Cancer Epidemiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

Sun exposure and skin cancer, and the puzzle of cutaneous melanoma
A perspective on Fears et al. *Mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States.* American Journal of Epidemiology 1977; 105: 420–427

Bruce K. Armstrong[a,b,*], Anne E. Cust[a,c]

[a] *Cancer Epidemiology and Prevention Research Group, School of Public Health, The University of Sydney, NSW, Australia*
[b] *School of Global and Population Health, The University of Western Australia, Perth, WA, Australia*
[c] *The Melanoma Institute Australia, North Sydney, NSW, Australia*

ARTICLE INFO

Article history:
Received 27 February 2017
Received in revised form 6 April 2017
Accepted 8 April 2017
Available online xxx

Keywords:
Sun exposure
Intermittent
Dual pathway
UV radiation
Melanoma
Skin cancer
Keratinocyte cancer
Nevi
Hypothesis
etiology
Risk factor

ABSTRACT

Sunlight has been known as an important cause of skin cancer since around the turn of the 20th Century. A 1977 landmark paper of US scientists Fears, Scotto, and Schneiderman advanced a novel hypothesis whereby cutaneous melanoma was primarily caused by intermittent sun exposure (i.e. periodic, brief episodes of exposure to high-intensity ultraviolet radiation) while the keratinocyte cancers, squamous cell carcinoma and basal cell carcinoma, were primarily caused by progressive accumulation of sun exposure. With respect to cutaneous melanoma, this became known as the intermittent exposure hypothesis. The hypothesis stemmed from analysis of measured ambient ultraviolet radiation and age-specific incidence rates of melanoma and keratinocyte cancers collected as an extension to the US Third National Cancer Survey in several US States. In this perspective paper, we put this novel hypothesis into the context of knowledge at the time, and describe subsequent epidemiological and molecular research into melanoma that elaborated the intermittent exposure hypothesis and ultimately replaced it with a dual pathway hypothesis. Our present understanding is of two distinct biological pathways by which cutaneous melanoma might develop; a nevus prone pathway initiated by early sun exposure and promoted by intermittent sun exposure or possibly host factors; and a chronic sun exposure pathway in sun sensitive people who progressively accumulate sun exposure to the sites of future melanomas.

Contents

* Corresponding author at: School of Global and Population Health, The University of Western Australia, 35 Stirling Hwy, Crawley, WA 6009, Australia.
E-mail address: bruce.armstrong@uwa.edu.au (B.K. Armstrong).

http://dx.doi.org/10.1016/j.canep.2017.04.004
1877-7821/

1. An hypothesis about sun exposure and skin cancer (Fears et al., 1977)

By comparatively simple modelling of cross-sectional descriptive epidemiological data from the US Third National Cancer Survey, Tom Fears, Joe Scotto and Marvin Schneiderman, US scientists working in the US National Cancer Institute's Biometry Branch, changed the paradigm for the nature of personal sun exposure that increases risk of skin cancer. In their words: "These observations suggest that non-melanomas [now referred to as keratinocyte cancers] and melanoma of the skin are related to UV [ultra violet radiation] in different ways. High rates of non-melanoma incidence may be associated with high cumulative UV exposure, while high melanoma incidence may be associated with brief exposure to high-intensity UV radiation" [1]. With respect to cutaneous melanoma (in this paper melanoma refers exclusively to cutaneous melanoma), their second sentence became known as the intermittent exposure theory or hypothesis [2].

Third National Cancer Survey melanoma data were collected with all other cancer data, except keratinocyte cancer data, from 1969 to 1971. Keratinocyte cancer data were collected in a 1971 to 1972 extension of the Survey in four Survey regions, which were distributed from north to south in the USA. Fears et al. [1] fitted weighted, least squares log-linear regression models to the Survey data, separately by cancer type and sex. The logarithm of the probability, specific to a particular region and age-group, of having keratinocyte cancer or melanoma diagnosed was the dependent variable and the logarithms of ambient erythemal solar UV radiation (denoted by U and measured by a network of Robertson-Berger meters in the four regions studied) and age at diagnosis (A, the middle of the age group range) were the independent variables. Thus the regression equation was: $\ln R_{ij} = c \ln U_i + k \ln A_j + \varepsilon_{ij}$, where ε_{ij} is an error term.

