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EVIDENCE THAT A LOW-FAT DIET REDUCES THE OCCURRENCE OF NON-MELANOMA SKIN CANCER

Homer S. BLACK[1,3,4], John I. THORNBY[3], John E. WOLF, JR.[1], Leonard H. GOLDBERG[1], J. Alan HERD[2], Theodore ROSEN[1], Suzanne BRUCE[1], Jaime A. TSCHEN[1], Lynne W. SCOTT[2], Suzanne JAAX[2], John P. FOREYT[2] and Brenda REUSSER[1]

Departments of [1]Dermatology and [2]Medicine, Baylor College of Medicine; and [3]Veterans Affairs Medical Center, Houston, TX, USA.

The effect of a low-fat diet on occurrence of non-melanoma skin cancer was examined in a 2-year dietary intervention trial. A total of 101 skin-cancer patients were randomized either to a control group that consumed, on average, 38% of caloric intake as fat, and in which no changes in dietary habits were introduced, or to a low-fat dietary-intervention group, in which patients were instructed to limit their calories from fat to 20% of total caloric intake. Patients were examined at 4-month intervals by dermatologists blinded to their dietary assignments. Nutrient analyses, conducted at each of the 4-month follow-up visits, indicated that the % calories of fat consumed in the intervention group had been reduced to 21% at 4 months and remained below this level throughout the 2-year period. There were no significant differences in total calories consumed, or in mean body weights, between the control and the intervention groups. Nor were there significant group differences in P/S ratios until month 24. Numbers of new skin cancers treated at each examination were analyzed in 8-month periods of the 2-year study. Comparisons of skin-cancer occurrences revealed no significant changes in the control group from baseline values. However, cancer occurrence in the low-fat intervention group declined after the first 8-month period and reached statistical significance by the last 8-month period. Patients in this group had significantly fewer cancers in the last 8-month period than did patients in the control group. In addition, there was a significant reduction in the number of patients developing skin cancer in the last 8-month period, as compared with the first 8-month period, within the low-fat intervention group. There were no significant changes in the control group. These data indicate that a low-fat diet can significantly reduce occurrence of a highly prevalent form of cancer.

Non-melanoma skin cancer represents a disease that occurs frequently in light-skinned populations. In fact, the incidence of new skin-cancer cases each year in the US currently approaches one million and roughly equals the annual incidence of all other malignancies combined (Miller and Weinstock, 1994). With its high prevalence and morbidity, substantial costs in treatment and management of this disease are incurred. Further, skin-cancer rates have been increasing over the past 25 years, particularly among younger age groups, and this is believed to reflect changes in life styles. A number of human cancers are thought to be induced and/or promoted by life-style or environmental factors and thus should be preventable to some extent (Higginson and Muir, 1976). Diet, particularly dietary fat, ranks high among factors associated with cancer (Weisburger *et al.,* 1977). Whereas solar UV radiation, an environmental factor difficult to avoid, is known to be the major cause of skin cancer (Mason *et al.,* 1975), a number of extrinsic factors, including dietary fat, have been shown in experimental models to influence the expression of this disease.

The first evidence of a relationship of diet and UV carcinogenesis was that of Baumann and Rusch (1939), who observed that animals fed high levels of dietary fat formed UV-induced tumors more rapidly than animals receiving lower levels of fat. More recently, Black *et al.* (1983, 1985), using the skin/UV-carcinogenesis hairless-mouse model, have demonstrated that, over a defined range, an approximate linear relationship exists between lipid level intake and tumor latency (*i.e.,* tumor latency decreased commensurably with incremental increases in lipid intake). Furthermore, with increasing dietary lipid level, the numbers of tumors per animal increased. It has now been shown that exacerbation of UV carcinogenesis by high dietary fat occurs during the post-initiation or promotion stage, and that modification to a low-fat diet after UV initiation can negate the exacerbating effects of high dietary fat (Black *et al.,* 1992). Experimentally, dietary lipid influences UV-induced skin cancer in animals and dietary modification through low-fat intervention can ameliorate UV-induced skin-cancer expression. Such observations provided the rationale for the current clinical trial, with the purpose of exploring the potential importance of dietary-fat modification as a prevention strategy for this highly prevalent cancer.

