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Comprehensive Review of Squamous Cell Carcinoma: Pathophysiology, Clinical Manifestations, Diagnostic Techniques, and Treatment Modalities

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ABSTRACT

Squamous cell carcinoma (SCC) is a prevalent form of skin cancer arising from the squamous cells of the epidermis. This malignancy primarily affects areas of the body exposed to ultraviolet radiation, but it can also develop in mucosal regions and internal organs. The pathophysiology of SCC involves a complex interplay between genetic mutations, environmental factors, and immune system dysregulation. Clinically, SCC presents with varied manifestations, ranging from indolent, well-differentiated lesions to aggressive, invasive tumors. Diagnostic techniques encompass a range of modalities, including dermoscopy, histopathological examination, and molecular profiling. Treatment strategies for SCC are multifaceted, involving surgical excision, radiation therapy, and emerging immunotherapies. This article aims to provide a detailed overview of SCC, focusing on its pathogenesis, clinical features, diagnostic approaches, and therapeutic options, highlighting recent advancements and ongoing research in the field.

KEYWORDS: Squamous Cell Carcinoma, Skin Cancer,Molecular Profiling

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INTRODUCTION:

Squamous cell carcinoma (SCC) represents the second most common type of skin cancer, characterized by the uncontrolled growth of abnormal squamous cells. These cells form the outermost layers of the skin and line various internal organs, including the lungs, esophagus, and cervix. SCC predominantly occurs in sun-exposed areas, with chronic ultraviolet (UV) radiation being a significant etiological factor. However, SCC can also arise in non-sun-exposed regions, influenced by factors such as human papillomavirus (HPV) infection, immunosuppression, and exposure to carcinogens.1,2

The pathogenesis of SCC is multifactorial, involving genetic mutations in tumor suppressor genes and oncogenes, alterations in cell signaling pathways, and immune evasion mechanisms. Clinically, SCC can manifest as a variety of lesions, ranging from erythematous, scaly plaques to ulcerative or nodular growths. The clinical course of SCC can be unpredictable, with some lesions remaining localized and others demonstrating aggressive behavior with potential for metastasis.1,2

Diagnostic evaluation of SCC involves a thorough clinical examination, supported by dermoscopic assessment and histopathological confirmation through biopsy. Advances in molecular diagnostics have enhanced our understanding of SCC at the genetic and epigenetic levels, facilitating the development of targeted therapies. Traditional treatment modalities for SCC include surgical excision, Mohs micrographic surgery, and radiation therapy. Recent advancements in immunotherapy and targeted therapy have opened new avenues for managing advanced and metastatic SCC, improving patient outcomes.2,3

This comprehensive review aims to elucidate the intricate pathophysiology, diverse clinical presentations, and advanced diagnostic and therapeutic approaches for SCC. By integrating current research and clinical practices, we seek to provide a holistic understanding of SCC, emphasizing the importance of early detection, accurate diagnosis, and effective treatment strategies.2,3

Epidemiology of Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the second most common type of non-melanoma skin cancer, following basal cell carcinoma (BCC). Globally, the incidence of SCC has been

rising, with substantial variations across different geographic regions, largely attributable to differences in UV radiation exposure, skin type, and population demographics. In the United States, SCC accounts for approximately 20% of all skin cancer cases, with an estimated 1.8 million new cases diagnosed annually. The incidence rate is notably higher in populations with fair skin and those residing in areas with high UV exposure, such as Australia and Southern Europe.2,3 The risk factors for SCC are multifactorial, with chronic exposure to ultraviolet (UV) radiation being the most significant. UV radiation induces direct DNA damage and promotes immunosuppression, facilitating carcinogenesis. Individuals with Fitzpatrick skin types I and II (those with fair skin, light eyes, and a propensity to burn rather than tan) are at the highest risk. Additionally, a history of extensive sunburns, particularly during childhood, significantly increases the lifetime risk of developing SCC.3,4

Other critical risk factors include:

