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Review Article

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The Association between Actinic Keratosis and Squamous Cell Carcinoma: A Comprehensive Narrative Review

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Abstract

Actinic keratosis is the predecessor that advances to becoming obtrusive squamous cell carcinoma. It is identified in 97% of squamous cell carcinomas as an underlining disease. Actinic keratosis holds great significance since substantial mortality rates every year occur in the count of undetected Squamous cell carcinoma [1]. Therefore, early detection via screening is crucial at an early state of Actinic keratosis, which is efficiently treatable and less invasive; especially before the lesion progress towards becoming squamous cell carcinoma with a less favorable prognosis.

The transformation and the association between these two lesions were spotted in the literature since the 19th century. Picascia and Robinson stated that squamous cell carcinoma of the lip is firmly associated with actinic keratosis, in which they are alike in most epidemiological data [2]. Further, in the late 19th century, Marks raised awareness of the fact that many carcinomas may resemble actinic keratosis [3].

This review addresses screening efficiency and controversies regarding the malignant potential of actinic keratosis. It is well established within the field specialists that actinic keratosis may progress to become invasive squamous cell carcinoma. However, it is still not known which histological subtypes are most susceptible towards transforming into an invasive malignancy. Thus, screening is crucial and potentially a life-saving process.

Also, this review addresses the current and the more profound evidence of the link between the evolvement of actinic keratosis and early-stage squamous cell carcinomas. Nevertheless, many have argued regarding the rate of malignant transformation, the efficiency and adequateness of screening, and the cost-effectiveness of early treatment of actinic keratosis. All have raised considerable debate within the field, in addition to recapitulating the similarities between the two lesions and describing the lesions by providing background, recognizing the clinical appearance, effectiveness of screening, manifestations, pathogenesis, and genetics involved to have profound reasoning for the importance of fully understanding the so-called differences between the two lesions.

Keywords: Actinic Keratosis, Oral Squamous Cell Carcinoma, Similarity, Clinical Manifestation, Histologic Appearance, Screening, Pathogenesis, Future View, Genetics, and Financial Implications.

Methodology

A search strategy based on the keywords "Actinic Keratosis, Oral squamous cell carcinoma, similarity, Clinical manifestation, histologic appearance, screening, Pathogenesis, Future view, genetics, and financial implications". was performed in various search engines, such as PubMed, NIH Public Access, Scopus, Google Scholar, Clarivate Analytics, and Cochrane Database of Systematic Reviews. Papers published between 1968 and December 2021 were scrutinized. Only articles that describe the terminology of Medical Subject Headings were selected, then obtained in full text and analyzed.

Background

Oral Squamous Cell Carcinoma

Oral cancer is a heterogeneous group of epithelial malignancies of the head and the neck. It originates from the mucosa of the oral cavity, pharynx, larynx, paranasal sinus, and nasal cavity, with a wide epidemiologic variety between various geographic populations [4]. Nonetheless, 95% of all oral cancer is squamous cell carcinoma, the eighth most occurring oral cancer. In the recent decade, the oral cancer incident rate has been increasing on a global scale, especially in underdeveloped countries. In addition, it possesses the lowest survival rate of 48-59% in five to ten years. Unfortunately, oral squamous cell carcinoma persisted without any significant changes in mortalities in the last 50 years [5].

Oral squamous cell carcinoma holds a multifactorial aetiology along with a well-established predisposing factor such as betel quid and tobacco chewing, excess consumption of alcohol, and prolonged exposure to ultraviolet rays. Notably, in the early stages, signs and symptoms are difficult to detect. However, some main symptoms are failure to heal sores, mobility of teeth without a visible cause, abnormal bleeding, Lymphadenopathy, and chronic earache. Nevertheless, most signs and symptoms in the early stages are painless and asymptomatic [6]. In particular, smoking and alcohol consumption are the major risk factors despite the denial of few studies about any relationship amongst survival rate and smoking. In addition, betel quid use is another crucial hazardous predisposing factor [7, 4].

Actinic Keratosis

Actinic Keratosis is a dysplastic epidermal anomaly and a potential precursor of squamous cell carcinoma. It is mostly well-recognized clinically and less often acknowledged histologically. It mostly appears on the lower lip and is seen as dryness, scaling, and epithelial erosion. White-skinned individuals (Caucasians) are more susceptible to this condition than those with darker skin [8, 9].