MATERIAL AND METHODS

Study protocol

The study protocol is represented diagrammatically by flow chart (Fig. 1). Patients presenting with a non-melanoma skin cancer (index carcinoma, either basal- or squamous-cell carcinoma) who had had no more than 2 previous non-melanoma skin cancers were eligible for the 2-year study. Previous skin-cancer occurrence was verified by pathology report, and the participating dermatopathologist made final diagnosis of the index and subsequent carcinomas based on accepted histologic criteria (Lever and Schaumburg-Lever, 1983). Patients were excluded from the study if they were Asian, black, Hispanic, or American Indian; if they were genetically predisposed to skin cancer; if they had had more than 2 previous skin cancers or currently had any non-skin cancer; if they had received photochemotherapy for psoriasis within the past 5 years; if they had received treatment with antimetabolites, systemic glucocorticoids, tretinoin, or isotretinoin; if they had received X-ray treatment for acne; if they were taking megavitamin or mineral supplements or were eating a therapeutic diet requiring a fat intake of more than 20% of total calories; or if they were diagnosed diabetics.

Patients who met the non-dietary inclusion criteria underwent pre-study evaluation prior to final admission to the study. The purpose of this evaluation was to provide baseline dietary, anthropometric and biochemical parameters by which a patient could be monitored for dietary compliance or for any untoward effects of the dietary regimen. Base-line (and follow-up) nutritional data were compiled from 7-day food records, from which 4 days (Monday, Wednesday, Saturday and Sunday) were pre-selected for analysis. The Nutrition Data System, developed at the University of Minnesota, was used for nutrient analysis. Food records were verified using standardized methods (Dennis *et al.,* 1980).

After the pre-study evaluation, patients were randomly assigned either to the control group or to the dietary-intervention group through a list of randomly generated numbers. The diet of the patients assigned to the control group

[4]To whom correspondence and reprint requests should be sent, at Photobiology Laboratory, Bldg. 109, Veterans Affairs Medical Center, 2002 Holcombe Blvd, Houston, TX 77030, USA. Fax: 713 794 7638.

