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Neurodegenerative Disease and Cancer: A Critical Role for Melanoma?

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In 2007, Baade et al. [1] reported excess mortality from amyotrophic lateral sclerosis (ALS) and Parkinson's disease among melanoma patients. Among Australian patients with melanoma in a national registry, the risk of death due to ALS was 70% higher than that of the general population. The risk of death due to Parkinson's disease was even higher in these patients, a threefold increase. The association between melanoma and both ALS and Parkinson's disease confirmed an earlier analysis of US Surveillance Epidemiology and End Results data [2]. Notably, these neurodegenerative diseases were not associated with an elevated risk of mortality from other cancers.

Surveillance bias is always a concern in studies of this type. For example, people with melanoma might be followed more carefully than nonpatients, allowing greater likelihood of discovery of ALS. However, most melanomas are detected at an early stage (<1.00 mm), and the recommended medical follow-up for these patients is 2 years. Since ALS mortality was increased 5 years after melanoma diagnosis, this bias is unlikely to account for the association. Likewise, it is possible that increased surveillance of people with ALS may have led to a greater likelihood of the melanoma diagnosis (that is patients developed ALS first and received the melanoma diagnosis later). But again, given the short survival associated with ALS, the increased risk of ALS mortality 5 or 10 years after melanoma diagnosis makes this reversal of onset extremely unlikely.

One source of bias left unexplored in the earlier papers is the effect of treatment of melanoma. Chemotherapeutic treatments for melanoma can have neurotoxic effects [3], and these may be responsible for the association between melanoma and neurodegenerative disease. The latest report from Baade et al. [4], published in this issue, excludes this possibility. Melanoma thickness at diagnosis, a proxy for greater likelihood of aggressive therapy, was not associated with ALS mortality.

The specificity of the association, replicated in large, well-controlled analyses, suggests a biological basis to the co-occurrence of melanoma and the two neurodegenerative diseases. Recent reviews confirm the association between Parkinson's disease and

skin cancers and conclude that the association is not related to levodopa treatment [5, 6]. The connection between melanoma and Parkinson's disease may involve mutations in parkin, PINK1 and perhaps other genes, which are involved in familial Parkinson's disease and also abnormally expressed in some cancers [7]. Whether an analogous genetic association will be found for ALS and skin cancer remains to be seen. More generally, the lack of an association between newly diagnosed cancers and other chronic diseases [8] again points to the specificity of the association reported for melanoma and the two neurodegenerative diseases.

These findings should be compared to research on the association between Alzheimer's disease and cancer. In prospective cohort studies, Alzheimer's patients have a lower risk of incident cancer diagnosis and cancer hospitalization than nondemented seniors [9, 10]. These findings were initially established in a clinical registry and were later replicated in the Cardiovascular Health Study cohort. The studies also showed that prevalent cancer was associated with a lower risk of incident Alzheimer's disease. Vascular dementia, by contrast, did not have this association with cancer. This difference in risk for the two types of dementia again suggests specificity in the association between cancer and neurodegeneration. A number of genetic mechanisms have recently been proposed to account for the inverse association between Alzheimer's disease and cancer [11, 12].

What should we conclude from these studies? Confidence in epidemiological findings depends on a variety of factors, repeated in every textbook. These studies effectively establish the strength, specificity and consistency of the association between certain kinds of cancer and neurodegeneration, ruling out the key biases that might threaten these claims. Still lacking, however, is a mechanistic understanding to provide biological plausibility for the association. Investigations of such mechanisms are under way but not fully developed. Until these studies reach maturity, the association between melanoma and neurodegeneration will remain tantalizing but not fully explained. However, if this mechanism, once established, helps in the development of therapies for these devastating neurodegenerative diseases, the epidemiological studies of Baade and others will have played an important role and should be acknowledged as such in advance.

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