Field cancerization: Definition, epidemiology, risk factors, and outcomes

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Learning objectives
After completing this learning activity, participants should be able to define field cancerization and discuss how this condition differs from actinic keratoses; explain the pathogenesis of field cancerization; and describe the morbidity, mortality, and cost considerations associated with untreated or undertreated field cancerization.

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Field cancerization was first described in 1953 when pathologic atypia was identified in clinically normal tissue surrounding oropharyngeal carcinomas. The discovery of mutated fields surrounding primary tumors raised the question of whether the development of subsequent tumors within the field represented recurrences or additional primary tumors. Since this initial study, field cancerization has been applied to numerous other epithelial tissues, including the skin. Cutaneous field cancerization occurs in areas exposed to chronic ultraviolet radiation, which leads to clonal proliferations of p53-mutated fields and is characterized by multifocal actinic keratoses, squamous cell carcinomas in situ, and cutaneous squamous cell carcinomas. In the first article in this continuing medical education series, we define field cancerization, review the available grading systems, and discuss the epidemiology, risk factors, and outcomes associated with this disease. (J Am Acad Dermatol 2020;83:709-17.)

Key words: actinic damage; actinic keratoses; cutaneous oncology; cutaneous squamous cell carcinoma; field cancerization; field change; field damage; field therapy; immunosuppression; keratinocyte carcinoma; actinic keratosis; *NOTCH*; *NOTCH1*; p53; p-53 clonal fields; squamous cell carcinoma; *TP53*.

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Abbreviations used:

AK:	actinic keratosis
AKASI:	Actinic Keratosis Area and Severity Index
AK-FAS:	Actinic Keratosis Field Assessment Scale
BCC:	basal cell carcinoma
CSCC:	cutaneous squamous cell carcinoma
FC:	field cancerization
KC:	keratinocyte carcinoma
QoL:	quality of life
SOTR:	solid organ transplant recipient
UVR:	ultraviolet radiation

The concept of field cancerization (FC) was first described in 1953 by Slaughter et al[1] in epithelial tissue surrounding oropharyngeal carcinomas. In that landmark study, 782 cases of oropharyngeal squamous cell carcinoma were examined and observed to have pathologic atypia in normal appearing adjacent tissue. Multiple new secondary tumors were found to subsequently arise within this field that were clinically suggestive of tumor recurrence, but were in fact second primary tumors. At the cellular level, FC is the growth of a mutant clone that creates a field of cells predisposed to subsequent tumor growth.[2] Since its inception, the concept of FC has become widely accepted in other tumors, including cancers of the vulva, head and neck, cervix, breast, and colon.[2]

Cutaneous tissue is uniquely susceptible to FC given the chronic ultraviolet radiation (UVR) exposure in sun-exposed areas. Areas affected by FC have an incredibly high burden of both clinical and subclinical actinic damage and, therefore, are at high risk for developing multiple cutaneous squamous cell carcinomas (CSCCs). Multiple CSCC formation leads to high morbidity for the patient from multiple surgical procedures and carries a high cost to society.[3,4]

The accurate identification of patients with cutaneous FC is of paramount importance because it identifies patients who are at highest risk for multiple CSCC formation and, thus, those at the greatest risk for developing poor disease-related outcomes.[5] Unfortunately, there is no standard or widely accepted definition for cutaneous FC. In addition, FC is not considered a distinct diagnosis from actinic keratosis (AK), as evidenced by the lack of separate *International Classification of Diseases, 10th revision, Clinical Modification* code for AK and FC. However, patients with FC have a disease process that behaves differently than those with multiple discrete AKs. A lack of understanding of FC may falsely lead clinicians to undertreat patients with FC when these patients require a more aggressive approach. In the first article in this continuing medical education series, we provide a clear definition of FC including visual examples of this disease, compare and contrast AKs with FC, and discuss the pathogenesis, risk factors, and outcomes of this condition.

