Advances in the Etiology, Detection, and Clinical Management of Seborrheic Keratoses

Mary D. Sun^a Allan C. Halpern^b

^aIcahn School of Medicine at Mount Sinai, New York, NY, USA; ^bDermatology Service, Memorial Sloan Kettering, New York, NY, USA

Keywords

Seborrheic keratosis · Oncogenic mutations · Dermoscopy · Artificial intelligence · Noninvasive diagnostics · Topical therapies

Abstract

Seborrheic keratoses (SKs) are ubiquitous, generally benign skin tumors that exhibit high clinical variability. While age is a known risk factor, the precise roles of UV exposure and immune abnormalities are currently unclear. The underlying mechanisms of this benign disorder are paradoxically driven by oncogenic mutations and may have profound implications for our understanding of the malignant state. Advances in molecular pathogenesis suggest that inhibition of Akt and APP, as well as existing treatments for skin cancer, may have therapeutic potential in SK. Dermoscopic criteria have also become increasingly important to the accurate detection of SK, and other noninvasive diagnostic methods, such as reflectance confocal microscopy and optical coherence tomography, are rapidly developing. Given their ability to mimic malignant tumors, SK cases are often used to train artificial intelligence-based algorithms in the computerized detection of skin disease. These technologies are becoming increasingly accurate and have the potential to significantly

augment clinical practice. Current treatment options for SK cause discomfort and can lead to adverse post-treatment effects, especially in skin of color. In light of the discontinuation of ESKATA in late 2019, promising alternatives, such as nitric-zinc and trichloroacetic acid topicals, should be further developed. There is also a need for larger, head-to-head trials of emerging laser therapies to ensure that future treatment standards address diverse patient needs.

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Introduction

Seborrheic keratoses (SKs) are the most common epithelial tumor encountered in clinical practice and diagnosed in teleconsultations [1–4]. These lesions are primarily benign, highly biopsied, and typically removed for cosmetic reasons, though eruptive presentations like the Leser-Trélat sign can indicate malignancy [5–8]. A national data profile of skin disease estimates that SK affects nearly 84 million Americans and incurs over USD 1.2B in annual medical costs [9]. Notably, 85% of all SK patients who seek medical treatment present to dermatologists [6]. SKs are, therefore, recognized as a frequent cause of dermatologic visits that create important opportunities

for detecting other skin disorders [10]. Despite their high prevalence and large cost burden, SKs are not widely discussed in the current literature. Furthermore, treatment options are often uncomfortable and have cosmetic sequelae. In this review, we highlight advances in SK pathogenesis, discuss novel noninvasive diagnostics, and provide an overview of emerging topical and laser therapies.

Clinical Presentation

SKs develop in hair-bearing areas and most commonly occur on the head, neck, trunk, and extremities, while sparing mucous membranes and the palms and soles [10, 11]. Rare cases of lesions in the external ear [12–14] and pedunculated tumors in perigenital areas have been reported [15–17], as well as truncal lesions along Blaschko's lines [18, 19]. SKs are generally asymptomatic and present as papules, macules, and plaques. Most variants range in color from tan to black and are well-demarcated with a verrucous, “stuck-on” appearance. Surface textures can be waxy, keratotic, scaly, or greasy appearing and may become rougher over time [10, 20]. SKs may also undergo exophytic, hyperplastic, and/or hyperpigmented change [21]. Lesions continue to develop over the lifespan and can grow to >5 cm in diameter [11]. Spontaneous regression is rare.

Patients presenting with SK are often concerned about the possibility of skin cancer and their aesthetic appearance, as an estimated one-third of SK patients present with greater than 15 lesions [10]. An observational study of 406 adult patients found that asymptomatic SK removals were due to nonmutually exclusive concerns about more serious illness (57%), cosmetic reasons (53%), tactile discomfort (44%), and irritation or itchiness (42%), with most patients having taken measures to “disguise, hide, or deal with” their SKs [22]. Individuals with multiple lesions on the face, hands, genitals, and other sensitive areas may suffer from perceived disfigurement and experience negative psychological impacts [23]. Furthermore, lesions may become inflamed (irritated SK) due to trauma or secondary infection and cause pain, pruritus, erythema, or crusting.

Epidemiology

SKs are highly prevalent in older populations and seem to increase with age. In a recent retrospective cohort study of 10,545 Brazilian patients older than 60 years, this dis-

order was the leading cause for dermatologic teleconsultations. Eighty-nine percent of lesions occurred in patients aged 80 years and above [2]. Previous studies of dermatology patients in Australia, the United Kingdom, the Netherlands, and Korea found similarly high, strongly age-related prevalence, as well as higher average numbers and diameters of SK lesions in geriatric individuals [24–27]. However, SKs can also develop at younger ages. Another Australian study of 170 people aged 15–30 years found that 24% had at least 1 lesion, 78% of which were truncal [24, 28]. Though pediatric dermatologists do not typically encounter SKs, the dermatosis papulosa nigra (DPN) variant has specifically been observed in children [10, 29–31].

SKs are mainly noted as coincidental findings in epidemiologic research, and relatively little is known about their demographic distribution. Recent studies have not found significant gender differences in SK incidence, though an observational study found that men exhibited more lesions on the trunk and arms than women [2, 11, 22, 24, 32]. While a Caucasian predominance has been assumed, SKs occur with near-equivalent incidence in Korean males (Fitzpatrick I–V) as in Caucasians and are generally known to occur in diverse skin types [26]. DPN is found more often in African American, East Asian, and South Asian populations (Fitzpatrick IV–VI) with a consistently reported predominance in women and is thought to be underrecognized [33–36]. There is a high likelihood of family history, especially in individuals with large numbers of lesions [37–41]. Autosomal dominant inheritance with incomplete penetrance has been proposed [11, 40, 42].

Etiology and Molecular Pathogenesis

Risk Factors

UV exposure has been implicated in the etiopathology of SK, though causality remains unclear. An Australian study found more frequent, flatter, and larger lesions in sun-exposed body sites, as well as higher SK prevalence when compared to other Caucasian populations in the United Kingdom [24]. Similarly, the aforementioned study of Korean males found lesions concentrated on the face and backs of the hands, as well as a 2.28-fold higher risk of SK associated with lifetime sunlight exposures of over 6 h/day versus less than 3 h/day [26]. A survey of 840 people in China also found a relationship between cumulative UV exposure and SK, noting that residents with Fitzpatrick II skin types were susceptible to more severe

photoaging than those with Fitzpatrick III and IV [43]. However, a cohort study of 966 individuals from the Netherlands found that neither lifetime sun exposure nor painful sunburns were associated with increased SK risk [27]. SKs frequently occur on clothing-covered sites and are found in perigenital and intertriginous areas. Interestingly, SKs are more represented in atrophic than hypertrophic photoaging [44].

Age is a widely acknowledged risk factor for SK. Amyloid precursor protein (APP), which plays an important role in the pathogenesis of age-related Alzheimer's disease, was recently shown to be elevated in SK tissues as compared to control. Expression levels were particularly high in UV-exposed skin sites and the older age group (61–85 years), though a positive age-related correlation was found in the epidermis but not the dermis [45]. The partial loss of presenilins 1 and 2, which help release amyloid beta from APP in neurologic disease, causes a SK-like cutaneous hyperplasia in mice [46]. Guanine deaminase (*GDA*) upregulation in SK has also been implicated in UV-induced keratinocyte senescence, where the production of uric acid generates reactive oxygen species and damages DNA [47]. Intriguingly, *GDA* also appears to promote melanogenesis by upregulating stem cell factor (SCF) and endothelin (EDN)-1 in epidermal keratinocytes and may, therefore, play a role in many hyperpigmentary skin disorders [48].

Viral etiologies have also been suggested, as human papillomavirus (HPV) DNA has been found in up to half of SK specimens across various studies [49–56]. However, rates of HPV detection tend to be much higher in genital versus nongenital SKs. A 2004 study found that SK had 79% HPV positivity on lesion surfaces versus 19% in biopsies, suggesting that positivity may simply reflect surface contamination [57]. Additionally, more recent studies could not replicate high levels of HPV detection in SKs [58–60]. Merkel cell polyomavirus was recently detected in 26% of reviewed SKs, but was ascribed to coincidental coinfection; these viruses replicate in rapidly dividing cells [51, 61].