A blend of hereditary tendency and chronic solar exposure are the most imperative predisposing factors. Their occurrence rate rises with progressed age. Therefore, it occurs generally in people who are routinely unprotected from daylight radiation. Since the lower vermilion is more susceptible to a straightforward beam of sun radiation, the main affected site of actinic cheilitis is -as a rulethe lower lip, rather than the upper lip, which is infrequently affected; naturally shielded from the sun rays [1]. Actinic keratosis manifests on the skin as a flesh coloured papule or plaque that is dry and erythematous and often has telangiec tasia, typically covered with brown or yellow adhering scales. It can appear singularly but more commonly develops in clusters. Actinic keratosis occurs in different proportions among people of different races, classes, sexes, ages, skin types, and places of birth [10, 11].

According to various studies, Actinic keratosis and skin cancer prevalence are significantly influenced by the type of skin. It has been demonstrated that those with a skin photo type of 1-3 are more likely to develop actinic keratosis. In addition, sixty per cent of adults over 40 with photo types I, II, or III skin will present a minimum of one Actinic keratosis, and this number rises to 80% of people over 60. Within the next 10-25 years, around 5–20 per cent of these lesions will develop into Squamous cell carcinoma [3].

The development of Squamous cell carcinoma has been connected to various well-known risk factors. They consist of the patient's skin type, the degree to which they have been harmed by the sun, and whether they are immunocompromised. In addition, several studies have demonstrated that sun-exposed skin, Actinic keratosis, and Squamous cell carcinoma all display mutations and alterations in gene expression brought on by UV radiation. Atypical keratosis is often the first lesion in the course of a disease that eventually leads to aggressive Squamous cell carcinoma. A variety of patient-related factors affect the likelihood that actinic keratosis will advance to Squamous cell carcinoma. Patients who have a history of extensive sun exposure, immuno-suppression, or advanced age have a greater chance of undergoing metastasis [12]. Actinic keratosis, Squamous cell carcinoma, and BCC are more likely to develop in patients using immuno-suppressant therapy for organ transplants, autoimmune illnesse.

Research suggests that sunscreen can slow the progression of actinic keratosis and Squamous cell carcinoma and even cause some cases to go into remission [13]. Sunscreen use has been proven to reduce the risk of actinic keratosis developing into Squamous cell carcinoma in clinical trials, arguing that using sunscreen routinely has decreased the likelihood of actinic neoplasia [14].

Clinical and Histologic Appearance

Oral Squamous Cell Carcinoma

The lesion appears clinically as well-defined, erythematous plaque in the initial primary stage. While the more invasive form of oral cancer may penetrate the basement membrane to become, nodular or plaque-like seen clinically as hyperkeratosis due to a variable quantity of keratin production, which may eventually ulcerate. Oral cancer can be divided into three categories: carcinomas of the lip vermilion (hard to distinguish from Actinic Keratosis), carcinomas of the oral cavity, and carcinomas arising in the oropharynx region [15, 8].

Actinic Keratosis

Actinic keratosis appears as limited and erythematous, And it papules with a hyperkeratotic surface. Distinguishable clinically as, a zone of a roughened surface of the skin. A few lesions of Actinic Keratoses may relapse suddenly. Actinic Keratosis is readily deductible by palpation and visual inspection. Additionally, it is distinctively seen in sun-uncovered body parts, and surrounding areas may indicate confirmation of sun-influenced harm. Contingent upon their thickness, there are five subtypes of Actinic Keratosis, which include acantholytic, hypertrophic, pigmented, atrophic, and Bowenoid [1].

The lesions appear pigmented, have abnormal redness, or are marked by thickening of the outer layer of the skin. They can sometimes actinic keratosise the form of plaques. Assessments obtained through palpation are frequently more accurate than those obtained solely through visual inspection when identifying Actinic keratosis. However, even though Actinic keratosis can typically be recognized based on the outward appearance of a lesion, there are situations in which Actinic keratosis cannot be distinguished from clinically aggressive squamous cell carcinoma (Squamous cell carcinoma). Therefore, under actinic keratosising skin biopsy is vital when differentiating between the two [16].

Histologic Appearance of Actinic Keratosis

Actinic keratosis is described in a current textbook on surgical pathology as the delimited proliferation of histologically atypical keratinocyte cells with concurrent changes in the keratinization process. The nuclei of individual keratinocytes have been described as packed, pleomorphic, and enlarged. The cytoplasm is eosinophilic. The epidermis thickens (acanthosis) as the number of neoplastic cells in the epidermis rises. Eventually, the lesions could become clinically apparent as a result of this. Neoplastic cells could subsequently separate from the epidermis and appear in the dermis as tumour nests. Squamous cell carcinomas that enter the dermis have identical histological alterations to actinic keratosis cells [17].

