

## EFFECT OF A LOW-FAT DIET ON THE INCIDENCE OF ACTINIC KERATOSIS

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**Abstract Background.** Actinic keratoses are premalignant lesions and are a sensitive and important manifestation of sun-induced skin damage. Studies in animals have shown that dietary fat influences the incidence of sun-induced skin cancer, but the effect of diet on the incidence of actinic keratosis in humans is not known.

**Methods.** We randomly assigned 76 patients with non-melanoma skin cancer either to continue their usual diet (control group) or to eat a diet with 20 percent of total caloric intake as fat (dietary-intervention group). For 24 months, the patients were examined for the presence of new actinic keratoses by physicians unaware of their assigned diets.

**Results.** At base line, the mean ( $\pm$ SD) percentage of

caloric intake as fat was  $40\pm 4$  percent in the control group and  $39\pm 3$  percent in the dietary-intervention group. After 4 months of dietary therapy the percentage of calories as fat had decreased to 21 percent in the dietary-intervention group, and it remained below this level throughout the 24-month study period. The percentage of calories as fat in the control group did not fall below 36 percent at any time. The cumulative number of new actinic keratoses per patient from months 4 through 24 was  $10\pm 13$  in the control group and  $3\pm 7$  in the dietary-intervention group ( $P = 0.001$ ).

**Conclusions.** In patients with a history of nonmelanoma skin cancer, a low-fat diet reduces the incidence of actinic keratosis. (N Engl J Med 1994;330:1272-5.)

NONMELANOMA skin cancer is the most common cancer among whites in the United States, with approximately one-half million new cases a year.<sup>1</sup> Nonmelanoma skin cancer includes, by definition, both basal-cell and squamous-cell carcinomas. However, lesions of actinic keratosis are the most frequent epidermal tumors and, as the name implies, are sun-induced.<sup>2,3</sup> They are premalignant lesions considered biologically to be either carcinoma in situ or squamous intraepidermal neoplasia.<sup>4</sup> Estimates of the rate of malignant transformation of an actinic keratosis to frank squamous-cell carcinoma range from 1 to 25 percent.<sup>5-7</sup> The latent period may exceed 10 years.<sup>8</sup> The predisposing factors for actinic keratosis are similar to those for basal-cell and squamous-cell carcinoma.<sup>9</sup> Due to its precancerous nature, actinic keratosis may be considered the most important manifestation of sun-induced skin damage.<sup>10</sup>

In animals, a high fat intake increases the likelihood of skin cancer after exposure to ultraviolet radiation, and changing to a low-fat diet after exposure can reduce the incidence of skin cancer.<sup>11-14</sup> We report the effects of a low-fat diet on the development of actinic keratosis in 76 patients with skin cancer during a 24-month study period.

### METHODS

#### Study Protocol

The study protocol was approved by the institutional review board. Patients presenting with a nonmelanoma skin cancer (index carcinoma) who had no more than two previous nonmelanoma skin cancers were eligible for the 24-month study. Previous skin cancers were verified by pathology report. The final diagnosis of the index carcinoma by the participating dermatopathologist was based on

accepted histologic criteria.<sup>15</sup> Patients were excluded from the study if they were of Asian, black, Hispanic, or American Indian ancestry; were genetically predisposed to skin cancer; had had more than two previous skin cancers or currently had any non-skin cancer; had received photochemotherapy for psoriasis within the past five years; had received treatment with antimetabolites, systemic glucocorticoids, tretinoin, or isotretinoin; had received x-ray treatment for acne; were taking megavitamin or mineral supplements or eating a therapeutic diet that required a fat intake of more than 20 percent of total calories; or had diabetes mellitus. After an explanation of the potential risks and benefits of participation, all the study patients gave written consent.