Immune factors are newly implicated in SK. Mast cells are significantly increased at the periphery of SK tumors, and mast cells, SCF, and cannabinoid receptor type 1 (CB1) are differentially expressed within them [62]. This novel mechanism suggests that immune components involved in inflammatory dermatoses may also play a role in SK pathogenesis. Another study found that while the paracrine cytokine SCF and its receptor c-KIT are surprisingly downregulated in SK, high levels of EDN-1 in lesional skin can be attributed to markedly upregulated

secretion of EDN-1 production-inducing cytokine TNF- α [63, 64]. EDN-1 is a keratinocyte-derived mitogen and strong melanogen in human skin cells [64]. Additionally, a recent study of 400 Chinese women found an association between SK incidence and smoking [65]. Meta-analyses have linked smoking to atopic dermatitis, psoriasis, and lupus erythematosus risk [66–68].

Oncogenic Activation

Despite their benign nature, a large proportion of SKs exhibit oncogenic mutations. A somatic mutation in fibroblast growth factor receptor 3 (*FGFR3*), identical to those associated with skeletal dysplasia and urinogenital neoplasms, is correlated with age and body site in SK patients [42, 69–71]. Though activated *FGFR3* and its receptors demonstrate oncogenic function in solid tumors [72–74], oncogene-induced senescence is not observed in SK [75]. Furthermore, the mild epidermal hyperplasia caused by *FGFR3* mutations cannot independently drive tumorigenesis [76]. This may be explained by a positive *FGFR3/FOXP1* feedback loop in SK, where increased *FGFR3* activity induces *FOXP1*-led differentiation and triggers a benign SK-like phenotype in previously malignant squamous cell carcinoma (SCC) cells. Conversely, *FOXP1* knockdown augments oncogenic RAS and results in SCC-like tumors [77, 78]. Fibroblast growth factor deficiency also causes epidermal defects associated with inflammatory dermatoses, and epidermal growth factor receptor (EGFR) has been implicated in abnormal keratinocyte proliferation and differentiation in SK [79–81].

In recent years, additional oncogenic mutations have been elucidated. A mutation in the p110 α catalytic subunit of phosphatidylinositol 3-kinase (*PIK3CA*), which co-occurs with *FGFR3* mutations in malignant bladder tumors, also co-occurs with *PIK3CA* mutations in SK [12, 40, 78, 82, 83]. A mutational screen of 175 SKs for *FGFR3*-RAS-MAPK and PI3K-AKT pathways found additional mutations in KRAS, HRAS, EGFR, and *AKT1* oncogenes. However, tumor suppressors TSC1 and PTEN were not mutated and, as previously illustrated in *FGFR3* studies, senescence and DNA damage responses were absent despite oncogenic activation. Unlike similarly mutated neoplasms, SKs are genetically stable [84].

SKs show increased rates of proliferation and apoptotic suppression when compared to normal keratinocytes [42, 85]. Akt kinase signaling, which interacts with *FGFR3* and p110 α proteins, inhibits the p53 pathway and FOXO-mediated apoptosis in SK. In contrast to cutaneous SCC, SK does not show mutations of p53, which suggests that this gene plays a differential role in sensitivity

Fig. 1. Proposed mechanisms of pathogenesis mediated by aging, UV exposure, and immune-related factors.

to Akt inhibition. Differential expression of tumor suppressors p16 and p27 is found in various SK subsets, especially clonal SK, and p53 and p16 overexpression in irritated SK may also indicate a pathway for malignant tumor transformation or adjacency (“collision tumors”) [61, 86–92]. Furthermore, elevated phosphorylated Akt in SK may confer hypersensitivity to apoptotic inhibition [89]. Paradoxical findings of “oncogenic driver” mutations in this benign disorder have profound implications for tumorigenesis research and the future treatment of skin tumors [93, 94].

These and other emerging theories of SK pathogenesis are speculatively summarized in Figure 1.

Noninvasive Diagnostics

SK lesions that resemble melanocytic neoplasms can be challenging to diagnose with the naked eye [5, 95, 96]. A clinicopathologic review of skin biopsies in 8,694 patients found that 30% of excised SKs were misdiagnosed as nonmelanocytic skin cancer and 3% as melanoma.

Fig. 2. Illustrated summary of key dermoscopic inclusion criteria for seborrheic keratosis (right), with accompanying dermoscopic images of milia-like cysts and fissures and ridges features (left). Images are adapted from Dermoscopedia.org under the Creative Commons Attribution 4.0 International License.

Twenty-one percent of all misdiagnosed cutaneous melanoma cases were determined to be SKs or benign nevi [97]. An assessment of 367 basal cell carcinoma (BCC) cases similarly found that 22% of misdiagnosed cases were SKs [98]. Malignancy tends to be overdiagnosed, reflecting a cautious approach to the management of skin tumors and an opportunity for advanced imaging techniques to augment clinical detection. Furthermore, data from SKs plays an important role in the development of artificial intelligence (AI)-based skin lesion detection technologies.

Dermoscopy

Dermoscopy is a powerful technique for visualizing clinically inapparent diagnostic features in real time. Though other methods have superior resolution, dermoscopy is the most widely used due to its ease of use and availability [99]. Notably, polarized and nonpolarized dermoscopy differ in their ability to visualize different features and should be used complementarily [100]. The two-step algorithm for dermoscopic SK diagnosis organizes features into (1) exclusionary criteria of a pigment network, aggregated globules, and homogenous patterns

of blue pigmentation and (2) inclusionary criteria of fissures and ridges, comedo-like openings, milia-like cysts, and brown fingerprint-like structures as shown in Figure 2 [101]. Subsequent studies report additional features, including hairpin vessels, sharp demarcation, moth-eaten borders, crypts, and exophytic papillary structures [102, 103]. A prospective study of 416 lesions found that the inclusion of a lack of blue-grey/white color, presence of yellowish color, and mica-like structure further optimizes SK identification [104].

In general, the above features constitute important findings for SK [20, 96, 100, 102, 105–107]. They are used in dermoscopic scoring methods shown to improve clinical accuracy for distinguishing between SKs and SK-like melanomas [108, 109]. A subgroup of these features, including hairpin vessels, a diffuse regular vessel arrangement, and 10% lesion coverage with white halos, can be used to differentiate irritated SK and SCC [110]. However, a global pattern has not been identified for atypical SKs. A study of 72 biopsies found that some of these lesions actually exhibit non-SK features, including a blue-whitish veil, polymorphous vessels, globules, and white streaks [111].

Several dermoscopy-dependent imaging techniques have been developed, including videodermoscopy (sequential digital dermoscopy) and computer-assisted digital dermoscopy. The latter involves an integrated approach for the objective measurement of multiple parameters in an assisted diagnosis model that are then analyzed as possible discriminant variables. This integration of numerical features, dermoscopic patterns, and personal metadata was initially performed in melanoma but could be replicated for SK [112]. In conjunction with dermoscopic data, information from multispectral digital skin lesion analysis devices has also been found to augment clinical decision-making [113].

Other Optical Techniques

Reflectance confocal microscopy (RCM) visualizes the epidermis and superficial dermis at the cellular level. In RCM analysis, a honeycomb epidermal pattern and densely packed, well-circumscribed dermal papillae at the dermo-epidermal junction indicate benign neoplasms, while SK-specific features include epidermal projections, keratin-filled invaginations, cords and bulbous projections, corneal pseudocysts, and a mixed vascular pattern [114–119]. In recent years, studies have identified the clinical variability of SKs and the restricted depth of imaging as challenges to accurate RCM-based diagnosis. In a retrospective analysis of 390 patients with clinically suspicious SK, dermatologists using RCM could not diagnose SK in 25% of participants [120]. SKs have previously been misdiagnosed as pigmented nevi, and RCM features have been reported as insufficient for distinguishing melanoacanthoma from melanoma [121–123].