Detection of the Lesion "Screening"

Oral Squamous Cell Carcinoma

"The oral cavity is an easily accessible site for screening by doctors, nurses, and health workers or for self-examination" [18]. Visual screening is the most appropriate way to recognize early oral cancer, if provided as a part of periodic checkups. The affectability of oral, visual investigation to recognize neoplastic differences changed from 57.7%–61.4% in past studies. However, Yeole et al., stated a specificity rate of 98.6 to 98.8% in recent publications [19]. Early detected cases of oral malignancy have a superior survival rate than those detected at late stages.

Prevention and early detections are the foundations to best control oral and head and neck neoplasms. Early recognition relies on observing the current manifestation in the initial periods, which can be done by clinician or patients themselves who may recognize a suspicious or continues growth. Nonetheless, in conducting routine oral examinations, it is evident that numerous clinicians, including dental specialists may overlook the predisposing components, performing initial working diagnosis, and early identification of growth and tumors [15].

The precancerous lesions and early intrusive growths are recognizable. Thus, screening for oral neoplasm may be extremely valuable. This will also enhance survival rate if treated at an initial progression state. As indicated by Neville and Day, visual oral investigation is a straightforward, worthy, and efficient screening technique for identifying oral neoplasia [15]. Meanwhile, other authors argued about the efficiency of the visual examination-based screening program in prompting a considerable decrease in oral malignancy mortality. Compared to visual screen, recognition of most oral malignancies in their initial asymptomatic stages quite often requires specific, expensive, and regularly traumatic means. For example, toluidine blue, Light-based detection systems, exfoliative cytology, biopsy, and histopathology [20]. It is noteworthy that visual screening for oral tumors is an uncomplicated and non-intrusive step, which demands only five minutes of visual oral tissue assessment. Thus, visual screening for oral neoplastic abnormalities is simple, efficient, affordable, and an effective tool to spare lives.

Actinic Keratosis

The same screening methods applied in squamous cell carcinomas apply to Actinic Keratosis. However, like Squamous cell carcinoma, there are other numerous diagnostic aids besides visual examination for Actinic Keratosis. Yet, the most reliable means in the Diagnosis of Actinic Keratosis depends on the common clinical routine of visual examination [1].

Nevertheless, the other available investigation screening methods for Actinic Keratosis are dermoscopy, optical coherence tomography, and confocal microscopy. Starting with dermoscopy, over the previous two decades, dermocopy served as a powerful apparatus for clinical evaluation, that further enhanced the efficiency for detecting Actinic Keratosis. On the other hand, optical coherence tomography is an optical imaging method that is quite valuable. Confocal Microscopy is an optical non-invasive symptomatic innovation with simihistological interpretation which has demonstrated high affectability and specificity for the detection of Actinic Keratosis [16].

Pathogenesis

It has been hypothesized that actinic keratosis is the first clinical manifestation of a disease continuum that ultimately results in the development of malignant skin cancer that is in its most advanced stage [21]. According to Lober, Lober and Accola, research, Actinic keratosis does not develop into skin cancer since the process is ongoing. Since solar keratosis neoplastic cells share the same cytologic characteristics with more aggressive Squamous cell carcinomas, they believe that Actinic keratosis is a malignant tumour, not a precancerous lesion. This indicates that actinic keratosis is, actually, a squamous cell carcinoma from the very outset.

Patients who suffer from Actinic keratosis as per findings of a scholarly work, almost eighty percent of individuals who had Actinic keratosis also had other types of skin lesions on their bodies. Patients often do not experience any symptoms as a result of these lesions because they are localized to the epidermis. These epidermis-localized lesions rarely generate symptoms. In a clinical setting, no precise morphometric traits identify whether an Squamous cell carcinoma has migrated into the dermis [22]. Even if they bleed or form ulcers, most people who have them are unaware that they have them. Finally, invasive Squamus cell carcinoma has the potential to spread to other organs and lymph nodes. Patients who have been ignored or undertreated are at a high risk of developing metastasis [23].

The multistage photo-carcinogenesis model created by Callen, Bickers and Moy, corresponds well with the clinical and histologic progression of actinic keratosis to invasive malignancy [22]. For abnormal cells to develop into cancer, they must be subjected to stimulating factors during the stages of inception, propagation, and advancement. Grossman and Leffell, have similarly given a multiple-stage paradigm for Squamous cell carcinoma in which an inducing factor creates an atypical clone, actinic keratosis, and biologically aggressive Squamous cell carcinoma [24]. In this model, Squamous cell carcinoma develops over the course of numerous stages.