After initial screening, the patients underwent an evaluation that included a nutritional assessment, anthropometric measurements, and biochemical tests. The base-line (and follow-up) nutritional data were compiled from seven-day food records, from which four days (Monday, Wednesday, Saturday, and Sunday) were preselected for analysis. The Nutrition Data System, developed at the University of Minnesota, was used for nutrient analyses. Food records were verified with the study patients with standardized methods.<sup>16</sup> Detailed individual printouts of the nutrient analysis were reviewed and used to counsel patients in the dietary-intervention group.

The patients were randomly assigned to either the control or the dietary-intervention group through a list of randomly generated numbers. In accord with general dermatologic practice, recommendations regarding the use of sunscreens and avoidance of the sun were made to all patients at base line and at all subsequent visits.

The diet of the patients assigned to the control group was not changed. Those assigned to the dietary-intervention group attended eight weekly classes during which they were instructed to limit their diet to low-fat foods. To maintain body weight, the intake of complex carbohydrates was increased. The objective was to limit calories from fat to 20 percent of total caloric intake. Calories from protein constituted about 15 percent of caloric intake, and calories from carbohydrate 65 percent. Foods containing sufficient vitamins and minerals to meet the recommended dietary allowances for adults were emphasized. The patients were taught behavioral techniques such as stimulus control, self-monitoring, and cognitive behavioral self-management<sup>17,18</sup> to help them comply with the dietary regimen.

#### Follow-up and Evaluation

The patients were examined at four-month intervals by dermatologists unaware of their treatment assignments. Four dermatologists participated in the study; each patient was followed by one dermatologist. It was recognized that biopsy of suspicious new lesions that did not prove to be carcinomas could influence the out-

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come of the study, particularly if the lesions were diagnosed as premalignant, because they would then have been removed or their progression to carcinoma interrupted. Likewise, a reluctance to undertake biopsies of suspicious lesions would also influence the validity of the results. To reduce variability among the participating dermatologists, clinical guidelines were established describing the lesions to be evaluated.

Although the study was designed to evaluate the effect of dietary fat intake on the incidence of skin carcinoma, annual assessment of the results indicated a striking effect on the occurrence of actinic keratosis. Because actinic keratoses are premalignant lesions, dietary intervention could influence not only their occurrence but also the subsequent incidence of squamous-cell and basal-cell carcinomas. Although ethical considerations required that actinic keratoses be treated, the numbers treated were recorded at four-month intervals. Since the lesions can be treated without histopathological diagnosis, we established morphologic criteria to diminish variability of clinical diagnosis between study dermatologists. Examination for suspicious lesions was limited to exposed cutaneous surfaces (i.e., the face, neck, head, arms, and hands); the lesions were characterized either by well-defined, erythematous, brownish, or grayish, round or irregular keratotic papules firmly attached to the skin or by a dry, adherent scale and an erythematous halo at the base of the lesion. Their diameter ranged from 1 or 2 mm to 1 cm or larger. In previous studies, diagnoses of actinic keratosis were made clinically with at least 90 percent certainty.<sup>19</sup>

All the patients were scheduled to see the dietitian at each follow-up visit. The purpose of these visits was to verify food records for dietary analyses. The patients in the dietary-intervention group also attended monthly classes designed to maintain adherence to the low-fat diet. Specific suggestions were given to address problems of compliance and short-term failures.<sup>20</sup>

### Statistical Analysis

To compare the incidence of actinic keratosis between groups, the cumulative number of new actinic keratoses from month 4 through month 24 was calculated for each patient. These numbers clearly did not follow a normal distribution (e.g., 25 of the 76 patients had no actinic keratoses), indicating the need for a nonparametric analytical approach. The Wilcoxon rank-sum test was therefore used initially to compare the results in the two groups. Since this test does not take into account risk factors in addition to diet, the SAS logistic-regression computer program for an ordinal dependent variable was subsequently used.<sup>21</sup> This program is ideal for a dependent variable that reflects a limited number of values.<sup>22</sup> An ordinal variable was created with a value of 0, 1, or 2 for cumulative numbers of new actinic keratoses of 0, 1 through 10, or more than 10, respectively. Twenty-five patients had a value of 0, 35 had a value of 1, and 16 had a value of 2. This three-point ordinal variable exploits the quantitative nature of the response more fully and is designed to provide more powerful estimates than the conventional dichotomous model. The SAS program also provides a test of the validity of the proportional odds assumptions inherent in the ordinal model.