Optical coherence tomography (OCT) also provides subsurface imaging with greater penetration but lower resolution than RCM. Existing use in SK management is limited, but reported criteria for SK include acanthosis, basal hyperpigmentation, visibility of the dermo-epidermal junction, a normal honeycomb pattern, loss of normal epidermal and dermal layering, and enlarged interpapillary spaces with edged papillae [124]. Given the ability of OCT to rapidly measure architectural changes in the epidermis and dermis, this technique was also used to measure the SK clearance of a topical hydrogen peroxide solution [125]. In the future, OCT may act as an alternative or useful adjunct to histopathological examinations of SK [126].

Several experimental photodynamic techniques have been used to identify SK. A pilot trial found that autofluorescence analysis using an RGB (red, green, blue) smartphone camera under 405-nm LED excitation was able to differentiate 15 SK lesions from 36 pigmented

Fig. 3. Accuracy of the top-ranked algorithm from the 2017 International Skin Imaging Collaboration challenge, specific to detection of seborrheic keratoses using a 150-image dataset. The receiving operator characteristic (ROC) curve, shown in black, demonstrates sensitivity and specificity of the model. The AUC result of 0.954 indicates excellent performance.

nevi, BCC, and melanoma with high sensitivity and specificity [127]. Near-infrared autofluorescence shows that SK lesions exhibit significantly brighter emissions than normal skin [128]. Raman spectroscopy uses structural alterations in lipid proteins to distinguish melanoma from pigmented nevi, BCC, and SK, and a low-cost portable device recently achieved moderate performance in differentiating SKs and melanomas [129, 130]. Photodynamic and thermovision methods demonstrate that SK lesions have lower mean temperatures than healthy skin and that temperature gradients differ significantly between SK and BCC [131].

Artificial Intelligence

SK images are often used to train AI-based algorithms capable of distinguishing malignant skin tumors from benign mimics. The test dataset of the 2017 International Skin Imaging Collaboration challenge included 50 melanoma, 50 nevi, and 50 SKs, leading to the top-ranked deep learning model with an area under the receiver operating characteristic curve (AUC) of 0.954 for SKs (Fig. 3) [132].

Machine- and deep learning-based systems that outperform clinician readers often include SK as a standalone category and report AUCs from 0.77 to 0.96 [133–141]. Others stratify results by increasing categories of risk and include SKs as low-risk designations [142]. Some algorithms, based on various deep learning frameworks, such as convolutional neural networks and Gabor wavelet-based learning, are trained on SK versus BCC or melanoma data only [143–146]. These computational tools show significant promise for augmenting clinical SK detection.

Emerging Therapeutics

Available treatments have largely been limited to destructive therapies and minor surgical techniques, including cryotherapy, shave dissection, and electrodesiccation and curettage [10, 41]. Many of these are not well tolerated in patients with multiple lesions and are more likely to cause postinflammatory pigmentation in skin of color [10, 147–149]. ESKATA, a 40% hydrogen peroxide topical solution and the first FDA-approved treatment for SK, was commercially discontinued in the USA in 2019 [150–152]. There is a need for more comfortable and cosmetically acceptable SK therapies.

Topical Treatments

Early studies of topical therapies show promise for treating SK (Table 1). Interventions of nitric-zinc solutions showed significant clearance in nearly all lesions with minimal patient discomfort and no reported relapse [153, 154]. A novel formula of trichloroacetic (TCA) and formic acid similarly showed complete response in 90% of patients, but was associated with more drug-related adverse events [155]. Focal TCA peels also showed good clinical response in darker-skinned patients (Fitzpatrick IV–V) [156]. Conversely, tazarotene 0.1% cream improved outcomes in less than half of patients, and 12% ammonium lactate lotion (Lac-Hydrin) only affected lesion elevation [157, 158]. SK clearance achieved using topical dobesilate [159], 5% imiquimod cream [160], and 3% diclofenac gel has also been reported [161]. A recent meta-analysis found no evidence for the efficacy of topical vitamin D analogues [162].

Laser and Light-Based Therapy

Ablative laser therapies, which can be relatively costly, have also been used to treat SK. In an observational study, carbon dioxide (CO₂) laser was used for lesions

that had not improved following treatment with a combination therapy of 4% hydroquinone-containing creams. Clinical improvement was scored using a subjective scale and the mean efficacy among 53 SK patients was 84% [163]. In several case series of DPN patients, the use of CO₂ laser treatment completely removed SK lesions without scar formation or significant discomfort [164–166]. CO₂ laser was also successfully used in 2 cases of irritated SK, with no evidence of recurrence at 6 and 12 months [167, 168]. Additionally, a comparative study of erbium:YAG (Er:YAG) laser and cryosurgery in 42 SK patients reported superior healing, less hyperpigmentation, and more erythema in laser-treated groups [169].

Nonablative laser therapies have also been reported. Two randomized, split-face studies comparing potassium-titanyl phosphate (KTP) laser and electrodesiccation in DPN patients found that KTP treatment was comparatively effective and better-tolerated. However, post-treatment hypo- and hyperpigmentation sequelae were observed in most patients [170]. Though another prospective, investigator-blinded pilot study of pulsed dye laser (PDL) treatment in 10 DPN patients found comparative effectiveness with curettage and electrodesiccation, PDL was rated the most painful of the treatment modalities and did not reduce post-treatment hyperpigmentation [148]. Another neodymium-doped:YAG (Nd:YAG) laser at 1,064 nm was successfully used to treat 2 cases of DPN with no post-treatment effects [171]. Fractional photothermolysis, intense pulsed light, and Q-switched and picosecond lasers have also been used [172–174]. Recently, the successful use of aminolevulinic acid photodynamic therapy (ALA-PDT) for giant SK was reported [175].

Conclusion

Recent advances in our understanding of immune- and oncogene-related SK pathogenesis have important implications for the treatment of both benign and neoplastic conditions. Given their ubiquity and clinical diversity, these lesions also pose an important diagnostic challenge that emphasizes their role in the development of AI-based technologies. To meet the needs of diverse patients and improve cosmetic outcomes, promising topical and laser-based treatments should be further developed.

Key Message

New therapeutic avenues and emerging topical and laser therapies could improve outcomes in SK patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no specific funding for this work.

Author Contributions

Mary D. Sun made substantial contributions to the design and acquisition, analysis, and interpretation of data for this work, drafted the work, and revised it critically for important intellectual content. Allan C. Halpern made substantial contributions to the conception of the work and agrees to be accountable for all aspects of the work. Both authors provided final approval of the version to be published.