Given that Actinic keratosis is Squamous cell carcinomas, distinguishing them on the basis of histopathology is not possible. According to Lober, Lober and Accola the world's leading dermatologists and dermatological pathologists were questioned to weigh the issue of where the line between thick Actinic keratosis and thin Squamous cell carcinoma lies, but their feedback was

inconsistent. From this, it can be deduced that the demarcation between Actinic keratosis and Squamous cell carcinoma is, at best unclear. Further, contend that the subjective assessment of a histopathologist ultimately determines whether a tumor is Actinic keratosis or Squamous cell carcinoma. Due to its inherent subjectivity in judgment, there is no way to reproduce the conclusions reliably, and if possible, they may be significantly inaccurate [17].

Chromosomal Abnormalities

The possibility for actinic keratosis to spread into the dermis is not unexpected. Nearly half of the actinic keratosis lesions studied by Rehman et al., showed indications of genetic instability in the form of loss of heterozygosity at four or more sites [25]. A DNA sequencing study by Taguchi et al., revealed that the tumor suppressor p53 protein is anomalous in Actinic keratosis, as were base substitutions and the resulting exon alterations [26]. Pennings, GrussendoreConen and Booking, used DNA single-cell cytometry to show that 69% of actinic keratosis exhibited DNA aneuploidy, a condition that has been linked with systematic development to aggressive cancer [27].

Between 25% and 80% of skin-invasive Squamous cell carcinoma exhibit chromosomal abnormalities [28]. Over 90% of dermal invasive Squamous cell carcinomas have p53 mutations. Ziegler et al., observed that these mutations are equally common in Actinic keratosis [29]. The p53 protein plays an essential role in the cell cycle, cell differentiation, and DNA damage repair, among many other functions. Because it prevents the development of cancerous tumors, this protein is called a tumor suppressor [24].

Similarities

Even though the frequency of the neoplastic transformation of Actinic Keratosis has been revealed to be low. Actinic Keratosis can be seen as an indicator of future development into squamous cell carcinoma. Thus, can give a promptly noticeable mark for early detection and effective intervention [30].

Resemblances between the two lesions can be observed on the histological, etiological, morphological, and the genetic levels. Padilla et al., 2010, affirmed that Actinic Keratosis is an originator of squamous cell carcinoma [31]. Since Actinic Keratosis and Squamous Cell Carcinoma are genetically linked. Likewise, Ortonne, uncovered a genetic interrelation between Actinic Keratosis aNd squamous cell carcinoma their findings propose a contiguous association of genetic factors amongst the two [32].

Under these circumstances, efforts have been made to rename Actinic Keratosis in relation to the linked association and advancement into squamous cell carcinoma. Nevertheless, the association remains debatable due to the rate of the neoplastic change in Actinic Keratosis and the pathogenesis of the resultant erosions [8].

Moreover, Actinic keratosis has been hypothesized to be Squamus cell carcinoma in situ [33]. Most cases of invasive Squamus cell carcinoma are caused by Actinic keratosis, which develops slowly over time in sun-damaged skin. Some studies, for this reason, have proposed an alternative classification system for actinic keratosis, which may be more accurate. It has been suggested that type Actinic keratosis1 be used for in situ Squamus cell carcinoma, type Actinic keratosis2 be used for in situ Squamous cell carcinoma, and type Actinic keratosis3 be used for in situ Squamous cell carcinoma [12].

The appearance of Actinic keratosis changes over time; therefore, ceroscopy may be useful in distinguishing it from Squamus cell carcinoma. When the differential diagnosis is unclear, a histopathologic analysis should be conducted [34]. Exposure to the sun has been identified as a major risk factor in the development of actinic keratosis into Squamous cell carcinoma; nevertheless, longitudinal studies are necessary to allow for a complete knowledge of the development of actinic Actinic keratosis into Squamous cell carcinoma. The exact risk of Actinic keratosis progressing to Squamous cell carcinoma varies from study to study, with some indicating an annual incidence of 0.075% or higher [35]. Possible confounders in the discrepancy of these data include a history of non-melanoma skin cancers; cumulative sun or radiation exposure; exposure to other recognized risk factors; previous use of immunosuppressive drugs; and sunscreen application [36].

