incidence of both melanoma and non-melanoma skin cancer in people with pigmented skin is several times lower than that in people with less pigmented skin.[2] How do the authors explain an apparent lack of association of lymphoma and leukaemia with skin colour?

The authors' reasoning is based on two assumptions: that the incidence of skin cancer can be used as a marker of exposure to ultraviolet radiation and that immunosuppression has a dominant role in the pathogenesis of cancer induced by ultraviolet radiation. Both assumptions may be false. Although ultraviolet radiation has an unequivocal role in the development of skin cancer, the pathogenesis of skin neoplasms is multifactorial. This is shown by the fact that exposure to the sun increases the relative risk of melanoma by only a factor of two to five, which is not impressive in comparison with the 85-1269 times higher risk in people with two family members with melanoma.[3] Moreover, recent evidence suggests that, in the pathogenesis of skin cancer, mechanisms other than immunosuppression are relevant, such as mutagenesis and suppression of apoptosis induced by ultraviolet radiation. Factors other than exposure to ultraviolet radiation—for example, genetic predisposition—probably better explain the association between skin cancer and the occurrence of lymphoma and leukaemia.

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Association may be iatrogenic

EDITOR,—Johanna Adami and colleagues postulate that exposure to ultraviolet light causes immunosuppression and, thereby, non-Hodgkin's lymphoma.[1] To support their hypothesis they report that patients with non-Hodgkin's lymphoma had a relative risk of 5·5 of developing squamous cell skin cancer. Conversely, patients with squamous cell skin cancer had a twofold excess risk of developing non-Hodgkin's lymphoma or the closely related chronic lymphocytic leukaemia. The relation between ultraviolet light and non-Hodgkin's lymphoma was therefore examined only indirectly.

Patients with non-Hodgkin's lymphoma are often treated with drugs, notably alkylating agents, that are inherently mutagenic. Although Adami and colleagues highlight the immunosuppressive effects of these agents, they do not mention their mutagenicity. In support of the importance of the latter mechanism of action, the authors show that patients with non-Hodgkin's lymphoma have an increased general risk of malignancy of 1·2 times normal (95% confidence interval 1·1 to 1·3), a finding referred to as "close to the expected" in their abstract. Indeed, this figure can be expected to rise with time as the latent period after chemotherapy for myeloid and lymphoid malignancies is shorter than that for most of the common solid tumours.[2]

It has been a puzzle for many years that immunocompromised transplant recipients are predisposed to develop only two types of malignancy, skin cancer and non-Hodgkin's lymphoma. Most of the cases of non-Hodgkin's lymphoma are caused by uncontrolled proliferation of lymphocytes infected with Epstein-Barr virus. Furthermore, lesions of non-Hodgkin's lymphoma in patients immunocompromised by HIV infection have been shown to contain the newly described herpesvirus-like agent that has been postulated to cause Kaposi's sarcoma.[3] This agent has now been reported in non-Kaposi's sarcoma skin lesions, notably squamous cell carcinoma, in transplant recipients.[4]

I find Adami and colleagues' explanation of their findings implausible. Alternative explanations are, firstly, the mutagenicity of agents used to treat non-Hodgkin's lymphoma and, secondly, infection with an agent that predisposes to malignant transformation in both skin and lymphoid cells.

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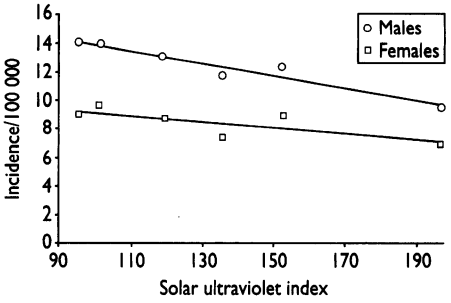
American data refute ultraviolet hypothesis

EDITOR,—Johanna Adami and colleagues suggest that an association between non-Hodgkin's lymphoma and skin cancer supports the hypothesis that exposure to ultraviolet light may be causally related to the development of non-Hodgkin's lymphoma.[1] Such an association would, however, be expected in a cohort of survivors of immunosuppressive treatment for cancer since it is well known that immunosuppression increases the risk of non-Hodgkin's lymphoma, squamous cell carcinoma of the skin, and malignant melanoma.[2,3] In the absence of information on exposure the relation cannot, therefore, be attributed to ultraviolet light.