References

- 1 Moreno-Ramírez D, Raya-Maldonado J, Morales-Conde M, Ojeda-Vila T, Martín-Gutiérrez FJ, Ruiz-de-Casas A, et al. Increasing Frequency of Seborrheic Keratosis Diagnoses as a Favorable Consequence of Teledermatology-Based Skin Cancer Screening: A Cross-sectional Study of 34,553 Patients. *Am J Clin Dermatol*. 2017;18(5):681–5.
- 2 Bianchi MG, Santos A, Cordioli E. Benefits of Teledermatology for Geriatric Patients: Population-Based Cross-Sectional Study. *J Med Internet Res*. 2020;22(4):e16700.
- 3 Ford JA, Pereira A. Does teledermatology reduces secondary care referrals and is it acceptable to patients and doctors?: a service evaluation. *J Eval Clin Pract*. 2015;21(4):710–6.
- 4 Mehrtens SH, Shall L, Halpern SM. A 14-year review of a UK teledermatology service: experience of over 40 000 teleconsultations. *Clin Exp Dermatol*. 2019;44(8):874–81.
- 5 Izikson L, Sober AJ, Mihm MC Jr, Zembowicz A. Prevalence of melanoma clinically resembling seborrheic keratosis: analysis of 9204 cases. *Arch Dermatol*. 2002;138(12):1562–6.
- 6 Duque MI, Jordan JR, Fleischer AB, Williford PM, Feldman SR, Teuschler H, et al. Frequency of seborrheic keratosis biopsies in the United States: a benchmark of skin lesion care quality and cost effectiveness. *Dermatol Surg*. 2003;29(8):796–801.
- 7 Chen TY, Morrison AO, Cockerell CJ. Cutaneous malignancies simulating seborrheic keratoses: An underappreciated phenomenon?. *J Cutan Pathol*. 2017;44(9):747–8.
- 8 Reddy R, Davidova L, Bhattacharyya I, Cohen DM, Islam MN, Fitzpatrick SG. Dermatologic Lesions Submitted to an Oral and Maxillofacial Pathology Biopsy Service: An Analysis of 2487 Cases. *Head Neck Pathol*. 2018;12(4):493–9.
- 9 Bickers DR, Lim HW, Margolis D, Weinstock MA, Goodman C, Faulkner E, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol*. 2006;55(3):490–500.
- 10 Jackson JM, Alexis A, Berman B, Berson DS, Taylor S, Weiss JS. Current Understanding of Seborrheic Keratosis: Prevalence, Etiology, Clinical Presentation, Diagnosis, and Management. *J Drugs Dermatol*. 2015;14(10):1119–25.
- 11 Requena L, Requena C, Cockerell CJ. Benign Epidermal Tumors and Proliferations. 4th ed. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. Elsevier; 2018.
- 12 De Loof M, Van Dorpe J, Van Der Meulen J, Lefever S, Dhooge I. Two cases of seborrheic keratosis of the external ear canal: involvement of PIK3CA and FGFR3 genes. *Int J Dermatol*. 2018;57(6):703–6.
- 13 Hong CE, Kim Y, Choi HS, Jeong J. Seborrheic Keratosis in the Auricle: A Rare Tumor. *Ear Nose Throat J*. 2019;98(9):560–1.
- 14 Kim KW, Chang J, Lee S, Im GJ, Chae SW, Jung HH, et al. Clinical analysis of seborrheic keratoses in the ear: a retrospective study and literature review. *Eur Arch Otorhinolaryngol*. 2015;272(5):1113–7.
- 15 Baer RL. Giant Pedunculated Seborrheic Keratosis. *Arch Dermatol*. 1979;115(5):627.
- 16 Thakur JS, Thakur A, Chauhan CG, Diwana VK, Chauhan DC. Giant pedunculated seborrheic keratosis of penis. *Indian J Dermatol*. 2008;53(1):37–8.
- 17 Bandyopadhyay D, Saha A, Mishra V. Giant perigenital seborrheic keratosis. *Indian Dermatol Online J*. 2015;6(1):39–41.
- 18 Mabuchi T, Akasaka E, Kondoh A, Umezawa Y, Matsuyama T, Ozawa A. Seborrheic keratosis that follows Blaschko's lines. *J Dermatol*. 2008;35(5):301–3.
- 19 Livingstone E, Hillen U, Hafner C, Piel S, Groesser L, Schadendorf D, et al. Segmentally arranged seborrheic keratoses with impending atypia and squamous cell carcinoma in an elderly woman. *Br J Dermatol*. 2015;172(6):1642–5.
- 20 Braun RP, Ludwig S, Marghoob AA. Differential Diagnosis of Seborrheic Keratosis: Clinical and Dermoscopic Features. *J Drugs Dermatol*. 2017;16(9):835–42.
- 21 Squillace L, Cappello M, Longo C, Moscarella E, Alfano R, Argenziano G. Unusual Dermoscopic Patterns of Seborrheic Keratosis. *Dermatology (Basel)*. 2016;232(2):198–202.
- 22 Del Rosso JQ. A Closer Look at Seborrheic Keratoses: Patient Perspectives, Clinical Relevance, Medical Necessity, and Implications for Management. *J Clin Aesthet Dermatol*. 2017;10(3):16–25.
- 23 Hirobe S, Otsuka R, Iioka H, Quan YS, Kamiyama F, Asada H, et al. Clinical study of a retinoic acid-loaded microneedle patch for seborrheic keratosis or senile lentigo. *Life Sci*. 2017;168:24–7.
- 24 Yeatman JM, Kilkenny M, Marks R. The prevalence of seborrheic keratoses in an Australian population: does exposure to sunlight play a part in their frequency?. *Br J Dermatol*. 1997;137(3):411–4.
- 25 Memon AA, Tomenson JA, Bothwell J, Friedman PS. Prevalence of solar damage and actinic keratosis in a Merseyside population. *Br J Dermatol*. 2000;142(6):1154–9.
- 26 Kwon OS, Hwang EJ, Bae JH, Park HE, Lee JC, Youn JI, et al. Seborrheic keratosis in the Korean males: causative role of sunlight. *Photodermatol Photoimmunol Photomed*. 2003;19(2):73–80.
- 27 Kennedy C, Bajdik CD, Willemze R, De Grujil FR, Bouwes Bavinck JN. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. *J Invest Dermatol*. 2003;120(6):1087–93.
- 28 Gill D, Dorevitch A, Marks R. The prevalence of seborrheic keratoses in people aged 15 to 30 years: is the term senile keratosis redundant?. *Arch Dermatol*. 2000;136(6):759–62.
- 29 Calcaterra R, Franco G, Valenzano M, Fazio R, Morrone A. Clinical features and treatment of dermatosis papulosa nigra in migrants to Italy. *Skinmed*. 2010;8(4):207–9.
- 30 Babapour R, Leach J, Levy H. Dermatitis papulosa nigra in a young child. *Pediatr Dermatol*. 1993;10(4):356–8.

