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Research Article

The Role of Dementia Diagnostic Delay in the Inverse Cancer–Dementia Association

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Abstract

Background: Cancer is inversely associated with dementia. Using simulations, we examined whether this inverse association may be explained by dementia diagnosis timing, including death before dementia diagnosis and differential diagnosis patterns by cancer history.

Methods: We used multistate Markov simulation models to generate cohorts 65 years of age and free of cancer and dementia at baseline; follow-up for incident cancer (all cancers, breast, prostate, and lung cancer), dementia, dementia diagnosis among those with dementia, and death occurred monthly over 30 years. Models specified no true effect of cancer on dementia, and used age-specific transition rates calibrated to U.S. population and cohort data. We varied the average lapse between dementia onset and diagnosis, including nondifferential and differential delays by cancer history, and examined observed incidence rate ratios (IRRs) for the effect of cancer on dementia diagnosis.

Results: Nondifferential dementia diagnosis delay introduced minimal bias (IRRs = 0.98–1.02) for all cancer, breast, and prostate models and substantial bias (IRR = 0.78) in lung cancer models. For the differential dementia diagnosis delay model of all cancer types combined, simulation scenarios with ≥20% lower dementia diagnosis rate (additional 4.5-month delay) in those with cancer history versus without yielded results consistent with literature estimates. Longer dementia diagnosis delays in those with cancer and higher mortality in those with cancer and dementia yielded more bias.

Conclusions: Delays in dementia diagnosis may play a role in the inverse cancer–dementia relationship, especially for more fatal cancers, but moderate differential delays in those with cancer were needed to fully explain the literature-reported IRRs.

Keywords: Alzheimer's disease, Bias, Markov model, Neoplasm, Simulation study

Cancer is inversely associated with dementia in robust literature; meta-analyses have reported hazard ratios (HRs) ranging from 0.62 to 0.85 (1–4). The explanation for this paradoxical inverse association is unclear and a subject of debate (5–7). This inverse link might be due to cancer-related physiologic changes that prevent dementia or due to shared etiologic factors that increase the risk of cancer while reducing the risk of dementia (5–7). If so, studying the association may offer a novel window into dementia etiology and inform future prevention and treatment strategies. While some research suggests such a shared common cause (5,8–11), proposed noncausal explanations for the cancer–dementia link include selective survival bias, bias from the competing risk of death preventing dementia onset, and dementia diagnosis patterns that are differential between older adults with and without a history of cancer (5–7). The utility of studying the inverse cancer–dementia relationship to

understand dementia etiology depends on ruling out these alternative noncausal explanations.

While selective survival bias and the competing risk of death do not appear to fully account for the reported inverse link, (12) prior work has not investigated potential contributions of dementia diagnosis patterns. Dementia has a long and insidious onset, making diagnosis complex and delays likely. As a result, this noncausal explanation is particularly relevant for studies using electronic health records. We thus examine 2 mechanisms related to dementia diagnosis that could influence the observed association between cancer and dementia. First, diagnostic delays that result in missed dementia cases yield underestimates of true dementia incidence rates. An inverse cancer–dementia association could be observed if elevated mortality in those with a cancer history exacerbates the underestimate of dementia incidence (because dementia cases remain undiagnosed at cancer death), even if dementia diagnostic practices are the same for those with and without cancer history. Second, dementia diagnostic practices may differ according to cancer history (6,7). This mechanism, often called diagnostic or ascertainment bias, could lead to either positive or inverse observed cancer–dementia associations, depending on whether dementia diagnosis occurs more quickly in those with a cancer history (eg, due to increased contact with the medical system), or more quickly in those without a cancer history (eg, if those with cancer are too frail for diagnostic workup, if their symptoms are attributed to other things like "chemobrain," or if physicians are not as concerned with diagnosing dementia in someone with a limited life expectancy due to cancer).

Even if there is no true effect of cancer on dementia, either nondifferential or differential dementia diagnosis delays could lead to an association between cancer and dementia. In this study, we use simulations to investigate the possibility that dementia diagnosis patterns among those with and without a cancer history can explain some of the inverse cancer–dementia link.

Method

Simulation Model Structure and Causal Scenarios

We used a multistate continuous-time Markov model to simulate a cohort of 65-year-olds starting free of both cancer and dementia and transitioning across states of disease and death. Multistate Markov models simulate how people transition across possible states (eg, disease progression), and have been used in a number of recent studies on dementia (13–18); although other simulation approaches exist, advantages of Markov models include that they are clear heuristics of disease processes and allow for excellent calibration of the data-generating model.