The logistic-regression model includes two intercept parameters and a slope parameter for each of the risk factors. In our description of the results we use only the intercept parameter representing the ratio of the probability of having no actinic keratosis to the probability of having one or more. The model, which predicts the ratio of the probability of nonoccurrence to that of occurrence, was estimated with dietary group (control or dietary intervention), history of actinic keratosis (no or yes), and the patients' actual ages as predictor variables. From the log of the reciprocal of the odds that an event would occur we calculated the odds, odds ratios, risks, and relative risks. The risk was calculated as the estimated probability of having one or more new actinic keratoses when various combinations of risk factors were present. Patients not at risk were defined as being in the dietary-intervention group, having no history of actinic keratosis, and being 40 years of age (the at-risk age was fixed at 65 years). The relative risk was calculated as the ratio of the risk if risk factors were present to the risk if no risk factors were present.

The body weight of the patients and the ratio of polyunsaturated fat to saturated fat in their diets were compared by analysis of

variance across each of the four-month evaluation periods. The significance of changes in these variables within and between groups was assessed with Dunnett's two-tailed t-test.

### RESULTS

To date, 133 patients have entered the two-year study, and 76 have completed it. Two patients in the control group and one in the dietary-intervention group died. Two patients in the dietary-intervention group were lost to follow-up because of extended hospitalization, and two patients in the control group were lost because of relocation. Data on three patients in the dietary-intervention group and one in the control group were censored because they failed to attend follow-up visits. No other patients withdrew from the study. Among the 38 patients in the control group who completed the study, 29 were men and 9 were women. Their mean ( $\pm$ SD) age was  $52 \pm 14$  years, their weight  $82 \pm 15$  kg, and their skin type  $2.6 \pm 0.8$  (on a numerical scale of 1 through 6 based on susceptibility to sun-induced erythema and tanning ability).<sup>23</sup> Among the 38 patients in the dietary-intervention group, 23 were men and 15 were women. Their mean age was  $51 \pm 10$  years, their weight  $80 \pm 20$  kg, and their skin type  $2.4 \pm 0.8$ . Twelve patients in the control group and 16 in the dietary-intervention group had a history of actinic keratosis.

Analysis of four-day food records indicated that the mean caloric intake as fat in the diets of the control and dietary-intervention groups at base line was  $40 \pm 4$  percent and  $39 \pm 3$  percent, respectively. The effect of the dietary-intervention program with respect to fat intake is shown in Figure 1. After the dietary training program, the percentage of calories consumed as fat decreased in the dietary-intervention group to 21 percent at month 4. Fat intake was maintained at or below this level throughout the 24-month period. The patients in this group lost weight during the first eight months of the study, after which their weight stabilized. There was, however, no significant difference in mean body weight between the groups at any time. The percentage of calories as fat in the control group did not fall below 36 percent at any time. There was a significant increase in the ratio of polyunsaturated fat to saturated fat in the dietary-intervention group ( $P < 0.001$  by analysis of variance), but there was no significant difference between groups until month 24, when the ratio was 0.66 in the control group and 0.81 in the dietary-intervention group.

The mean cumulative number of new actinic keratoses per patient from month 4 through month 24 was  $10 \pm 13$  in the control group and  $3 \pm 7$  in the dietary-intervention group ( $P = 0.001$ ). The incidence of actinic keratosis at four-month intervals is shown in Figure 2.