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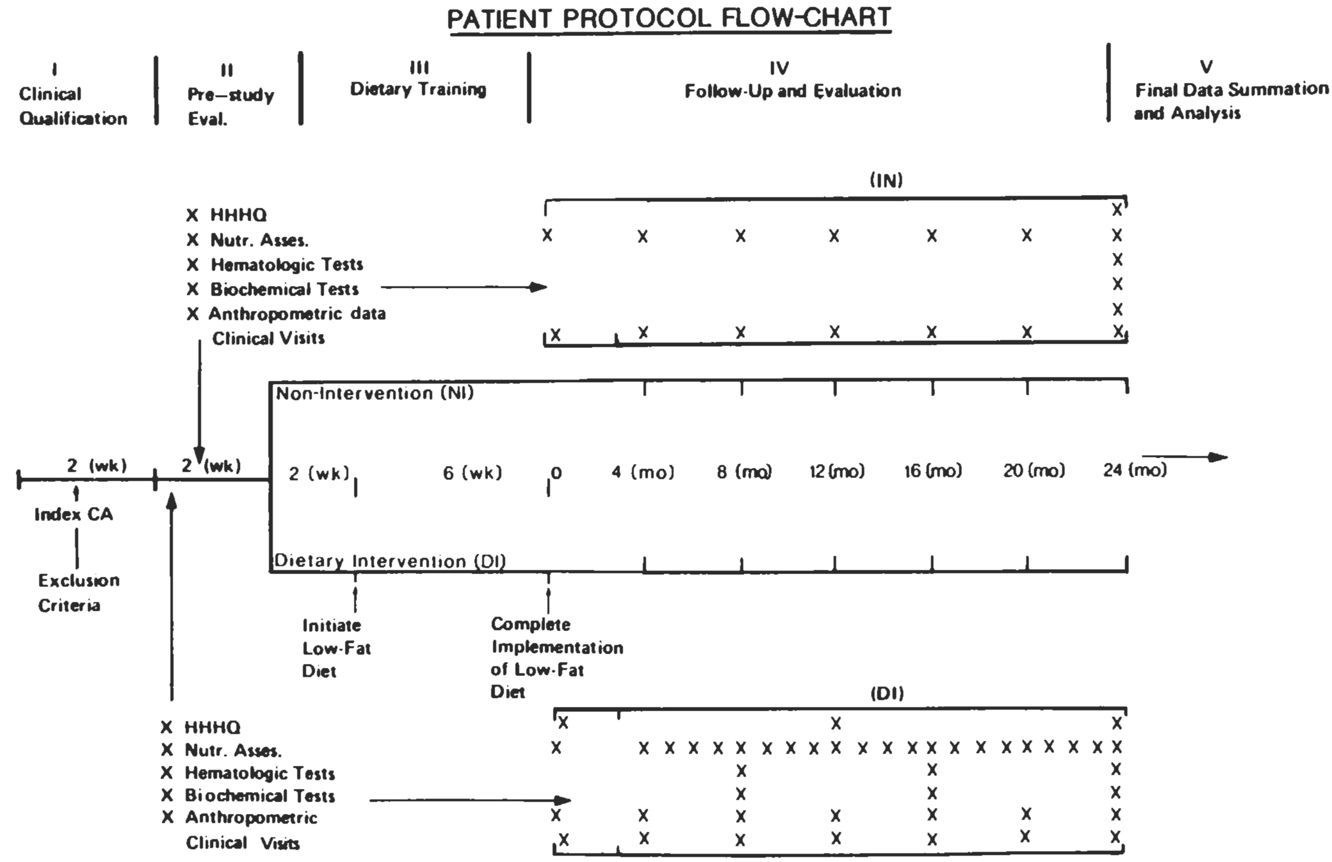

FIGURE 1 – Study Design. NI, non-intervention, control arm; DI, dietary-intervention arm of the study; X, time when respective tests, measurements and evaluations were scheduled; HHHQ, Human Health Habits Questionnaire (Block *et al.,* 1986).

was not changed. Those assigned to the dietary-intervention group attended 8 weekly classes during which they were instructed to reduce intake and to maintain low intake of foods containing any type of fat. To maintain body weight, the reduced caloric intake from fat was compensated by increased intake of complex carbohydrates. The dietary objective was to limit calories from total fat to 20% of total caloric intake. Generally, calories from protein constituted about 15% and from carbohydrates 65% of the total caloric intake. Adequate sources of vitamins and minerals to meet the recommended dietary allowances for adults were emphasized.

All patients were examined at 4-month intervals by dermatologists unaware of their treatment assignments. Patients were instructed to refrain from disclosing this information. Each patient was followed by one dermatologist. To reduce variability among the participating dermatologists, clinical guidelines were established describing the lesions to be evaluated. Examination for suspicious lesions was limited to those anatomic sites habitually and/or intermittently exposed to sunlight (*i.e.,* face, neck, head, arms, hands, legs, and upper torso). Pre-malignant lesions of actinic keratosis and non-melanoma skin cancers were treated at each follow-up visit. Recommendations regarding the use of sunscreens and avoidance of sun exposure were made to all patients, of both groups, at baseline and at all subsequent follow-up clinical visits.

At each 4-month follow-up visit, all patients were scheduled to see the dietitian to verify food records for dietary analyses. In addition, the patients in the dietary-intervention group attended monthly classes designed to maintain adherence to the low-fat diet. Detailed nutrient analyses were used to counsel patients in the intervention group, and a number of behavioral techniques were taught to help patients comply with the dietary regimen (Foreyt and Kondo, 1984).