The coefficients of UV for keratinocyte cancers and melanoma were quite similar (keratinocyte cancer 2.96 males and 2.45 females; melanoma 2.45 males and 2.23 females) but the coefficients of age were quite different (keratinocyte cancer 3.71 males and 3.06 females; melanoma 0.80 males and 0.29 females) (Fig. 1). That is, the effect of attained age, which is also the total period of accumulation of UV exposure, was much weaker for melanoma than for keratinocyte cancer. The data and lines of best fit are shown in Figs. 2 and 3. With respect to the different age coefficients, Fears et al. [1] stated: "If we regard the product of age and total annual ultraviolet radiation as a measure of cumulative life-time exposure, then such a common coefficient ($k = c$) suggests that the age-specific risks of non-melanoma skin cancer are related to cumulative UV exposure. By contrast, we see that in the regression of melanoma incidence on ln age and ln annual UV count, the differences between the regression coefficients is large relative to the standard deviations for males and for females. While the coefficient for ln UV is still large, the coefficient for ln age is now small. If we again regard the product of age and total annual ultra-violet radiation as a measure of cumulative exposure then this large discrepancy between regression coefficients implies that the age-specific risks of melanoma are related to annual dose [as measured by annual UV count] rather than to cumulative lifetime exposure."

In introducing their paper, Fears et al. [1] summarised evidence that sun exposure causes skin cancer. Briefly, skin cancers occur most frequently on exposed parts of the body; those who have skin cancer tend to sunburn easily; skin cancer is more common among those outdoors much of the time or who live closer to the equator; and skin cancer can be produced in animals in experimental studies by exposure to ultraviolet radiation. They also noted that basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) occur predominantly on sun-exposed skin, SCC more so than BCC, and that while melanomas occur often on exposed sites they are also common on unexposed sites, particularly the trunk in men. This anomaly, they noted in their discussion, might be explained by their finding that high melanoma incidence may be associated with brief exposure to high intensity UV.

John Lee, a medical epidemiologist in the School of Public Health at the University of Washington, Seattle, and doyen of US melanoma epidemiology at the time, raised issue with Fears et al. [3]. He argued that a birth-cohort based temporal increase in melanoma incidence, which was observable in data from the long-running Connecticut Cancer Registry, could explain the lack of any strong association of melanoma incidence with age in the Third National Cancer Survey data. Lee concluded: "... it seems reasonable to adopt the working hypothesis that, whatever their other differences, both melanomas and non-melanomas [keratinocyte cancers] in white populations are related to cumulative doses of ultraviolet light.' In response, Fears et al. observed that if both melanomas and keratinocyte cancers in white populations are related to cumulative dose of UV their "rates should mirror one another even for cross-section annual incidence rates' [4]; a proposition we think is more likely to be true than Lee's conclusion. Lee's argument against the new findings may have been, in part, due to his championing the existence of a 'solar circulating factor' that could be produced in exposed skin and operate to increase melanoma risk in unexposed skin and thereby explain the frequency of melanoma on infrequently exposed sites [5].

TABLE 3

*Summary of weighted least squares analysis**

Disease	Sex	Percent variation "explained"	t^c	$\hat{a} \pm$ SD (constant)	$\hat{k} \pm$ SD (age coefficient)	$\hat{c} \pm$ SD (UV coefficient)
Nonmelanoma	Males	87	5.0†	−50.6 ± 8.6	3.71 ± .45	2.96 ± .59
	Females	80	3.9†	−41.3 ± 9.3	3.06 ± .49	2.45 ± .63
Melanoma	Males	74	5.4†	−35.6 ± 6.5	.80 ± .31	2.45 ± .45
	Females	62	4.6†	−30.5 ± 6.9	.29 ± .34	2.23 ± .48

* $\ln R_{ij} = a + c \ln U_i + k \ln A_j + \epsilon_{ij}$

† $p \leq .01$

Fig. 1. (Table 3 from Fears et al., 1977). The key results of Fears et al. reproduced here in facsimile from their 1977 paper [1].

Please cite this article in press as: B.K. Armstrong, A.E. Cust, Sun exposure and skin cancer, and the puzzle of cutaneous melanoma, Cancer Epidemiology (2017), http://dx.doi.org/10.1016/j.canep.2017.04.004