Chemoprevention of Head and Neck Cancer With Retinoids

A Negative Result

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Objective: To determine whether isotretinoin (or 13-cis-retinoic acid) decreases the risk of second primary cancers in patients previously treated for cure of head and neck squamous cell carcinoma.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Two head and neck multidisciplinary cancer clinics in university teaching hospitals taking cases from 4 to 5 million people in Queensland, Australia, combined to enter appropriate patients into this trial.

Patients: One hundred fifty-one patients with their first head and neck squamous cell carcinoma treated with high expectation for cure and living close by. They were randomized into 3 arms to receive 3 years of treatment.

Interventions: Patients took isotretinoin at a high dose (1.0 mg/kg per day) or a moderate dose (0.5 mg/kg per day) or placebo. Group 1 took the high dose for 1 year and then the moderate dose for 2 years. Group 2 took the moderate dose for 3 years. Group 3 took placebo for 3 years.

Main Outcome Measures: The diagnosis of a second primary malignancy of the head and neck, lung, or bladder was regarded as the end point signifying failure of therapy. Issues of drug adverse effect profile and impact on survival were measured.

Results: There was no significant difference in the occurrence of second primary disease (P=.90), the recurrence of primary disease (P=.70), or disease-free time (P=.80) between the treatment and nontreatment arms. Numbers were too small to find differences in survival.

Conclusion: With evidence that retinoid treatment adversely affects survival of lung cancer and with this drug not significantly decreasing the incidence of second primary tumors of head and neck squamous cell carcinoma, the use of this drug in head and neck cancer patients for second cancer prophylaxis is not indicated.


The retinoids are analogues of vitamin A, first identified in the 1920s. It was soon noted that people with a dietary lack of vitamin A were prone to malignant and premalignant changes in the skin and mucosal surfaces. In 1983, Shah et al used topical retinoid for premalignant changes in the oral cavity, with moderate improvement. In 1986, Hong et al from the University of Texas M. D. Anderson Cancer Center, Houston, reported similar results for the more convenient tablet form of retinoid, 13-cis-retinoic acid or isotretinoin. The drug was taken at 1 or 2 mg/kg per day for as long as 3 months, with no difference in response between the 2 doses. In both of the mentioned series, approximately two thirds of patients with significant oral premalignant changes had good improvement clinically, with many recurrences on cessation of therapy. In another study from the University of Texas M. D. Anderson Cancer Center group, 66 patients with premalignant oral cavity mucosal disease were initially treated with isotretinoin for 3 months at 1.5 mg/kg per day, and then randomized to receive either beta carotene (30 mg/d) or low-dose isotretinoin (0.5 mg/kg per day) for 9 months. While there was a significant clinical response in only 55% of individuals after the initial 3 months of therapy, there was a 92% “stabilization of the lesions” in those receiving isotretinoin maintenance therapy compared with 45% in those receiving beta carotene. Because most patients with head and neck mucosal malignancy do not notice premalignant changes before presenting with their invasive cancers, the role of agents that reverse pre-
malignancy did not create much interest among head and neck surgeons.

The observation that patients cured of head and neck mucosal malignancy have a high rate of second and even third primary lesions was made in 1953 by Slaughter et al,7 who coined the term condemned mucosa. The accurate collection of cancer registry data has revealed a high second cancer rate, possibly as high as 5% to 7% per year, that may not decrease with time.6 This predisposition to second cancers may be a greater cause of mortality in head and neck cancer patients with small lesions at a young age than their initial lesions.

A pilot study by Hong et al in 19907 created much interest in the head and neck field. One hundred three head and neck cancer patients treated for cure received either high-dose isotretinoin or placebo for 12 months. One third of the treatment group did not complete their course of therapy because of the adverse effects of the drug at the high doses given to the patients enrolled in the early phase of the trial. The dose was decreased for those enrolling in the trial later. The median follow-up was 32 months. Of the 49 patients who took isotretinoin for the full 12 months, only 2 developed second primary cancers, compared with 12 of the 51 patients in the placebo group. More than 30% of patients developed recurrence of their first tumor, so that only 34 in each group were fully evaluable. This study failed to reach statistical significance. If proved beneficial, isotretinoin therapy could have been a major leap forward in head and neck cancer cure and a potent cancer prophylactic for ex-smokers.