Several clinical characteristics, including lesion size, degree of ulceration, bleeding, induration, enlargement in diameter, and erythema, are predictive of disease development. Lesions with induration, inflammation, a diameter more than 1cm, rapid growth, bleeding, erythema, and ulceration have been linked to an elevated risk of cancer in patients with actinic keratosis [37].

Karyomeric evaluation can allow for quantitative tracking of the development of skin solar damage. Micro assay profiling analysis has found that actinic keratosis and Squamous cell carcinoma share the expression of nine unique genes [37]. Actinic keratosis are pre-malignant lesions thought to originate from squamous cells whose genes have been altered by exposure to ultraviolet light [33]. As UV radiation from the sun accumulates, more nuclei will show altered chromatin patterns. Moreover, a sizable subset of Squamous cell carcinomas has similarities to actinic keratosis [37]. Actinic keratosis can develop into invasive Sequamus cell carcinoma because it penetrates the skin's basement membrane. Also, actinic keratosis and Squamous cell carcinoma look quite similar from the outside, Actinic keratosising diagnosis challenging. Unfortunately, this also means they are more likely to be misdiagnosed or unrecognized [13, 36].

Discussions

The rate at which Actinic keratosis (intraepidermal Squamous cell carcinoma) spreads to the dermis varies depending on a plethora of factors. These factors include the state of the patient's immune system as well as the degree to which the sun has damaged the patient's skin, amongst others. Because of this, it differs from patient to patient and varies with the length of the observation. The literature provides estimates as high as 20%. According to Lober, Lober and Accola the precise number of Actinic keratosis infiltrating the dermis is influenced by the length of time that passes. If the Actinic keratosis are allowed to go untreated for a longer time, it is possible that most of them will enter the dermis. Without treatment, a sizeable portion of patients with actinic keratoses will develop one or more lesions that infiltrate the dermis, as stated in the actinic keratosis treatment guidelines by the American Academy of Dermatology [38].

Lober, Lober and Accola, mentions that 12–13% of patients with Actinic keratosis will develop aggressive Squamous cell carcinoma if they do not receive treatment [39]. Marks et al., found one dermally invasive Squamous cell carcinoma for every 429 actinic keratoses identified one year previously [40]. This results in a yearly incidence rate of 0.24% for each Actinic keratosis observed at the outset of their analysis. On average, 7.7 Actinic keratosis were discovered in each patient that they examined. With the help of data provided by Dodson et al., were able to establish that the patient had 7.7 Actinic keratosis and that 10.2% of them would infiltrate the dermis during the subsequent 10 years [41].

In addition, Marks et al., discovered that although 25.9% of the Actinic keratosis diagnosed at the beginning of their analysis had clinically vanished, 44.0% of the 1,040 patients they had tracked had developed a minimum one new lesion [40]. No biopsies were performed on lesions that had disappeared clinically. Schwartz, notes that an untreated Actinic keratosis is indicative of a possibly curable and deadly cancer [21]. He also notes that certain Actinic keratosiss may become clinically inapparent, most likely as a result of immunological resistance or perhaps by having their external surface accidentally scratched off. To clarify, Marks, Rennie, and Selwood assert not all cases of Actinic keratosis inevitably develop into an aggressive malignancy [42]. A review by Hurwitz and Monger found that out of 459 patients with dermally invasive Squamous cell carcinoma, 97% were associated with a persistent Actinic keratosis either at the peripheral or within the borders of the Squamous cell carcinoma [43]. In a study involving 165 cases of invasive cutaneous Squamous cell carcinoma, Mittelbronn et al. revealed that 136 patients also had simultaneous actinic keratosis [30]. This figure represents 82.4% of the total (defined as within 8 mm). Within an Actinic keratosis was found to be the location of the squamous cell carcinoma in 44 cases (26.7%). Actinic keratosis was observed in the same histologic section in 31 of the 53 patients (58.5%) who were diagnosed with invasive Squamous cell carcinoma, as reported in the scholarly works by Actinic keratosisemiya, Ohtsuka and Miki, [44]. These patients all had invasive Squamous cell carcinoma. Robin Marks, Rennie, and Selwood, discovered that Actinic keratosis was present in 60% of the Squamous cell carcinoma cases in their cohort; these had been diagnosed within the previous year [42].

These percentages may be skewed artificially for a couple of reasons: (I) Actinic keratosis may have been completely hidden by the advancement to a dermally intrusive Squamous cell carcinoma, which may have excluded any prospective traces of Actinic keratosis; and (II) additional histological portions of the dermally invasive Squamous cell carcinoma may have disclosed foci of Actinic keratosis that were previously undetected [17]. Guenthner et al., published the results of their histologic analysis of 1,011 cases of Squamous cell carcinoma [45]. They discovered that 983 patients, or 97.2 percent, displayed alterations consistent with Squamous cell carcinoma in situ at the peripheral or inside the boundaries of the existing Squamous cell carcinoma.

