Nonablative Fractional Laser Treatment Is Associated With a Decreased Risk of Subsequent Facial Keratinocyte Carcinoma Development

Travis A. Benson, MD,* Brian P. Hibler, MD,†‡ Dylan Kotliar, MD, PhD,§‖ and Mathew Avram, MD, JD‡

BACKGROUND Keratinocyte carcinoma (KC) is the most common type of nonmelanoma skin cancer. Currently, prophylactic treatment options are limited. Nonablative fractional lasers (NAFL) have received the Food and Drug Administration approval for the treatment of actinic damage; however, their role in KC prophylaxis is not known.

OBJECTIVE The aim of this study is to determine whether NAFL treatment is associated with a decrease in subsequent facial KC development.

MATERIALS AND METHODS A retrospective cohort study of patients with a history of facial KC treated at the Massachusetts General Hospital Dermatology Laser and Cosmetic Center between 2005 and 2021 was conducted.

RESULTS Forty-three NAFL-treated patients with a history of facial KC and 52 matched control subjects were included in the study. The rate of subsequent facial KC development was 20.9% in NAFL-treated patients and 40.4% in control subjects (RR 0.52, $p = .049$). Control subjects developed new facial KC significantly sooner than NAFL-treated patients ($p = .033$). When controlling for age, gender, and skin type, control subjects were more likely to develop new facial KC than NAFL-treated patients (hazard ratio 2.65, $p = .0169$).

CONCLUSION NAFL treatment was associated with a decreased risk of subsequent facial KC development and may have a benefit for KC prophylaxis.

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), collectively known as keratinocyte carcinoma (KC), are the most common types of nonmelanoma skin cancer. In 2012 alone, there were an estimated 5.4 million cases of KC diagnosed in 3.3 million patients, 80% of which were BCC and nearly 20% were SCC.[1] In white populations, the lifetime risk of developing BCC is 30%, far exceeding any other form of cancer. In individuals with a history of KC, the 3-year cumulative risk of developing a subsequent KC is 35%, whereas the 5-year cumulative risk is 50%.[2]

KCs can place a large financial burden on the health care system, accounting for an estimated 4% of malignant tumor expenditures in the United States.[3] In 2012, there were an estimated 3.3 million individuals treated for KC in the United States.[4] Cutaneous SCC alone accounts for 6.2 of every 100,000 hospitalizations with each hospital stay lasting an average of 5.8 days and costing an average of $66,841.[5] With a large aging population, the prevalence and cost are expected to rise, emphasizing the need for improved prophylactic therapies.

The most common risk factor for the development of KC is chronic ultraviolet radiation exposure. There has been a push to identify prophylactic therapies to prevent KC, which could offer benefit for a large population of individuals who have accumulated significant actinic damage. Nonablative fractional lasers (NAFL) have been shown to treat actinic damage, including precancerous actinic keratoses (AK).[6–9] Although ablative laser treatment has been shown to reduce KC incidence, it is unknown whether NAFL therapy provides similar benefit. The aim of this study is to determine whether NAFL treatment might confer prophylaxis against the development of subsequent KC in patients with a history of facial KC. A retrospective cohort study comparing the rates of subsequent facial KC development between NAFL-treated patients and matched control subjects was conducted.

Methods

Following exemption from the Mass General Brigham (MGB) institutional review board (#2020P002417), a retrospective chart review of patients was performed. The treatment group is defined as patients who have a history of facial KC and have received NAFL therapy at the Massachusetts General Hospital Dermatology Laser and Cosmetic Center (MGH DLCC). At the MGH DLCC, NAFL therapy was performed using topical anesthetic (lidocaine 23%, tetracaine 7%) for 1 hour, which was removed before treatment. Each area of the face (right, left,

*From the *Harvard Medical School, Boston, Massachusetts; †Schweiger Dermatology Group, New York, New York; ‡Dermatology Laser and Cosmetics Center, Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts; §Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts; and‖Broad Institute of MIT and Harvard, Cambridge, Massachusetts*

The authors have indicated no significant interest with commercial supporters.

Address correspondence and reprint requests to: Travis Benson, MD, Massachusetts General Hospital Laser and Cosmetics Center, 50 Staniford Street, Suite 250, Boston, MA 02114 travisarmondbenson@gmail.com

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forehead, nose) was treated by making 2 passes of the laser in the vertical direction, followed by 2 horizontal passes, and 2 additional vertical passes. Ice packs and a sunscreen moisturizer were applied posttreatment. Repeat treatments are performed as early as 1 month; however, most patients had repeat treatment at least 1 year after the initial treatment.

