

The Kinetics of Skin Cancer: Progression of Actinic Keratosis to Squamous Cell Carcinoma

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BACKGROUND Actinic keratoses (AKs) are intraepidermal skin tumors that have the potential to progress to squamous cell carcinomas (SCCs). SCCs are the second most common cancer with more than 200,000 cases each year in America. Approximately 10% of AKs will progress to SCCs. This progression is thought to be due to chronic sun exposure, specifically ultraviolet B sunlight.

OBJECTIVE Understanding the kinetics of this developmental process can help physicians better evaluate and subsequently treat precancerous AKs.

METHODS To determine the time scale of AK progression, we conducted a retrospective electronic medical record study of all patients diagnosed histopathologically with an SCC between July 1, 2003, and June 30, 2005.

RESULTS Of a total patient population of 6,691, 91 had a histopathologically confirmed diagnosis of an AK at the same site as the subsequent SCC. The length of time for an AK to progress to an SCC was determined to be 24.6 months (95% confidence interval, 21.04–28.16 months).

CONCLUSIONS Although a more controlled *in vivo* study is indicated, these data provide a good estimate of the time course from an AK to an SCC. In summary, of the estimated 10% of AKs that will develop into an SCC, the progression will take approximately 2 years.

Aaron Fuchs, BA, and Ellen Marmur, MD, have indicated no significant interest with commercial supporters.

The kinetics of actinic keratosis (AK) progression to a squamous cell carcinoma (SCC) is an important principle in understanding the process of malignancy. Knowledge of the time required for AKs to progress to SCCs will educate physicians about the nature of this disease course and may even reduce the 1,300 to 2,300 annual deaths in the United States attributed to SCCs.¹

AKs are considered an incipient form of SCCs. They appear as rough, scaly, hyperkeratotic macules or papules with discrete borders.² Histologically, AKs present with atypical keratinocytes in the deeper portions of the epidermis.² Clinically, AKs become tender and inflamed before SCC progression.³ Once AKs have become palpable, indurated, or ulcerated, they can be considered to have undergone malignant transformation.⁴ Advanced, invasive SCCs may be nodular or plaque-like and show hyperkeratosis.²

Clinical studies have established that between 0.025 and 16% of AKs progress to invasive SCCs, with extrapolation studies suggesting the risk of progression at approximately 8%.⁵ This progression has been attributed to p53 mutations caused by ultraviolet B (UVB)-induced DNA damage. UV exposure causes the formation of pyrimidine dimers in the DNA of keratinocytes. If the p53 tumor suppressor gene is mutated by UVB damage, there is a decrease in G1 cell cycle arrest and thus release of cells with damaged DNA from apoptotic control.⁶ Chronically sun-exposed skin has been shown to have larger and more numerous epidermal p53 clones compared to skin that is intermittently sun-exposed or sun-shielded.⁷ Mutations of the p53 gene, on chromosome 17p13.2, have been found in 53% of AKs and 69% of SCCs.⁸ Progression from AK to SCC has also been correlated with the deletion of the 9p21 region encoding the p16^{INK4a} tumor suppressor protein.⁷

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Additionally, UVA radiation has been implicated in AK progression to SCC by causing reactive oxygen species such as superoxide anions, singlet oxygen, and hydrogen peroxide.⁹ Thus, although the mechanisms of progression from an AK to a SCC have been identified, the kinetics of this conversion process have not been acknowledged before this study.

Methods

To determine the time scale for progression from an AK to an SCC, we conducted a retrospective electronic medical record (EMR) review. We examined the clinical histories of all 6,191 patients at Mount Sinai's Dermatology Faculty Practice who were diagnosed pathologic with an SCC between July 1, 2003, and June 30, 2005. The clinical histories were subsequently examined for previous pathologically confirmed AKs at the site of the subsequent SCC. Lesion locations were matched using physician descriptions of the surgical site. Only those patients with extensive, descriptive matching locations were included in the study. The paper charts of patients with SCC, but without pathology proven precursor AK, were not examined due to the large number of medical records in the study.

