Actinic Keratoses: Reconciling the Biology of Field Cancerization with Treatment Paradigms

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This Perspective briefly reviews the relationship between UV-induced mutations in habitually sun-exposed human skin and subsequent development of actinic keratoses (AKs) and skin cancers. It argues that field therapy rather than AK-selective therapy is the more logical approach to cancer prevention and hypothesizes that treatment early in the process of field cancerization, even prior to the appearance of AKs, may be more effective in preventing cancer as well as more beneficial for and better tolerated by at-risk individuals. Finally, the Perspective encourages use of rapidly advancing DNA analysis techniques to quantify mutational burden in sun-damaged skin and its reduction by various therapies.


Actinic keratoses (AKs) are a discrete stage in the progression of normal skin to invasive squamous cell carcinoma (SCC) as a result of prolonged intermittent sun exposure (Criscione et al., 2009; Marks et al., 1988b; Ortonne, 2002). AKs have been subclassified on the basis of clinical and histologic features, resistance to therapy, and presumptive risk of near-term progression to SCC (Fernández-Figueras et al., 2015). AKs are chronic, recurring lesions and represent a substantial burden to the health care system owing to their high prevalence, treatment costs, and associated risk of frank malignancy (Rosen and Lebwohl, 2013; Stockfleth, 2017; Warino et al., 2006; Yeung et al., 2018). AKs are also quite distressing to many individuals as a cosmetic liability occurring by definition on habitually exposed body sites, especially the face and bald scalp.

Molecular abnormalities present in apparently normal habitually sun-exposed skin are well-documented and include the common driver mutations for cutaneous SCC (Albibas et al., 2018; Chitsazzadeh et al., 2016; Martincorena et al., 2015), albeit at lower frequencies than in SCCs (Ratushny et al., 2012). Not surprisingly, there appears to be a clear dose response for UV-induced mutations in habitually exposed skin with increasing age and also with frequency of sun exposure (intermittent vs. daily), measured as the burden of passenger mutations in excised basal cell carcinoma (BCC) specimens (Jayaraman et al., 2014). AKs appear to be intermediate in the mutational burden between normal habitually sun-exposed (photodamaged) skin and SCCs (Albibas et al., 2018). The best studied mutations are those that inactivate the tumor suppressor protein p53 (Brash et al., 1991; Ziegler et al., 1994), detectable in histologic cross-sections of skin as patches of positive immunostaining for the resulting nonfunctional but stabilized protein (Brash et al., 1991; Jonason et al., 1996). Unfortunately, as clearly relevant as these mutations are to malignant progression, at present, there are no data in man linking the mutation burden to clinical features of AKs or the response of AKs to therapy. Of interest, however, in chronically UV-irradiated hairless mouse skin, 0.05% ingenol mebutate gel (two daily applications), an AK therapy shown to be effective in man (Jansen et al., 2019), reduced premalignant papilloma formation as well as the number of p53-positive immunostained patches, both by approximately 70% (Cozzi et al., 2012), suggesting that reduction in epidermal mutation burden parallels clinical improvement.

The known etiologic role of sun exposure, specifically UV light exposure, in producing signature mutations in the TP53 gene that encodes p53 (Brash et al., 1991; Einspahr et al., 1997; Kanjilal et al., 1995; Ziegler et al., 1994) and many other genes critical to orderly epidermal proliferation and maturation (Chitsazzadeh et al., 2016; Jayaraman et al., 2014) makes sun protection the logical cornerstone of prevention of AKs, SCCs, and BCCs (Nehal and Bichakjian, 2018). Ideally, but alas rarely, lifelong sun protection with appropriate clothing and sunscreen use begins in early childhood (Robinson et al., 2000; Stern et al., 1986). Fortunately, beginning regular use of a sun protection factor 15 or higher sunscreen even in an already severely sun-damaged population with a history of at least one skin cancer reduced the development of new skin cancers by 40% over a 5-year follow-up period (Green et al., 2011, 1999; van der Pols et al., 2006). Similarly, regular sunscreen use in a cohort with AKs only reduced the number of clinically detectable lesions within 1 year (Thompson et al., 1993). Conversely, continued unprotected sun exposure of already moderately to severely photodamaged skin, as evidenced by the presence of AKs, greatly increases the risk of new AKs and invasive SCCs as well as BCCs, not known to have a clinically identifiable
previously, within an affected area such as the face or bald scalp (Marks et al., 1988a). SCCs may arise from pre-existing AKs, and all the three lesions (AKs, SCCs, and BCCs) may arise from clinically nonlesional photodamaged skin, a process termed field cancerization (Dakubo et al., 2007; Vanharanta and Massagué, 2012; Willenbrink et al., 2020).