Control subjects are defined as patients who have a history of facial KC, have never received facial NAFL therapy, and have been seen at DLCC. The cohort was assembled using the MGB Research Patient Data Registry (RPDR) Query Tool. To identify eligible participants for the treatment group, a query was generated based on International Classification of Diseases (ICD) 10 codes for facial KC, a search for the term "Fraxel" (Solta Medical, Hayward, CA) in the electronic medical record to identify NAFL treatment, and at least 1 documented visit to DLCC:

"Basal cell carcinoma of skin of other and unspecified parts of face" (ICD 10:C44.31), "Squamous cell carcinoma of skin of other and unspecified parts of face" (ICD 10: C44.32), "Basal cell carcinoma of skin of lip" (ICD 10: C44.01) AND "visit notes search for any Fraxel" AND "location MGH Laser and Cosmetic Center."

The query generated one hundred seventy patients. An initial screen was performed, and 90 patients were excluded for not receiving NAFL treatment. A thorough chart review was then conducted for each patient, and age, gender, Fitzpatrick skin type, NAFL history (dates, parameters, locations), pathology-confirmed facial BCC and SCC dates, history of immunosuppressive medication use, and most recent total body skin examination (TBSE) were documented. Patients who received NAFL treatment at an outside clinic (n = 12), received NAFL treatment in a location other than the face (n = 6), only received NAFL treatment before first diagnosed KC (n = 4), or lacked a pathology-confirmed KC diagnosis (n = 7) were excluded. None of the patients were found to have a medical history predisposing to KC (organ transplantation, radiation exposure, hematologic malignancy, genetic syndrome, long-term immunosuppressive medication use). Of the one hundred seventy patients returned in the RPDR query, 51 were initially included in the study.

A second RPDR query was generated to identify matched control subjects based on ICD 10 codes for facial KC and at least 1 documented visit to the DLCC:

"Basal cell carcinoma of skin of other and unspecified parts of face" (ICD 10:C44.31), "Squamous cell carcinoma of skin of other and unspecified parts of face" (ICD 10: C44.32), "Basal cell carcinoma of skin of lip" (ICD 10: C44.01) AND "location MGH Laser and Cosmetic Center."

This initial query returned one thousand one hundred seventy-sixth control subjects. To exclude NAFL-treated patients from the control cohort, an RPDR-matched control query was generated by matching control subjects based on age and sex to the initial query generated for NAFL-treated patients while excluding the NAFL-treated patients from the set of matched control subjects, ensuring that no NAFL-treated patients were included in the control cohort. This returned 176 control subjects. Control subjects who were matched to an excluded participant (n = 134) were excluded. A thorough chart review was then conducted for each control, and age, gender, Fitzpatrick skin type, pathology-confirmed facial BCC and SCC dates, history of immunosuppressive medication use, and most recent TBSE were documented. Control subjects who lacked a pathology-confirmed KC diagnosis (n = 6) or had a single KC diagnosis at the time of most recent TBSE (n = 3) were excluded. Nineteen unused control subjects were then matched to the remaining unmatched participants based on age and sex. After control matching, an additional 8 NAFL-treated patients were excluded because they received NAFL treatments that predated a diagnosis of facial KC, leaving a final sample size of 43 NAFL-treated patients and 52 control subjects.

A survival analysis was conducted to determine whether there was a difference in the time to developing an additional facial KC between NAFL-treated patients and control subjects. For NAFL-treated patients, time point zero was defined as the date of first pathology-confirmed facial BCC or SCC diagnosis before NAFL treatment. For control subjects, time point zero was defined as the date of first pathology-confirmed facial BCC or SCC diagnosis. The end point was defined as the date of next pathology-confirmed facial BCC or SCC diagnosis or the most recent documented TBSE. If a participant reached the TBSE end point without developing an additional facial KC, they were censored at that time point.

Survival analyses were conducted using the Python package Statsmodels version 0.13.1. A logrank test was performed to determine a difference in development time between NAFL-treated patients and control subjects. A Cox proportional hazards model was then used to determine a difference in development time while controlling for age, gender, and Fitzpatrick skin type. Subgroup survival analyses and logrank tests were then conducted among NAFL-treated patients to ascertain whether there is a significant difference in development time based on gender, the number of NAFL treatments, the type of NAFL-treatment, and Fitzpatrick skin type.