The data collected for each patient included length of time to conversion, sex of the patient, age of the patient, and location of the lesion. The locations of the lesions were categorized into groups that included the scalp, temple, forehead, eyebrow, nose, cheek, ear, trunk, or extremities. Statistical analysis using the one-tailed *t*-test was utilized to compare time scales between the sexes of patients. The ANOVA (analysis of variance) test was used to statistically compare time scales between locations and between different age groups.

Results

Our study identified 6,691 patients with pathologically confirmed SCCs in the 2-year time scale. Of these patients, only 91 were determined to have

pathologically confirmed AKs at the same site of the subsequent SCC. The mean time for an AK to progress to an SCC in this patient population was found to be 24.6 months (95% confidence interval, 21.04–28.16 months). The range for conversion was found to be 1.97 to 75.6 months.

Analysis of the data showed that there were 46 men identified by the study with a mean time scale to conversion of 23.77 months. The 45 women identified in the study had a mean time scale to conversion of 25.45 months. A one-tailed *t*-test analysis showed no significant difference in mean time of progression between men and women in this study ($p = .323$).

Analysis of the patient populations by age yielded similar results. Patients between the ages of 50 and 59 ($n = 11$) had a mean time to conversion of 26.65 months. The age group of patients between the ages of 60 and 69 ($n = 21$) had a mean time of 29.39 months. Patients between 70 and 79 years ($n = 31$) had a mean time of 22.54 months, and patients older than 80 years ($n = 28$) had a mean time of 22.48 months. ANOVA analysis of these data showed that there is no statistically significant difference between time of AK progression to SCC in the different age groups ($p = .77$).

The time scale of conversion was also compared between different locations of the lesions. As shown

TABLE 1. Comparison by Lesion Location of Time Scale for AK Progression to SCC

Location of lesion	Mean time to conversion (months)	Number of patients
Scalp	22.54	17
Temple	16.75	5
Forehead	33.57	15
Eyebrow	15.86	6
Nose	28.24	19
Cheek	23.18	14
Ear	25.51	4
Trunk	28.54	3
Extremities	15.56	9

in Table 1, the mean times to conversion ranged from 15.56 to 33.57 months. ANOVA analysis showed no significant statistical difference between time to conversion among the different lesion sites ($p = .26$).

Discussion

Our data show that the progression of an AK to a SCC takes approximately 2 years. We also discovered that there is no significant statistical difference in the time to progression based on sex or age of the patient or location of the lesion. Therefore, our data illustrate that all AKs must be treated soon after diagnosis. Any delay in treatment may result in an AK progressing into a SCC.

The limitations of this study include the possible lag time to biopsy and diagnosis of the AK or SCC. Additionally, location errors are possible in which diagnosis of AK and SCC were made at separate locations. The small size of the study is also a limitation of the study. One further limitation of the study is the use of the EMR system. The Mount Sinai Dermatopathology department instituted EMRs in 1997. Therefore, any AKs that were biopsied before 1997 were excluded from the study. This could potentially skew the data to a shorter time scale. Although a more controlled *in vivo*, human study is indicated to reduce inherent study limitations, the data do provide a good estimate of the progression time course for AK conversion to SCC.

Conclusion

This study showed that of the estimated 10% of AKs that will develop into SCCs, the progression takes approximately 2 years. To impede progression to an SCC, physicians must treat AKs swiftly after diagnosis. The quick time scale for progression may help

improve patients' willingness to undergo the treatments for AKs, because current treatments of AKs are often opposed by patients due to irritation and slow healing. This information can also be utilized by physicians when educating patients about the relationship between sun exposure and skin cancer. A better understanding of the kinetics of conversion of precancer to cancer may improve treatment plans as well as sun protection habits and lead toward a decrease in incidence of SCC.

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