Our simulation model builds directly on prior work (12), in which we used a similar multistate Markov model to simulate a cohort of cancer- and dementia-free individuals transitioning across 5 states (combinations of history of cancer no/yes, dementia no/yes, and death) and showed that mortality due to cancer (ie, survival bias) could not yield a strong enough inverse cancer–dementia association to explain empirical findings. In this analysis, we expand our simulation model to 7 states, and specifically model dementia diagnosis (none, undiagnosed, and diagnosed) in addition to cancer history (no/yes) and death (Figure 1). This allowed us to examine differential dementia diagnosis rates as an alternative source of bias yielding an inverse cancer–dementia association. In our main analysis, the simulated cohort members all started in State A (neither cancer nor dementia), and were followed monthly over 30 years.

State transitions during follow-up denoted incidence of an event (cancer, dementia, dementia diagnosis, or mortality). For example, a transition from State A to D denoted incidence of cancer without dementia, and a transition from State B to State C indicated incidence of a diagnosis of dementia in the absence of cancer (Figure 1). Transitions were irreversible; individuals could not revert to a state free of cancer history, dementia, dementia diagnosis, or death once they had experienced any of these events. Consistent with all Markov models, transition rates varied by age (ie, follow-up time) but not by length of time spent in a state (19).

Because our objective was to evaluate the extent to which dementia diagnosis patterns among those with and without a cancer history can explain the inverse cancer–dementia link, in all scenarios cancer had no effect on dementia incidence. We first simulated a scenario in which cancer was unrelated to time to transition from undiagnosed to diagnosed dementia ("Nondifferential Delay Scenario"). In this scenario, even though cancer was unrelated to transition time from undiagnosed to diagnosed dementia (ie, delay in dementia diagnosis), cancer accelerated transition to death, which precluded dementia diagnosis. This scenario characterized the estimated effect of cancer on diagnosed dementia absent any differential delay by cancer history. We next simulated a set of scenarios in which cancer influenced time to diagnosis, that is, transition from undiagnosed to diagnosed dementia, in addition to accelerating transition to death ("Differential Delay Scenario"). With these models, we aimed to determine under what circumstances such differential delay could lead to estimated effects of cancer on diagnosed dementia similar to those reported in the literature.

All analyses were conducted in R version 4.0.2. The model was specified using differential equations corresponding to the states shown in Figure 1, and solved using the "ode45" solver in the deSolve package (20). The code, which generates and analyzes all data, is available at https://github.com/Mayeda-Research-Group/CancerAD-diagnosissims. The simulations did not involve human participants and Institutional Review Board approval was therefore not required.

Model Parameters and Data Sources

The simulation required specifying parameters for transition rates corresponding to each arrow in Figure 1. We parameterized the

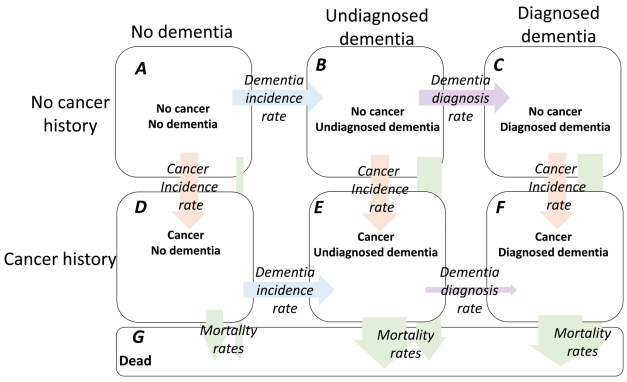

Figure 1. Schematic of simulation model. Arrow thicknesses qualitatively represent relative magnitude of incidence rates. Blue arrows, transition from no dementia to dementia. Purple arrows, transition from undiagnosed to diagnosed dementia (showing Differential Delay Scenario). Orange arrows, transition from no history of cancer to history of cancer. Green arrows, transition to death. Transition rates were obtained from real-world data (Supplementary Table 1).

model using age-specific real-world data, most of which has been reported in detail previously (12); details on parameters and data sources are reiterated below and summarized in Supplementary Table 1. Importantly, model parameters were age-specific for each cancer type and were additionally sex-specific for breast and prostate cancer models. Most information on dementia, cancer, and mortality rates was provided in 5-year age bands. To calibrate the model to this input data, we converted these to monthly estimates using the pracma package (21) in R, which allowed us to fit smooth polynomials to the age band-specific estimates to obtain transition rates in each month of follow-up in the simulation model (input parameters and smooth polynomials shown in sections 1 and 2 of Supplementary Material).