Results

Of the initial One hundred seventy patients identified in the initial RPDR query, 43 NAFL-treated patients met all inclusion criteria. The mean age was 67.88 years for NAFL-treated patients and 66.75 years for control subjects. The gender distribution was 23.3% male and 76.7% female for the NAFL-treated group and 21.2% male and 78.8% female for the control group (OR 0.89, p = .810) (Table 1).

Among the NAFL-treated patients, 20.9% developed an additional facial KC compared with 40.4% of control subjects (RR 0.52, p = .049–Fisher exact test) (Table 1). When comparing the length of time to develop a new facial KC, control subjects developed new facial KC significantly sooner than NAFL-treated patients (p = .033, logrank Test) (Table 2, Figure 1A). In a subgroup survival analysis of the NAFL-treated group, no significant difference in survival time was found between genders (p = .409), the type of NAFL treatment (p = .283), the number of NAFL

TABLE 1. Participant Characteristics				
	NAFL Treated	**Matched Controls**	**Odds Ratio**	***p***
N	43	52		
Gender				
M	10	11	0.89	.810
F	33	41		
Mean age (SD)	67.88 (±7.79)	66.75 (±12.66)		
Skin type				
I	4	3		
II	33	39		
III	5	7		
Unknown	1	3		
NAFL type				
1,550 nm	21			
1927 nm	17			
Both	5			
NAFL treatments				
1–2	29			
3 or more	14			
Mean NAFL fluence (mJ/cm^2)				
1,550 nm	59.24 (±12.29)			
1927 nm	10.43 (±1.51)			
Mean NAFL energy (kJ)				
1,550 nm	1.95 (±1.75)			
1927 nm	1.12 (±0.83)			
Subsequent KC development				
Development (%)	9 (20.93)	21 (40.38)	0.52 (RR)	.049
No development (%)	34 (79.07)	31 (59.62)		
Mean time to subsequent KC diagnosis (d)	2,361.33 (±1800.85)	2,255.19 (±1968.64)		

KC, keratinocyte carcinoma; NAFL, nonablative fractional laser.

treatments (p = .124), or Fitzpatrick skin type (p = .877) (Table 2, Figure 1). When controlling for age, gender, and Fitzpatrick skin type, control subjects were found to be more likely to develop a new facial KC than patients treated with NAFL (hazard ratio 2.65, p = .0169) (Table 2).

Discussion

In this retrospective cohort study of patients with a history of facial KC, it was found that those treated with NAFL had about half the risk of developing a subsequent facial KC compared with those who did not receive NAFL. In addition, the time to develop subsequent facial KC was significantly longer in patients treated with NAFL compared with untreated control subjects. These findings suggest that NAFL may serve an important role in KC prophylaxis in individuals with a history of KC. Although not statistically significant, there was a trend toward reduced risk of developing subsequent facial KC with increasing number of treatments, warranting future investigation.

Regaerding treatment, destructive therapy has long been the gold standard in the treatment of AKs.[10] Currently, available treatments for actinic damage include medications, such as 5-fluorouracil (5-FU), nicotinamide, retinoids, imiquimod, ingenol mebutate, and diclofenac. Cryotherapy and photodynamic therapy are frequently used as well.[11] However, these modalities can be limited by pain and significant downtime with an often unpredictable response. In the case of 5-FU, upward of 100% of patients experience some degree of morbidity in the form of pain and erosions, whereas nearly 60% of patients were found to have new or recurrent AKs 1 year following the treatment.[10] Nicotinamide has been shown to reduce the rate of AK and KC development; however, the chemoprotective benefit of the supplement does not persist following discontinuation. Data regarding the use of oral retinoids, such as acitretin, in KC prevention are variable, and side effects of treatment (mucositis, lipid abnormalities, teratogenicity) can be a major limiting factor.[11]

TABLE 2. Differences in Development Time

			X^2	*p*
NAFL treated v. matched controls			4.527	.033
Gender (NAFL treated)			.680	.409
Number of treatments (NAFL treated)			2.363	.124
NAFL type (NAFL treated)			1.154	.283
Skin type (NAFL treated)			.263	.877
Cox proportional hazards model	HR	*t*	*p*	confidence interval
NAFL treated vs matched controls	2.65	2.39	.0169	1.19, 5.89
Gender	1.82	1.27	.2038	.72, 4.58
Skin type				
II	1.93	0.83	.4047	.41, 9.09
III	3.24	1.29	.1970	.54, 19.33
Unknown	1.51	0.31	.7548	.12, 19.64
Age	1.00	0.15	.8778	.97, 1.03

HR, hazard ratio; NAFL, nonablative fractional laser.

