Journal of Integrative Oncology

Black, J Integr Oncol 2014, 3:2
http://dx.doi.org/10.4172/2329-6771.1000 e107

Editorial Open Access

Role of Dietary Fat in Ultraviolet Light–Induced Carcinogenic Expression

Homer S Black*

Department of Dermatology, Baylor College of Medicine, Houston, Texas 77030, USA

***Corresponding author:** Homer S Black, Department of Dermatology, Baylor College of Medicine, Houston, Texas 77030, USA, Tel: 832-741-1052; E-mail: hblack@bcm.tmc.edu

Received date: Oct 24, 2014; **Accepted date:** Oct 25, 2014; **Published date:** Nov 1, 2014

Editorial

The indictment of fat as a dietary constituent that potentiates carcinogenesis arose from a study of Watson and Mellanby in 1930 [1]. Animal diets containing high levels of butterfat (12.5-25%) were shown to enhance coal tar-induced skin tumor formation. After this seminal observation, intense investigations of the effects of dietary fat on chemically-induced carcinogenesis were conducted during the 1930s through the 1950s. There were several conclusions from these studies that are noteworthy [2]. These, however, must be tempered by the fact that many of these early studies failed to control for major dietary parameters, e.g., caloric density. And although much of the exacerbation of fat on tumor formation reported in these early studies could be explained on the basis of increased caloric intake, fat, per se, increased the rate of tumor formation, particularly when total caloric intake was restricted. Also, much of the exacerbation by fat on tumor formation occurred during the post initiation stage of carcinogenesis.

Baumann and Rusch [3] first demonstrated that dietary fat also had an influence on ultraviolet light (UVL) induced carcinogenesis. These investigators employed a high-fat diet that contained up to 30% hydrogenated cottonseed oil. This resulted in a four week shorter tumor latent period than that which occurred in low-fat controls. However, this line of investigation ended with the advent of World War II and was not resumed for nearly 45 years. This was unfortunate as UVL-carcinogenesis is the main etiologic agent in skin carcinogenesis. Nearly 90% of all human skin cancers are the result of solar UVL [4]. Thus, studies of skin carcinogenesis employing UVL are the most relevant to the clinical condition. There are other advantages to employing a physical carcinogenic agent over chemical carcinogens in dietary studies. UVL involves no activation/detoxification of the presumed carcinogenic species; no competitive chemical inhibition; no binding to target molecules; and no transport to respective target sites. Changing the cells chemical milieu through dietary modification could have an impact on any of these activities affecting chemical carcinogenesis. UVL allows investigation of the direct underlying mechanisms of dietary modification of the skin cancerization process.

Dietary lipid was further implicated in cancer when Denham Harmon [5] developed the Free Radical Theory of disease. Cognizant of the vulnerability of polyunsaturated fatty acids to free radical attack, he recommended that dietary levels of PUFA be reduced in order to reduce cancer risk [6]. Indeed, the first report on diet and UVL carcinogenesis following the seminal observation in 1939, appeared to be in agreement with Harman's recommendation. Mice were fed semi-defined, isocaloric diets containing 0.75 to 4.0 % (w/w) omega-6 fatty acid (Corn oil), and subjected to a UVL regimen. The tumor latent period was dramatically lengthened and tumor multiplicity reduced as the dietary PUFA level was reduced [7].These tumor parameters were altered in a near linear fashion with dietary lipid level. Further, when animals were fed a diet containing 4% corn oil that was partially hydrogenated (60%), tumor latency was markedly lengthened and tumor multiplicity reduced when compared to the normal 4% corn oil diet. Later, Reeve et al. [8] found that feeding a diet supplying totally saturated sunflower oil (hydrogenated) completely abolished the UVL carcinogenic response, whereas those animals receiving the polyunsaturated sunflower oil exhibited 100% tumor incidence. As noted, these results supported Harman's recommendation of reducing PUFA intake to reduce cancer risk. Further supporting evidence was obtained when it was shown that antioxidants inhibited the level of cutaneous lipid peroxidation and produced an inhibitory effect on carcinogenesis almost equal to the exacerbation of these parameters by increasing dietary lipid level [9].

