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Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure

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Abstract

A systematic revision of the literature was conducted in order to undertake a comprehensive meta-analysis of all published observational studies on melanoma. An extensive analysis of the inconsistencies and variability in the estimates was performed to provide some clues about its Epidemiology. Following a systematic literature search, relative risks (RRs) for sun exposure were extracted from 57 studies published before September 2002. Intermittent sun exposure and sunburn history were shown to play considerable roles as risk factors for melanoma, whereas a high occupational sun exposure seemed to be inversely associated to melanoma. The country of study and adjustment of the estimates adjuste for phenotype and photo-type were significantly associated with the variability of the intermittent sun exposure estimates ($P = 0.024$, 0.003 and 0.030, respectively). For chronic sun exposure, inclusion of controls with dermatological diseases and latitude resulted in significantly different data ($P = 0.05$ and 0.031, respectively). Latitude was also shown to be important ($P = 0.031$) for a history of sunburn; studies conducted at higher latitudes presented higher risks for a history of sunburns. Role of country, inclusion of controls with dermatological diseases and other study features seemed to suggest that "well conducted" studies supported the intermittent sun exposure hypothesis: a positive association for intermittent sun exposure and an inverse association with a high continuous pattern of sun exposure.

Keywords: Melanoma; Sunlight; Sunburn; Meta-analysis; Epidemiology; Review literature

1. Introduction

Malignant melanoma of the skin (melanoma) is one of the few forms of cancer whose incidence and mortality rates are rising in many parts of the world where light-skinned populations live. The reasons for this increase are thought to be linked to changing sun exposure patterns, although many aspects of the aetiology of melanoma are not understood or are poorly quantified.

The present paper describes the results of a meta-analysis on the cutaneous melanoma risk and ultraviolet sun radiations, which was included in a wider project investigating all major risk factors for melanoma [1].

In 1991, the "Consensus Development Conference on Sunlight, Ultraviolet Radiation, and the Skin" stated that the only established exogenous causal factor for cutaneous melanoma in white populations is sun exposure [2]. Similar conclusions were reached by the

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International Association for Research on Cancer (IARC) [3], which has reviewed in great detail the relationship between melanoma and sun exposure and has accepted sun exposure as the main cause of cutaneous melanoma in humans. However, complete or more convincing answers to a number of questions on sun exposure are still needed. Such questions include whether the pattern of sun exposure is really important and acts independently of the amount of sun exposure and whether sunburn makes a specific contribution to the risk of skin cancer. It is often difficult to separate the interrelations between sunburn history, sun exposure habits, ability to tan and other phenotypic factors. Ultraviolet (UV) radiation may act as both an initiator through sunburn, for example, and a promoter, producing naevi and having promoting action on them, as well as a possible promoting action on other initiated melanocytes that do not proliferate at an early stage to form naevi [4].

Assessment of sun exposure has been investigated in this study looking at differences in patterns of sun exposure and the possible association with sunburns. Many studies showed positive associations between the melanoma risk and a history of sunburn, but a straightforward interpretation of this association is complicated. In fact, many studies consider sunburn a marker of acute sun exposure [5]. Furthermore, this inflammatory reaction may represent an increased risk for those with a high susceptibility rather than a direct effect of the presence of sunburn. Therefore, both questions, unusually intense sun exposure and skin sensitivity, must be considered in order to render the data meaningful.

Several publications have investigated sun exposure in association with melanoma, producing results that appear conflicting. In point of fact, they used different methods of information ascertainment and statistical analyses, and considered completely different populations. Furthermore, most of the evidence relevant to the effects of different patterns of sun exposure epidemiological studies and it is not easy to separate the effects of different patterns of exposure using epidemiological methods. Several methodological problems may bias the association between sunlight exposure and melanoma risk [6]. We have carried out an in-depth exploration of between-study heterogeneity and possible sources of bias searching for significant differences in study features, definitions adopted, characteristics of the populations and of the types of analyses conducted.

2. Patients and methods

2.1. Definition of outcome and exposures

The outcome of this systematic meta-analysis was histologically confirmed melanoma.

Sun exposure was classified as intermittent, chronic or total. Intermittent exposure indicated "an intermittent pattern of sun exposure" and it was generally assessed by posing questions about specific activities that would be likely to represent relatively severe intermittent exposure such as recreational activities: sunbathing, water sports, and vacations in sunny places. Chronic exposure indicated "a continuous or more continuous pattern of sun exposure" and it was measured essentially entirely as occupational exposure. Total exposure was evaluated as sun exposure of all kinds.

Sunburn is an inflammatory reaction that arises following acute exposure of the skin to intense solar radiation. Sunburn is considered by many authors [5,7,8] a biological marker of high dose of ultraviolet radiation penetrating to the melanocytes at the base of the epidermis, regardless of the degree of pigmentation in the epidermis.

In this paper, we refer to *Intermittent sun exposure* as the amount of intermittent pattern of sun exposure, to *Chronic sun exposure* as the amount of a more continuous pattern of sun exposure, to *Total sun exposure* as the amount of sun exposure of all kinds and to *Sunburns* as the number of episodes of sunburn. Where a study presented multiple measures for one or more of the four exposures categories, we chose the measure that covered exposure for the longest period of adult life. In cases where, for the chosen measure, there were more than two levels of exposure, we used the relative risk (RR) estimates for the highest level, in order to reduce the possibility of misclassification. When the decision about the most appropriate definition is not straightforward, the definition that presented the highest prevalence among controls was chosen. The choice of definitions, and of the corresponding risk estimates to be included, was evaluated in the sensitivity analysis by looking at the influence of single studies. The choice of which measure and which exposure to use was made independently of knowledge of the measure and level specific RR.

Between childhood exposure and adulthood exposure, the second option was chosen because there is evidence that self-reported childhood exposure is less reproducible than exposure at older ages [9]. This choice was checked in the heterogeneity analysis by looking at the relevance of the latent period considered and at the influence of age for sunburn history.

Thus, two further meta-analyses on sunburns in childhood and in adulthood were carried out. To assess sunburn in adulthood, it was decided to include studies with a clear indication that experiences occurred at an adult age (>19 years of age). "Childhood" was defined as considering subjects of no more than 15 years of age. Weinstock *et al.* [8] was not included in this sub group analysis because the age period considered was "15–20 years" and it was not coherent with the other definitions of childhood sunburns.