Furthermore, there is no strong evidence that the incidence of non-Hodgkin's lymphoma is increased in people living in places where exposure to solar ultraviolet light is likely to be high. Published data on the incidence of cancer[4] and measures of exposure to solar ultraviolet light at six locations in the United States (Seattle, Detroit, Iowa, Utah, Atlanta, and New Mexico)[5] suggest that the incidence of non-Hodgkin's lymphoma declines, rather than increases, with increasing exposure, both in men (regression coefficient −0·044; 95% confidence interval −0·030 to −0·058) and in women (−0·022; 0·003 to −0·047) (figure). Taken at face value, these data do not support the hypothesis that exposure to ultraviolet light increases the risk of non-Hodgkin's lymphoma. The analyses must, however, be viewed with caution because they take no account of possible confounding factors, such as socioeconomic status.



Incidence of non-Hodgkin's lymphoma at six centres in United States related to exposure to solar ultraviolet light

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1 Adami J, Frisch M, Yuen J, Glimelius B, Melbye M. Evidence of an association between non-Hodgkin's lymphoma and skin cancer. *BMJ* 1995;**310**:1491-5. (10 June.)
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Author's reply

EDITOR,—Peter Sasieni and Veronique Bataille argue that the relative risk after exposure to ultraviolet light should be of the same magnitude for subsequent non-Hodgkin's lymphoma and malignant melanoma for a causal association between ultraviolet light and non-Hodgkin's lymphoma to be plausible and for ultraviolet light to explain part of the increase in the incidence of non-Hodgkin's lymphoma. This argument is problematic, because the size of the relative risks cannot be interpreted in such a simplistic way. Theoretically, if ultraviolet light has a directly causal role in the pathogenesis of malignant melanoma (that is, no other components are needed to generate malignant melanoma or, alternatively, the component causes are ubiquitous) whereas it is only one of several component causes of non-Hodgkin's lymphoma, the relative risks for the two malignancies need not be identical. The relative risk for non-Hodgkin's lymphoma would depend on the prevalence of the other component causes.

Furthermore, if non-Hodgkin's lymphoma has important causes other than ultraviolet light, the incidence of non-Hodgkin's lymphoma would correlate only poorly with measures of the intensity of the ultraviolet light. This could explain why the incidences of malignant melanoma and non-Hodgkin's lymphoma show little covariation in different geographical areas, as discussed by Sassieni and Bataille and by Robert Gniadecki. Unlike Gniadecki, however, we believe that there is good evidence that coloured people have lower incidences of non-Hodgkin's lymphoma than white people.[1] This is compatible with the hypothesis that ultraviolet light has an impact on the incidence of non-Hodgkin's lymphoma, a theory that is further supported by the observation of an increasd risk of non-Hodgkin's lymphoma in people with outdoor occupations.[2]

Mark Vickers adds the mutagenic action of alkylating agents to the possible explanations of the high risk of skin cancer in patients with non-Hodgkin's lymphoma. Such iatrogenic mutagenicity might contribute to the much stronger associations observed between initial systemic malignancies and subsequent skin cancers but is unlikely to contribute to the reverse sequence. Sasieni and Bataille suggest that immunodeficiency predating the squamous cell skin cancer could explain this finding. Malignancies that antedate the squamous cell skin cancer or the immunosuppressive mutagenic treatment of such antedating malignancies could explain part of this association. However, in a large scale analysis of cancers after basal cell carcinoma, which may be equally useful as a proxy for exposure to ultraviolet light, the subsequent risk of non-Hodgkin's lymphoma remained virtually unchanged whether