- 31 Veraitch O, Rickaby W, Robson A, Higgins E, Mellerio JE. Early-onset dermatosis papulosa nigra. *Br J Dermatol*. 2016;174(5):1148–50.
- 32 El-Sayed MH, Saleh HM, El Zawahry KMA, Mostafa AE. The dermoscopic features of facial aging among Egyptians: A comparative study between males and females. *J Cosmet Dermatol*. 2019;18(6):1803–13.
- 33 Kundu RV, Patterson S. Dermatologic conditions in skin of color: part II. Disorders occurring predominately in skin of color. *Am Fam Physician*. 2013;87(12):859–65.
- 34 Metin SA, Lee BW, Lambert WC, Parish LC. Dermatitis papulosa nigra: a clinically and histopathologically distinct entity. *Clin Dermatol*. 2017;35(5):491–6.
- 35 Zhu MY, Wang P, Li LY, Sun YP, Shen H. [Clinical-pathological analysis of 71 cases of dermatosis papulosa nigra of Han Chinese people]. *Zhonghua Yi Xue Za Zhi*. 2019; 99(37):2903–6. Chinese.
- 36 Bhat RM, Patrao N, Monteiro R, Sukumar D. A clinical, dermoscopic, and histopathological study of Dermatitis Papulosa Nigra (DPN) – An Indian perspective. *Int J Dermatol*. 2017;56(9):957–60.
- 37 Uwakwe LN, Souza B, Subash J, McMichael AJ. Dermatitis Papulosa Nigra: A Quality of Life Survey Study. *J Clin Aesthet Dermatol*. 2020;13(2):17–9.
- 38 Grimes PE, Arora S, Minus HR, Kenney JA Jr. Dermatitis papulosa nigra. *Cutis*. 1983;32(4): 385–92.
- 39 Xie F, Wang R, Chen Y, Jia Y, Jia X, Chen M, et al. A Case of Seborrheic Keratosis and Family Survey. *West Indian Med J*. 2015; 65(1):219–21.
- 40 Hafner C, Vogt T, Landthaler M, Müsebeck J. Somatic FGFR3 and PIK3CA mutations are present in familial seborrheic keratoses. *Br J Dermatol*. 2008;159(1):214–7.
- 41 Hafner C, Vogt T. Seborrheic keratosis. *J Dtsch Dermatol Ges*. 2008;6(8):664–77.
- 42 Hafner C, Hartmann A, van Oers JM, Stoehr R, Zwarthoff EC, Hofstaedter F, et al. FGFR3 mutations in seborrheic keratoses are already present in flat lesions and associated with age and localization. *Mod Pathol*. 2007;20(8): 895–903.
- 43 Wang YN, Fang H, Zhu WF. Survey on skin aging status and related influential factors in Southeast China. *J Zhejiang Univ Sci B*. 2009; 10(1):57–66.
- 44 Sachs DL, Varani J, Chubb H, Fligel SEG, Cui Y, Calderone K, et al. Atrophic and hypertrophic photoaging: Clinical, histologic, and molecular features of 2 distinct phenotypes of photoaged skin. *J Am Acad Dermatol*. 2019; 81(2):480–8.
- 45 Li Y, Wang Y, Zhang W, Jiang L, Zhou W, Liu Z, et al. Overexpression of Amyloid Precursor Protein Promotes the Onset of Seborrheic Keratosis and is Related to Skin Ageing. *Acta Derm Venereol*. 2018;98(6):594–600.
- 46 Tournoy J, Bossuyt X, Snellinx A, Regent M, Garmyn M, Serneels L, et al. Partial loss of presenilins causes seborrheic keratosis and autoimmune disease in mice. *Hum Mol Genet*. 2004;13(13):1321–31.
- 47 Cheong KA, Lee AY. Guanine Deaminase Stimulates Ultraviolet-induced Keratinocyte Senescence in Seborrheic Keratosis via Guanine Metabolites. *Acta Derm Venereol*. 2020; 100(8):adv00109.
- 48 Jung JM, Noh TK, Jo SY, Kim SY, Song Y, Kim YH, et al. Guanine Deaminase in Human Epidermal Keratinocytes Contributes to Skin Pigmentation. *Molecules*. 2020;25(11).
- 49 Zhao YK, Lin YX, Luo RY, Huang XY, Liu MZ, Xia M, et al. Human papillomavirus (HPV) infection in seborrheic keratosis. *Am J Dermatopathol*. 1989;11(3):209–12.
- 50 Zhu WY, Leonardi C, Penneys NS. Detection of human papillomavirus DNA in seborrheic keratosis by polymerase chain reaction. *J Dermatol Sci*. 1992;4(3):166–71.
- 51 Tsambaos D, Monastirli A, Kapranos N, Georgiou S, Pasmatzi E, Stratigos A, et al. Detection of human papillomavirus DNA in nongenital seborrheic keratoses. *Arch Dermatol Res*. 1995;287(6):612–5.
- 52 Bai H, Cviko A, Granter S, Yuan L, Betensky RA, Crum CP. Immunophenotypic and viral (human papillomavirus) correlates of vulvar seborrheic keratosis. *Hum Pathol*. 2003; 34(6):559–64.
- 53 Gushi A, Kanekura T, Kanzaki T, Eizuru Y. Detection and sequences of human papillomavirus DNA in nongenital seborrheic keratosis of immunopotent individuals. *J Dermatol Sci*. 2003;31(2):143–9.
- 54 Li YH, Chen G, Dong XP, Chen HD. Detection of epidermodysplasia verruciformis-associated human papillomavirus DNA in nongenital seborrheic keratosis. *Br J Dermatol*. 2004;151(5):1060–5.
- 55 Tardío JC, Bancalari E, Moreno A, Martín-Fragueiro LM. Genital seborrheic keratoses are human papillomavirus-related lesions. A linear array genotyping test study. *Apmis*. 2012;120(6):477–83.
- 56 Wu YH, Hsiao PF, Chen CK. Seborrheic keratosis with bowenoid transformation: the immunohistochemical features and its association with human papillomavirus infection. *Am J Dermatopathol*. 2015;37(6):462–8.
- 57 Forslund O, Lindelöf B, Hradil E, Nordin P, Stenquist B, Kirnbauer R, et al. High prevalence of cutaneous human papillomavirus DNA on the top of skin tumors but not in “Stripped” biopsies from the same tumors. *J Invest Dermatol*. 2004;123(2):388–94.
- 58 Lee ES, Whang MR, Kang WH. Absence of human papillomavirus DNA in nongenital seborrheic keratosis. *J Korean Med Sci*. 2001; 16(5):619–22.
- 59 Reutter JC, Geisinger KR, Laudadio J. Vulvar seborrheic keratosis: is there a relationship to human papillomavirus?. *J Low Genit Tract Dis*. 2014;18(2):190–4.
- 60 Kambiz KH, Kaveh D, Maede D, Hossein A, Nessa A, Ziba R, et al. Human papillomavirus deoxyribonucleic acid may not be detected in non-genital benign papillomatous skin lesions by polymerase chain reaction. *Indian J Dermatol*. 2014;59(4):334–8.
- 61 Hillen LM, Rennspieß D, Speel EJ, Haugg AM, Winnepeninckx V, Zur Hausen A. Detection of Merkel Cell Polyomavirus in Seborrheic Keratosis. *Front Microbiol*. 2017;8: 2648.
- 62 Yamanaka-Takaichi M, Sugawara K, Sumitomo R, Tsuruta D. The Mast Cell-SCF-CB1 Interaction Is a Key Player in Seborrheic Keratosis. *J Histochem Cytochem*. 2020;68(7): 461–71.
- 63 Takenaka Y, Hoshino Y, Nakajima H, Hayashi N, Kawashima M, Imokawa G. Paracrine cytokine mechanisms underlying the hyperpigmentation of seborrheic keratosis in covered skin areas. *J Dermatol*. 2013;40(7):533–42.
- 64 Manaka L, Kadono S, Kawashima M, Kobayashi T, Imokawa G. The mechanism of hyperpigmentation in seborrheic keratosis involves the high expression of endothelin-converting enzyme-1 α and TNF- α , which stimulate secretion of endothelin 1. *Br J Dermatol*. 2001;145(6):895–903.
- 65 Peng F, Xue CH, Hwang SK, Li WH, Chen Z, Zhang JZ. Exposure to fine particulate matter associated with senile lentigo in Chinese women: a cross-sectional study. *J Eur Acad Dermatol Venereol*. 2017;31(2):355–60.
- 66 Kantor R, Kim A, Thyssen JP, Silverberg JL. Association of atopic dermatitis with smoking: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2016;75(6):1119–e1.
- 67 Armstrong AW, Harskamp CT, Dhillon JS, Armstrong EJ. Psoriasis and smoking: a systematic review and meta-analysis. *Br J Dermatol*. 2014;170(2):304–14.
- 68 Speyer CB, Costenbader KH. Cigarette smoking and the pathogenesis of systemic lupus erythematosus. *Expert Rev Clin Immunol*. 2018;14(6):481–7.
- 69 Hafner C, Hartmann A, Real FX, Hofstaedter F, Landthaler M, Vogt T. Spectrum of FGFR3 mutations in multiple intraindividual seborrheic keratoses. *J Invest Dermatol*. 2007; 127(8):1883–5.
- 70 Hafner C, van Oers JM, Hartmann A, Landthaler M, Stoehr R, Blaszyk H, et al. High frequency of FGFR3 mutations in adenoid seborrheic keratoses. *J Invest Dermatol*. 2006; 126(11):2404–7.
- 71 Logié A, Dunois-Lardé C, Rosty C, Levrel O, Blanche M, Ribeiro A, et al. Activating mutations of the tyrosine kinase receptor FGFR3 are associated with benign skin tumors in mice and humans. *Hum Mol Genet*. 2005; 14(9):1153–60.
- 72 Nakanishi Y, Akiyama N, Tsukaguchi T, Fujii T, Satoh Y, Ishii N, et al. Mechanism of Oncogenic Signal Activation by the Novel Fusion Kinase FGFR3-BAIAP2L1. *Mol Cancer Ther*. 2015;14(3):704–12.

