Cancer and Dementia
It's Complicated

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Abstract: The relationship between dementia and cancer is complex. A wealth of observational data suggest (1) reduced risk of certain cancers in Alzheimer and Parkinson diseases; and (2) increased risk of other cancers in Parkinson disease. These relationships persist despite correcting for reporting artifacts and survival bias. Several potential mechanisms have been proposed and warrant further investigation. Aging is a risk factor for both. Common environmental exposures, such as smoking, may play roles. Common mechanisms such as chronic inflammation and immunosenescence, and common risk factors such as diabetes and obesity, have been implicated. Shared genetic pathways are a major focus, particularly those favoring apoptosis and cell proliferation at opposite ends of the spectrum. To complicate the picture further, certain cancer chemotherapy and adjuvant therapy agents have neurotoxic effects, whereas animal studies show other cancer drugs reducing neurodegeneration, raising the possibility of repurposing those agents for use in Alzheimer disease. These multiple potential lines of evidence must be disentangled to investigate underlying mechanisms, the end-game being to develop and to test potential prevention and treatment strategies.

Key Words: risk factor, protective factor, aging, immune mechanisms, genetic pathways, competing risks

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Particularly over the past decade, evidence has steadily emerged of intriguing relationships between cancer and neurodegenerative diseases.[1–3] This rapidly growing body of literature ranges from population and case-control studies, to genetic and immunologic studies, to treatment studies. These findings may have attracted less interest than expected because cancer and dementia are both common disorders of aging, the signals appear mixed, the underlying mechanisms are not straightforward, and the potential for bias in the findings seems substantial. A translational epidemiology framework is well placed to transmit and interpret the information across research disciplines and eventually into clinical and public health practice.[4] This article provides an overview of the observational/epidemiologic data, and some cautious speculation about their implications.

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OBSERVATIONAL STUDIES: POSITIVE (DIRECT) OR NEGATIVE (INVERSE) ASSOCIATIONS?

Both direct and inverse associations have been reported between cancer and neurodegeneration. A cornerstone of understanding this literature is the heterogeneity of both kinds of disorders, that is, that different cancer types represent different disease processes, as do different neurodegenerative disorders.

Cancer and Alzheimer Disease (AD)

A consistent inverse association has been found in epidemiologic studies between AD and overall cancer, particularly but not exclusively those cancers classified as smoking-related (cancers of the oral cavity, pharynx, larynx, esophagus, stomach, pancreas, lung, cervix, and kidney). To date, no studies have reported direct associations between cancer and AD.

One of the earliest reports came from a prevalence study of dementia within a cohort of atom bomb survivors in Japan, which found an inverse association between overall cancer and AD (odds ratio, 0.3) but not vascular dementia, and unrelated to radiation exposure.[5] In the same year, a population-based cohort study in the rural Monongahela Valley of southwestern Pennsylvania reported on causes of death on the death certificates of study participants. For individuals with AD, cancer was listed as the immediate, underlying, or contributory cause of death significantly less often it was for individuals without dementia (odds ratio, 0.395).[6] This finding has been recently replicated in a large Spanish population-based study of over 5000 people, in which there was a significantly reduced cancer mortality risk [relative risk (RR), 0.53] in individuals with AD, even adjusting for demographics and comorbid conditions.[7]

Meanwhile, a case-control study within an urban Alzheimer Disease Research Center cohort at Washington University in St Louis (Missouri) had reported that risk of cancer was reduced [hazard ratio (HR), 0.39] among participants with AD, whereas risk of AD was reduced (HR, 0.4) among participants with a history of cancer.[8] Similarly, a recent investigation of 1609 participants in the multisite Alzheimer Disease Neuroimaging Initiative found that individuals with a history of cancer was inversely associated with AD at baseline and with later age of AD onset, independent of *APOE*4* status.[9]

Similar results have been found in studies in which cancer diagnosis or treatment is the outcome. In a multicenter population study (the Cognition Substudy of the Cardiovascular Health Study), the presence of AD or mixed AD-vascular dementia was associated with significantly reduced risk of hospitalization for cancer (HR, 0.57 for pure AD and 0.72 for mixed AD); no association was found with pure vascular dementia.[10] A cancer registry in Sweden looking at 18 cancer types, with over 19,000 cases and over

147,000 controls, found a significantly reduced risk (RR, 0.60) of dementia diagnosis 9 to 45 months before the diagnosis of cancer.[11] Similarly, a tumor registry including over 21,000 participants in Northern Italy (Milan Health Authority), looking at reported diagnoses of AD, found significantly reduced risk of cancer in AD (RR, 0.57) and of AD in cancer (RR, 0.65).[12] In a recent population-based study of almost 7000 patients with AD in Taiwan's National Health Insurance database, compared with the general population, patients with AD had a significantly lower standardized incidence ratio (SIR) of overall cancer (SIR = 0.88) and specifically of lung cancer (SIR = 0.75).[13]