EPIDEMIOLOGY AND RISK FACTORS

Key points

- **The prevalence of AKs and FC is rising across the world**
- **Risk factors for the development of FC include male sex, light skin, increasing age, immunosuppression, and exposure to UVR**

Prevalence and incidence

As there are limited data regarding the epidemiology of FC, both AK and CSCC are proxies that may be used to estimate the prevalence and incidence of FC. AK epidemiologic figures are calculated based on patients with ≥1 AK.[6] Unfortunately, these data rarely stratify patients with 1 versus extensive AKs, which is a more clinically relevant measure for patients with FC.

AKs represent the most common dermatologic diagnosis in patients ≥45 years of age in the United States,[7] with an estimated 5.2 million visits annually.[8] The number of treated AKs per 1000 Medicare patients rose 14.6% (917.2 to 1051.1) from 2007 to 2015, demonstrating the increasing prevalence of this disease.[9]

Incidence data on AKs is sparse given the difficulty in tracking individual AKs over time.[6] In a study from South Wales of patients >60 years of age, there was an incidence of 149 AKs per 1000 person-years.[10] Incidence rates of AKs were as high as 60% in Australian patients who had a history of previous AKs.[11]

There was a 35% increased incidence of keratinocyte carcinoma (KC) in the United States between 2006 and 2012.[12] While the risk of transformation of individual AKs to invasive CSCC is low (0-0.53% per lesion-year; 2.88% at 5 years),[13,14] patients with FC carry significantly higher risks of invasive CSCC because of the high burden of actinic damage.[15]

At-risk populations

The risk factors for FC are similar to the risk factors for AK and CSCC, namely exposure to UVR, fair skin, increasing age, male sex, and immunosuppression.

Age. AKs have been shown in many studies to increase significantly with age.[16-20] A study of 1,375 patients in Baltimore showed a >5-fold increase in AKs in patients 70 to 79 years of age versus those 50 to 59 years of age.[20] A German study of >90,000 patients demonstrated a 4-fold increased risk of AKs in persons 61 to 70 years of age compared with the total study population.[19]

Sex. Males have consistently higher rates of AKs compared with females.[16,17,20-25] In a population-based German study, there was a nearly 4-fold increased risk of AKs in men.[17] Males also have a 3 times higher prevalence of extensive actinic damage (defined as ≥10 AKs) compared with females,[25] which is more likely related to differences in sun exposure and protection behaviors between the 2 groups rather than inherent susceptibility.

Body site. AKs are seen almost exclusively in sites of extensive sun exposure, including the scalp, face, dorsal aspects of the hands, and the forearms.[26-29] The density of AKs is 18 times higher on the face than the trunk and extremities.[26] In a population-based study from the Netherlands, the single strongest risk factor for the development of ≥10 AKs was severe baldness in males.[25]

Skin type. Fair-skinned patients have a significantly higher risk of developing AKs because of their susceptibility to UVR.[17-19,21,25,30] In a case-control, multicenter study across 8 European countries, there was a 9- and 4-fold increased risk of AKs in Fitzpatrick type I and II skin, respectively.[18]

UVR. AKs and CSCCs are related to the amount of cumulative UVR an individual experiences over his or her lifetime.[31-33] The amount of ambient UVR exposure has repeatedly been shown to affect the incidence of CSCCs,[33-36] with those living closer to the equator being exposed to more UVR. Occupations with high rates of daily sun exposure have also been shown to have increased rates of actinic damage.[18,32,37,38]

Immunosuppression. The risk for AKs and CSCCs is significantly increased in immunosuppressed patients, such as solid organ transplant recipients (SOTRs) or patients with chronic lymphocytic leukemia.[15,39-41] In the authors' experience, this group of patients is at the highest risk of developing FC. Decreased immune surveillance allows for high rates of skin tumorigenesis and predisposes patients to the development of FC.[6]

A 2015 study of 452 SOTRs showed a 17% prevalence rate of FC, which increased with the length of immunosuppression.[42] Furthermore, SOTRs with FC were shown to be 4 times more likely to develop CSCCs compared with those with AKs, but without FC.[42] Although there are no studies evaluating FC in patients with chronic lymphocytic leukemia, these patients have a 5- to 8.6-fold increased risk of CSCC[43-45] with significantly elevated rates of recurrence, metastasis, and death from CSCC.[46-49]