They found that it appeared that 2.8% of the samples did not have Squamous cell carcinoma in situ at the periphery or inside the boundaries of the Squamous cell carcinoma and concluded that this was a result of poor sampling of the neoplasm during the biopsy process and thus inferred that in specimens that had acceptable margins, 100% encapsulated Squamous cell carcinoma in situ at the periphery or inside the boundaries of the Sequamus cell carcinoma. Hence, they state that Actinic keratosis is an Squamous cell carcinoma in situ.

According to Kwa, Campana and Moy, findings, actinically produced Squamous cell carcinoma possesses a limited but significant potential for metastasis [28]. On the other hand, it is very clear from the research that Squamous cell carcinomas begin as Actinic keratosis have the potential to metastasize at some point in the future.

Equipped with this useful indication, management approaches premeditated to treat Actinic keratosiss before they progress to Squamous cell carcinoma should be advised. It would also be sensible to enlighten Actinic keratosiss patients on the consequence of chronic sun radiation exposure and recommend some behavior modification to avoid direct rays' exposure. Such patients might be introduced and advised on self-examination to recognize primary malignancies; they ought to be encouraged to visit routine public oral cancer screening procedures [1].

In some cases, Actinic keratosis can develop into cancerous squamous cell tumors. Several investigations have shown that Actinic keratosis carries a potential for invasive Squamous cell carcinoma. Although data is insufficient on the specific percentage that may progress, estimates range from 0.025 % to 16 % and the risk was found to augment over time [58, 48].

Histology results show Actinic keratosis bordering Squamous cell carcinoma in the absence of clinically obvious lesions further complicate these findings. This could be an indication of a delayed propensity to the emergence of invasive Squamous cell carcinoma and subsequent field cancerization [40, 41, 59, 60]. Referring to Criscione et al., where they contended that several researchers have debunked the theory that Actinic keratosis is capable of complete regression [48]. Although they discovered that atypical keratinocytes with a single p53 mutation had a chance of reversal, regression became highly improbable if a cell line had attained multiple gene mutations. They note that there is no histology data to suggest that Actinic keratosis can subside and that even while Actinic keratosis may be asymptomatic or absent from visit to visit, they are not expected to progress to a less destructive form. Clinically determining whether Actinic keratosis may develop into aggressive Squamous cell carcinomas remains a challenge. There are no widely accepted clinical indicators that can reliably detect higher-risk Actinic keratosis, despite evidence from the literature detailing that Actinic keratosis can advance into invasive Squamous cell carcinoma. Inflammation, redness, more than 1cm diameter, bleeding, ulceration, and rapid growth have all been proposed as potential risk factors.

Pain that occurs on its own or in response to pressure may signal that the lesion is an Squamous cell carcinoma and not an Actinic keratosis [61]. In addition to an increased likelihood of developing into an invasive Squamous cell carcinoma, a diagnosis of melanoma or non-melanoma skin cancer is also associated with a follicular expansion of Actinic keratosis [62, 63]. Immunocompromised people are already at a higher risk of developing Actinic keratosis and Squamous cell carcinoma; therefore, this danger may be amplified in them [64].

When discussing Actinic keratosis, Fukamizu et al., mentioned that four out of ten lesions developed in solar keratosis started spreading to lymph nodes or salivary glands [46]. According to the researchers, the four cases of metastatic Squamous cell carcinoma were distinguished by aggressive lymphatic metastasis that did not involve additional tissue and had early lesions that were amenable to treatment. In a histological study of primary lesions from individuals with dermally invasive Squamous cell carcinoma carried out by Dinehart et al., the researchers found that 44 percent of the primary lesions had continuous epidermal involvement (actinic keratosis) [47].

Actinic keratosis is the immediate cause that results in the emergence of Squamous cell carcinoma. The epidermis is where Ultraviolet damage first manifests as lesions [42, 48]. Research on the development of single actinic keratosis lesions demonstrated a significant risk factor in its progression to Squamous cell carcinoma [13].