An obvious potential explanation to be considered in these studies is survival bias. Developing cancer reduces the likelihood that an individual will live long enough to develop dementia. There is also the possibility of competing risks[14]; given several risk factors common to both AD and cancer, some individuals would be at risk for both conditions. Among them, those who die of cancer before they can develop AD would be excluded from studies of cancer survivors, thus skewing the sample toward those at lesser risk of AD. A pragmatic, albeit mechanistically less interesting, explanation is that health care providers may choose not to undertake cancer screening in individuals with dementia and vice versa, thus leading to systematic underascertainment and underreporting. However, if these biases were the entire explanation, we would not expect to observe selective associations of AD with certain cancers but not others. A further argument against ascertainment bias was provided by an earlier autopsy study showing a significantly lower proportion of cancer deaths among patients with AD than in patients without AD.[15] Here, it should be noted that the autopsied subjects were a sample of residential patients at a long-stay state psychiatric facility and thus subject to its own selection bias.

These potential sources of bias were substantially overcome in a landmark investigation within the population-based Framingham Heart Study. Here, independent prospectively data collected over 22 years revealed that survivors of "smoking-related cancers" had a significantly reduced risk of incident AD (HR, 0.67); further, in a nested case-control study, incident AD cases had a significantly reduced risk (HR, 0.39) of subsequent cancer. Sensitivity analyses took survivor bias into account without changing the results.[16]

The Framingham Study also highlighted the importance of recognizing the heterogeneity of cancer by demonstrating that smoking-related cancers showed stronger relationships than smoking-unrelated cancers. Notably, this study excluded skin cancers other than melanoma from the analysis. Nonmelanoma skin cancers are typically distinguished from other cancers because they are more readily detected and are less likely to metastasize. Shortly thereafter, a report from the Einstein Aging Study in the Bronx (New York) revealed that older adults with nonmelanoma skin cancer had a reduced risk (HR, 0.21) of developing AD; this finding was specific to AD and did not extend to other dementias or all-cause dementia.[17] In the Alzheimer Disease Neuroimaging Initiative study mentioned earlier, nonmelanoma skin cancer was the largest cancer category, and the major driver of the observed inverse effect. However, invasive cancers, rather than skin cancers, drove their additional finding of cancer-associated lower gray matter density in the right superior frontal gyrus.[9] The Northern Italian Study had sufficient power to disaggregate cancers and examine the RRs separately by cancer site as well as type, with the strongest effects seen with epithelial cancers (colorectal and lung).[12]

Cancer and Parkinson Disease (PD)

Moving on to PD, the evidence appears mixed at first glance, with both direct and inverse associations reported; however, it is in fact more consistent when cancer type is considered. A historical cohort study from the Mayo Clinic's Rochester Epidemiology Project found a significant direct association between PD and all cancers (RR, 1.64); looking at cancer types, the association was only significant for nonmelanoma skin cancer, and adjustment for smoking did not alter the results.[18] A systematic review and meta-analysis of 107,598 subjects across 29 studies of PD, published in 2010, showed significantly reduced risk of overall cancer (RR, 0.73), nonskin cancers (RR, 0.69), and in both smoking-related cancers (RR, 0.61), and smoking-unrelated cancers (RR, 0.76), albeit with greater risk reduction in the former.[19] The Danish National Hospital Register followed over 20,000 people with PD for 30 years. Compared with the general population, individuals with PD had significantly *low*er SIR of overall cancer (SIR = 0.86), and both smoking-related cancers (SIR = 0.65) and smoking-unrelated cancers (SIR = 0.79). However, they had significantly *higher* incidence of malignant melanoma (SIR = 1.41), nonmelanoma skin cancer (SIR = 1.29), and female breast cancer (SIR = 1.17).[20] The Utah Cancer Registry, a statewide genealogical database, found almost 3000 cases of PD, who had significantly *lower* than expected numbers and RRs of colorectal cancer (RR, 0.55), lung/bronchus (RR, 0.22), pancreas (RR, 0.26), and stomach (RR, 0.22) cancers.[17] In contrast, these patients and their first-degree relatives had *elevated* risks of melanoma (RR, 1.95 for self and 1.23 for relatives) and prostate cancer (RR, 1.71 for self and 1.25 for relatives).[21] The association between PD and melanoma has been known for years and replicated over several studies and better established than the associations with breast and prostate cancer.[21–24] A massive meta-analysis of cancer incidence across 50 observational studies (encompassing 577,013 participants in either cohort or nested case-control studies) found significantly lower pooled effect sizes (ES) for cooccurring cancer in all neurodegenerative disorders (ES = 0.80), in AD (ES = 0.32), PD (ES = 0.83), multiple sclerosis (ES = 0.91), and Huntington disease (ES = 0.53).[3]