DEFINING AND ASSESSING FIELD CANCERIZATION

Key points

- **The clinical manifestations of FC lie on a continuum between AK and CSCC**
- **A clear and concise definition of FC is lacking**
- **Multiple grading systems for FC have recently been developed**

Definition of FC

FC has been used to describe actinic dysplasia and KCs of the skin, but a clear and concise definition is lacking. There are several proposed definitions of cutaneous FC with most studies requiring a subclinical mutated field as a defining feature of the disease.[50-54] While it is clear that UVR-induced subclinical atypia surrounds visible AKs and likely precedes their development, this has limited clinical utility because obtaining a biopsy specimen from the skin would be required to diagnose FC. Furthermore, it would not be possible to identify the field margins without evidence of visible AKs. Other proposed definitions of FC require a history of CSCC within the actinically damaged field.[54,55] Although visible field change is paramount, the necessity of invasive CSCC may exclude patients with FC who have yet to develop their first CSCC and preclude these high-risk patients from receiving early field-directed intervention.

We have developed an updated definition of FC to help guide and standardize both the discussion and treatment of this disease. We define FC as multifocal clinical atypia characterized by AKs or squamous cell carcinomas in situ with or without invasive disease, occurring in a field exposed to chronic UVR. Compared with patients with diffuse AKs, patients with FC are more likely to have broad and hyperkeratotic scaly lesions, suggesting progression to squamous cell carcinoma in situ or early invasive CSCC, although this is not a required feature for diagnosis. These patients may have a history of multiple invasive CSCCs within the involved field if the FC was not diagnosed early. Clinical examples of FC are provided in Fig 1.

Current grading systems for FC

Despite the ubiquitous nature of AKs in dermatology, effective systems to grade FC are limited.

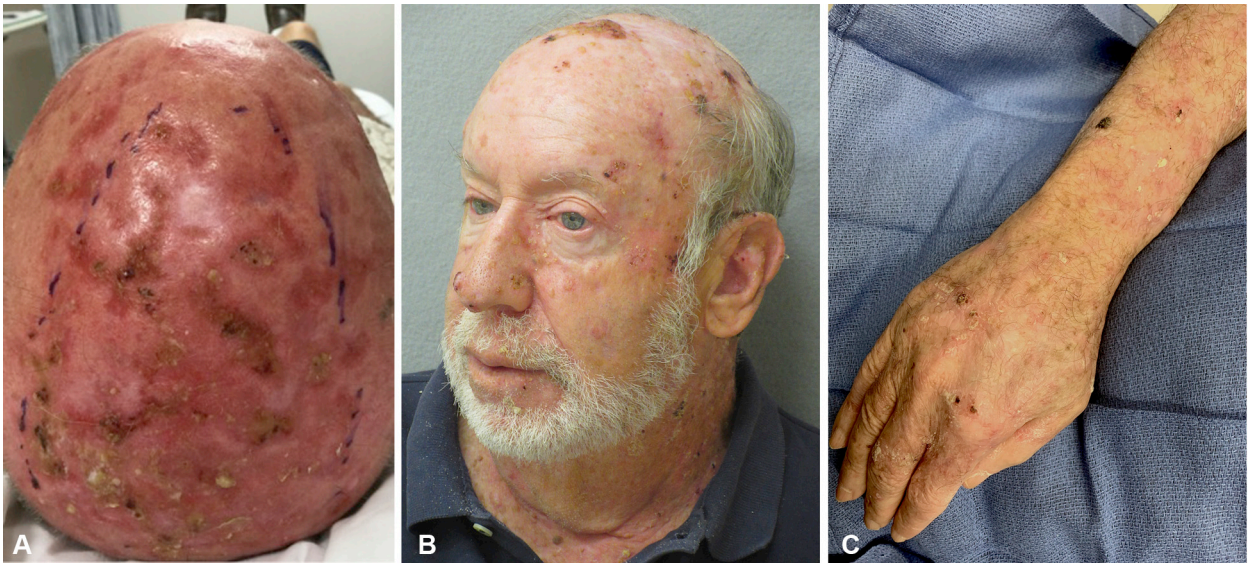

Fig 1. Field cancerization. Examples of field cancerization of the (**A**) scalp, (**B**) face, and (**C**) upper extremity in 3 patients. Note the extensive, confluent hyperkeratotic actinic keratoses and squamous cell carcinomas in situ.