1. **Immunosuppression:** Organ transplant recipients and patients with chronic lymphocytic leukemia (CLL) have a significantly increased risk of developing SCC due to long-term immunosuppressive therapy, which impairs immune surveillance against oncogenic viruses and tumor cells.3,4
2. **Human Papillomavirus (HPV) Infection:** Certain high-risk HPV strains, particularly HPV 16 and 18, are implicated in the pathogenesis of SCC in mucosal regions, such as the oropharynx, anogenital area, and cervix.4,5
3. **Chronic Inflammatory and Scarring Conditions:** Conditions like chronic wounds, burns, and scars (Marjolin ulcers) predispose individuals to SCC due to persistent inflammation and cellular turnover.4,5
4. **Exposure to Carcinogens:** Prolonged exposure to chemical carcinogens, such as arsenic, coal tar, and tobacco, is associated with an increased risk of SCC. Occupational exposure in industries like mining, construction, and chemical manufacturing also contributes to elevated risk.4,5
5. **Genetic Predispositions:** Genetic syndromes such as xeroderma pigmentosum, characterized by defective DNA repair mechanisms, significantly elevate the risk of developing SCC.4,5

Clinical Manifestations of Squamous Cell Carcinoma

Squamous cell carcinoma exhibits a wide range of clinical presentations, influenced by the site of origin, degree of differentiation, and aggressiveness of the tumor. SCC typically arises in sun-exposed areas of the skin, such as the face, ears, neck, scalp, hands, and arms. However, it can also occur in non-sun-exposed regions, including the oral cavity, esophagus, lungs, and anogenital area.5,6

Cutaneous SCC:

- **Actinic Keratosis:** Often considered a precursor to SCC, actinic keratosis presents as rough, scaly patches on sun-exposed skin. These lesions are usually erythematous and may evolve into SCC over time.5,6
- **Intraepidermal SCC (Bowen's Disease):** This in situ form of SCC appears as well-demarcated, erythematous plaques with a scaly or crusted surface. Bowen's disease can progress to invasive SCC if left untreated.5,6
- **Invasive SCC:** Characterized by a variety of morphologies, invasive SCC may present as nodular, ulcerative, or verrucous lesions. Nodular SCC typically manifests as firm, skin-colored to erythematous nodules that may ulcerate or bleed. Ulcerative SCC appears as non-healing sores with raised, indurated edges, often exuding blood or serous fluid. Verrucous SCC presents as warty, exophytic growths that can be mistaken for benign verrucae.5,6

Mucosal SCC:

- **Oral Cavity:** SCC of the oral cavity commonly affects the tongue, floor of the mouth, and buccal mucosa. Lesions may present as white (leukoplakia) or red (erythroplakia) patches, ulcers, or exophytic masses, often associated with pain, bleeding, and difficulty in swallowing.5,6
- **Esophagus:** Esophageal SCC typically presents with progressive dysphagia, odynophagia, weight loss, and retrosternal pain. Advanced disease may cause obstruction and aspiration.5,6
- **Anogenital Region:** SCC in the anogenital region, including the penis, vulva, and perianal area, often presents as ulcerative or exophytic masses, which can be painful and prone to bleeding. HPV infection is a significant etiological factor in these cases.5,6

Metastatic Potential:

SCC has a higher propensity for metastasis compared to BCC, particularly when arising in high-risk areas such as the lips, ears, and non-sun-exposed sites. Metastasis typically occurs via the lymphatic system, presenting as regional lymphadenopathy. Distant metastasis to organs such as the lungs, liver, and bones is less common but signifies advanced disease with a poor prognosis.6,7

Aggressive Variants:

- **Keratoacanthoma:** This variant is characterized by rapid growth, presenting as a dome-shaped nodule with a central keratin-filled crater. Although keratoacanthoma often exhibits spontaneous regression, its aggressive growth warrants prompt treatment to rule out invasive SCC.6,7
- **Desmoplastic SCC:** This rare, aggressive variant infiltrates deeply into the dermis and subcutaneous tissues, often presenting as indurated plaques or

nodules. Desmoplastic SCC has a higher recurrence rate and potential for metastasis.6,7

The epidemiology and clinical manifestations of squamous cell carcinoma underscore the importance of early detection, accurate diagnosis, and timely intervention. Understanding the diverse presentations and risk factors associated with SCC is crucial for clinicians to implement effective preventive measures and therapeutic strategies.8,9

Diagnostic Methods

Squamous cell carcinoma (SCC) of the skin, as well as mucosal surfaces, requires prompt and accurate diagnosis to ensure effective treatment and improve patient outcomes. Traditional diagnostic methods, including clinical examination, dermoscopy, and histopathological biopsy, remain the gold standard. However, advancements in diagnostic technologies have introduced novel methods that enhance accuracy, provide rapid results, and offer non-invasive options for patients. This section explores the latest diagnostic innovations in the field of SCC.8,9