- 73 Costa R, Carneiro BA, Taxter T, Tavora FA, Kalyan A, Pai SA, et al. FGFR3-TACC3 fusion in solid tumors: mini review. *Oncotarget*. 2016;7(34):55924–38.
- 74 Czyz M. Fibroblast Growth Factor Receptor Signaling in Skin Cancers. *Cells*. 2019;8(6).
- 75 Hida Y, Kubo Y, Arase S. Activation of fibroblast growth factor receptor 3 and oncogene-induced senescence in skin tumours. *Br J Dermatol*. 2009;160(6):1258–63.
- 76 Duperret EK, Oh SJ, McNeal A, Prouty SM, Ridky TW. Activating FGFR3 mutations cause mild hyperplasia in human skin, but are insufficient to drive benign or malignant skin tumors. *Cell Cycle*. 2014;13(10):1551–9.
- 77 Mandinova A, Kolev V, Neel V, Hu B, Stonely W, Lieb J, et al. A positive FGFR3/FOXN1 feedback loop underlies benign skin keratosis versus squamous cell carcinoma formation in humans. *J Clin Invest*. 2009;119(10):3127–37.
- 78 Heidenreich B, Denisova E, Rachakonda S, Sanmartin O, Dereani T, Hosen I, et al. Genetic alterations in seborrheic keratoses. *Oncotarget*. 2017;8(22):36639–49.
- 79 Meyer M, Ben-Yehuda Greenwald M, Rauschendorfer T, Sanger C, Jukic M, Iizuka H, et al. Mouse genetics identifies unique and overlapping functions of fibroblast growth factor receptors in keratinocytes. *J Cell Mol Med*. 2020;24(2):1774–85.
- 80 Groves RW, Allen MH, MacDonald DM. Abnormal expression of epidermal growth factor receptor in cutaneous epithelial tumours. *J Cutan Pathol*. 1992;19(1):66–72.
- 81 Nanney LB, Ellis DL, Levine J, King LE. Epidermal growth factor receptors in idiopathic and virally induced skin diseases. *Am J Pathol*. 1992;140(4):915–25.
- 82 Hafner C, López-Knowles E, Luis NM, Toll A, Baselga E, Fernández-Casado A, et al. Oncogenic PIK3CA mutations occur in epidermal nevi and seborrheic keratoses with a characteristic mutation pattern. *Proc Natl Acad Sci U S A*. 2007;104(33):13450–4.
- 83 Hafner C, Landthaler M, Mentzel T, Vogt T. FGFR3 and PIK3CA mutations in stucco keratosis and dermatosis papulosa nigra. *Br J Dermatol*. 2010;162(3):508–12.
- 84 Hafner C, Toll A, Fernández-Casado A, Earl J, Marqués M, Acquadro F, et al. Multiple oncogenic mutations and clonal relationship in spatially distinct benign human epidermal tumors. *Proc Natl Acad Sci U S A*. 2010;107(48):20780–5.
- 85 Simionescu O, Popescu BO, Costache M, Manole E, Spulber S, Gherghiceanu M, et al. Apoptosis in seborrheic keratoses: an open door to a new dermoscopic score. *J Cell Mol Med*. 2012;16(6):1223–31.
- 86 Omman RA, Speiser J, Robinson S, Lapadat R, Mudaliar K. Clonal highlights: Clonal seborrheic keratoses often demonstrates p16 expression. *J Cutan Pathol*. 2019;46(6):411–7.
- 87 Bruecks AK, Kalia S, Trotter MJ. Overexpression of p27KIP1 in seborrheic keratosis. *J Cutan Med Surg*. 2007;11(5):174–8.
- 88 Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. *Cell*. 2007;129(7):1261–74.
- 89 Neel VA, Todorova K, Wang J, Kwon E, Kang M, Liu Q, et al. Sustained Akt Activity Is Required to Maintain Cell Viability in Seborrheic Keratosis, a Benign Epithelial Tumor. *J Invest Dermatol*. 2016;136(3):696–705.
- 90 Smolyannikova VA, Aleksandrova AK. [Impaired expression of cell-cycle regulatory proteins in seborrheic keratosis]. *Arkh Patol*. 2020;82(2):30–4.
- 91 Bahrani E, Sithinamsuwan P, McCalmont TH, Pincus LB. Ki-67 and p16 Immunostaining Differentiates Pagetoid Bowen Disease from “Microclonal” Seborrheic Keratosis. *Am J Clin Pathol*. 2019;151(6):551–60.
- 92 Nasiri S, Azhari V, Bidari-Zerehpoush F, Asadi-Kani Z, Talebi A. The diagnostic value of p63, p16, and p53 immunohistochemistry in distinguishing seborrheic keratosis, actinic keratosis, and Bowen’s disease. *Dermatol Ther*. 2021;34(2):e14817.
- 93 Adashek JJ, Kato S, Lippman SM, Kurzrock R. The paradox of cancer genes in non-malignant conditions: implications for precision medicine. *Genome Med*. 2020;12(1):16.
- 94 Kato S, Lippman SM, Flaherty KT, Kurzrock R. The Conundrum of Genetic “Drivers” in Benign Conditions. *J Natl Cancer Inst*. 2016;108(8):djw036.
- 95 Carrera C, Segura S, Aguilera P, Takigami CM, Gomes A, Barreiro A, et al. Dermoscopy improves the diagnostic accuracy of melanomas clinically resembling seborrheic keratosis: cross-sectional study of the ability to detect seborrheic keratosis-like melanomas by a group of dermatologists with varying degrees of experience. *Dermatology*. 2017;233(6):471–9.
- 96 Minagawa A. Dermoscopy-pathology relationship in seborrheic keratosis. *J Dermatol*. 2017;44(5):518–24.
- 97 Heal CF, Raasch BA, Buettner PG, Weedon D. Accuracy of clinical diagnosis of skin lesions. *Br J Dermatol*. 2008;159(3):661–8.
- 98 Mohammad EA, Mansour M, Parichehr K, Farideh D, Amirhossein R, Ahmad SA. Assessment of clinical diagnostic accuracy compared with pathological diagnosis of basal cell carcinoma. *Indian Dermatol Online J*. 2015;6(4):258–62.
- 99 Weber P, Tschandl P, Sinz C, Kittler H. Dermatoscopy of neoplastic skin lesions: recent advances, updates, and revisions. *Curr Treat Options Oncol*. 2018;19(11):56.
- 100 Gülseren D, Hofmann-Wellenhof R. Evaluation of dermoscopic criteria for seborrheic keratosis on non-polarized versus polarized dermoscopy. *Skin Res Technol*. 2019;25(6):801–4.
- 101 Argenziano G, Soyer HP, Chimenti S, Talamini R, Corona R, Sera F, et al. Dermoscopy of pigmented skin lesions: Results of a consensus meeting via the Internet. *J Am Acad Dermatol*. 2003;48(5):679–93.
- 102 Braun RP, Rabinovitz HS, Krischer J, Kreusch J, Oliviero M, Naldi L, et al. Dermoscopy of pigmented seborrheic keratosis: a morphological study. *Arch Dermatol*. 2002;138(12):1556–60.
- 103 Malvey J, Puig S, Argenziano G, Marghoob AA, Soyer HP. Dermoscopy report: Proposal for standardization: Results of a consensus meeting of the International Dermoscopy Society. *J Am Acad Dermatol*. 2007;57(1):84–95.
- 104 Lin J, Han S, Cui L, Song Z, Gao M, Yang G, et al. Evaluation of dermoscopic algorithm for seborrheic keratosis: a prospective study in 412 patients. *J Eur Acad Dermatol Venereol*. 2014;28(7):957–62.
- 105 Takenouchi T. Key points in dermoscopic diagnosis of basal cell carcinoma and seborrheic keratosis in Japanese. *J Dermatol*. 2011;38(1):59–65.
- 106 Sakakibara A, Kamijima M, Shibata S, Yasue S, Kono M, Tomita Y. Dermoscopic evaluation of vascular structures of various skin tumors in Japanese patients. *J Dermatol*. 2010;37(4):316–22.
- 107 Zalaudek I, Kreusch J, Giacomel J, Ferrara G, Catricalà C, Argenziano G. How to diagnose nonpigmented skin tumors: A review of vascular structures seen with dermoscopy: Part II. Nonmelanocytic skin tumors. *J Am Acad Dermatol*. 2010;63(3):377–86.
- 108 Carrera C, Segura S, Aguilera P, Scalvenzi M, Longo C, Barreiro A, et al. Dermoscopic clues for diagnosing melanomas that resemble seborrheic keratosis. *JAMA Dermatol*. 2017;153(6):544–51.
- 109 Dinnes J, Deeks JJ, Chuchu N, Ferrante di Ruffano L, Matin RN, Thomson DR, et al. Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults. *Cochrane Database Syst Rev*. 2018;12(12):CD011902.
- 110 Papageorgiou C, Spyridis I, Manoli SM, Busila I, Nasturica IE, Lallas K, et al. Accuracy of dermoscopic criteria for the differential diagnosis between irritated seborrheic keratosis and squamous cell carcinoma. *J Am Acad Dermatol*. 2020;S0190-9622(20)30227-9.
- 111 Mazzeo M, Manfreda V, Diluvio L, Dattola A, Bianchi L, Campione E. Dermoscopic Analysis of 72 “Atypical” Seborrheic Keratoses. *Actas Dermosifiliogr*. 2019;110(5):366–71.
- 112 Rubegni P, Feci L, Nami N, Burrioni M, Taddeucci P, Miracco C, et al. Computer-assisted melanoma diagnosis: a new integrated system. *Melanoma Res*. 2015;25(6):537–42.
- 113 Winkelmann RR, Farberg AS, Tucker N, White R, Rigel DS. Enhancement of International Dermatologists’ Pigmented Skin Lesion Biopsy Decisions following Dermoscopy with Subsequent Integration of Multi-spectral Digital Skin Lesion Analysis. *J Clin Aesthet Dermatol*. 2016;9(7):53–5.