Although the aforementioned therapies are available for the treatment of AKs, this does not necessarily translate into efficacious KC prophylaxis. The most effective and safest approach for skin cancer prophylaxis is strict photoprotection, using broad-spectrum sunscreens and photoprotective behaviors.[12] Evidence has shown that high-dose topical tretinoin is ineffective in the prevention of KC.[13] In addition, 5-FU and imiquimod have been shown to be ineffective in the prevention of subsequent site-specific KC.[14] Given these limitations, there is a great need for other prophylactic options. Emerging evidence suggests that laser therapy could play a role in the prophylaxis of AKs and KCs. A retrospective study of 24 patients with widespread facial actinic damage treated with ablative lasers, such as carbon dioxide (CO_2) or erbium-doped yttrium aluminum garnet (Er:YAG), demonstrated a 94% reduction in AKs. In addition, 87% of patients did not have recurrence of AKs or KCs for a year following laser therapy.[15] Another study found a ten-fold reduction in the number of new subsequent KC in areas treated with CO_2 laser compared with control subjects.[16] However, full facial laser resurfacing with CO_2 or Er:YAG lasers have decreased in popularity as a result of prolonged downtime, wound care, and risk for scarring and permanent dyschromia.

In comparison, NAFL is generally better tolerated with fewer complications. In 2013, the Food and Drug Administration approved Fraxel DUAL 1550/1927 nm Laser System (*Solta Medical, Hayward, CA*), a NAFL device, for the treatment of AKs.[17] Combined treatment with 1,550 nm NAFL and 0.025% tretinoin cream has shown to have a 54% reduction in AK severity at 4 weeks and 46% reduction at 24 weeks.[6] As monotherapy, 1 study found a 55.6% reduction in AKs at 6 months following 5 treatments with 1,550 nm NAFL.[7] Similarly, another study demonstrated an 86.6% reduction in AKs at 6 months following one 1927 nm NAFL treatment.[8] Most recently, a study found a 79% improvement in AK severity at 6 months following treatment with 1,540 nm NAFL.[9]

Although the mechanism of NAFL's use in AK treatment is not completely understood, it is believed that fibroblast stimulation may play an important role. In patients with chronic ultraviolet B (UVB) exposure, the age of an individual contributes to the development of KCs through suboptimal UVB damage repair mechanisms. In elderly skin, fibroblasts become senescent, which results in decreased levels of insulin-like growth factor (IGF-1)—a hormone that plays an important role in keratinocyte regulation. In vitro studies have shown that IGF-1 inhibits UVB-damaged keratinocyte proliferation and local injections of exogenous IGF-1 can have an anticarcinogenic effect.[18,19]

Coagulation of the epidermis and papillary dermis by cosmetic skin rejuvenation techniques, such as NAFL, have been shown to upregulate IGF-1 levels in skin fibroblasts in geriatric skin,[20] providing a plausible physiologic mechanism for NAFL in the reversal of the procarcinogenic response to UVB-induced DNA damage. A study of topical IGF-1 receptor inhibitor on a human skin/immunodeficient mouse xenograft model revealed increased histological features of AKs and increased keratinocyte proliferation compared with control subjects, further suggesting that IGF-1 is a regulator of a procarcinogenic response to UVB exposure.[21]

It is hypothesized that the effect of 1,550 nm compared with 1927 nm NAFL (Figure 1D) could be due to the deeper penetration of thermal injury from the 1,550 nm laser and therefore elicit a more robust intratumoral immune response leading to increased immune surveillance. In addition, lidocaine has been shown to potentiate the thermal sensitivity of S-phase cells in the skin,[22] potentially creating a dose–response effect among precancerous cells with thermal injury induced by the 1,550 nm laser. Repeat