1. Dermoscopy and Digital Dermoscopy

Dermoscopy has long been an essential tool for dermatologists, aiding in the visualization of subsurface skin structures that are not visible to the naked eye. Digital dermoscopy takes this a step further by integrating digital imaging and analysis software. This technology allows for the capture of high-resolution images, which can be stored, compared over time, and analyzed using artificial intelligence (AI) algorithms. AI-driven analysis helps in distinguishing SCC from other skin lesions by identifying characteristic patterns and features with high sensitivity and specificity.8,9

2. Reflectance Confocal Microscopy (RCM)

Reflectance confocal microscopy (RCM) is a non-invasive imaging technique that provides cellular-level resolution images of the skin in vivo. RCM uses a low-power laser to create detailed images of the epidermis and superficial dermis. This method allows for the real-time examination of suspicious lesions without the need for a biopsy. RCM has proven particularly useful in identifying features of SCC, such as atypical keratinocytes, disrupted epidermal architecture, and increased vascularization. Its non-invasive nature makes it a valuable tool for monitoring treatment response and detecting recurrences.10,11

3. Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) is another non-invasive imaging modality that uses light waves to capture cross-sectional images of the skin. OCT provides detailed information about the epidermis, dermis, and superficial subcutaneous tissue. It is particularly effective in identifying the depth of invasion and the margins of SCC, which are critical for treatment planning. OCT is increasingly being used in conjunction with RCM to enhance diagnostic accuracy, providing complementary information about the lesion's morphology and depth.10,11

4. High-Frequency Ultrasound (HFUS)

High-frequency ultrasound (HFUS) utilizes sound waves to create detailed images of the skin and underlying tissues. HFUS is particularly useful for assessing the thickness and extent of SCC, helping to guide surgical planning and evaluate the response to therapy. Recent advancements in HFUS technology have improved image resolution and depth penetration, making it a valuable tool for diagnosing and managing SCC.10,11

5. Raman Spectroscopy

Raman spectroscopy is an emerging diagnostic technique that analyzes the molecular composition of tissues based on their vibrational energy states. This non-invasive method can differentiate between benign and malignant lesions by detecting biochemical changes associated with cancer. Raman spectroscopy has shown promise in identifying SCC with high accuracy, offering a rapid and non-destructive alternative to traditional biopsy.10,11

6. Multiphoton Microscopy (MPM)

Multiphoton microscopy (MPM) is an advanced imaging technique that uses two-photon excitation to produce high-resolution, three-dimensional images of the skin. MPM allows for the visualization of cellular and subcellular structures in vivo, providing detailed information about the architecture and composition of SCC lesions. This technique is particularly valuable for assessing tumor margins and detecting early-stage SCC.10,11

7. Liquid Biopsy

Liquid biopsy is a minimally invasive method that analyzes circulating tumor DNA (ctDNA), RNA, and other biomarkers in blood or other body fluids. This technique offers a real-time snapshot of the tumor's genetic and molecular profile, helping to identify mutations, monitor treatment response, and detect minimal residual disease. Liquid biopsy is especially useful for patients with advanced or metastatic SCC, providing critical information for personalized treatment planning.12,13

8. Molecular and Genetic Profiling

Advancements in molecular biology and genomics have led to the development of comprehensive profiling techniques that analyze the genetic and molecular characteristics of SCC. Techniques such as next-generation sequencing (NGS) and microarray analysis allow for the identification of specific mutations, gene expression patterns, and epigenetic modifications associated with SCC. These insights can guide targeted therapies and improve prognostication.12,13

9. Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning (ML) are revolutionizing the field of dermatology by enhancing diagnostic accuracy and efficiency. AI algorithms can analyze large datasets of dermoscopic images, histopathological slides, and clinical information to identify patterns and predict outcomes with high accuracy. These technologies are being integrated into clinical practice to

assist dermatologists in diagnosing SCC, triaging cases, and optimizing treatment strategies.14,15

The landscape of diagnostic methods for squamous cell carcinoma is rapidly evolving, driven by technological advancements and innovations in imaging, molecular biology, and artificial intelligence. These emerging diagnostic tools offer significant benefits, including non-invasive options, enhanced accuracy, and personalized insights, ultimately improving patient care and outcomes. As these technologies continue to develop and integrate into clinical practice, they hold the promise of transforming the early detection, diagnosis, and management of SCC.15,16

