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Guilty by association? The complex relationship between immunosuppressants and cancer

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Immunosuppressants are commonly used for attenuation of the potent effects of the immune system. From treatment of inflammatory diseases to solid organ transplantation (SOT), immunosuppressive drugs are established as a mainstay of pharmacological therapy. For example, in the context of SOT, they are essential for prevention of acute allograft rejection and attenuation of long-term chronic immunological injury.[1] However, a careful balance is required between efficacy vs potential side effects and/or complications. One complication commonly associated with immunosuppressants is development of cancer. By weakening the immune system, immunosuppressive drugs make it less able to detect and destroy cancerous cells or fight off oncogenic infections that contribute to cancer risk. Observational studies support this link but may be confounded by indication-for-treatment bias. This is because the underlying disease or condition may itself be associated with an intrinsically higher risk of cancer, or patients with most severe disease are more likely to receive immunosuppressive treatment.

In this issue of *BMJ Oncology*, Buchanich and colleagues challenge our established viewpoint with their analysis of the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study.[2] Study recruits had ocular inflammatory diseases and were recruited from the USA between 1 January 1996 and 31 December 2010. Participation was excluded if they had infectious ocular inflammation, HIV infection or a known cancer diagnosis. Probabilistic data linkage was facilitated with 12 state cancer registries (covering 84% of study recruits) and median follow-up was approximately 10 years. No evidence of any increased risk of overall or site-specific cancer incidence was observed with multiple immunosuppressive drugs, regardless of stratification into eye-limited disease or presence of concomitant systemic disease.

These findings are of great interest to a wider audience of clinicians beyond ophthalmologists who frequently use immunosuppressive drugs. Immunosuppressants that did not show any association with cancer incidence in this analysis are commonly associated with increased risk for many cancers (eg, skin cancer and lymphomas) in different patient cohorts.[3–5] Therefore, translating these data to other settings requires careful reflection. First, there will be an underlying selection bias and the SITE cohort may reflect a low-risk group who warrant immunosuppression but are deemed fit enough for the exposure. This can be extrapolated from the relatively few cases of cancer or deaths observed over 10 years. Ophthalmological treatment may be of shorter duration, which will differ to other settings like SOT where lifelong immunosuppression is warranted for the life of the allograft. It is unclear if there is a 'Goldilocks' point regarding dose-dependent exposure, where a critical threshold for cumulative immunosuppression burden is required for cancer development.

However, it seems clear we must reappraise the association between immunosuppressants and cancers. These data confirm we have an incomplete understanding of how immunosuppressants contribute to cancer risk and they may not be the main driver despite mechanistic plausibility. For example, in the setting of SOT where all allograft recipients receive immunosuppression, not all cancers have amplified risk after transplantation.[6] Risk for some cancers is no different to the general population (eg, breast or prostate), while some cancers occur in excess among subgroups of transplant patients due to underlying medical conditions.[7] In a systematic review and meta-analysis of 16 studies, use of immunosuppressive therapy for a variety of

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conditions in people with previous cancer demonstrates no increased risk for cancer recurrence.[8]

Based on this insight, we can surmise that not everybody who receives immunosuppression develops cancer. This risk heterogeneity may relate to exposure, genetics, demographic or geographical variation, underlying disease states, etc. Something akin to the two-hit hypothesis may be necessary; either immunosuppression serves as the second hit for an individual predisposed to cancer, or an immunosuppressed individual is predisposed to developing cancer after a pathophysiological second hit. For example, cancers with an oncogenic viral aetiology are more common and likely relate to an immune-deficient state. Grulich *et al* demonstrated similar risk for cancer when comparing kidney transplant recipients and people with HIV/AIDS.[9] Risk was increased for 20/28 cancers studied, with those of infectious aetiology more common while epithelial cancers occurred at similar rates to the general population for both cohorts. The exception was kidney cancer, which was increased for both cohorts but exceptionally so for kidney transplant recipients (likely influenced by dialysis exposure after kidney failure).[10]

This work exposes our incomplete understanding of the complex relationship between immunity, inflammation and cancer.[11] As stated by the authors, epidemiological research would be enhanced with a national cancer registry to facilitate maximum record linkage to study cohorts of interest. However, even in countries where national cancer registries exist, progress to link datasets has been slow.[12] Only by overcoming these obstacles, and studying exposure in detail, can we tease out the relationship between immunosuppression and cancer. Until then, the data from Buchanich and colleagues have challenged us to re-examine the guilty verdict for immunosuppression.[2]

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