Interpreting the Signals from the Observational Studies

The first order of business is to look for sources of bias, the most obvious of which is survival bias resulting from selective mortality discussed earlier. A second is ascertainment bias, from selective underdiagnosis of cancer in people with dementia, and of dementia or cognitive impairment in people with cancer. The Framingham Study[16] stands out in its efforts to address these possibilities and demonstrate that the inverse association persisted nonetheless. Selection bias is less of an issue in population-based studies, compared with case-control studies of AD and PD which may exclude individuals with preexisting cancer from enrollment.

The next step is to look for sources of confounding, meaning that the apparent association between the 2 associations is completely explicable by a common factor related to both, such as age, or smoking. Again, studies

have adjusted for these factors as covariates. As noted, distinctions have been made between smoking-related and smoking-unrelated cancers. Treatment effects, discussed later, are potential confounders of the observed direct associations, but also provide potential avenues to investigate underlying pathways.

Next, observational studies can identify putative risk factors to illuminate potential underlying mechanisms. It is relatively simple to suggest possible mechanisms for the direct associations. Shared risk factors common to both cancer and AD include diabetes and obesity.[25,26] Here, the special case of competing risks, mentioned earlier, is potentially relevant. For the inverse associations, ready explanations are elusive. Smoking is a known risk factor for several cancers but also has a "protective" effect (ie, inverse association) against PD[22]; thus, smoking is a candidate for explaining the inverse associations with smoking-related cancers.

POSSIBLE IMMUNE MECHANISMS

Shared immune mechanisms appear more likely to explain direct associations between cancer and neurodegeneration than inverse associations. Autoimmune and inflammatory mechanisms have been implicated in AD,[27,28] and in conditions which increase risk of AD, such as obesity and type 2 diabetes.[25,26] Smoking has been shown to have both proinflammatory and anti-inflammatory effects in vitro[29]; whereas chronic smoking is associated with inflammation, very–short-term smoking appears to acutely reduce some inflammatory responses, suggesting that dose and duration may influence the effect.[30] With respect to cancer risk, the immune response (effective vs. ineffective immune surveillance) has been discussed by Cramer and Finn[31] as "a unifying and non–site-specific determinant (both positive and negative)." These authors review evidence that immunosenescence (the deterioration with age in the innate and adaptive immune responses) is the immune mechanism behind the association between cancer and aging. The triggering of innate immune mechanisms is also said to be emerging as a major driving force in neurodegeneration.[32] Protein complexes called inflammasomes are activated in several conditions including cancer,[33,34] and mediate the innate neuroinflammatory responses in the central nervous system.[35] The NLRP inflammasomes are implicated in obesity, type 2 diabetes, as well as neuroinflammation and neurodegeneration.[35] The NLRP3 inflammasome also appears to be activated by amyloid-β and to contribute to AD pathology in APP/PS1 mouse models of AD.[36] The term "cancer immunoediting" has been used to describe the dual role of the immune system in both inhibiting and promoting tumor growth; this process is reported to be enhanced in certain neurodevelopmental and neurodegenerative disorders.[37] Useful information may also come from the paraneoplastic syndromes, where cancer survivors who have developed immunity to their cancers go on to develop nonmetastatic brain effects; these effects are caused by autoimmunity to brain tissue due to shared epitopes between their tumor antigens and their brain antigens.[38]

POSSIBLE GENETIC MECHANISMS

Shared genetic predispositions to cancer and PD were suggested by the Utah Cancer Registry study cited earlier.[21] Beyond the population studies, an area of considerable current interest is shared genetic pathways, for example, the *PIN1* gene which is overexpressed in certain cancers but is also necessary for tau phosphorylation, and the *PARK2* gene which encodes an E3 ubiquitin ligase and may also be a tumor suppressor.[1] Other relevant genetic pathways implicated in AD include *Wnt* and *P53*.[39] Examples in other neurodegenerative disorders include the gene mutation for ataxia-telangectasia which increases risk of breast and blood cancers, and the amyloid precursor protein gene that is overexpressed in Down syndrome, predisposes to AD, and also increases risk of leukemia.[40] The genetic studies and potential mechanisms involving differential regulation of common genes and pathways have been extensively reviewed elsewhere.[1,39–42]