Most studies measure AK counts[56]; however, because of the varied morphology of AKs, counts are challenging and multiple studies have shown that they are imprecise.[57,58] In patients affected by FC, AK counts are also impractical because these lesions often coalesce, and individual lesions are hard to identify and can spontaneously regress.

The Actinic Keratosis Area and Severity Index (AKASI) was developed with the intent of classifying actinic damage across a field.[59] This tool stratifies FC on the face and scalp in a similar manner to the Psoriasis Area Severity Index score in psoriasis.[59] A score is calculated by taking into account 3 parameters: area (scalp, forehead, right face, and left face), percentage of actinically damaged skin in each area, and the extent of clinical AK severity, including erythema, thickness, and distribution, with higher scores indicating worse actinic damage. Studies show that higher AKASI scores are associated with a greater risk of CSCC and basal cell carcinoma (BCC) (AKASI score 6.9 for CSCC vs 3.3 for BCC).[51] A second scale, the Actinic Keratosis Field Assessment Scale (AK-FAS), was created with the similar goal of evaluating FC of the skin.[60] This tool applies to the face and scalp and uses a combination of sun damage and hyperkeratosis to determine the extent of actinic damage. To date, this gradation system has only been tested in photographs and has not been applied in clinical settings.

The main disadvantage of both AKASI and AK-FAS is that the scoring systems are time-consuming and cumbersome for routine clinical practice. Neither tool fully measures FC because they do not account for the burden of squamous cell carcinomas in situ or invasive CSCCs within the sun-damaged field. Furthermore, neither tool has been validated in a large, prospective fashion. A simple, validated tool to evaluate FC in the clinical setting could help to better stratify those patients at greatest risk of CSCC progression.

PATHOGENESIS

Key points

- **Chronic UVR is the primary carcinogen responsible for the formation of FC and KC**
- **p53-clonal fields are key to the formation of FC**
- ***TP53* and *NOTCH* are recognized as early driver mutations in the progression from AK and FC to KC**

Gene mutations caused by chronic UVR exposure are the main driver of FC. The mutagenic signature of UVB, C-T and CC-TT substitutions at dipyrimidine dimer sites, has been identified in several key driver genes in sun-exposed skin, AKs, and CSCCs.[61-64]

TP53 is the most common driver mutation found in CSCCs, identified in >90% of specimens,[62] and is suspected to be the key player in the formation of FC. P53 plays critical roles in both apoptosis and cell cycle arrest following DNA damage, and UVR-related loss of function leads to the resistance of apoptosis.[65,66] Multiple studies

have shown that the clonal expansion of p53-mutated fields occurs in an exponential fashion in response to chronic UVR.[67,68] This expansion occurs secondary to low doses of UVR at or below the energy needed to cause erythema.[69] In murine models, the number of p53-mutant clonal fields decreases 60% to 70% 2 to 4 weeks after removal of a chronic UVB stimulus.[68] These findings support epidemiologic data that actinic damage and CSCCs occur in response to chronic UVR, not short, high intensity events.[68]

TP53 mutations have been identified in clinically normal sun-exposed skin, as well as photodamaged skin and AKs, but are nearly absent in sun-protected areas.[70-75] The clonal expansion of p53-mutated fields in clinically normal tissue indicates that *TP53* mutations occur early in the progression towards FC and CSCC. Furthermore, subclones of other key CSCC driver mutations have been identified within these p53-mutant clonal patches, but not in adjacent skin outside of the clonal fields.[76] *NOTCH* (present in 75% to 82% of CSCCs)[61,77-81] and *MAPK*[82-86] have been identified as key driver mutations. Other notable driver mutations that are suspected to play a role in the progression to CSCC include *CDKN2A*,[61,87] *FAT1*,[61,88] *RAS*,[87,89] *RIPK4*,[87] and *MMP1*.[90,91] CSCCs possess the second highest (BCCs have the highest) mutational burden of any human malignancy with 33.3 to 50 mutations per megabase of coding DNA,[61,92,93] and therefore it is difficult to determine which of the above mutations are key to the development of FC and CSCC.

