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Review Article

Exploring the nexus of Alzheimer's disease and related dementias with cancer and cancer therapies: A convening of the Alzheimer's Association & Alzheimer's Drug Discovery Foundation

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Abstract Recent population studies suggest an intriguing inverse relationship between several types of cancer and neurodegenerative diseases, including Alzheimer's disease. Understanding the intersection of the underlying biology for these two distinct families of diseases with one another may offer novel approaches to identify new therapeutic approaches and possible opportunities to repurpose existing drug candidates. The Alzheimer's Association and the Alzheimer's Drug Discovery Foundation convened a one-day workshop to delve into this discussion. Workshop participants outlined research focus areas, potential collaborations, and partnerships for future action.

Keywords: Alzheimer's disease; Oncology; Cancer; Repurpose therapy; Epidemiology; Biological mechanisms; Genetics

1. Introduction

Over the past decade, several population-based studies have suggested an intriguing relationship between many types of cancer and neurodegenerative diseases, including

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Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [1]. Both cancer and AD are heterogeneous diseases of aging that cause substantial morbidity and mortality. They receive substantial investment from both the National Institutes of Health and the biotechnology/pharmaceutical industry. Success in translating biological discoveries about AD into new therapies lags far behind those achieved to date within the cancer field, an area of major foment with an explosion of interest in effective immune approaches.

The nexus of cancer and neurodegenerative disease may offer novel opportunities to expand the understanding of disease-related mechanisms and identify new therapeutic targets. Recognizing these possibilities, the Alzheimer's Association and the Alzheimer's Drug Discovery Foundation convened a one-day think tank on May 25, 2016. Its purpose was to delve into the biological underpinnings that may provide further context for the inverse relationship between cancer and later-life neurodegenerative diseases, particularly AD and PD. Furthermore, we explored whether and how these insights may be exploited to advance drug discovery. Participants in this discussion spanned the disciplines of biostatistics, epidemiology, genetics, immunology, neurology, neuropsychology, oncology, radiation oncology, psychiatry, and surgery.

2. Epidemiologic evidence linking cancer with neurodegenerative disease

Evidence from multiple epidemiologic studies suggests a negative or inverse association, that is, a lower risk of some cancers among persons with AD and PD [2], as well as a lower risk of subsequent AD among cancer survivors [3]. Additional work has identified associations between other cancers and AD [4]. Reduced risk of cancer has also been identified in patients with ALS [5], although no effect has been found on the risk of incident ALS after a diagnosis of cancer [6,7]. These associations appear across many individual types of cancer, including both smoking-related cancers (oral, breast, lung, pancreas, and so forth) and smoking-unrelated cancers. However, in PD, studies have also suggested positive or direct associations with melanoma and prostate cancer [8,9].

Observational findings, even when remarkably consistent, are only signals; the challenge is to understand what mechanisms they represent. Methodological explanations may account for some of the observed reduced risk of cancer in patients with neurodegenerative disease. Three types of bias are particularly germane to this discussion. First, a competing risk or survival bias could result from poorer survival among patients with both AD or PD and cancer, compared with those with neurodegenerative disease alone. A second type of bias—ascertainment bias—would result from a difference in the likelihood of screening or detection of one disease after the diagnosis with the other. Indeed, a study by Freedman et al. [10] suggested that PD patients are less likely to receive cancer screening and aggressive diagnostic procedures, and they concluded that the data do not support a biological relationship between PD and cancer. Finally, nonpopulation-based studies may suffer from selection bias if, for example, people with cancer do not volunteer for dementia research and vice versa.

When analyzing risk relationships between cancer and AD, the type of data available (e.g., from large database or multiple studies), study design, and analytic approaches, all influence results. For example, to take into account the relatively low frequency of both individual cancer types and the various neurodegenerative disorders, the sample must be large enough and follow-up sufficiently long with adequate assessment of both outcomes. The study may have a prospective cohort, nested case-control, or cross-sectional design, depending on the data available and the selected study population (e.g., cancer registry, AD registry, or population-based cohort or registry). Analytic methods and inferences should vary according to the sample and design. For a time-to-event or survival analysis, the baseline must be clearly specified.

Interpreting signals from epidemiologic studies is challenging for multiple reasons in addition to the issues of bias discussed previously. Multiple overlapping mechanisms and common risk factors appear to underlie both cancer and neurodegenerative disease. Further complicating this scenario is the fact that risk factors may be associated with either an increased or diminished risk of both some cancers and some neurodegenerative diseases. Epidemiologic studies also point to possible biological factors that could explain the observed association between cancer and neurodegenerative diseases, including common risk factors such as stress, obesity, diabetes, chronic inflammation, and immunosenescence [1]. Stress itself can alter cancer immunity. For other risk factors, such as smoking, the associations may be in opposite directions: smoking is associated with a higher risk for some cancers and in some studies for AD, but a lower risk for PD [11,12]. Ethnicity and other environmental factors also play important roles in disease pathogenesis. In a Taiwanese study, for example, PD showed a positive rather than negative relationship with increased risk of all cancers [13]. One possibility is that cultural bias, especially in terms of dementia, could affect diagnosis rates and thus the overall results. Vascular interactions could also play important roles, related to whether cancer survivors have an increased risk of metabolic disorders that may, in turn, increase their risk of vascular disease.

Interactions among risk factors further complicate the picture. For example, the association between melanoma and PD appears to be biologically plausible, given that melanocytes and neurons both arise from a common embryonic cell type. In addition, levodopa (the predominant treatment for PD) serves as a substrate for the syntheses of both dopamine and melanin. Some studies have suggested that pigmentation gene polymorphisms may explain the increased risk of melanoma in PD patients [14]. However, another study found no association between PD single-nucleotide polymorphisms and melanoma [15], and yet another study found no association of pigmentation phenotypes with PD [16]. Thus, current evidence does not clearly support a genetic