The aims of the present study were first to try to confirm that treatment with isotretinoin is more effective than placebo in preventing second primary tumors in those with head and neck squamous cell carcinoma (HNSCC). Second, the study sought to determine whether treatment with high-dose (approximately 1.0 mg/kg per day) isotretinoin for 12 months followed by maintenance low-dose treatment (approximately 0.5 mg/kg per day) for a further 24 months is more effective in preventing second primary tumors than low-dose treatment for the full 36 months. These doses of isotretinoin were used and found effective in previous studies.2,3,7 Also to be examined were disease-free and absolute survival and the tolerability of these regimens.

The 2 major head and neck cancer clinics in Brisbane review most of the HNSCC patients diagnosed in 4 to 5 million people who live in Brisbane or come to Brisbane for tertiary medical services. With funding and technical support of the Queensland Cancer Fund, Fortitude Valley, Queensland, and Hoffmann La Roche Pharmaceutical Company, Basel, Switzerland, a study was undertaken to emulate the indications, selection criteria, drug dosage, and follow-up used by Hong et al7 to hopefully confirm their findings, this time with statistical significance. One previous study2 had shown no difference in the resolution of premalignant change using 1 mg/kg per day compared with 2 mg/kg per day, while a 0.5-mg maintenance dose was found effective in stabilizing or reversing oral premalignancy.7 Because the dosage and duration of drug treatment were unknown, and the cost and adverse effects of therapy are significant, a 3-armed randomized, double-blind, placebo-controlled trial was initiated. Given an estimated second primary cancer incidence of 5% per year, and an expected therapeutic effect being an 80% reduction in second primary cancer,7 enrollment of 125 patients per treatment arm would detect the expected therapeutic effect with a power of at least 90% and with no more than 5% chance of type I error.

During a 7-year period, all patients presenting to the head and neck clinics at the Princess Alexandra Hospital and the Royal Brisbane Hospital (both with new patient numbers of ≥250 per year) were reviewed for possible enrollment. This included a cohort assessed and treated at the Royal Brisbane Hospital but followed up at Rockhampton Hospital. Only those with invasive HNSCC were included. Patients needed to live close by for ease of monitoring and be self-sufficient, with a Karnofsky score of at least 60. In fact, all participants had a Karnofsky score of 100. All had to have a reasonable expectation of cure and be clinically free of disease at recruitment. In fact, few developed recurrent disease (15 [9.9%] of 151 patients) compared with patients in the study by Hong et al7 (>30%). Patients with pathological N3 advanced nodal disease were excluded, as were those thought to be unreliable, substance abusers, those older than 70 years or younger than 18 years, and those with a history of other cancer, except the nearly ubiquitous nonmelanomatous skin cancers that occur regularly on pale-skinned Queenslanders living in the tropics. Also excluded were those who, in the past, had routinely taken vitamin A or who had received investigational new drugs within the previous 3 months. Only postmenopausal women and women taking contraceptive measures were considered because isotretinoin is highly teratogenic. A thorough medical history and physical examination, kidney and liver function tests, and chest radiography were performed before informed written consent was obtained in accordance with the respective institution’s ethics committees and the principles of the Declaration of Helsinki. Any concomitant medications taken for other diseases were recorded.

The trial had 3 arms. Two of the arms were to mimic those of the study of Hong et al7 of high-dose 1-mg/kg per day isotretinoin (80 mg/d for men and 60 mg/d for women) or placebo for 12 months, but those in the treatment arm received a further 2 years of a low dose (0.5 mg/kg per day), potentially lesion stabilizing.7 Thus, those in the nontreatment arm took their placebo for a 36-month period. The third group of patients took 40 mg/d for the 36-month period.

