Effect of eicosapentaenoic acid, an omega-3 polyunsaturated fatty acid, on UVR-related cancer risk in humans. An assessment of early genotoxic markers

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Dietary omega-3 polyunsaturated fatty acids (ω-3 PUFAs) protect against photocarcinogenesis in animals, but prospective human studies are scarce. The mechanism(s) underlying the photoprotection are uncertain, although ω-3 PUFAs may influence oxidative stress. We examined the effect of supplementation on a range of indicators of ultraviolet radiation (UVR)-induced DNA damage in humans, and assessed effect on basal and post-UVR oxidative status. In a double-blind randomized study, 42 healthy subjects took 4 g daily of purified ω-3 PUFA, eicosapentaenoic acid (EPA), or monounsaturated, oleic acid (OA), for 3 months. EPA was bioavailable; the skin content at 3 months showing an 8-fold rise from baseline, $P < 0.01$. No consistent pattern of alteration in basal and UVR-exposed skin content of the antioxidants glutathione, vitamins E and C or lipid peroxidation, was seen on supplementation. Sunburn sensitivity was reduced on EPA, the UVR-induced erythemal threshold rising from a mean of 36 (SD 10) mJ/cm² at baseline to 49 (16) mJ/cm² after supplementation, $P < 0.01$. Moreover, UVR-induced skin p53 expression, assessed immunohistochemically at 24 h post-UVR exposure, fell from a mean of 16 (SD 5) positive cells/100 epidermal cells at baseline to 8 (4) after EPA supplementation, $P < 0.01$. Peripheral blood lymphocytes (PBL) sampled on 3 successive days both pre- and post-supplementation, showed no change with respect to basal DNA single-strand breaks or oxidative base modification (8-oxo-dG). However, when susceptibility of PBL to _ex vivo_ UVR was examined using the comet assay, this revealed a reduction in tail moment from 84.4 (SD 3.4) at baseline to 69.4 (3.1) after EPA, $P = 0.03$. No significant changes were seen in any of the above parameters following OA supplementation. Reduction in this range of early markers, i.e. sunburn, UVR-induced p53 in skin and strand breaks in PBL, indicate protection by dietary EPA against acute

Abbreviations: CPD, cyclobutane pyrimidine dimers; EPA, eicosapentaenoic acid; MDA, malondialdehyde; MED, minimal erythemal dose; MM, malignant melanoma; ω-3 PUFAs, omega-3 polyunsaturated fatty acids; ROS, reactive oxygen species; SSB, single-strand breaks; TM, tail moment; UVR, ultraviolet radiation.

UVR-induced genotoxicity; longer-term supplementation might reduce skin cancer in humans.

Introduction

Skin provides a protective barrier against environmental insults and is the primary target for ultraviolet radiation (UVR) effects. Skin cancer is now the commonest form of cancer in white Caucasian populations, and the incidence continues to rise due to the trend for greater recreational exposure to ambient UVR (1). Basal cell carcinoma (BCC), arising from the basal epidermal layer, is the commonest skin cancer, followed by squamous cell carcinoma (SCC), derived from supra-basal keratinocytes, whereas malignant melanoma (MM), derived from melanocytes, is less common but carries a high mortality rate. UVR is implicated as the main aetiological factor in all three types.

The mechanisms of UVR-induced carcinogenesis have been extensively reviewed (2,3). UVR is a complete carcinogen, capable of the initiation and promotion of cancer, inducing both DNA damage and immunosuppression. DNA may be damaged directly by UVR, or indirectly via UVR induction of free radicals and reactive oxygen species (ROS). While the shorter wavelength ultraviolet-B (UVB, 290–320 nm) typically causes direct damage and ultraviolet-A (UVA, 320–400 nm) causes indirect damage, there is considerable overlap of effects. The commonest DNA lesions caused by direct damage are cyclobutane pyrimidine dimers (CPD), while a range of types of oxidative DNA damage have been observed including single-strand breaks (SSB) and base modifications. When UVR-induced DNA damage is not removed from the genome, this may lead to mutations and cancer development. In normal skin, the transcription factor p53 is a key element in the response to UVR-induced DNA damage, facilitating either repair by regulation of the cell cycle, or destruction of the pre-cancerous cells by apoptosis (4,5). Mutations in the p53 tumour suppressor gene, causally linked to UVR exposure, are a very early event in skin cancer induction (6). The data suggest an important role for p53 mutations in SCC and BCC, as they are present in the majority of these lesions and also in the pre-malignant actinic keratoses, and a smaller association with MM (2,3).

Strategies to protect against UVR-induced skin damage include topical sunscreens (7), but studies that have examined sunscreen application methods by consumers have consistently found these lacking, with insufficient amounts applied and uneven spread (1). A systemic means of protection, particularly a safe dietary method, would therefore have much appeal (7). While dietary agents seem unlikely to be capable of intervening to reduce direct DNA damage by UVR, they could potentially influence DNA damage due to free radicals/ROS. In addition, they might intervene at the promotion stage of photocarcinogenesis by modulating immunosuppression.