Earlier studies had suggested that the primary effect of dietary fat on the carcinogenic continuum occurred in the post-initiation phase [2]. The segment, at which dietary fat exerted its primary effect on UVL carcinogenesis, was examined by a cross-over feeding study design. Animals were placed on semi-defined, isocaloric diets containing low (0.75 %) or high (12%) levels of corn oil. Immediately after a cancer causing dose of UVL was administered, but before tumors appeared, some of the dietary groups were crossed to the opposing diet. The resulting tumor incidence plots (tumor latent period) and tumor multiplicity (number of tumor /animal) values provided clear evidence that the principal exacerbation of carcinogenic expression by high levels of omega-6 PUFA occurred during the post-initiation, or promotion, stage of carcinogenesis [10]. Perhaps more important, crossing from a high fat to a low-fat diet, even after a cancer causing dose had been administered, negated the exacerbating influence of the high fat diet and provided a rationale for the undertaking of a clinical intervention trial. Such a trial was undertaken and has been described in more detail [11]. Briefly, 133 skin patients met the inclusion criteria, of which 115 completed the two-year study. Fifty-eight were randomly assigned to the Control arm in which no dietary changes were introduced. The 57 patients randomly assigned to the Intervention arm learned how to adopt low-fat eating habits to their food preferences and lifestyles. Each patient was given a "fat gram goal" that defined the grams of fat that would provide 20% of calories as fat. At four months into the study, patients in the Intervention arm had reduced their % of calories from fat from 39% to 21% where it remained to the end of the two-year study. As this study was designed to determine the influence of dietary fat on non-melanoma skin cancer (NMSC), stability of body weight and calorie intake was maintained in order to prevent confounding effects due to these variables. The influence of dietary fat became apparent early in the study, as a significant number of actinic keratoses (pre-malignant lesions) between groups occurred [12]. Patients in the control arm were found to be at 4.7 times greater risk of having one or more actinic keratosis during the two-year period than similar patients in the low-fat intervention arm. The influence of the reduction in calories from fat on NMSC (squamous and basal cell carcinomas) was observed after 101

patients had completed the study [13] and became even stronger after all 115 patients completed [14]. NMSC occurrence in the control arm, when measured in 8-month intervals of the two year study, did not change significantly from the baseline period. NMSC occurrence in the intervention arm was significantly lower ($p < .02$) in the last 8-month evaluation period. The cumulative rate of occurrence of NMSC (cumulative skin cancers/patient/time period) was .21 and .19 during the first 8-month period of the study and 0.26 and 0.02 during the last 8-month evaluation period for control and intervention arms, respectively. In this study there was no effort to alter the types of fat consumed by the patient nor the type of PUFA. Effort was made to maintain the polyunsaturated/saturated fatty acid ratio (P/S ratio), however.

With respect to the latter, the degree of unsaturation and the reduction of PUFA level in the diet to reduce cancer risk became moot points when studies with omega-3 PUFA demonstrated that these PUFA dramatically inhibited UVL carcinogenesis, compared to the exacerbation of carcinogenesis resulting from high levels of omega-6 intake. [15]. Both linoleic acid (omega-6 PUFA) and eicosapentaenoic acid (omega-3 PUFA) exhibit similar iodine numbers that reflect similar degrees of unsaturation. Assessment of early genotoxic markers in humans indicates that omega-3 PUFA protected against UVL-induced genotoxicity and suggested that longer term supplementation might reduce NMSC occurrence [16]. A population-based case-control study found a consistent tendency for a lower risk of squamous cell carcinoma (SCC) with higher intakes of omega-3 PUFA [17]. Their data also suggested a tendency toward reduced risk of SCC with diets containing high omega-3/omega-6 PUFA ratios.

Recently, a review and meta-analysis was conducted to determine the relationship between skin cancer and dietary omega-3 intake [18]. While the data were limited, the investigators reported that intake of high omega-3 was inversely associated with melanoma (only one estimate) and SCC, although the latter was not significant. The investigators concluded that these data were suggestive but inadequate to support the hypothesis that omega-3 PUFA protects against skin cancer. The most direct approach to address this issue is through intervention trials in populations with high and known risk, for NMSC. It has been proposed that a study design be adopted that is similar to that in which a reduction in the % of calories consumed as fat was shown to reduce NMSC occurrence in NMSC patients [19].

It has been suggested that one potential mechanism of omega-3 PUFA inhibition of UVL carcinogenesis is mediated through immune modulation. It was shown that plasma prostaglandin E2 (PGE2) levels are directly related to the intake of omega-6, which, in turn, induced the greatest exacerbation of carcinogenesis. Omega-3 PUFA reduced the PGE2 level below that of the lowest level of omega-6 intake. PGE2 is known to be pro-inflammatory and immunosuppressive. Importantly, omega-3 PUFA provides striking protection against UVL-induced immunosuppression [20, 21]. Indeed, a preliminary double-blind, randomized controlled study of UVL suppression of nickel contact hypersensitivity in humans indicated that oral omega-3 PUFA abrogated photoimmunosuppression [22].

A considerable body of evidence has accrued that indicates the influence of omega-6,-3 PUFA on UVL carcinogenesis is predicated upon the differential metabolites of the cyclooxygenase pathway [19]. The different effects upon UVL carcinogenic expression, the differences in eicosanoid intermediates, the differences in immune responsiveness of omega-6 and omega-3 PUFA precludes the general indictment of dietary PUFA in cancer risk and this recommendation must be refined, based on individual PUFA [23]. In summary, the implementation of a low-fat diet and omega-3 supplementation show the greatest promise as dietary strategies for the management and prevention of the highly prevalent NMSC.

