How do solar UV irradiance and smoking impact the diagnosis of second cancers after diagnosis of melanoma?

No answer yet

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It may be useful to look at the risk patterns for developing a second primary malignancy after a first primary melanoma diagnosis in order to understand the etiology and mortality due to melanoma. In this volume, W.B. Grant has proposed the interesting hypothesis that solar UV radiation and smoking may be inversely associated with the development of melanoma through the presence of dermal or solar elastosis. However, this association is inconsistent and may be explained by confounding by outdoor activity, physical exercise, obesity, diet and underlying immune or genetic factors.

The paper by William B. Grant[1] in this issue presents an interesting hypothesis: That UV and smoking are independently protective for melanoma incidence and that the types of second primary cancers after the diagnosis of melanoma support this suggestion. Grant suggests that the mechanism through which UV and smoking may work is elastosis, the breakdown of elastin and collagen under the surface of the skin, demonstrated clinically by deep wrinkles and histologically by "tangled fibers."[2]

Although the argument veers off in different directions, there are a number of interesting points made:

(1) Several cancers that have smoking and vitamin D associated with their etiology have a reduced risk after the diagnosis of melanoma: cervical cancer, colorectal cancer, laryngeal cancer and rectal cancer.

(2) Several cancers that are usually suspected of being smoking related also have a reduced risk when diagnosed after a melanoma: hypopharynx, nonlymphocytic leukemia, liver cancer, lung, bronchus and tracheal cancer, myeloid, monocytic leukemia and pharyngeal cancer.

(3) Cancers that are suspected of being vitamin D sensitive seem to have an **increased** risk after a diagnosis of melanoma: brain, nervous system tumors, female breast cancer, chronic lymphocytic leukemia, non-Hodgkin lymphoma, prostate cancer, and thyroid cancer.

(4) Those with unknown UV sensitivity are also increased after a diagnosis of melanoma: bones and joint, soft tissue sarcoma.

(5) Those that are generally considered to be UV sensitive are also increased after a diagnosis of melanoma: melanoma, ocular melanoma, salivary gland tumors, and nonepithelial skin cancers.

These are data analyzed by Spanogle et al.[3] and re-categorized by Grant in the paper. It is questionable as to whether these SIRs are adequate for hypothesis generation of the type attempted here. In fact, Spanogle and colleagues strongly suggest that surveillance bias may account for many of the associations in all but the case of prostate, soft tissue sarcoma, salivary gland tumor and bone sarcomas—none of which are noted to be inversely associated with risk after a diagnosis with melanoma. Data are readily available to refine the hypotheses that Grant has developed. For example, in the absence of a mechanism relating elastosis to improved survival or reduced incidence, it would be of great interest to evaluate melanomas of the head and neck as those are most likely to be

associated with smoking; however, they only account for 16–19% of all melanoma in SEER data.[4,5]

In a study that found reduced mortality among melanoma patients who had solar elastosis at diagnosis,[6] those with head and neck melanoma were more than three times as likely to die from melanoma as those with truncal melanoma; they were older and less educated. There were also few individuals, only 36 out of 650, diagnosed with head and neck melanoma. Those with solar elastosis on the head and neck had a non-significant hazard ratio of 0.44 [95% Confidence Interval (CI) 0.12–1.65] while those with solar elastosis on the trunk had a highly significant hazard ratio for dying from melanoma of 0.34 (95% CI 0.16–0.79). It is unlikely that smoking would have an effect on the trunk through elastosis.

In the large cohort study by DeLancey et al.[7] the association between smoking and melanoma incidence is confined to current smokers compared with never smokers. These categories were developed at baseline 24 y prior to the end of follow up. The authors cite as a limitation the lack of follow up information and the potential residual confounding due to lack of adequate information on screening, ascertainment, sun exposure and socioeconomic status. Mortality was significantly reduced in men but not in women; however, for a subset of persons there were updated data and an analysis of these data found a non-significant effect of smoking in males but a significant decrease in mortality among women; however, this was based on only 16 cases. These authors look for mechanistic explanations and cite both Odenbro[8] and Grant[9] who suggest immunosuppression and elastosis, respectively, as being responsible for the reduction in risk and hazard ratios. However, the authors also clearly state that "the absence of clear dose response relationships with respect to duration of smoking and cigarettes per day complicate the interpretation of results."

Grant suggests that ecological studies supply evidence that solar UV radiation is associated with reduced risk for melanoma. Conversely, migrant studies,[10,11] have shown that age of arrival and duration of residence in Australia or Israel are related to increased risk for melanoma. In order to reduce confounding, it is critical in 2012 to look at factors beyond latitude, such as individual behavior, anatomic site of melanoma development, age of incidence, and gender. All but the first are available through SEER data.

Because smoking is associated with dermal elastosis and because high levels of sun exposure lead to solar elastosis (shown to have an inverse association with melanoma mortality), it does not follow that both smoking and high levels of sun exposure are protective for the development of UV sensitive and smoking sensitive tumors. UV sensitive and vitamin D sensitive are not interchangeable. It is highly speculative as to which tumors noted are in fact UV sensitive. There are multiple potential confounders to explain these associations, including outdoor activity, physical exercise, obesity, diet and underlying immune or genetic factors. These confounders need explanation as research moves forward to understand the inverse association between smoking and melanoma incidence and mortality.

Disclosure of Potential Conflicts of Interest

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