Patients received their medication in 10-mg or matching placebo capsules. Thus, all men took 8 capsules orally per day for 12 months while women took 6 capsules per day. Then, men and women took 4 capsules a day for a further 24 months. The capsules were given to the patients in 2 marked bottles. The bottles were individually made for each patient. All capsules in 1 bottle were the same, being either isotretinoin or placebo. Patients were seen by blinded assessors (C.F.P., M.S., I.R., and W.C.) every 6 weeks in the first year, every 8 weeks in the second year, and every 12 weeks in the third year. Capsule numbers were counted. If doses were forgotten, patients were asked not to catch up their doses. All possible adverse effects were recorded. Because of the hepatotoxicity of retinoids, heavy alcohol use was discouraged. Blood samples were taken to monitor liver function test results and cholesterol levels, because both may increase with retinoid use. If dietary advice failed, patients discontinued the trial if the cholesterol level could not be kept below 271 mg/dL (<7 mmol/L). For quality control, retinoid blood assays were done in Sydney by Hoffmann...
La Roche Pharmaceutical Company to confirm that levels were appropriate for the dosage of drug each patient had been randomized to receive.

Patients were followed up for signs of recurrent or residual disease and second primary tumors. For those with recurrent disease requiring further surgery, the trial drugs were discontinued for up to 1 month before surgery when possible, because of the possibility that isotretinoin delayed healing. Patients were regarded as having a second primary tumor of the upper airway if disease occurred more than 3 cm or 3 years from the original lesion; if that happened, further medication with isotretinoin or placebo was discontinued. For patients who developed a lung malignancy during the trial, a panel of 3 blinded assessors (an otolaryngologist [C.F.P.], a respiratory physician, and a medical oncologist) determined as accurately as possible from the available deidentified clinical, radiological, and histological information whether the tumor was a second primary lung lesion or a metastasis.

STUDY DESIGN

The study was randomized, prospective, double-blind, and placebo controlled. Standard computer randomization, performed in Sydney, assigned patients. The investigators were blinded. The investigator and pharmacy received sealed envelopes for each subject in the trial, identifying the subject’s treatment group. A second set of code envelopes was retained by Hoffmann La Roche Pharmaceutical Company when an interim analysis of the data revealed no significant difference between the treatment and nontreatment groups. Initially, 54 patients were randomized to group 1, 48 to group 2, and 49 to group 3. However, the numbers taking the drug for longer than 3 months were as follows: 47 patients in group 1, 45 in group 2, and 33 in group 3.

The demographic data (age, sex, weight, ethnicity, smoking status, alcohol consumption, medical examination findings, and treatment modalities) of the groups were equivalent. Sites of origin of cancer were slightly different between groups (Table 1).

Of the patients, 31.1% had a T1 tumor, 39.1% had T2, 19.8% had T3, and 7.3% had T4. Four patients had an undefined T classification. Of the patients, 70.1% had N0 disease, 13.2% had N1, and 15.9% had N2 (6 had N2a, 8 had N2b, and 4 had N2c); 1 patient was recorded with undefined N classification. Of the patients, 70.1% had N0 disease, 13.2% had N1, and 15.9% had N2 (6 had N2a, 8 had N2b, and 4 had N2c); 1 patient was recorded with undefined N classification.

Approximately two thirds of the patients (100/151) failed to complete 3 years of therapy. This differed somewhat across groups: 74.1% in group 1, 58.3% in group 2, and 65.3% in group 3. Adverse events were given as a reason for withdrawal for 27.7% of patients in group 1, 20.4% in group 2, and 34.7% in group 3. Of these adverse events, most were possibly or probably related to study medication use. A few patients were unavailable for follow-up or experienced treatment failure. Six had significant protocol violations leading to withdrawal. One patient died during the study; this was unrelated to treatment or disease. The many incompletely treated patients are a reflection of the long time the patients were expected to take their drug (3 years) and the early cessation of this trial, with its disappointing results.