- 114 Ahlgrim-Siess V, Cao T, Oliviero M, Laimer M, Hofmann-Wellenhof R, Rabinovitz HS, et al. Seborrheic keratosis: reflectance confocal microscopy features and correlation with dermoscopy. *J Am Acad Dermatol*. 2013;69(1):120–6.
- 115 Longo C, Zalaudek I, Argenziano G, Pellacani G. New directions in dermatopathology: in vivo confocal microscopy in clinical practice. *Dermatol Clin*. 2012;4(30):799–814, viii.
- 116 Pellacani G, Pepe P, Casari A, Longo C. Reflectance confocal microscopy as a second-level examination in skin oncology improves diagnostic accuracy and saves unnecessary excisions: a longitudinal prospective study. *Br J Dermatol*. 2014;171(5):1044–51.
- 117 Gill M, González S. Enlightening the Pink: Use of Confocal Microscopy in Pink Lesions. *Dermatol Clin*. 2016;34(4):443–58.
- 118 Pezzini C, Mandel VD, Persechini F, Ciardo S, Kaleci S, Chester J, et al. Seborrheic keratoses mimicking melanoma unveiled by in vivo reflectance confocal microscopy. *Skin Res Technol*. 2018;24(2):285–93.
- 119 Navarrete-Dechent C, DeRosa AP, Longo C, Liopyris K, Oliviero M, Rabinovitz H, et al. Reflectance confocal microscopy terminology glossary for nonmelanocytic skin lesions: A systematic review. *J Am Acad Dermatol*. 2019;80(5):1414–e3.
- 120 Guo A, Chen J, Yang C, Ding Y, Zeng Q, Tan L. The challenge of diagnosing seborrheic keratosis by reflectance confocal microscopy. *Skin Res Technol*. 2018;24(4):663–6.
- 121 Shahriari N, Grant-Kels JM, Rabinovitz HS, Oliviero M, Scope A. In vivo reflectance confocal microscopy features of a melanoacanthoma. *Dermatol Pract Concept*. 2016;6(4):27–30.
- 122 Tang Z, Huang J, Lu J, Chen J, Guo A, Ding S. Application and challenge of reflectance confocal microscopy in the diagnosis of pigmented nevus. *Skin Res Technol*. 2020;26(5):690–5.
- 123 Porto ACS, Blumetti TP, Macedo MP, Braga JCT. Melanoacanthoma: a potential pitfall of reflectance confocal microscopy. *An Bras Dermatol*. 2019;94(6):747–50.
- 124 Oliveira A, Zalaudek I, Arzberger E, Hofmann-Wellenhof R. Seborrheic keratosis imaging in high-definition optical coherence tomography, with dermoscopic and reflectance confocal microscopic correlation. *J Eur Acad Dermatol Venereol*. 2017;31(2):e125–7.
- 125 Forouzandeh M, Rajabi-Estarabadi A, Williams NM, Avanaki MRN, Nouri K. The efficacy and morphological effects of hydrogen peroxide 40% topical solution for the treatment of seborrheic keratoses, evaluated by dynamic optical coherence tomography. *Skin Res Technol*. 2020;26(1):142–5.
- 126 Serban ED, Farnetani F, Pellacani G, Constantin MM. Role of in vivo reflectance confocal microscopy in the analysis of melanocytic lesions. *Acta Dermatovenereol Croat*. 2018;26(1):64–7.
- 127 Lihachev A, Lihacova I, Plorina EV, Lange M, Derjabo A, Spigulis J. Differentiation of seborrheic keratosis from basal cell carcinoma, nevi and melanoma by RGB autofluorescence imaging. *Biomed Opt Express*. 2018;9(4):1852–8.
- 128 Wang S, Zhao J, Lui H, He Q, Zeng H. In vivo near-infrared autofluorescence imaging of pigmented skin lesions: methods, technical improvements and preliminary clinical results. *Skin Res Technol*. 2013;19(1):20–6.
- 129 Gniadecka M, Philipsen PA, Sigurdsson S, Wessel S, Nielsen OF, Christensen DH, et al. Melanoma diagnosis by Raman spectroscopy and neural networks: structure alterations in proteins and lipids in intact cancer tissue. *J Invest Dermatol*. 2004;122(2):443–9.
- 130 Bratchenko IA, Bratchenko LA, Moryatov AA, Khristoforova YA, Artemyev DN, Myakinin OO, et al. In vivo diagnosis of skin cancer with a portable Raman spectroscopic device. *Exp Dermatol*. 2021;30(5):652–63.
- 131 Cholewicka A, Stanek A, Kwiatek S, Sieroń A, Drzazga Z. Does the temperature gradient correlate with the photodynamic diagnosis parameter numerical colour value (NCV)? *Photodiagnosis Photodyn Ther*. 2013;10(1):33–8.
- 132 Marchetti MA, Liopyris K, Dusza SW, Codella NCF, Gutman DA, Helba B, et al. Computer algorithms show potential for improving dermatologists' accuracy to diagnose cutaneous melanoma: Results of the International Skin Imaging Collaboration 2017. *J Am Acad Dermatol*. 2020;82(3):622–7.
- 133 Liu Y, Jain A, Eng C, Way DH, Lee K, Bui P, et al. A deep learning system for differential diagnosis of skin diseases. *Nat Med*. 2020;26(6):900–8.
- 134 Tschandl P, Codella N, Akay BN, Argenziano G, Braun RP, Cabo H, et al. Comparison of the accuracy of human readers versus machine-learning algorithms for pigmented skin lesion classification: an open, web-based, international, diagnostic study. *Lancet Oncol*. 2019;20(7):938–47.
- 135 Hosny KM, Kassem MA, Foad MM. Classification of skin lesions using transfer learning and augmentation with Alex-net. *PLoS One*. 2019;14(5):e0217293.
- 136 Lai Z, Deng H. Medical image classification based on deep features extracted by deep model and statistic feature fusion with multilayer perceptron. *Comput Intell Neurosci*. 2018;2018:2061516.
- 137 Al-Masni MA, Al-Antari MA, Choi MT, Han SM, Kim TS. Skin lesion segmentation in dermoscopy images via deep full resolution convolutional networks. *Comput Methods Programs Biomed*. 2018;162:221–31.
- 138 Han SS, Kim MS, Lim W, Park GH, Park I, Chang SE. Classification of the clinical images for benign and malignant cutaneous tumors using a deep learning algorithm. *J Invest Dermatol*. 2018;138(7):1529–38.
- 139 Shimizu K, Iyatomi H, Celebi ME, Norton KA, Tanaka M. Four-class classification of skin lesions with task decomposition strategy. *IEEE Trans Biomed Eng*. 2015;62(1):274–83.
- 140 Jinnai S, Yamazaki N, Hirano Y, Sugawara Y, Ohe Y, Hamamoto R. The development of a skin cancer classification system for pigmented skin lesions using deep learning. *Biomolecules*. 2020;10(8).
- 141 Chang WY, Huang A, Yang CY, Lee CH, Chen YC, Wu TY, et al. Computer-aided diagnosis of skin lesions using conventional digital photography: a reliability and feasibility study. *PLoS One*. 2013;8(11):e76212.
- 142 Cascinelli N, Ferrario M, Bufalino R, Zurrida S, Galimberti V, Mascheroni L, et al. Results obtained by using a computerized image analysis system designed as an aid to diagnosis of cutaneous melanoma. *Melanoma Res*. 1992;2(3):163–70.
- 143 Huang K, He X, Jin Z, Wu L, Zhao X, Wu Z, et al. Assistant diagnosis of basal cell carcinoma and seborrheic keratosis in Chinese population using convolutional neural network. *J Healthc Eng*. 2020;2020:1713904.
- 144 Serte S, Demirel H. Gabor wavelet-based deep learning for skin lesion classification. *Comput Biol Med*. 2019;113:103423.
- 145 Mahbod A, Schaefer G, Ellinger I, Ecker R, Pitiot A, Wang C. Fusing fine-tuned deep features for skin lesion classification. *Comput Med Imaging Graph*. 2019;71:19–29.
- 146 Esteve A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature*. 2017;542(7639):115–8.
- 147 Molinar VE, Taylor SC, Pandya AG. What's new in objective assessment and treatment of facial hyperpigmentation? *Dermatol Clin*. 2014;32(2):123–35.
- 148 Garcia MS, Azari R, Eisen DB. Treatment of dermatosis papulosa nigra in 10 patients: a comparison trial of electrodesiccation, pulsed dye laser, and curettage. *Dermatol Surg*. 2010;36(12):1968–72.
- 149 Kao S, Kiss A, Efimova T, Friedman AJ. Managing seborrheic keratosis: evolving strategies and optimal therapeutic outcomes. *J Drugs Dermatol*. 2018;17(9):933–40.
- 150 Baumann LS, Blauvelt A, Draelos ZD, Kempers SE, Lupo MP, Schlessinger J, et al. Safety and efficacy of hydrogen peroxide topical solution, 40% (w/w), in patients with seborrheic keratoses: Results from 2 identical, randomized, double-blind, placebo-controlled, phase 3 studies (A-101-SEBK-301/302). *J Am Acad Dermatol*. 2018;79(5):869–77.
- 151 Keaney T. Eskata (40% hydrogen peroxide solution) for the treatment of seborrheic keratoses. *J Drugs Dermatol*. 2019;18(7):s172.