POSSIBLE TREATMENT EFFECTS

Both inverse and direct associations between cancer and neurodegeneration are potentially susceptible to confounding by treatment effects, if a drug used to treat one group of disorders influences risk of developing the other. Patients undergoing certain forms of cancer chemotherapy are known to experience cognitive impairment, a phenomenon referred to as "chemo-brain" for which early empirical evidence was lacking and current evidence is mixed. A subgroup of breast cancer patients appears vulnerable to posttreatment cognitive changes, although not exclusively related to chemotherapy.[43] Frontal gray matter reduction and associated executive dysfunction have been shown in patients after breast cancer chemotherapy.[44] However, a meta-analysis of studies examining cognitive functioning in breast cancer patients, at least 6 months after chemotherapy, showed that residual effects were of small magnitude and limited to verbal and visuospatial ability.[45] In a prospective study of over 62,000 older women with breast cancer in the SEER program, there was no significant association between chemotherapy and drug-induced dementia or "other cognitive disorders" and in fact a significant reduction in the incidence of AD and vascular dementia.[46]

A treatment-related effect which might shed light on mechanisms is exemplified by estrogen, which has demonstrable neuroprotective activity.[47] The use of postmenopausal estrogen therapy for at least 10 years, and at least 10 years before the onset of dementia, has been found to reduce incidence of AD.[48] However, in later life, the use of estrogens, especially opposed estrogens, increases the risk of dementia as shown both in the same population study[49] and in a clinical trial.[50] Thus, it would be reasonable to anticipate adverse neurocognitive effects from the adjuvant treatment of breast cancer in younger women, whether with aromatase inhibitors which block estrogen production, or selective estrogen receptor modulators.[51] Evidence is mixed as to whether tamoxifen is neuroprotective or neurotoxic.[52,53] Another, earlier, example was the implication of PD treatment with levodopa as a risk factor for melanoma; however, this appears not to be supported by recent studies.[54]

In contrast, some cancer chemotherapy agents may have neuroprotective effects. Taxanes stabilize microtubules and have been proposed as potential therapeutic agents for AD and "related tauopathies."[55] In animal studies, the *APOE*-directed cancer chemotherapy drug bexarotene was effective in clearing amyloid from the brains of mouse models of AD and also in improving their cognition[56]; the

cancer drug carmustine with chronic administration also reduced β-amyloid generation and plaque burden in mice.[57] These findings have led to interest in repurposing oncology drugs for the treatment of AD.[58] Conversely, it has been proposed that if proteasome inhibitors are effective against cancer, then proteasome activators, including antioxidants, may be effective against neurodegeneration.[1]

OTHER PROPOSED MECHANISMS

It is beyond the scope of this article to delve deeply into the potential mechanisms underlying these various observations, but several promising signals have been reported. An umbrella concept is that cancer and neurodegeneration are at opposite ends of a spectrum that ranges from abnormal cell death (apoptosis) to abnormal cell proliferation.[42] Tumorigenesis and neurodegeneration have been described as 2 sides of the same coin, with regard to genes that control cell-cycle progression and cell-cycle repair but also contribute to degeneration of postmitotic neurons.[39,40] Functional microRNA that are expressed differently in AD and cancer show some inversely associated pathways (proliferation and apoptosis) as well as some parallel functions (immune activation and inflammation).[59] Age-related metabolic deregulation and reprogramming may initiate both neurodegeneration and carcinogenesis. Both disorders are associated with pathways and genes involved in bioenergetics, inflammation, DNA damage and repair, oxidative stress, and aberrant cell-cycle activation.[1,60] Yet, neurones differ sharply from other cell types in that they do not divide and therefore follow different pathways to repair their own DNA and meet their energy needs.[1] More specifically, synucleins have been described as potential 2-edged swords, in that α-synucleins are implicated in PG and γ-synucleins in breast and colorectal cancer.[61] Cyclin-E, usually expressed in proliferating cells, may regulate synaptic plasticity and memory formation.[62] Apoptosis-inducing aβ is extruded by increased ABC transporter activity at the blood-brain barrier in the brains of cancer survivors.[63] It has been suggested that β-amyloid may be toxic to natural killer cells, which may contribute to β-amyloid-induced microglial activation.[64]

