

Milestones And Challenges In Skin Cancer Carcinogenesis

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Editorial

The skin represents one of the largest organ systems of the human body – constituting about one-twelfth of our total body weight. Positioned as the interface between the internal systems of the body and its environment, the skin acts as a barrier to an expansive array of extrinsic agents and provides the foremost target for environmental insult [1]. Thus, it is not surprising that skin cancer, in some light-skinned populations, such as Australia, United Kingdom, and the United States represents the most frequently occurring neoplastic disease. In fact, a descriptive analysis of population-based fees-for-service physicians' claims and National Ambulatory Medical Care service database found that the total number of procedures increased by 76.9% from 1,158,298 in 1992 to 2,048,517 in 2006. Further, the total number of Non-Melanoma Skin Cancers (NMSC) in the U.S. population in 2006 was estimated at 3,507,693 and total number of persons in the U.S. treated for NMSC estimated at 2,152,500 [2]. NMSC is the most frequently occurring cancer with an estimated 5.4 million new cases each year – more than all other types of cancers combined [3].

Major milestones in the study of cancer development have been achieved through investigations of the carcinogenic potential of various agents on skin – the skin offering an unique model and direct approach to carcinogenesis studies. Indeed, the first association of skin cancer to excessive exposure to external agents occurred in 1775 [4]. Sir Percival Pott observed that excessive exposure to “soot” was associated with unusually high skin cancer incidence (Epithelial cancer of the scrotum) in chimney sweeps. It was not until 1918 that Yamagiwa and Ichikawa successfully produced cancer (skin) in experimental animals with coal tar [5]. Berenblum was instrumental in the development of the two-stage theory of carcinogenesis, defined as initiation and promotion – a factitious segmentation of the carcinogenic continuum that has been invaluable in allowing dissection and definition of the biochemical steps in the cancer process [6]. At this point, these accomplishments were achieved with chemical carcinogens. However, about 90% of all NMSC are due to ultraviolet radiation (UVR) exposure [7].

More than a hundred years after Pott had associated excessive exposure to soot with skin cancer occurrence, the association of skin cancer with UVR began to develop. First, with Unna (1894) who associated the severe degenerative changes of sun-exposed areas of the skin with the development of skin cancer, referred to as “Carcinome der Seemannshaup” and the association confirmed two years later through association of “la Lumiere solaire” (sunlight) exposure with keratoses and skin cancer by

vineyard workers in southern France [8]. This association was observed in light-skinned populations exposed in areas of high sun-exposure [9]. The first experimental evidence of the causal role of UVR was provided by Findlay (1928) when it was shown that daily UVR exposure from a quartz mercury-vapor lamp produced skin cancers in mice [10]. Blum and colleagues carried-out extensive quantitative studies on the induction of tumors in mice with UVR [11]. Roffo (1939), an Argentine, confirmed that radiation from a mercury arc lamp produced skin cancer in rats and extended the study to show that sunlight would do the same [12]. Roffo also demonstrated that the offending wavelengths of UVR were excluded by clear window glass, thus setting an approximate limit of effectiveness in producing skin cancer to those wavelengths of 320 nm, or less. Eleven years later, Roffo was the first to conduct an epidemiological study of skin cancer in humans, a study in which skin cancer occurrence was analyzed with respect to anatomical site, gender, nationality, and occupation.

After the delimitation of the most carcinogenic wavelengths of UVR to 320 nm, or less, numerous efforts to define an action spectrum for UVR carcinogenesis, and especially in humans, were undertaken. After evaluation of extensive animal data, the Commission Internationale de l'Eclairage (CIE, International Commission on Illumination, Vienna, Austria) accepted the recommendations of the CIE Technical Committee (TC-32) and adopted (2006) an action spectrum for human NMSC. This spectrum was adjusted for optical differences between murine and human epidermis and with qualifying caveats. The spectrum can be viewed in [1]. Although the data seem relevant in the UVB (280-320 nm) range, there is about 20-30 times more UVA (320-400 nm) in sunlight than UVB and there is less confidence in the contribution wavelengths greater than 340 nm make. Whereas UVA is carcinogenic, the quantum efficiency is about a 1000-times less than that of UVB. Questions arose regarding the real risks from excessive prolonged sun exposure of persons protected with effective UVB sunscreens, or from tanning parlors – questions that roiled the sunscreen industry. There was also a question regarding the action spectra of UVA versus UVB for melanoma skin cancer and the WHO, IARC (2009) found that use of tanning beds before the age of 30 led to a 75% increase in melanoma!