In each of the treatment groups, 85% to 95% of patients were assessed as having reliably taken their study medication. The median length of exposure for patients in group 1 was 622 days (range, 1-1132 days); group 2,

**Table 1. Demographic Characteristics of the 3 Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (n = 54)</td>
<td>2 (n = 48)</td>
<td>3 (n = 49)</td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td></td>
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<td>16 (29.6)</td>
<td>11 (22.9)</td>
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<td>47 (97.9)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
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<td>1 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
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<td>0</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Smoker</td>
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<td>38 (80.9)</td>
</tr>
<tr>
<td></td>
<td>Nonsmoker</td>
<td>8 (15.1)</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Previous tumor site</td>
<td>Oral cavity</td>
<td>26 (48.1)</td>
<td>19 (39.6)</td>
</tr>
<tr>
<td></td>
<td>Oropharynx</td>
<td>6 (11.1)</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td></td>
<td>Hypopharynx</td>
<td>3 (5.6)</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td></td>
<td>Larynx</td>
<td>19 (35.2)</td>
<td>18 (37.5)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of each group. Percentages are based on the total for each category. Group 1 received 1.0 mg/kg per day of isotretinoin for 1 year and then received 0.5 mg/kg per day of isotretinoin for an additional 2 years; group 2, 0.5 mg/kg per day of isotretinoin for 3 years; and group 3, placebo for 3 years.

A total of 151 patients were randomized to enroll into the study. Although we initially wanted larger numbers in each study arm (125 patients), the size of each arm was close to that of the study we were trying to confirm. The study was stopped early by Hoffmann La Roche Pharmaceutical Company when an interim analysis of the data revealed no significant difference between the treatment and nontreatment groups. Initially, 54 patients were randomized to group 1, 48 to group 2, and 49 to group 3. However, the numbers taking the drug for longer than 3 months were as follows: 47 patients in group 1, 45 in group 2, and 33 in group 3.

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Efficacy Data

Twenty patients experienced a secondary primary cancer. This included 5 of 54 patients in group 1, 8 of 48 patients in group 2, and 7 of 49 patients in group 3 (Table 3). There was no statistically significant association between the occurrence of second primary cancers and treatment group (for the intention-to-treat group: \( \chi^2 = 1.3, P = .50 \); and for the \( \geq 90 \)-day group: \( \chi^2 = 2.6, P = .30 \)). Five patients in the placebo group (group 3) were diagnosed as having second primary tumors in the post-study period, compared with 3 patients in group 2 and 1 patient in group 1. That is, in most of those taking high-dose isotretinoin in whom treatment failed, the failure occurred while the patient was taking the drug.

Recurrence of primary cancers was noted for 15 patients. Again, there was no statistically significant association between the recurrence of primary cancers and treatment group (for the intention-to-treat group: \( \chi^2 = 1.7, P = .40 \); and for the \( \geq 90 \)-day group: \( \chi^2 = 2.1, P = .30 \)).

Disease-free status (ie, no recurrence of primary cancer or occurrence of a secondary primary cancer) did not differ significantly between treatment groups (for the intention-to-treat group: \( \chi^2 = 2.3, P = .30 \); and for the \( \geq 90 \)-day group: \( \chi^2 = 2.0, P = .40 \)).

One patient died during the study, while a further 5 died after discontinuing treatment. There were too few deaths recorded during the study to make any statistical statements regarding absolute survival. This low death rate possibly reflects the care we took in selecting relatively younger and more healthy patients with prognostically better tumors to enroll into the trial.

Time to occurrence of a second primary tumor, time to recurrence of a primary tumor, and time without either primary or secondary disease were analyzed, and there were no statistically significant differences (log-rank test results, \( P = .90 \), \( P = .70 \), and \( P = .80 \), respectively). Because of sparse data, few of the median survival times could be calculated.

Using Cox proportional hazards regression models to adjust for the possible effects of age and time since previous diagnosis, there was no statistically significant difference in survival between treatment groups (\( P = .1 \)).