Statistical analysis

Numbers of new, confirmed skin cancers per patient were totalled in 8-month intervals of the 2-year study period. Each of the last two 8-month periods, within each dietary group, was compared with the respective initial 8-month period, using the Wilcoxon signed rank test. In addition, the corresponding 8-month periods of the 2 dietary groups were compared using the Wilcoxon rank-sum test with adjustments for tied observations. In all comparisons, significance was based on 2-tailed tests with $p \leq 0.05$.

Numbers of patients with skin cancers in the last 8-month period were compared between groups using Fisher's exact (2-tail) test. Significance of improvement between the first and last 8-month periods within dietary groups was determined by the McNemar test.

Patient body weight, total calories, percentage calories as fat, and the polyunsaturated/saturated fat ratios (P/S ratio) within the control and the intervention groups were compared by ANOVA across each of the 4-month evaluation intervals. Significance of changes in these parameters, within and between groups, was assessed using Dunnett's *t*-test.

RESULTS

Initially, 982 skin-cancer patients were approached to participate in the study. Of this number, 774 patients did not meet the inclusion criteria, over 40% having had more than 2 previous skin cancers, and 93 were not interested in or could not commit to participation in the study. Of the 115 patients entered, 101 completed the 2-year study. Of the 14 patients that failed to complete, 2 in the control group and one in the dietary-intervention group died; 3 patients in the dietary-intervention group and one in the control group were lost to follow-up due to hospitalization or extended illness; 2 patients in the control group relocated and were lost to follow-up; data on 3 patients in the dietary-intervention group and 2 in the control group were censored because they failed to attend follow-up visits. Among the 50 patients in the control group completing, 14 were female. The mean (±SD) age of this group was 54 ± 13 years and weight, 81 ± 19 kg. Among the 51 patients in the dietary-intervention group, 21 were female. The mean age of this group was 51 ± 9 years and weight, 81 ± 15 kg. There were no significant differences ($p > 0.05$) in patients of either group with respect to age, weight or gender.

Analysis of 4-day food records indicated that the mean caloric intake as fat at baseline was 40 ± 4 and 39 ± 4 per cent for the control and the dietary-intervention groups respectively. The success of the dietary-intervention program with respect to fat intake is shown in Figure 2. At the end of the dietary training program (first 4-month assessment interval), the percentage of calories consumed as fat decreased in the dietary-intervention group to 21 ± 7 per cent. Fat intake was maintained at or below this level throughout the 24-month study period. The percent calories consumed as fat in the control group never dropped below 37% and averaged 38 ± 6 per cent for the 24-month period. There were significant increases ($p = 0.01$) in the P/S ratios within the dietary-intervention group beginning at month eight, although there were no significant differences between the control and the dietary-intervention groups until the 24-month assessment, when values were 0.64 and 0.78 ($p = 0.01$) for the control and the dietary-intervention groups respectively.

Baseline values for daily total calorie intake were 2310 ± 688 calories for the control group and 2455 ± 649 for the dietary-intervention group. Although there was a significant decrease in total calorie intake within the dietary-intervention group ($p < 0.001$ by analysis of variance), there was no significant difference between groups throughout the 24-month study. Mean values were 2254 ± 705 and 2033 ± 663 calories for the control and the intervention groups, respectively. Nor were there significant differences in mean body weights between the 2 groups at any time, although there was a significant weight loss ($p < 0.001$ by ANOVA) within the dietary-intervention group. This loss occurred primarily during the first 8-month period (Fig. 3).

Skin-cancer occurrence in the control group did not change significantly from the baseline period, *i.e.,* the first 8-month period (Fig. 4). However, cancer occurrence in the dietary-intervention group declined after the first 8-month period and reached statistical significance ($p < 0.05$) by the last 8-month period. Further, patients in the intervention group had significantly fewer cancers ($p < 0.05$) in the last 8-month period than did patients in the control group (0.02 *vs.* 0.22 cancers/patient). Although differences between the 2 groups in the numbers of patients with new skin cancers in the last 8-month period approached significance, comparisons of the first and last 8-month periods within each group exhibited a significant ($p < 0.05$) improvement in the dietary-intervention group (*i.e.,* 8 patients had skin cancers in the first 8-month period as compared with only one in the last 8 months). No improvement occurred in the control group (*i.e.,* 6 patients had skin cancers in the first 8-month period and 6 in the last 8 months).