Diet was one of the first extrinsic factors shown to modify the carcinogenic response to UVR. In 1939, Baumann and Rusch reported that high levels of dietary fat exacerbated skin cancer development [13]. This line of investigation lay dormant until re-initiated in the 1980's [14]. A low-fat dietary intervention study was initiated with NMSC patients in 1991. Early in the study evidence of an effect by low-fat intervention on actinic keratosis (AK), a pre-malignant lesion, was observed. There were three-times more AK in the Control group that was at 4.7 times greater risk to develop AK than the low-fat intervention group [15]. This effect carried over to NMSC as there was a significant reduction in NMSC in the intervention group during the last eight-month period of the two-year study [16].

One of the major milestones in the study of skin carcinogenesis was the demonstration that UVR was an immunosuppressive agent [17]. UVR-induced skin tumors are highly antigenic and, when transplanted into normal non-irradiated mice, are quickly rejected. However, if the recipients are pre-irradiated with UVR, the animals are immunosuppressed and

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the tumors take and grow the same as in animals that have their thymus removed. UVR diminishes the animal's ability to mount T-cell-mediated immune suppression and abrogates an animal's capacity to reject the highly antigenic UVR-induced skin tumors. This effect results from the development of suppressor T-lymphocytes, of which the presence or absence determines whether primary skin cancers develop in UVR-irradiated skin.

Dietary fat also modulates immunity in UVR-irradiated mice [18, 19]. UVR-irradiated animals fed an omega-3 FA source demonstrated a reduced inflammatory response and a greater (4.5-fold) delayed hypersensitivity (DH) to dinitrochlorobenzene than animals fed omega-6 FA. DH is a T-cell mediated immune response in UVR-irradiated animals. High dietary lipid level of omega-6 FA was shown to completely suppress the DH after three weeks of UVR; significantly increase tumor rejection rates of transplanted animals compared to those on low-fat diet; and high-fat diet exerted a significant reduction in median tumor rejection times. Dietary lipid, both type and level, exerts profound influence over specific immune responses and probably represents a major mode of action for dietary fat to influence tumor occurrence.

Other milestones in UVR-carcinogenesis include the direct, and indirect, effects of UVR on DNA; the molecular events of UVR damage, such as p53 and Ras mutations; and the potential role of free radicals in carcinogenic expression. Shorter UVR wavelengths induce DNA damage, e.g. cis-syn cyclobutadipyrimidines and pyrimidine (6-4) pyrimidone photoadducts, in the presence or absence of O_2 , implying direct DNA damage [20, 21]. Studies have also shown that longer wavelengths, i.e., UVA, causes various types of DNA damage including cyclobutene-type pyrimidine dimers, strand breaks, and DNA cross-links [22]. Just as there are numerous endogenous UVA chromophores that may initiate cellular oxidative reactions, endogenous antioxidant constituents have been identified that inhibit these reactions [23].

Many NMSC cells carry a high level of DNA mutations induced by UVR. Brash et al [24] reported that 58% of skin squamous cell carcinomas (SCC) contain mutations in the p53 tumor suppressor gene. There is a relatively high frequency (45-68%) of the tumor promoter gene, ras, found in NMSC – localized primarily to pyrimidine rich sequence areas [25]. The genes c-fos and c-jun are induced early after Solar Simulated Radiation (SSR) [26]. Their gene products are components of the nuclear transcription factor AP-1.

Free radical formation in skin exposed to UVR was first observed by Norins in 1962 [27]. Although the potential for involvement in carcinogenesis was recognized, no direct evidence has been forthcoming. There are, however, four lines of indirect evidence that free radicals, or free radical mediated reactions, are involved in the etiology of UVR-induced carcinogenesis. First, free radicals are formed in UVR-exposed skin [27]. Conditions that exemplify oxidative stress inhibit natural antioxidant defenses [28]. Conditions that increase the free radical load of the host enhances UVR-carcinogenesis [29]. Supplementation with antioxidants inhibit UVR-carcinogenesis [30]. It should be emphasized that each agent that exhibits antioxidant properties must be assessed individually as their mode of action may differ under different circumstances, e.g., β -carotene may exacerbate UVR carcinogenesis [31].

Major milestones have been examined in the progress of UVR-induced skin carcinogenesis research. Only the surface of this immensely complex problem has been presented with the hope of placing in perspective some of the major effects of UVR as it relates to skin carcinogenesis. UVR is a complete carcinogen comprised of UVB and UVA. UVR increases oxidative stress and reduces antioxidant defense. At the same time, it produces DNA photoproducts. UVR is immunosuppressive and skin lipids can be peroxidized and may act as tumor promoters. DNA photoproducts may be repaired but UVR may also cause mutations in repair enzymes that lead to cell death or allow mutations that transform cells to yield papillomas.

Oncogenes may be activated that regulate transformation. UVR may mutate tumor suppressor genes that allow the conversion of papillomas to frank malignancy. The outgrowth of papillomas is suppressed by the immune system in the promotion/progression phase along the carcinogenic continuum. All the factors addressed occur with exposure to UVR and potentiate and modulate carcinogenic expression [32].

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