Adverse Events

All patients in the study for more than 3 months experienced adverse events. There was no statistically significant difference in the rate of patients experiencing adverse events probably or possibly related to study medication (\( P = .4 \)). The more commonly listed adverse events include back pain; bleeding in the gums, lips, mouth, and nose; blurry vision; brushing of hands and arms; chest infections; constipation; dry and cracked lips/mouth; slow healing of cuts; diarrhea; dizziness; dry eyes and skin; elevated cholesterol and triglyceride levels; fatigue; flu and flulike symptoms; headaches; increased liver enzyme levels; mood changes; pink facial complexion; rashes; sore and watering eyes; and sun sensitivity.

There is no doubt that isotretinoin has significant adverse effects. The lack of a significantly different adverse event profile is a reflection of the common finding of dry and cracked skin, increased liver function test results and cholesterol level, and arthritis in this treatment group of generally sun-damaged, hard-living, older Australians residing in the tropics who develop HNSCC, compared with younger people taking this drug for acne. Apart from 2 patients with persistent trouble with wicklows (staphylococcal infection of the fingernail) and 1 with a severe staphylococcal skin infection of the lower eyelid, the patients experienced few serious effects and could not be differentiated into treatment groups by their treating physicians based on adverse effect profile.

There were 6 deaths noted during the study or as part of the study follow-up. None of these were coded as being related to the study medication: 3 were heart related, 1 was lung cancer, 1 was respiratory failure, and 1 was a gut obstruction. Three life-threatening events (prostate cancer, syncope, and myocardial infarction) were not related to study medication.

The results of this study are illuminating. The use of this drug for the prevention of second primary cancers in a patient previously diagnosed as having HNSCC does not work. Obviously, the study could be criticized for its lack of numbers. The study by Hong et al. had 49 and 51 patients in its 2 arms (high-dose drug and placebo, respectively). Recurrences occurred in 30% of those patients compared with 9.9% of our patients, and consequently 34 patients in each group were evaluable. We had 34 patients having similar high doses and 33 having lower doses for longer than 12 months and then those taking placebo, with only 15 recurrences out of 151 people. Thus, we had similar numbers receiving the drug at the high dose and a further group receiving it at a moderate dose. We were more selective in whom we approached to be involved in the trial, and did not restrict ourselves to only recruit people within 10 to 16 weeks of the cessation of
therapy. Because the rate of second primary tumors is said not to decrease with time, we recruited people who had their first tumor after the date of starting the trial but sometimes more than a year after the cessation of active treatment for their primary disease. The previous study had patients initially taking 1.5 mg/kg per day, with the dose later being decreased to 1 mg/kg per day because of the adverse effects of the drug. Although our statistical results suggest it was clinically difficult for the blinded physician to differentiate what treatment arm a particular patient had being randomized to, anecdotally those taking the study medication, when they had dry skin, had extremely dry skin, and those who had cheilitis and flu-like symptoms tended to have more severe and long-lasting symptoms when taking the drug at high doses.

Those with wicklows and significant staphylococcal skin infections were taking the drug. A potential for subjectivity existed in the assessment of whether a lesion was a recurrence or a second primary tumor. When a solitary squamous cell cancer lesion is found in the lung, it could be a secondary primary tumor or a solitary metastasis. When an upper airway mucosal lesion occurs within 3 years close to a previous cancer, is it a recurrence or a second primary tumor? Hong et al. used the criterion of greater than 3 years or 2 cm, whereas we used more than 3 years or 3 cm, from the site of the original tumor as the indication of a new primary tumor. As noted previously, the solitary lung metastases were differentiated from second primary disease by a blinded panel using the available clinical data, which were previously deidentified. The panel needed to adjudicate on 6 lesions.

The few patients recruited for the study out of the many seen at the combined clinics of these 2 large institutions is a reflection of our selectivity as to the curability and reliability of the patients. The study was stopped after 7 years by the funding drug company, while several patients had at that stage received treatment for inadequate periods. Our aim of 3 years’ drug therapy was, in retrospect, too ambitious.