DISCUSSION

This dietary-intervention trial not only provides evidence that a large decrease in calories consumed as fat can reduce the occurrence of non-melanoma skin cancer, but also addresses other important questions regarding low-fat diets and skin cancer. For example, recent studies of the influence of dietary fat on UV-induced skin cancer in experimental animals have dealt exclusively with effects on the formation of squamous-cell carcinomas. The lack of a model in which basal-cell carcinoma can be induced by UV had resulted in uncertainty regarding the influence of dietary fat on this type of skin cancer, the most prevalent form of non-melanoma skin cancer occurring in Caucasians. In the current study, the combined ratio (*i.e.,* both treatment groups) of squamous- to basal-cell carcinomas was 0.09 (46 basal; 4 squamous), much less than that predicted for this latitude (30°N) (Urbach, 1969). However, actinic keratoses were treated at 4-month intervals in this

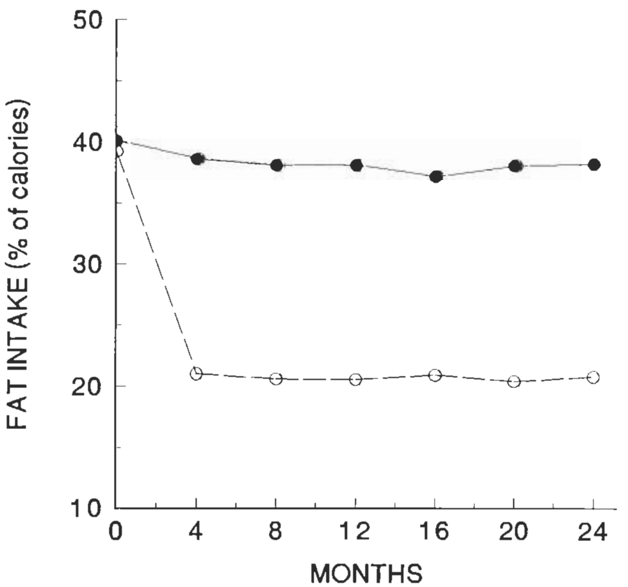

FIGURE 2 – Mean per cent of calories consumed as fat. Control, closed circles; dietary intervention, open circles.

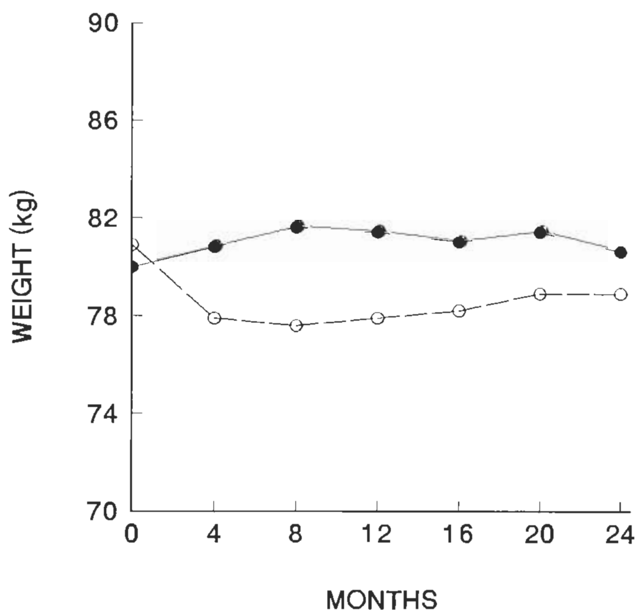

FIGURE 3 – Mean body weights. Control, closed circles; dietary intervention, open circles.