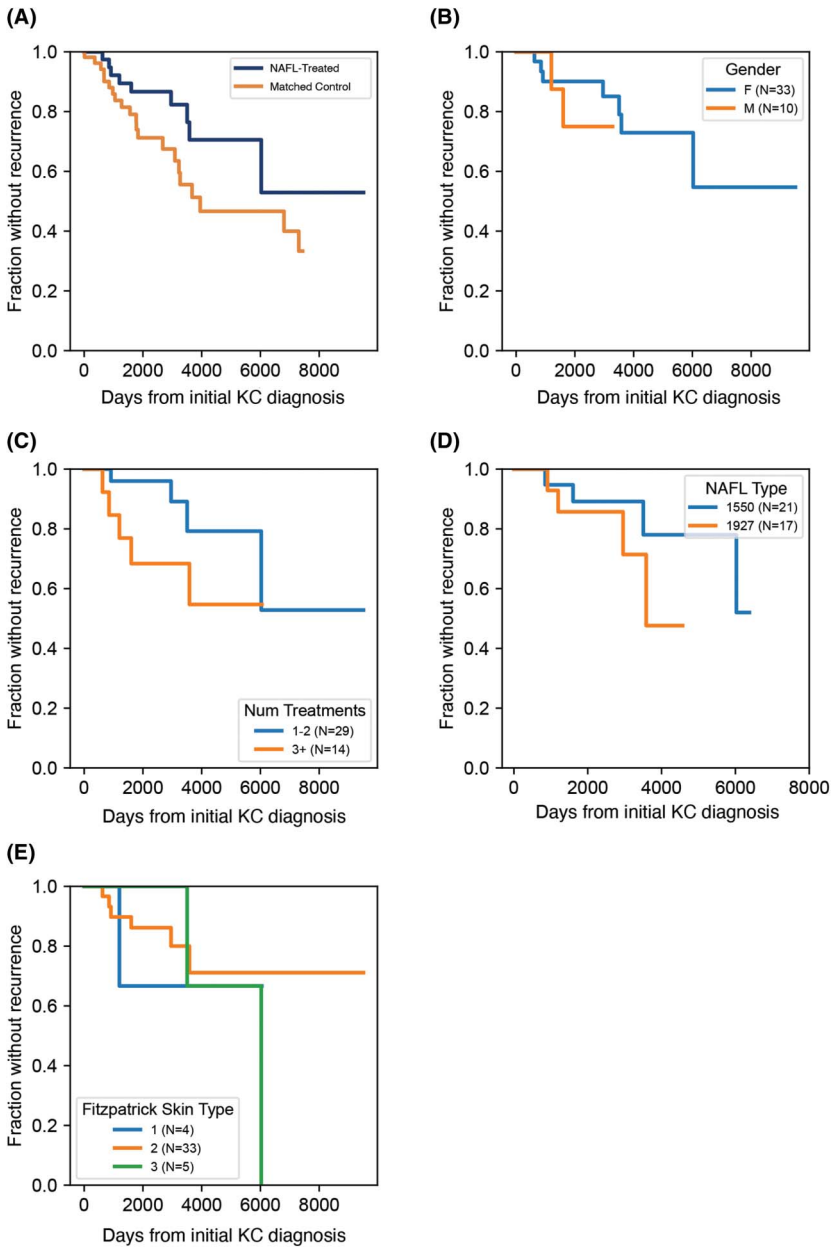

Figure 1. (A) Differences in recurrence time between NAFL-treated patients and matched control subjects. (B) Differences in development time in NAFL treated by gender. (C) Differences in development time in NAFL treated by number of treatments. (D) Differences in development time in NAFL treated by NAFL type. (E) Differences in development time in NAFL treated by skin type. NAFL, nonablative fractional lasers.

fractional CO_2 laser treatments in a mouse model yielded decreased SCC formation and prevented photodamage,[23] likely from increased immune surveillance, restoration of IGF-1 levels, and repeated regeneration of dysplastic skin. With these findings in mind, it is suspected that NAFL treatment would reduce the overall burden of photodamaged keratinocytes and may promote a wound healing response, which gives healthy epidermal cells a selective advantage. A standardized prospective study is needed to evaluate the longevity of NAFL's protective effects.

Limitations

There are several important limitations of this study worth noting. First, this is a retrospective cohort survival analysis and does not standardize treatment parameters, such as time from initial KC diagnosis, laser wavelength, laser fluence, total energy per treatment, number of laser passes, and frequency of treatment over time. Second, this study only looks at the development of a second facial KC. Further investigation should be done to evaluate whether NAFL therapy is associated with fewer KC development over a longer period. Third, the patient population was racially and ethnically homogeneous, with most patients having a Fitzpatrick skin type of II and therefore may not be generalizable to the entire population. This study does not account for unreported KC or NAFL treatments where participants were seen at an outside facility. Finally, it can be argued that patients who seek laser treatments may

engage in a greater level of skin surveillance than the general population. However, this theory further supports the potential role for NAFL therapy in KC prophylaxis because the NAFL-treated patients would be more likely to report a new facial KC.

Conclusion

In addition to the treatment of AKs, NAFL may have a benefit for KC prophylaxis in patients with a history of facial KC. Further controlled, prospective studies are warranted to more critically assess the role of NAFL, the duration of protective effects, and optimal treatment parameters in KC prevention.

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