Dementia incidence parameters

Dementia incidence rates were obtained from cohort studies with active dementia case-finding and gold-standard assessment: the Adult Changes in Thought study (ACT) for ages <90 and the 90+ Study for ages ≥90 (22,23). ACT is a cohort study of 4 445 dementia-free community-dwelling members aged 65+ recruited between 1994 and 2010 from Kaiser Permanente Northwest (formerly Group Health); participants are assessed biannually for dementia with the Cognitive Abilities Screening Instrument followed by complete diagnostic evaluation (physical, neurological, and neuropsychological testing, and lab/imaging studies) for low-scoring individuals. Published incidence estimates include 3 605 participants with at least 1 follow-up visit to date (median follow-up 6.3 years) (22). The 90+ Study is a cohort study of 330 dementia-free participants age 90+ at baseline who had previously participated in the Leisure World Cohort Study of a retirement community in California (23). Dementia assessments included neurological exam and neuropsychological test battery (every 6 months) or informant questionnaires/Cognitive Abilities Screening Instrument (annually), as available, with average 2.3 years of follow-up for incidence estimates (23).

In all simulations, we specified no true effect of cancer history on dementia incidence rates to quantify the magnitude of bias induced in the scenarios described above.

Dementia diagnosis parameters

A key parameter in our models was the time that elapsed between when an individual met clinical criteria for dementia and when dementia was diagnosed, which determined the transition rate from undiagnosed to diagnosed dementia. In our models, this transition rate was taken from a recent analysis comparing dementia diagnoses in members of the ACT study described above (which had biannual active case-finding) to diagnoses in electronic health records for the same individuals for the 2 years prior to the ACT diagnosis (24). Using the findings of this paper, we calculated an average time from dementia onset to dementia diagnosis of approximately 2 years (calculation in section 3 of the Supplementary Material). However, this likely represented a pessimistic estimate of the time to diagnosis (because the calculation assumed that cases of dementia identified in ACT had dementia during the entire 2-year period prior to the ACT diagnosis), so our model for the Nondifferential Delay Scenario used an average lapse of 1.5 years, regardless of cancer history. The average lapse was varied in sensitivity analyses (see below).

In the Differential Delay Scenario, we allowed cancer history to affect rate of dementia diagnosis. The effect of cancer history on dementia diagnosis rates reflected the net of 2 opposing processes: history of cancer could increase rate of diagnosis of dementia (decreasing delay, eg, due to more frequent contact with clinicians who could refer patients for a dementia assessment) or decrease rate of dementia diagnosis (increasing delay, eg, due to those with cancer being too unwell to complete an assessment, attribution of cognitive symptoms to effects of cancer and treatment, or fewer dementia diagnoses for people with limited life expectancy due to cancer). Estimates for this relative rate are not available in the literature, so a key question in our analyses was how different dementia diagnosis rates would need to be to produce estimated effects of cancer on dementia similar in magnitude to those in the prior research. We thus varied the relative rate of diagnosis between those with and without cancer history from 0.5 (50% lower rate of diagnosis) to 1.5 (50% higher rate of diagnosis).

The upper limit of 1.5 was based on an analysis of the Health and Retirement Study (HRS, a nationally representative longitudinal study of approximately 20 000 adults age 50+ (25)) linked to Medicare claims comparing health care utilization before and after diagnosis of incident cancer. The analysis included 2 682 individuals with incident cancer who were at least 67 years of age and free of dementia at the time of cancer diagnosis (see section 4 of the Supplementary Material for details).

Cancer incidence parameters

Cancer incidence rates (overall and type-specific for female breast, prostate, and lung) were obtained from the Surveillance Epidemiology and End Results 21 Area (SEER 21) registry for 2012–2016 using standard SEER cancer site coding (26–28). SEER is a national registry and authoritative source of cancer incidence and survival data in the United States; data are aggregated from population-based cancer registries covering nearly half the U.S. population, and the covered population is comparable to the U.S. population on education and poverty (29,30).