- 152 Aclaris Therapeutics. Aclaris Therapeutics Reports Second Quarter 2019 Financial Results, Provides Business Strategy Update and Provides Update on Clinical and Commercial Developments. 2019 [cited 2021]. Available from: <https://investor.aclaristx.com/news-releases/news-release-details/aclaris-therapeutics-reports-second-quarter-2019-financial>.
- 153 Lacarrubba F, Nasca MR, Verzi AE, Micali G. A novel topical agent in the treatment of seborrheic keratoses: A proof of concept study by clinical and dermoscopic evaluation. *Dermatol Ther*. 2017;30(5):e12526.
- 154 Tribó MJ, Aladren S, Garre A, Granger C. A novel Nitrizinc Complex[®] solution for topical treatment of seborrheic keratosis: an interventional clinical study. *Eur J Dermatol*. 2019;29(2):203–8.
- 155 Levy-Nissenbaum E, Thio HB, Burstein P, Thaci D. Seborrheic keratosis removal in a multicentre phase I/II clinical trial using a novel topical formulation (BL-5010). *Br J Dermatol*. 2015;173(1):247–9.
- 156 Chun EY, Lee JB, Lee KH. Focal trichloroacetic acid peel method for benign pigmented lesions in dark-skinned patients. *Dermatol Surg*. 2004;30(4 Pt 1):512–6; discussion 516.
- 157 Herron MD, Bowen AR, Krueger GG. Seborrheic keratoses: a study comparing the standard cryosurgery with topical calcipotriene, topical tazarotene, and topical imiquimod. *Int J Dermatol*. 2004;43(4):300–2.
- 158 Klaus MV, Wehr RF, Rogers RS, Russell TJ, Krochmal L. Evaluation of ammonium lactate in the treatment of seborrheic keratoses. *J Am Acad Dermatol*. 1990;22(2 Pt 1):199–203.
- 159 Cuevas P, Angulo J, Salguero I, Giménez-Gallego G. Clearance of seborrheic keratoses with topical dobesilate. *BMJ Case Rep*. 2012;2012.
- 160 Karadag AS, Ozlu E, Uzuncakmak TK, Akdeniz N, Cobanoglu B, Oman B. Inverted follicular keratosis successfully treated with imiquimod. *Indian Dermatol Online J*. 2016;7(3):177–9.
- 161 Aktaş H, Ergin C, Keseroğlu HÖ. Diclofenac gel may be a new treatment option for seborrheic keratosis. *Indian Dermatol Online J*. 2016;7(3):211–2.
- 162 Wat H, Dytoc M. Off-label uses of topical vitamin D in dermatology: a systematic review. *J Cutan Med Surg*. 2014;18(2):91–108.
- 163 Takekawa C, Fukumoto T, Haraoka G, Terashi H. Combination treatment algorithm for pigmentary disorders of the face: A prospective observational study in Asian patients. *J Plast Reconstr Aesthet Surg*. 2021;74(2):370–76.
- 164 Furukawa F, Mizawa M, Shimizu T. Treatment of dermatosis papulosa nigra using a carbon dioxide laser. *J Cosmet Dermatol*. 2020;19(10):2572–75.
- 165 Bruscinio N, Conti R, Campolmi P, Bonan P, Cannarozzo G, Lazzeri L, et al. Dermatitis Papulosa Nigra and 10,600-nm CO₂ laser, a good choice. *J Cosmet Laser Ther*. 2014;16(3):114–6.
- 166 Ali FR, Bakkour W, Ferguson JE, Madan V. Carbon dioxide laser ablation of dermatosis papulosa nigra: high satisfaction and few complications in patients with pigmented skin. *Lasers Med Sci*. 2016;31(3):593–5.
- 167 Lee JP, Kim YJ. A Case of irritated seborrheic keratosis associated with a previous incision site. *Korean J Ophthalmol*. 2010;24(3):173–4.
- 168 Cevizci R, Bezgin SÜ, Altın G, Oran G, Bayazıt YA. Treatment of seborrheic keratosis in bilateral external auditory canal using fiber CO₂ laser. *Kulak Burun Bogaz Ihtis Derg*. 2016;26(5):304–6.
- 169 Gurel MS, Aral BB. Effectiveness of erbium: YAG laser and cryosurgery in seborrheic keratoses: Randomized, prospective intraindividual comparison study. *J Dermatolog Treat*. 2015;26(5):477–80.
- 170 Kundu RV, Joshi SS, Suh KY, Boone SL, Huggins RH, Alam M, et al. Comparison of electrodesiccation and potassium-titanylphosphate laser for treatment of dermatosis papulosa nigra. *Dermatol Surg*. 2009;35(7):1079–83.
- 171 Schweiger ES, Kwasniak L, Aires DJ. Treatment of dermatosis papulosa nigra with a 1064 nm Nd:YAG laser: report of two cases. *J Cosmet Laser Ther*. 2008;10(2):120–2.
- 172 Katz TM, Goldberg LH, Friedman PM. Dermatitis papulosa nigra treatment with fractional photothermolysis. *Dermatol Surg*. 2009;35(11):1840–3.
- 173 Piccolo D, Di Marcantonio D, Crisman G, Cannarozzo G, Sannino M, Chiricozzi A, et al. Unconventional use of intense pulsed light. *Biomed Res Int*. 2014;2014:618206.
- 174 Tran M, Richer V. Elective treatment of dermatosis papulosa nigra: a review of treatment modalities. *Skin Therapy Lett*. 2020;25(4):1–5.
- 175 Zhang H, Wei G, Zhang C, Xu Q, Zhang C. Aminolevulinic photodynamic therapy (ALA-PDT) for giant seborrheic keratosis of the head: A case report. *Photodiagnosis Photodyn Ther*. 2020;32:102015.
- 176 DuBois J, Grande K, Rhodes T, Schnyder J, Shanler SD. Assessing patients' satisfaction with hydrogen peroxide topical solution, 40% for treatment of raised seborrheic keratoses. *J Drugs Dermatol*. 2020;19(12):1184–91.
- 177 Wood LD, Stucki JK, Hollenbeak CS, Miller JJ. Effectiveness of cryosurgery vs curettage in the treatment of seborrheic keratoses. *JAMA Dermatol*. 2013;149(1):108–9.