Novel Treatment Modalities for Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is a prevalent form of skin cancer that necessitates timely and effective treatment to prevent progression and metastasis. While traditional treatment options such as surgical excision, Mohs micrographic surgery, radiation therapy, and cryotherapy remain fundamental, recent advancements in medical science have introduced novel therapeutic modalities. These innovations aim to enhance treatment efficacy, reduce side effects, and offer alternatives for patients with advanced or refractory SCC. This section delves into the latest treatment methods for SCC, emphasizing their mechanisms, clinical applications, and potential benefits.17,18

1. Immunotherapy

Checkpoint Inhibitors:

Checkpoint inhibitors have revolutionized cancer treatment by unleashing the immune system to attack tumor cells. These drugs target immune checkpoints such as PD-1/PD-L1 and CTLA-4, which are exploited by tumor cells to evade immune surveillance. Pembrolizumab and nivolumab, both PD-1 inhibitors, have shown promising results in treating advanced and metastatic SCC, leading to durable responses and prolonged survival in some patients. Avelumab, a PD-L1 inhibitor, has also demonstrated efficacy in clinical trials.18,19

Cytokine Therapy:

Interleukin-2 (IL-2) and interferon-alpha (IFN-α) are cytokines that enhance the anti-tumor activity of the immune system. IL-2 therapy can stimulate the proliferation and activation of T cells, which are crucial for targeting and destroying SCC cells. IFN-α has antiviral and anti-proliferative properties, making it effective in treating SCC, particularly those associated with human papillomavirus (HPV) infection.18,19

2. Targeted Therapy

Epidermal Growth Factor Receptor (EGFR) Inhibitors:

EGFR is often overexpressed in SCC, promoting tumor growth and survival. Targeted therapies such as cetuximab, an EGFR monoclonal antibody, inhibit EGFR signaling pathways, thereby reducing tumor proliferation and inducing apoptosis. Cetuximab has been used in combination with radiation therapy and chemotherapy, showing improved outcomes in locally advanced and metastatic SCC.18,19

Tyrosine Kinase Inhibitors (TKIs):

TKIs such as erlotinib and gefitinib target EGFR and other tyrosine kinases involved in SCC pathogenesis. These oral agents block the phosphorylation of tyrosine residues, interrupting key signaling pathways that drive tumor growth. TKIs are particularly beneficial for patients with mutations or overexpression of EGFR.18,19

3. Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) combines a photosensitizing agent with a specific wavelength of light to induce cytotoxicity in cancer cells. The photosensitizer, applied topically or systemically, preferentially accumulates in SCC cells. Upon activation by light, it generates reactive oxygen species that cause direct cell death and damage to the tumor vasculature. PDT is effective for treating superficial SCC and actinic keratosis, offering a non-invasive option with excellent cosmetic outcomes.18,19

4. Gene Therapy

Gene therapy aims to correct or modulate the genetic abnormalities driving SCC. Techniques such as CRISPR-Cas9, RNA interference (RNAi), and viral vector-mediated gene delivery are being explored to target oncogenes, tumor suppressor genes, and pathways involved in SCC development. For example, CRISPR-Cas9 can be used to knock out mutant TP53 or HRAS genes, potentially restoring normal cell function and reducing tumor growth.18,19

5. Oncolytic Viral Therapy

Oncolytic viruses selectively infect and kill cancer cells while sparing normal tissues. Talimogene laherparepvec (T-VEC) is an FDA-approved oncolytic herpes simplex virus engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF). T-VEC selectively replicates in SCC cells, causing direct lysis and stimulating a systemic anti-tumor immune response. Clinical trials are investigating the efficacy of T-VEC and other oncolytic viruses in SCC.18,19

6. Combinatorial Approaches

Combining different therapeutic modalities can enhance treatment efficacy and overcome resistance. For instance, the combination of immunotherapy with targeted therapy or radiation can produce synergistic effects. Clinical trials are exploring the combination of checkpoint inhibitors with EGFR inhibitors, PDT, and oncolytic viruses to improve outcomes in SCC patients.18,19

7. Nanotechnology-Based Therapies

Nanotechnology offers innovative approaches to drug delivery and cancer treatment. Nanoparticles can be engineered to deliver chemotherapeutic agents, siRNA, or gene editing tools directly to SCC cells, minimizing systemic toxicity and enhancing therapeutic efficacy. Nanoparticles can also be conjugated with targeting ligands to improve specificity for SCC cells.20