According to a systematic review done by Werner et al., patients diagnosed with a type of skin cancer that is non-melanoma, Actinic keratosis carry a risk of developing into Squamous cell carcinoma ranging from 0% to 0.53% per lesion every year [13]. After one year, the rates of remission for a single lesion ranged from 15% to 63%, whereas the rates of recurrence after one year ranged from 15% to 53%. Corresponding to the findings of another study by Bickers et al., sixty percent of skin cancers originated from preexisting lesions such as solar keratosis, and forty percent of Squamous cell carcinomas grew on clinically considered normal skin [35]. Furthermore, Frost, Green and Williams, argued that the risk of actinic keratosis developing into Squamous cell carcinoma increases at yearly rates ranging from 0.025 percent to 20 percent [49]. According to the findings of one study, the risk of progression from Actinic keratosis to primary Squamous cell carcinoma after one year was 0.60%, and the risk after four years was 2.57%. Whereas the incidence of primary invasive Squamous cell carcinoma at one year was 0.39 percent, while the risk at four years was 1.97 percent.

A hospital-based population survey found that patients with a history of non-melanoma skin cancers had a risk of progression of 0.53% every year. However, the chance of malignant transition from Actinic keratosis to Squamous cell carcinoma is less than 1 in 1000 [48].

Notably, there is a significant gap in the diagnosis of Actinic keratosis cases made based on clinical criteria and those made based on histology, as indicated by research conducted in the scientific community and proved by those findings. Additionally, 5% of the 22 cases of Actinic keratosis clinically diagnosed were histopathologically identified as basal cell carcinoma, and 12% of the 514 cases of suspected BCC were diagnosed as Actinic keratosis [50, 51].

Warino et al., research has indicated that most actinic keratosis-derived Squamous cell carcinomas develop in the same spot as the Actinic keratosis or a nearby site [51]. Also found that 65% of all Squamous cell carcinomas develop from Actinic keratosis, whilst found that 60% of Squamous cell carcinomas emerged at the exact locations where actinic keratosis lesions were present. A study conducted in the United States found that chronic sun exposure, especially from UVB sunlight, caused 10% of actinic keratosis cases to develop into Squamous cell carcinoma. Based on the findings of a retrospective study, the average time that passes between the onset of Actinic keratosis and the development of skin cancer is 24.6 months [33].

The Financial Aspects

The disease burden associated with Actinic keratosis may be far higher than estimated. As predicated on the results of a prior study, it has been estimated that the worldwide value for alleviating Actinic keratosis symptoms is worth $2.4 billion [48]. Actinic keratosis is an expensive illness to manage. It was shown in the study that of the anticipated 5.2 million annual visits to doctors for actinic keratosis, 60% were made by individuals who were enrolled in Medicare. Annual expenditures for treating actinic keratosis amount to $920 million, with 43% going toward doctor's visits, 51% to invasive procedures, and the remaining 6% to topical therapies [36].

Despite this, a paucity of evidence elucidates the cost-benefit analysis of treating Actinic keratosis, which is urgently needed to influence subsequent treatment decisions. However, by calculating the number of visits made by patients with a diagnosis of Squamous cell carcinoma to a healthcare practitioner and the cost of managing patients who have Sequamus cell carcinoma, one can gain a more thorough understanding of whether solar or actinic keratosis should in fact, be treated as Squamous cell carcinoma [34]. In addition, investigations are required to estimate the condition's prevalence, economic cost, and influence on life quality. Nevertheless, the currently available evidence has argued that destructive treatments, compared to topical medications, offer a higher rate of care for patients, are more effective, and help keep costs down [34]. Consequently, lesions brought on by Actinic keratosis must be treated with a lesion or field-directed therapy to stop the disease from propagating further [52]. Furthermore, the rate of complete spontaneous regress of Actinic keratosis is low, and the risk of recurrence is considerable.

Future Directions

Referring to a paper by Rosso et al., the existing research contains inconsistencies; specialists advise conducting more in-depth studies on the following three topics: (I) the natural history and clinical manifestations of high-risk Actinic keratosis; (II) the effectiveness of therapies that are consisted of a confluence of various patient-applied therapies; and (III) patientapplied therapy's efficacy on unresearched sites and conditions [53]. Future research should clarify their evolutionary background to understand Actinic keratosis further. Given that the quantifiable risk of progression to invasive Squamous cell carcinoma is not yet well defined, a paradigm to select those lesions at the heightened rate of advancement is necessary. Existing studies have demonstrated combining lesion-directed treatment with field therapy has additional favorable impacts [54, 55]. However, there is a dearth of information regarding the efficacy of combination therapy regimens, particularly those involving several mechanisms of action. In addition, it may be reasonable to research the potential benefits of using topical corticosteroids or another adjuvant therapy to decrease LSRs and increase adherence [56]. Finally, individual alternative treatments might be further refined, and patient care could be improved if future studies were to validate the effectiveness of patient-applied treatments for actinic cheili-

tis or other parts of the body, such as the lateral hands or forearms and chest. Also, it would be advantageous to do off-label trials of medications for keratinocyte dysplastic processes such as Squamous cell carcinoma in situ, Bowenoid papulosis, vulvar dysplasia, verruca, and molluscum contagiosum [53].