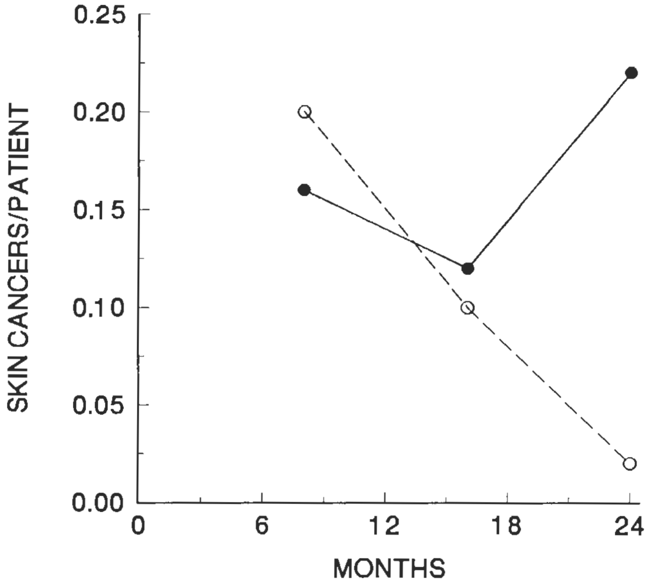

FIGURE 4 – Effect of a low-fat diet on the occurrence of skin cancer. Closed circles, control group; open circles, low-fat dietary-intervention group. Data points reflect numbers of tumors per patient for each 8-month period.

study. These pre-malignant lesions occur with very high frequency in patients over 60 years of age and can undergo malignant transformation to squamous-cell carcinoma (Graham and Helwig, 1966; Callen, 1991). Treatment would, of course, have interrupted the progression of these pre-malignant tumors and might explain the low incidence of squamous-cell carcinoma we observed. In addition, we have reported that the current low-fat dietary intervention reduces the incidence of actinic keratosis, the precursor lesion (Black *et al.,* 1994). In any case, it is clear that a low-fat diet reduces the occurrence of basal-cell carcinoma, as it has been shown to do for UV-induced squamous-cell carcinomas in experimental animals.

In addition, these data provide insight with respect to the time required for the dietary intervention to exert influence upon cancer expression. It is clear that occurrence of skin cancer was not significantly influenced by reduction in percent of calories as fat until after month 12 (Fig. 4). This is slightly longer than the time previously observed for the low-fat diet to affect incidence of actinic keratosis (Black *et al.,* 1994). For the latter, significant effects were observed after 8 months of dietary intervention.

Further insight from this study relates to the distinction between the effects of fat and of calorie restriction on cancer development. Although the ameliorating effect of caloric restriction on tumorigenesis has long been recognized (Tannenbaum, 1942), recent interest has focused upon the relative importance of calorie *vs.* fat restriction, with some evidence suggesting that the major effects of dietary fats relate primarily to their caloric contribution (Welsch, 1992; Weindruck *et al.,* 1991). However, evaluation of the experimental animal 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 (Freedman *et al.,* 1990). In addition, analysis of international data found that associations between total fat consumption and the incidence of human breast, colon and prostate cancer appeared to be independent of total caloric intake or of the P/S ratio (Hursting *et al.,* 1990). Certainly, the effect on the incidence of non-melanoma skin cancer reported here appears to be related predominately to the reduction of fat intake. There were no significant differences in caloric intake or body weights between our control and intervention groups. Nor was the type (*i.e.,* degree of saturation) of fat consumed an apparent contributing factor, since the P/S ratios of the 2 groups were not significantly different until the end of the 2-year study.

In summary, our study indicates that a large decrease in percentage of calories consumed as fat reduces the occurrence of a prevalent form of cancer, *i.e.,* non-melanoma skin cancer. Reductions in skin-cancer occurrence were observed after one year of the low-fat dietary intervention and appeared, for the most part, to be calorie-independent. These data, supported by the earlier finding that a reduction in fat intake reduced the incidence of pre-malignant lesions of actinic keratosis, suggest that implementation of a low-fat diet could play an important role in the management and prevention of this highly prevalent form of cancer.

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