Previously, the relationship of clinically detectable AKs to SCC development was recognized (Jonason et al., 1996), but before the concept of field cancerization was widely appreciated, clinicians began to advocate the destruction of individual AKs as a cancer prevention measure (Ceilley and Jorizzo, 2013). During the period 2007–2015, destructive therapies (cryotherapy, curettage, electrocautery, and chemical peels) accounted for 77% of patient visits for AK and cost the healthcare systems an estimated $413.1 million annually (Yeung et al., 2018). Liquid nitrogen (LN2) cryotherapy remains the most widely used modality, accounting for perhaps 50% of all patient care visits for AKs (Hagele et al., 2012; Kirby et al., 2017). Unfortunately, recurrence rates for individual AKs treated with cryotherapy are high, strongly influenced by lesion thickness and location (Krawtchenko et al., 2007; Simon et al., 2015) as well as the aggressiveness of the freeze, which is limited by patient pain tolerance and scarring risk (Thai et al., 2004). In formal studies, 3-month complete clearance rates vary from 39% to 83% for nonhypertrophic AKs (Thai et al., 2004). In practice, for most patients with more than an occasional clinically detectable AK, cryotherapy sessions are usually scheduled at 3- to 6-month intervals and are required indefinitely.

When 5-fluorouracil (5-FU) was introduced as a systemic cancer chemotherapeutic agent in the 1950s (Longley et al., 2003; Rutman et al., 1954), it was observed in patients with moderate to severe photodamage that multiple AKs first appeared or became more readily visible during chemotherapy and that some lesions resolved completely after the 5-FU course (Falkson and Schulz, 1962; Johnson et al., 1987). Subsequently, trials of topical 5-FU therapy established it as safe and effective for the management of relatively large areas with multiple AKs, such as the entire face or scalp (Gupta et al., 2012; Jansen et al., 2019; Pomerantz et al., 2015). As a field therapy, it was an attractive approach for patients with multiple AKs at high risk of progression to invasive skin cancer. Predictably, however, the treatment proved very difficult and distressing for many patients because it produced widespread and often marked erythema as well as discomfort of the treated area for many months (Ceilley and Jorizzo, 2013; Erntoft et al., 2016; Shergill et al., 2013). Repeat prolonged courses were required to control new and recurrent AKs in most patients (Pomerantz et al., 2015). Numerous modifications of the original 5-FU protocol have only partially addressed these issues (Epstein, 1998; Werschler, 2008).

More recently, several other therapies that preferentially destroy the abnormal cells in a photodamaged field have been approved as safe and effective by the Food and Drug Administration. For example, 5% imiquimod cream applied twice weekly for up to 16 weeks resulted in complete clearance of nonhypertrophic AKs after 1 year in 50% of patients in a meta-analysis of clinical trials (Hadley et al., 2006; Hashim et al., 2019), albeit at a cost of frequent to near-constant erythema, crusting or scabbing, and other local adverse effects during the period of use (Hadley et al., 2006). Roughly similar clearance rates and side effect profiles have been reported for 0.05% ingenol mebutate, 3% diclofenac, and photodynamic therapy with either methyl aminolevulinate or aminolevulinic acid, allowing for differences in treatment protocols and outcome measures among trials (Gupta et al., 2012; Jansen et al., 2019). Whereas some patients and their physicians find these agents easier to use than they find 5-FU owing to shorter duration of treatment and/or less severe local skin reactions during and after treatment, these characteristics nevertheless have limited the use of all field therapies among highly motivated patients with relatively advanced field cancerization considered to be at far higher risk of short-term progression to cancer than patients with only one or a few AKs.

The above experience, in combination with an appreciation of the dynamics and implications of field cancerization, suggests a different approach to managing the huge societal burden of UV-induced skin cancer in the United States. The underlying logic and hypothetically expected results from this approach are shown in Figure 1. The schema assumes that cumulative sun damage occurs in essentially everyone beginning in infancy and progresses at a variable rate throughout life determined by intensity and frequency of sun exposure, patient compliance, and other factors influencing resistance to UV-induced mutations (solid blue line in Figure 1). This progression of damage is shown as exponential on the basis of the assumption that early UV-induced mutations such as those in the tumor suppressor gene TP53 impair epidermal ability to repair or eliminate subsequent UV damage (Ziegler et al., 1994), accelerating the accumulation of mutations. With minimal damage, the skin’s appearance remains normal for most individuals at least into early adulthood. As damage continues to accumulate, clinical changes of photodamage (dyspigmentation, roughness, etc.) appear and then gradually progress. By mid to late adulthood, many fair-skinned individuals begin to develop AKs within the fields of photodamage. The rate of malignant transformation to SCC per individual AK lesion per year has been estimated to range from 0.025% to 16% and usually <1% (Criscone et al., 2009; Fuchs and Marmur, 2007; Glogau, 2000; Marks et al., 1988a, 1988b), but up to 60% of SCC arise from pre-existing AKs (Criscone et al., 2009; Marks et al., 1988b), justifying therapy. If an effective field therapy is first instituted when multiple AKs are present (the later Rx1 in Figure 1), this schema assumes that the clinical and molecular severity of field cancerization is reduced, presumably through the destruction of the most severely damaged (mutated) epidermal stem cells, resulting in the temporary disappearance of all AKs in many patients (solid red line in Figure 1). Then, with continued UV exposure, cancerization again resumes an upward trajectory and AKs again appear after a few months. If instead, field treatment is given earlier in the accumulation of damage and before the
appearance of AKs (the earlier RX1 in Figure 1), the initial treatment-associated improvement in mutational burden leads to a temporary reduction in signs of photoaging and a considerable delay in appearance of AKs. In both instances, treatment often delays or prevents the appearance of SCCs and other cutaneous malignancies throughout the remaining lifespan. Whether patients and their physicians would favor earlier or later field treatment or even repeated treatments (RX2 in Figure 1) should logically depend on their cost and effectiveness as well as the duration and severity of expected adverse effects such as erythema and other local skin reactions. The prospect of many years of improved skin appearance and delayed or eliminated appearance of AKs and skin cancer would however argue for early and possibly repeated intervention. Early intervention might also encourage scrupulous sun protection, leading to attractive cancer-free skin over the remaining lifespan, as indicated by a slower rate of damage progression (dashed blue lines in Figure 1).