8. Anti-Angiogenic Therapy

Angiogenesis, the formation of new blood vessels, is critical for tumor growth and metastasis. Anti-angiogenic agents such as bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), inhibit tumor angiogenesis and disrupt the blood supply to SCC cells. These agents can be used alone or in combination with other treatments to enhance anti-tumor effects.21

The advent of novel treatment modalities for squamous cell carcinoma marks a significant advancement in oncologic care. Immunotherapies, targeted therapies, photodynamic therapy, gene therapy, oncolytic viral therapy, combinatorial approaches, nanotechnology-based therapies, and anti-angiogenic agents offer promising alternatives and adjuncts to traditional treatments. These innovations hold the potential to improve patient outcomes, reduce recurrence rates, and provide options for those with advanced or refractory SCC. Ongoing research and clinical trials will continue to refine these therapies, optimizing their efficacy and expanding their applicability in the management of SCC.

CONCLUSION

Squamous cell carcinoma (SCC) remains a significant public health concern due to its rising incidence, particularly among populations with increased UV exposure and those with compromised immune systems. As the second most common type of non-melanoma skin cancer, SCC poses unique challenges in its clinical management, necessitating a comprehensive understanding of its pathophysiology, epidemiology, clinical manifestations, diagnostic techniques, and treatment modalities.

The pathogenesis of SCC is complex and multifactorial, involving genetic mutations, environmental influences, and immune system interactions. Chronic exposure to ultraviolet (UV) radiation is the primary etiological factor, but other risk factors, such as human papillomavirus (HPV) infection, immunosuppression, and exposure to chemical carcinogens, also contribute significantly to SCC development. Understanding these risk factors is crucial for implementing effective preventive measures and early detection strategies.

Clinically, SCC presents with a wide spectrum of manifestations, ranging from indolent, well-differentiated lesions to aggressive, invasive tumors with metastatic potential. Accurate clinical assessment, supplemented by advanced diagnostic techniques, is essential for the early identification and appropriate management of SCC. Traditional diagnostic methods, such as histopathological examination, remain the gold standard. However, emerging technologies, including dermoscopy, reflectance confocal microscopy (RCM), optical coherence tomography (OCT), high-frequency ultrasound (HFUS), Raman spectroscopy, multiphoton microscopy (MPM), liquid biopsy, molecular and genetic profiling, and artificial intelligence (AI)-based tools, are revolutionizing SCC diagnosis. These innovations offer non-invasive, rapid, and highly accurate diagnostic options, enhancing the ability to detect SCC at earlier stages and monitor treatment response effectively.

The treatment landscape for SCC has also evolved significantly, with novel therapies complementing traditional modalities like surgical excision, Mohs micrographic surgery, and radiation therapy. Immunotherapy, particularly checkpoint inhibitors such as pembrolizumab and nivolumab, has emerged as a promising option for advanced and metastatic SCC, offering durable responses and improved survival rates. Targeted therapies, including epidermal growth factor receptor (EGFR) inhibitors and tyrosine kinase inhibitors (TKIs), provide precision treatment by targeting specific molecular pathways involved in SCC pathogenesis. Photodynamic therapy (PDT), gene therapy, oncolytic viral therapy, combinatorial approaches, nanotechnology-based therapies, and anti-angiogenic agents represent additional innovative treatment modalities that enhance therapeutic outcomes and reduce adverse effects.

Despite these advancements, challenges remain in managing SCC, particularly in high-risk populations and those with advanced disease. Continued research is essential to further elucidate the molecular mechanisms underlying SCC, identify novel biomarkers for early detection, and develop more effective and personalized treatment strategies. Clinical trials and real-world studies will play a critical role in validating the efficacy and safety of emerging therapies, ultimately guiding evidence-based clinical practice.

In conclusion, the ongoing advancements in the understanding, diagnosis, and treatment of squamous cell carcinoma hold great promise for improving patient outcomes. By integrating cutting-edge diagnostic technologies and novel therapeutic approaches, clinicians can offer more precise, effective, and personalized care to patients with SCC. Collaborative efforts among researchers, clinicians, and healthcare systems are vital to overcoming the remaining challenges and achieving optimal outcomes in the fight against this pervasive and potentially life-threatening cancer.

