in normal human melanocytes induced by UVB and metal uptake--a basis for the pro-oxidant state of melanoma. Photochem Photobiol. 84(3):556–564.

Gómez M, Guillem V, Pereira A, et al. 2016. Risk factors for non-melanoma skin cancer in patients with essential thrombocythemia and polycythemia vera. European Journal of Haematology. 96(3):285-290.

Grossman D, Leffell DJ. 2008. Squamous cell carcinoma. Fitzpatrick's Dermatology in General Medicine. New York: McGraw-Hill. 1028–1036.

Guy GP, Thomas CC, Thompson T, et. al. 2015. Vital Signs: Melanoma Incidence and Mortality Trends and Projections — United States, 1982–2030. Morbidity and Mortality Weekly Report. 64(21);591-596. Figures 2, 3.

Jhappan C, Noonan FP, Merlino G. 2003. Ultraviolet radiation and cutaneous malignant melanoma. Oncogene. 22(20):3099–3112.

Kennedy C, ter Huurne J, Berkhout M, Gruis N, Bastiaens M, Bergman W, et al. 2001. Melanocortin 1 receptor (MC1R) gene variants are associated with an increased risk for cutaneous melanoma which is largely independent of skin type and hair color. J Invest Dermatol. 117(2):294–300.

Kimmel JN, Taft TH, Keefer L. 2016. Inflammatory Bowel Disease and Skin Cancer: An Assessment of Patient Risk Factors, Knowledge, and Skin Practices. *Journal of Skin Cancer*. 1-7.

Mallipeddi R, Stark J, Xie XJ, Matthews M, Taylor RS. 2008. A novel 2-hour method for rapid preparation of permanent paraffin sections when treating melanoma in situ with mohs micrographic surgery. Dermatol Surg. 34(11):1520–1526.

Nassiripour L, Amirsadri M, Tabatabaeian M, Maracy MR. 2016. Cost-effectiveness of surgical excision versus Mohs micrographic surgery for nonmelanoma skin cancer: A retrospective cohort study. J Res Med Sci. 2016;21:91.

Radespiel-Troger M, Meyer M, Pfahlberg A, Lausen B, Uter W, Gefeller O. 2009. Outdoor work and skin cancer incidence: a registry-based study in Bavaria. Int Arch Occup Environ Health. 82(3):357–363.

Raghunath A, Sambarey A, Sharma N, Mahadevan U, Chandra N. 2015. A molecular systems approach to modelling human skin pigmentation: identifying underlying pathways and critical components. BMC Research Notes. 8(1):1-12.

Riker AI, Zea N, Trinh T. 2010. The epidemiology, prevention, and detection of melanoma. Ochsner J. 10(2):56–65.

Scherer D, Kumar R. 2010. Genetics of pigmentation in skin cancer--a review. Mutat Res. 705(2):141–153.

Situm M, Bolanca Z, Buljan M. 2010. Lentigo maligna melanoma--the review. Coll Antropol. 34(Suppl 2):299–301.

Skoda AM, Simovic D, Karin V, Kardum V, Vranic S, Serman L. 2018. The role of the Hedgehog signaling pathway in cancer: A comprehensive review. Bosn J Basic Med Sci. 18(1):8-20.

Terenziani M, Spreafico F, Serra A, Podda M, Cereda S, Belli F. 2003. Amelanotic melanoma in a child with oculocutaneous albinism. Med Pediatr Oncol. 41(2):179–180.

Tlholoe MM, Khammissa RA, Bouckaert M, Altini M, Lemmer J, Feller L. 2015. Oral Mucosal Melanoma: Some Pathobiological Considerations and an Illustrative Report of a Case. Head Neck Pathol. 9(1):127–134.

Wong SY, Dlugosz AA. 2014. Basal cell carcinoma, Hedgehog signaling, and targeted therapeutics: the long and winding road. J Invest Dermatol. 134(e1):E18–22.