FUTURE DIRECTIONS

Epidemiology has been described as the epicenter of translational science, in the sense that epidemiologic methods and perspectives span research from discovery to effective interventions and ultimately to their dissemination and implementation.[65] Epidemiological studies have yielded a remarkably consistent set of signals suggesting complex relationships between cancer and neurodegeneration. This is particularly striking because the data which generated these signals were not collected primarily to examine these relationships. The mechanisms underlying these associations are far from clear, in part because of the heterogeneity of both cancer and neurodegeneration. It is important to tease out the effects of bias and confounding, including neurocognitive effects of cancer therapies. However, the consistency of the findings warrants a variety of mechanistic studies including genetic and immunologic investigations. In humans, these might be conducted with the greatest efficiency in large established cohorts well characterized for one or other group of disorders, adding in appropriate assessments for the other. Cancer should of course be disaggregated and examined by type and site.[12]

As so many potential signals have been observed, careful hypothesis generation will be needed to reduce noise: signal ratio. For example, cohorts of high-risk patients being followed for specific incident cancers (eg, women at risk of familial breast cancer), and of patients already diagnosed with specific cancers, can be tested for biomarkers for specific neurodegenerative diseases, such as β-amyloid and tau proteins in the cerebrospinal fluid which are putative biomarkers for preclinical AD.[66] Similarly, cohorts being followed for AD or PD could incorporate appropriate cancer biomarkers. Both cancer cohorts and AD cohorts could be systematically examined for genes upregulated in one group of disorders and downregulated in the other, such as *Pin1*, *P53*, and *Wnt*.[39] Such studies can all be carried out using biobanked specimens from existing cohorts of well-characterized participants. However, moving forward, ongoing cohort studies of cancers of interest should incorporate not only genetic and biomarker studies for specific neurodegenerative diseases but also neuroimaging and neuropsychological assessments over time to identify their structural and functional trajectories.

To overcome the difficulties encountered to date with power, bias, and confounding, samples for future studies should be population-based, prospective, and large enough to detect small effects. Passive surveillance (eg, using claims data or death certificate data) is likely to introduce ascertainment bias. Ascertainment should be a process of active screening and diagnosis for both the cancers and the neurodegenerative disorders of interest, using current diagnostic criteria and biological markers. Data should be gathered on relevant risk factors and their timing and duration, for example, smoking, occupational exposures, and cancer treatments. Attrition should be carefully tracked. Statistical modeling should include appropriate techniques for dealing with issues such as selection bias, attrition, competing risks, and nonignorable missing data, in particular taking mortality (survival bias) into account. It would be important to conduct these studies in ethnically diverse populations and different geographic areas where different cancers are prevalent and may be related to different exposures. The cost of such studies would be balanced by embedding both cancer and dementia studies within the same cohorts, sharing recruitment, and infrastructure costs.

Treatment effects could be assessed by conducting neurocognitive and neuroimaging assessments before and after delivery of different chemotherapy and adjuvant agents; these effects could be accounted for in analyses of the relationships between cancer and dementia. Progress which has already been made in understanding these treatment-related effects in their own right[43–46] warrants more attention with regard to the possibility of developing less neurotoxic cancer therapies.

Some of the signals reported above lend themselves to generation and testing of specific hypotheses. For example, the selective inverse association of smoking-related cancers with AD and PD deserves further investigation. Smoking increases the risk of many cancers and appears to reduce the risk of PD. Among the multiple substances contained in tobacco smoke, it is possible that while the known carcinogens such as polycylic hydrocarbons increase the risk of cancer, nicotine may reduce the risk of PD. As noted, while chronic smoking causes inflammation, acute smoking may

have anti-inflammatory effects[30]; nicotine also acutely improves cognition.[67] It may be possible to explore this area further by following cohorts using nicotine patches and/or electronic cigarettes. Other potential leads may come from studying the paraneoplastic syndromes where shared antigens between the cancer and brain result in autoimmune nonmetastatic effects on brain tissue.[38] In contrast, studies to define targets of successful immune surveillance could allow immunophenotyping of individuals as a risk assessment tool.[31] The end-game here would be the development of appropriate vaccines for disease prevention, of both cancer and neurodegeneration. Cancer treatment-related hypotheses, such as those related to neural effects of antiestrogen therapies in breast cancer patients, and to anti-AD effects of certain cancer chemotherapy agents, appear ready for testing. Further investigations are clearly warranted of promising genetic pathways, for example, Pin1 and PARK2 discussed earlier in the contexts of AD and PD. Functional miRNA studies, already well established in cancer research, may hold promise in neurodegeneration research as well.[59]

Translational research generally refers to the application of basic science discoveries to the clinical setting (bench to bedside). However, translation can be bidirectional and move from population science to the clinical setting and the laboratory.[68] Besides gains in understanding of key mechanisms, this broad research topic could yield substantial potential payoff in terms of prevention and therapeutics.

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