This is not the first trial to show no gain by the use of retinoids in the chemoprevention of second primary tumors. The EUROSCAN study showed no benefit using retinyl palmitate or n-acetylcysteine as chemopreventive agents for second primary tumors in patients previously treated for head and neck or lung cancer.5 Another retinoid, etretinate, used for 24 months, when compared with placebo, failed to show any survival or second primary tumor advantage in patients previously treated for early-stage head and neck cancer and followed up for 5 years. The Physicians’ Health Study showed no decrease in cancer rates in those taking beta carotene.10 While it may be argued by some that the drug is safe and, therefore, worth giving a try, several studies are a cause of serious concern.

For patients with smoking-induced lung cancer, isotretinoin (≤30 mg/d, depending on toxic effects) was associated with a statistically significant higher rate of mortality in smokers (P = .01, log-rank test) and a statistically nonsignificant higher rate of recurrence (P = .15) in an article by Lippman et al.11 This study did not show the same harmful effects of retinoids in those patients who stopped smoking, and while there were lower rates of recurrence and mortality in the patients who were no longer smoking, the P values for improvement (P = .12 and P = .14, respectively) were not statistically significant. Similar results were found in the CARET study of chemoprevention for lung cancer using the naturally occurring retinoid, beta carotene.12,13 In this study, the mortality rate of lung cancer was 17% higher in the active treatment group than in the placebo group (P = .02). The death rates from cardiovascular disease were also higher in the treatment group. Consequently, this study was stopped early because these retinoids showed a potentially harmful effect. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group observed a similarly higher incidence of lung cancer and lung cancer–related deaths among the 29,133 male smokers from Finland who took this retinoid vs those taking placebo.

A multicentered group from the United States and Canada has recently indicated that they have recruited, since 1991, 1,190 head and neck cancer patients and randomized them to receive 30 mg/d of isotretinoin or placebo and observed them for second primary lesions.15 Their results were given at the 2003 general meeting of the American Society of Clinical Oncology. They concluded that 30 mg/d of isotretinoin was not effective in preventing second primary tumors.16

<table>
<thead>
<tr>
<th>Group</th>
<th>Second Primary Tumor</th>
<th>Synchronous Tumor†</th>
<th>During the Study‡</th>
<th>After the Study§</th>
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<td>1 (n = 54)</td>
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<td>2 (n = 48)</td>
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<td>1 (2.1)</td>
<td>4 (8.3)</td>
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<td>3 (n = 49)</td>
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<td>2 (4.1)</td>
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<td>≥90-d population</td>
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<tr>
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<td>2 (6.1)</td>
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</tr>
</tbody>
</table>

*Data are given as number (percentage) of each group. The groups are described in the first footnote to Table 1.
†Occurred within the first 180 days of taking study medication.
‡Occurred after 180 days from the start of study medication administration.
§Occurred more than 30 days after study termination.
||Population that stayed in the study for 90 days or longer.
Because lung cancer is common in the head and neck cancer population, this well-demonstrated effect of an increased mortality rate for lung cancer patients taking retinoids is a serious problem. Other retinoids are being tested in in vitro studies and may prove efficacious in the future. Retinoids are being used in combination with interferons and chemotherapeutic agents, and may prove to have a positive statistical advantage as a treatment of HNSCC.\(^\text{17}\) However, the use of retinoids (as single agents) to prevent future primary cancers in the lung, head and neck mucosa, and elsewhere in patients already treated for cure for one lesion in the head and neck is ineffective and potentially dangerous in active smokers, and there are no reasonable grounds to support their routine recommendation. Patients with HNSCC do not receive the benefit of a decrease in their high lung cancer rate when receiving isotretinoin therapy, but would have a lower cure rate for their lung cancers if they took it and continued to smoke. Retinoids should not be used as chemoprevention agents for those who, by previously having an HNSCC or by lifestyle or family history, are prone to lung cancer or further head and neck squamous malignancy.

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REFERENCES