References

1. Watson AF, Mellanby E (1930) Tar cancer in mice. II. The condition of the skin when modified by external treatment or diet, as a factor in influencing this cancerous reaction. Br. J Exp Pathol 11: 311-322.
2. Tannenbaum A (1953) Nutrition and Cancer in Pathophysiology of Cancer, Homburger F, Fishman WH, Eds., Harper (Hoeber), New York, 392-437.
3. Baumann CA, Rusch HP (1939) Effects of diet on tumors induced by ultraviolet light. Am J Cancer 35: 213-221.
4. Koh HK, Lew RA, Geller AC, Miller DR, Davis BE (1995) Skin Cancer: prevention and control in Cancer Prevention and Control. Greenwald P, Kramer BS, Weed DL, Eds. Dekker, New York, 611-640.
5. HARMAN D (1962) Role of free radicals in mutation, cancer, aging, and the maintenance of life.Radiat Res 16: 753-763.
6. Harman D (1982) The free radical theory of aging. In Free Radicals in Biology, Pryor WA, Ed. Academic Press, NY, 255-275.
7. Black HS, Lenger W, Phelps AW, Thornby J (1983) Influence of dietary lipid upon ultraviolet-light carcinogenesis.Nutr Cancer 5: 59-68.
8. Reeve VE, Matheson M, Greenoak GE, Canfield PJ, Boehm-Wilcox C, et al. (1988) Effect of dietary lipid on UV light carcinogenesis in the hairless mouse.Photochem Photobiol 48: 689-696.
9. Black HS, Lenger WA, Gerguis J, Thornby J (1985) Relation of antioxidants and level of dietary lipid to epidermal lipid peroxidation and ultraviolet carcinogenesis.Cancer Res 45: 6254-6259.
10. Black HS, Thornby J, Gerguis J, Lenger W (1992) Influence of dietary omega-6, -3 fatty acid sources on the initiation and promotion stages of photocarcinogenesis.Photochem Photobiol 56: 195-199.
11. Black HS Skin Cancer (2006) in Nutritional Oncology, Second Ed. Heber D, Blackburn GL, Go VLW, Milner J. Eds. Academic Press, San Diego, CA, 405-422.
12. Black HS, Herd JA, Goldberg LH, Wolf JE Jr, Thornby J, et al. (1994) Effect of a low-fat diet on the incidence of actinic keratosis.N Engl J Med 330: 1272-1275.
13. Black HS, Thornby J, Wolf JE Jr, Goldberg LH, Herd JA, et al. (1995) Evidence that a low-fat diet reduces the occurrence of non-melanoma skin cancer.Int J Cancer 62: 165-169.
14. Jaax S, Scott LW, Wolf JE Jr, Thornby J, Black HS (1997) General guidelines for a low-fat diet effective in the management and prevention of nonmelanoma skin cancer.Nutr Cancer 27: 150-156.
15. Orengo IF, Black HS, Kettler AH, Wolf JE Jr (1989) Influence of dietary menhaden oil upon carcinogenesis and various cutaneous responses to ultraviolet radiation.Photochem Photobiol 49: 71-77.
16. Rhodes LE, Shahbakhti H, Azurdia RM, Moison RM, Steenwinkel MJ, et al. (2003) Effect of eicosapentaenoic acid, an omega-3 polyunsaturated fatty acid, on UVR-related cancer risk in humans. An assessment of early genotoxic markers.Carcinogenesis 24: 919-925.
17. Hakim IA, Harris RB, Ritenbaugh C (2000) Fat intake and risk of squamous cell carcinoma of the skin.Nutr Cancer 36: 155-162.
18. Noel SE, Stoneham AC, Olsen CM, Rhodes LE, Green AC (2014) Consumption of omega-3 fatty acids and the risk of skin cancers: a systematic review and meta-analysis.Int J Cancer 135: 149-156.
19. Black HS, Rhodes LE (2006) The potential of omega-3 fatty acids in the prevention of non-melanoma skin cancer.Cancer Detect Prev 30: 224-232.
20. Fischer MA, Black HS (1991) Modification of membrane composition, eicosanoid metabolism, and immunoresponsiveness by dietary omega-3 and omega-6 fatty acid sources, modulators of ultraviolet-carcinogenesis.Photochem Photobiol 54: 381-387.
21. Moison RM, Beijersbergen Van Henegouwen GM (2001) Dietary eicosapentaenoic acid prevents systemic immunosuppression in mice induced by UVB radiation.Radiat Res 156: 36-44.

22. Pilkington SM, Massey KA Bennett, SP, Al-Aasswad NM, Roshdy, K, et al. (2013) Randomized controlled trial of oral omega-3 PUFA in solar-simulated radiation-induced suppression of human cutaneous immune responses. Am J Clin Nutr 97: 646-652.

23. Black HS (2012) Nutritional lipid and antioxidant supplements: risks versus benefits. Expert Rev Dermatol 7: 483-492.