There are corollaries of this schema for the development of new AK therapies. First, it would be highly desirable to better document and quantify the progressive mutational burden associated with nonlesional photodamaged skin, AK-bearing skin, and cancer-bearing skin as well as the presumed decrease in mutational burden after specific field therapies. Recent advances in whole-exome sequencing methodologies and the development of a noninvasive nonscarring epidermal sampling technique for quantifying mutation burden (Muradova et al., 2020) should permit such data collection. Second, and far easier, would be to document improvement in photodamaged skin appearance after treatment (Touma et al., 2004) because this would provide strong motivation for patient compliance.

Solid organ–transplant recipients are at greatly increased risk of developing AKs and SCCs, presenting an enormous management challenge (Euvrard et al., 2003). A recent review found 2–6 months complete clearance rates of AKs for multiple current therapies that were similar to those achieved in standard AK trials (Heppt et al., 2019). However, the problem of AKs progressing to SCCs, with their high metastatic and fatality rates in this population (Lanz et al., 2019; Lott et al., 2010), is clearly unresolved. A prospective trial of intermittent field therapy beginning immediately after transplantation before the expected appearance of multiple AKs and including repeated measurement of mutation burden as well as the number of AKs and SCCs would be very informative. Preferably, such a trial would include an untreated control area such as one arm, an ethical proposal given that no therapy other than sunscreen use is currently the standard of care for virtually all patients who have undergone or will undergo transplantation not yet experiencing the development of SCC and other skin cancers. Photographic documentation of the patients’ habitually exposed skin areas to
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determine both the rate of progression from normal or mildly photodamaged skin to AKs and SCCs, as well as the impact of repeated field therapy, would provide important additional confirmation of the Figure 1 schema.

AKs represent a highly prevalent premalignant condition and a reliable risk factor for the development of SCC and other skin cancers. Whereas the understanding of field cancerization has greatly increased in recent decades, promoting the more rational use of field therapy over traditional AK-specific treatment modalities such as LN2 cryotherapy, for patients with multiple lesions, current treatment paradigms do not reflect current biologic understanding. Even in severely affected individuals, cryotherapy sessions remain the most common approach, accounting for nearly half of AK-related treatment costs. This seemingly curious choice, which fails to treat the majority of skin in a clearly carcinized field, all of which is at risk of developing AKs and/or invasive malignancies, surely reflects long-established physician reimbursement policies but also the current arguable practice of reserving field therapy for patients with advanced disease. This practice in turn reflects the higher short-term cost and resulting reluctance of third-party payers to reimburse for field therapy but also patients’ concerns for downtime related to uncomfortable highly visible local skin reactions to current broad-area treatments. Not part of the decision-making process currently is the likelihood that treating patients earlier in the natural history of their disease would result in far less severe skin reactions owing to the lesser mutational burden in their skin as well as decreased lifetime risk of developing invasive malignancies (Figure 1) with their higher morbidity and associated treatment costs.

Over the past century, there has been a profound increase in our understanding of carcinogenesis. As expected, cancer prevention and treatment approaches have evolved to at least partially incorporate this knowledge base, albeit with a delay attributable to the development of needed new drugs, as well as more meaningful documentation of their effectiveness and cost effectiveness. As argued earlier, AK treatment and skin cancer prevention protocols are now poised to benefit more fully from an integration of current biologic understanding into new drug development and approval metrics.

Data availability statement
No datasets were generated or analyzed in preparing this perspective.

CONFLICT OF INTEREST
BAG is not currently a paid consultant to any company involved in the diagnosis or treatment of AKs but has in the past served on the advisory board of several.

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REFERENCES