The parameter estimates of the logistic-regression model and the odds ratios demonstrated a significantly higher incidence of actinic keratosis among the patients in the control group ( $P < 0.001$ ; odds ratio, 9.6; 95 percent confidence interval, 3.1 to 29.9), among those with a history of actinic keratosis ( $P < 0.001$ ;

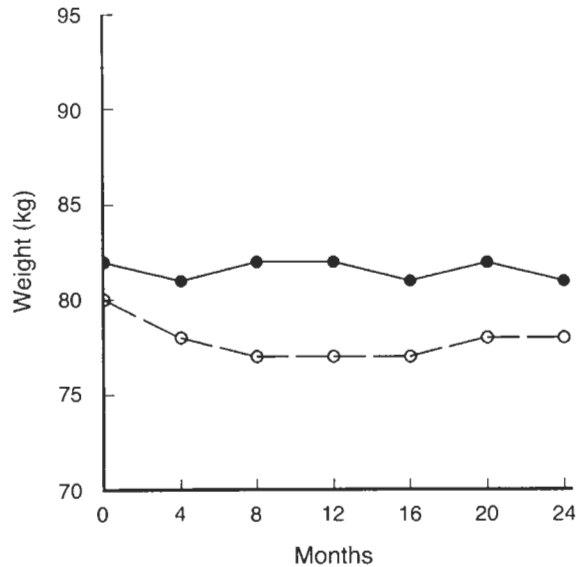
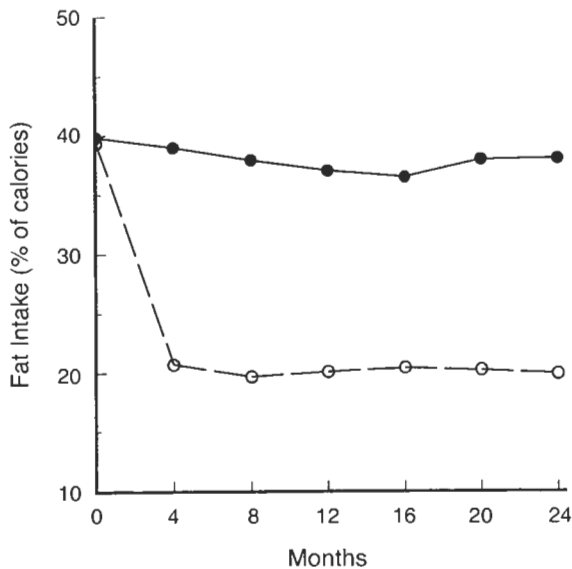


Figure 1. Changes in Fat Intake and Body Weight in the Control (●) and Dietary-Intervention (○) Groups during the Study Period.

odds ratio, 7.6; 95 percent confidence interval, 2.4 to 24.0), and among those 65 years of age or older ( $P < 0.001$ ; odds ratio, 14.4; 95 percent confidence interval, 4.0 to 51.7). A patient in the control group with neither of the other two risk factors (a history of actinic keratosis or older age) was estimated to have a 56 percent chance of having one or more actinic keratoses during the 24-month study period, a risk 4.7 times greater than that of similar patients in the dietary-intervention group. A patient with a history of actinic keratosis but no other risk factors had an estimated 51 percent chance, with a relative risk of 4.3 as compared with a patient with no such history, and a 65-year-old

patient with no additional risk factors had an estimated chance of 66 percent, with a relative risk of 5.6 as compared with a 40-year-old patient. When all three risk factors were present (i.e., usual diet, history of actinic keratosis, and age of 65 years or more) the estimated risk of having one or more actinic keratoses was 99 percent (relative risk, 8.4). It should be emphasized that the proportional odds assumption of the regression model was validated for our data ( $P = 0.52$ ).

## DISCUSSION

Epidemiologic studies indicate that many cancers in humans arise largely from lifestyle factors.<sup>24</sup> Among the factors associated with cancer, dietary fat intake ranks high.<sup>25</sup> Dietary fat is particularly associated with cancers of the breast, prostate, ovary, and colon.<sup>26</sup> With respect to skin cancer, in one case-control study no association with dietary fat was found.<sup>27</sup> Epidemiologic studies of diet and cancer, however, are fraught with methodologic problems that lead to equivocal inferences.<sup>28</sup> Many of these problems are circumvented in dietary-intervention trials, which are specifically designed to provide evidence of whether a reduction in dietary fat consumption influences the incidence of disease.<sup>29</sup>