OUTCOMES

Key points

- **FC is associated with a significantly higher risk of CSCC formation compared with discrete AKs**
- **Recognition and treatment of FC before transformation to CSCC could provide significant cost reduction**
- **FC impacts quality of life similar to other chronic dermatologic diseases**

Morbidity, mortality, and multiple skin cancer formation

The risk of CSCC increases with greater numbers of AKs. In SOTRs, those with 1 to 49 and ≥50 AKs had a 4.1- and 12.1-fold increased risk of CSCC formation, respectively.[15] Similarly, in a study of immunocompetent patients, those with ≥15 AKs carried a 5.7 times increased risk of invasive CSCC on the face and ears compared with those without AKs.[94] Given the confluent nature of the actinic damage, patients with FC are at even higher risk of CSCC formation compared with patients with multiple AKs.

In FC, the extensive subclinical premalignant change lends itself to the development of multiple primary skin cancers in the cancerized field.[1] Eighty-two percent of patients with ≥2 KCs will develop a new KC compared with only 43% of patients with 1 KC.[95] As patients develop multiple skin cancers, the morbidity associated with numerous surgical procedures increases substantially and the risk of metastatic CSCC also increases. Patients with ≥10 CSCCs have a 3.8 and 4.2 times increased risk for local recurrence and nodal metastasis, respectively, compared with those with 1 previous CSCC.[5] Once metastatic disease develops, the mortality is high, with a median survival of 2.19 years for patients with stage IV CSCC.[96]

Based on the above data, patients with FC are at higher risk of developing multiple CSCCs and often suffer significant morbidity and mortality from their disease. In our experience, early diagnosis of these patients is of paramount importance. Aggressive, early intervention to decrease premalignant change in the cancerized field and early CSCC detection can prevent the negative sequelae of untreated disease.

Cost

Given the high prevalence of AKs and an aging population, it is not unexpected that management of AKs and FC comes with a large economic cost. The combined management of AKs and KC accounts for >15% of all medical costs related to skin disease, with an estimated cost in the United States of $1.68 and $4.59 billion for AK and KC treatment, respectively.[97] However, overall, the treatment of AKs is less costly than the treatment of CSCCs. In Medicare patients, the per patient cost of KC ($791) was almost $650 more per year than the cost of treating AKs ($143).[98] Field therapy for AKs in the form of topical chemotherapies and immunomodulators, a treatment often reserved for patients with FC, increased by 32% between 2011 to 2015.[99] In a study of high-risk Veterans Health Administration patients, there was a 3-year, $741 savings in patients treated with 5-fluorouracil vs placebo.[100] Given the high prevalence of AK and CSCC in our society, the identification of patients with FC and aggressive treatment of AKs and early CSCCs may lead to significant cost reductions to the health care system.

Patient perception

While dermatologists often consider AK to be a premalignant diagnosis, the ongoing sequelae from chronic UVR suggests that actinic damage may also be viewed as a chronic disease.[101] Actinic damage

can affect patient quality of life (QoL) in a number of ways, including fear about progression to cancer, cosmesis, and clinical symptoms.[102] QoL scores for patients with AKs are comparable to other chronic diseases, including psoriasis and atopic dermatitis.[102]

Patients with AKs have been shown to have a significantly lower QoL than those without AKs.[101,103] While there are no studies examining the QoL in patients with FC, multiple studies have shown that QoL decreases as the number of AKs increases,[101,102,104,105] suggesting that patients with FC may have a worse QoL than those patients without FC. Previous treatment with 5-fluorouracil, suggesting FC, is also strongly associated with lower QoL scores.[101] Other factors associated with lower QoL in patients with actinic damage include female sex and age <60 years.[102,106,107]

FUTURE DIRECTIONS

Given the high morbidity associated with FC, it is imperative that dermatologists understand this condition and the aggressive management required for these patients. A clear, widely accepted definition of FC will allow for these patients to be identified early. Future studies are needed that focus on identification of FC, risk factors, outcomes, and efficacy of clinical interventions.

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Answers to CME examination

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