REFERENCES

I. Stern RS. Prevalence of a history of skin cancer in 2007: results of an inci- dence-based model. Arch Dermatol 2010; 146:279-82.

II. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population, 2012. JAMA Dermatol 2015;151:1081-6.

III. Karia PS, Han J, Schmults CD. Cuta- neous squamous cell carcinoma: estimat- ed incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol 2013; 68:957-66.

IV. Brougham NDLS, Dennett ER, Cam- eron R, Tan ST. The incidence of metasta- sis from cutaneous squamous cell carci- noma and the impact of its risk factors. J Surg Oncol 2012;106:811-5.

V. Mourouzis C, Boynton A, Grant J, et al. Cutaneous head and neck SCCs and risk of nodal metastasis — UK experience. J Craniomaxillofac Surg 2009;37:443-7.

VI. Joseph MG, Zulueta WP, Kennedy PJ. Squamous cell carcinoma of the skin of the trunk and limbs: the incidence of me- tastases and their outcome. Aust N Z J Surg 1992;62:697-701.

VII. Tokez S, Wakkee M, Kan W, et al. Cu- mulative incidence and disease-specific survival of metastatic cutaneous squa- mous cell carcinoma: a nationwide cancer registry study. J Am Acad Dermatol 2022; 86:331-8.

VIII. Garrett GL, Blanc PD, Boscardin J, et al. Incidence of and risk factors for skin cancer in organ transplant recipients in the United States. JAMA Dermatol 2017; 153:296-303.

IX. Genders RE, Weijns ME, Dekkers OM, Plasmeijer EI. Metastasis of cutaneous squamous cell carcinoma in organ trans- plant recipients and the immunocompe- tent population: is there a difference? a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2019;33: 828-41.

X. Clayman GL, Lee JJ, Holsinger FC, et al. Mortality risk from squamous cell skin cancer. J Clin Oncol 2005;23:759-65.

XI. Robsahm TE, Helsing P, Veierød MB. Cutaneous squamous cell carcinoma in Norway 1963–2011: increasing incidence and stable mortality. Cancer Med 2015;4: 472-80.

XII. Tokez S, Hollestein L, Louwman M, Nijsten T, Wakkee M. Incidence of multi- ple vs first cutaneous squamous cell car- cinoma on a nationwide scale and estima-tion of future incidences of cutaneous squamous cell carcinoma. JAMA Derma- tol 2020;156:1300-6.

XIII. Muzic JG, Schmitt AR, Wright AC, et al. Incidence and trends of basal cell carci- noma and cutaneous squamous cell car- cinoma: a population-based study in Olmsted County, Minnesota, 2000 to 2010. Mayo Clin Proc 2017;92:890-8.

XIV. Kosmadaki MG, Gilchrest BA. The de- mographics of aging in the United States: implications for dermatology. Arch Der- matol 2002;138:1427-8.

XV. Stang A, Khil L, Kajüter H, et al. Inci- dence and mortality for cutaneous squa- mous cell carcinoma: comparison across three continents. J Eur Acad Dermatol Venereol 2019;33:Suppl 8:6-10.

XVI. Gray DT, Suman VJ, Su WP, Clay RP, Harmsen WS, Roenigk RK. Trends in the population-based incidence of squamous cell carcinoma of the skin first diagnosed between 1984 and 1992. Arch Dermatol 1997;133:735-40.

XVII. Higgins S, Nazemi A, Chow M, Wysong A. Review of nonmelanoma skin cancer in African Americans, Hispanics, and Asians. Dermatol Surg 2018;44:903-10.

XVIII. Gloster HM Jr, Neal K. Skin cancer in skin of color. J Am Acad Dermatol 2006; 55:741-60.

XIX. Armstrong BK, Kricker A. The epide- miology of UV induced skin cancer. J Pho- tochem Photobiol B 2001;63:8-18.

XX. Stern RS; PUVA Follow-Up Study. The risk of squamous cell and basal cell can- cer associated with psoralen and ultravio- let A therapy: a 30-year prospective study. J Am Acad Dermatol 2012;66:553-62.

XXI. Wehner MR, Shive ML, Chren M-M, Han J, Qureshi AA, Linos E. Indoor tan- ning and non-melanoma skin cancer: sys- tematic review and meta-analysis. BMJ 2012;345:e5909.