Conclusion

Advancement of Actinic Keratosis to an intrusive squamous cell carcinoma in any individual has a low prognosis. These nascent malignancies serve as a distinguisher of persons who have the hereditary susceptibility or individuals maintaining chronic sun exposure. Early detection of Actinic Keratosis is critical because it is a subsequent predisposing factor in the transformation sequence. According to Mittelbronn et al., 26.7% of these cases had squamous cell carcinoma emerging from Actinic Keratosis reflects a solid connection between these two diseases [30]. 82.4% of performed biopsies showed a predominance of clear similarities between Actinic Keratosis and cutaneous squamous cell carcinoma. Therefore, that signifies the importance of early recognition and the viability of the early intervention or treatment.

Lober, Lober and Accola, argued that, Actinic keratosis does not develop into skin cancer since the process is ongoing. Since solar keratosis neoplastic cells share the same cytologic characteristics with more aggressive Squamous cell carcinomas, they believe that Actinic keratosis is a malignant tumour, not a precancerous lesion. They stated that actinic keratosis is a squamous cell carcinoma from the outset. Furthermore, Mittelbronn et al., Stated that Actinic keratosis serves as an alarm to prevent malignancy occurrence and to decrease the accompanying mortality, as well as belligerent treatment of clinically recognized Actinic keratosis would lessen the occurrence of cutaneous (Squamous cell carcinoma), consequently, restrain the upcoming neoplastic changes [30]. Yet, there has been a persistent evolution from Actinic Keratoses to Squamous Cell Carcinoma, so it is hard to meticulously distinguish between these growths. The fact that various lesions treated as Actinic Keratosis may perhaps be early Squamous Cell Carcinomas indicates that these patients must be observed and treated belligerently to stop the development of Squamous Cell Carcinoma.

“The fact that many lesions being treated as actinic keratosis could be early squamous cell carcinomas suggests that treatment should be aggressive and that patients should be monitored closely so that the eventual progression from actinic keratosis to squamous cell carcinoma may be stopped” [57]. Therefore, early detection via routine screening may interrupt undesirable progression from Actinic Keratosis to Squamous Cell Carcinoma [1]. Thus, oral screening could be focused on susceptible individuals, and controlled visual screening is a sensible initiative to restrain oral neoplasm. Furthermore, as a key preventive measure, it is highly recommended that oral screening be ingrained in routine check-ups.

Actinic keratosis should be treated to minimize unnecessary morbidity and mortality due to the high likelihood of Actinic keratosis development into invasive Squamous cell carcinoma and the lack of clinical and pathological indicators to determine which Actinic keratosis would progress to aggressive disease. This statement encompasses not only the treatment of overt Actinic keratosis but also the investigation and care for Actinic keratosis that are not yet noticeable clinically [53].

Actinic keratosis exhibits the same clinical, histological, and molecular hallmarks as Squamous cell carcinoma. Initial signs of this cancer include actinic keratosis. The word "actinic keratosis" is misleading because it does not accurately describe the malignant aspect of this lesson. The unfortunate reality is that the term has become standard in medical sciences. Efforts to rename this lesion such that it more correctly reflects its biological behaviour have been hampered by worries over reimbursement and insurance difficulties. Actinic keratosis, Squamous cell carcinoma, or whatever one names it, must be Actinic keratosis seriously [17].

This report reveals that opinions are divided on whether Actinic keratosis is keratolytic intraepithelial neoplasia or real epithelial neoplasia. According to the findings of several studies, 10% of cases of Actinic keratosis develop into Squamous cell carcinoma. Because it is so hard to tell Actinic keratosis from Squamous cell carcinoma, treating it can be challenging. Thus, when clinicians are perplexed about a lesion's diagnosis, obtaining histological information is crucial. Most investigations have shown a continuum between actinic and solar keratosis, suggesting that intensive early therapy and monitoring of lesions may be warranted. There is a significant financial expense connected with actinic keratosis; hence, it is important to conduct a cost-benefit analysis when considering treatment options [10, 36, 65].

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