Our dietary-intervention trial clearly indicates that a large decrease in calories consumed as fat reduces the incidence of actinic keratosis. Studies in animals demonstrate that caloric restriction inhibits the development and growth of certain tumors, a finding that leads to the suggestion that the effects of high-fat diets are related to increased caloric intake.<sup>30</sup> An evaluation of these studies supports the hypothesis that, at least for the development of mammary tumors, there is a specific enhancing effect of dietary fat as well as a general effect of calories.<sup>31</sup> In an analysis of interna-

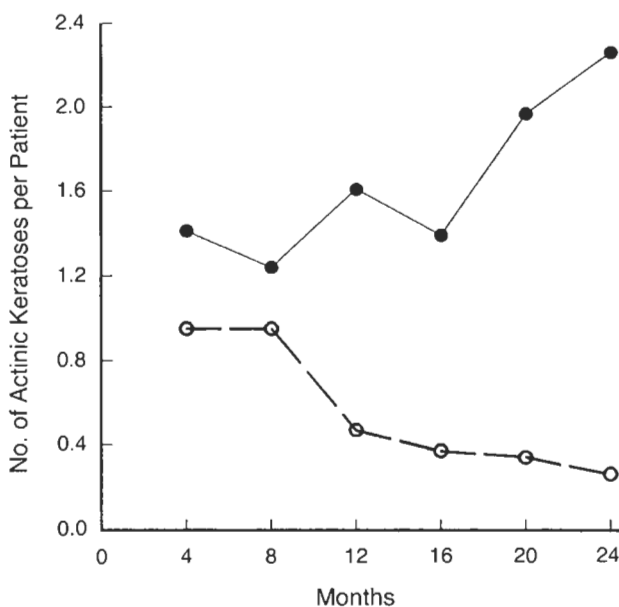


Figure 2. Incidence of Actinic Keratosis Measured at Four-Month Intervals in the Control (●) and Dietary-Intervention (○) Groups.

tional data, Hursting et al.<sup>32</sup> reported that associations between total fat consumption and the incidence of breast, colon, and prostate cancer appeared to be independent of total caloric intake or the ratio of polyunsaturated fat to saturated fat. In general, the effects of calories are thought to be restricted largely to tumor initiation,<sup>33</sup> whereas fat exerts its principal effect on tumor promotion and growth. Certainly, the effect on the incidence of actinic keratosis reported here appears to be related predominantly to the reduction in fat intake and to be independent of caloric intake. In the dietary-intervention group calories from fat were replaced with calories from other sources to prevent reductions in body weight. Nor was the type of fat consumed a contributing factor, since the ratio of polyunsaturated fat to saturated fat averaged 0.66 in the control group and 0.67 in the dietary-intervention group over the two-year period.

For the 76 patients who completed the study, the mean number of new skin cancers (basal-cell and squamous-cell carcinomas) was 0.54 per patient in the control group and 0.36 per patient in the dietary-intervention group. No inferences regarding the influence of this dietary intervention on the incidence of skin cancer can be drawn, because not enough patients have completed the study. It is evident, however, that the dietary intervention had a marked influence on the most common of skin tumors, actinic keratosis. Actinic keratosis occurs with very high frequency in patients over 60 years old, and even if one assumes a 1 percent rate of malignant transformation, the magnitude of the reduction in the incidence of actinic keratosis by dietary intervention would be expected to have a pronounced influence on the incidence of skin cancer.

The widespread implementation of a low-fat diet could reduce the substantial costs associated with the treatment of this common skin tumor and might also convey other health benefits associated with dietary fat reduction.<sup>34,35</sup> Indeed, the Committee on Diet and Health of the National Research Council has recommended that the general North American adult population reduce total fat intake to 30 percent of calories or less.<sup>36</sup> A reduced incidence of a prevalent form of skin tumor, actinic keratosis, may now be added to the list of potential benefits of a low-fat diet.

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