Mortality parameters

Mortality rates were parameterized such that cumulative survival matched U.S. lifetables for the cohort born 1919–1921 from age 65 to 95 (31). Lifetables are records maintained by the National Vital Statistics system, and report age-specific death rates and survival proportions based on death registrations observed for a given birth cohort over time (31). The effect of cancer on mortality was obtained by converting 5-year relative survival estimates for each cancer type from SEER 18 (2009–2015) to rate differences (26,28). (SEER 18 is a geographic subset of SEER that includes 18 (out of 21) geographic areas and is used to report survival data (28).) The effect of dementia on mortality was obtained from published estimates of the effect of dementia on mortality in a cohort of 273 843 dementia-free Kaiser Permanente Northern California health plan members aged 64+ with up to 13 years of follow-up starting in 2000 (32).

The combined effects of cancer and dementia on mortality in the models were obtained from an analysis of data from the HRS. The analyzed sample included 15 526 participants 65+ in the 1998–2014 surveys, with average follow-up time of 10 years (see section 5 of the Supplementary Material for more details). The analyses suggested an interaction HR of 0.50. For example, if for a given age, cancer increases mortality rates by 3-fold, and dementia increases mortality rates by 4-fold, an interaction HR of 0.5 would mean that having both cancer and dementia yields a 3 * 4 * 0.50 = 6-fold increase in mortality relative to those with neither cancer nor dementia. Additional details are in section 4 of the Supplementary Material, and this input was subject to sensitivity analyses as outlined below.

Quantification of Bias

Because we specified the true effect of cancer on dementia incidence to be null, any deviation from a null rate ratio (ie, 1.00) in our simulations was

bias due to delays in dementia diagnosis. We estimated instantaneous incidence rate ratios (IRRs) for cancer on diagnosed dementia: for each month of follow-up we divided the rate of dementia diagnosis among all those with a history of cancer (number of dementia diagnoses among those with cancer/person-time with cancer) by the rate of dementia diagnosis in those without a history of cancer (number of dementia diagnoses among those without cancer/person-time without cancer). To obtain IRRs over the duration of follow-up, we exponentiated the average of the natural log of the instantaneous rate ratios in each month. Only *diagnosed* dementia cases would be seen in empirical studies and were included in the numerators of rate calculations for comparison to prior published associations. We quantified the amount of bias as the difference between the true value of 1.00 and the value observed in our simulations.

We compared results from our simulations to literature-reported values for the inverse cancer–dementia association, expressed as standardized IRRs or HRs, for each of the 4 cancer types we examined (all types combined, breast, prostate, and lung). Specifically, we compared to findings from the most recent systematic review and meta-analysis, as well as the most recent large cohort study of multiple cancer types (4,33). The simulation scenarios for each cancer type that best-matched the empirical data were determined by the weighted least mean-squared error (LMSE) for each simulation scenario, where the weighted LMSE was taken as the mean of the squared differences between each cancer-specific simulated IRR and the corresponding empirical estimates, weighted equally between the meta-analysis and cohort study.

Sensitivity Analyses

We conducted sensitivity analyses to determine robustness of the results to key model input parameters. First, we assessed the sensitivity of the results to the interaction effect of cancer and dementia on mortality in the model. As described above, this effect's parameter value in the main analyses (interaction HR = 0.50) came from an analysis of HRS data. In sensitivity analyses, we varied this parameter from 0.40 to 0.70 (ie, assuming joint effects of cancer and dementia on mortality were 40% to 70% of multiplicative). In addition, we varied the lapse between onset of meeting clinical criteria for dementia and diagnosis among those without cancer by approximately half-year increments, examining average lapses between 0.05 years (~2.5 weeks, the smallest computationally feasible lapse in the multistate model) and 2 years (the upper bound derived from ACT study data (24), shown in section 3 of the Supplementary Material). Finally, we conducted a sensitivity analysis in which we allowed cancer type-specific prevalent cancer at baseline (age 65); prevalence at age 65 was estimated from SEER 13 data (the subset SEER uses to report prevalence) (26,28), using the prevalence for ages 50–64 and 65–74 at their midpoints (ie, 57 and 70) and assuming a constant percent change over time (details in section 6 of the Supplementary Material).

Results

Across all simulated cohorts, models were well-calibrated to cumulative survival from U.S. lifetables and cancer and dementia incidence (from SEER and the ACT and 90+ studies, respectively). Example calibration results (smooth polynomials) are shown in section 2 of the Supplementary Material. Figure 2 shows an example of the cumulative incidence of dementia, dementia diagnosis, and death for a simulated cohort (model for all cancer types combined in the Nondifferential Delay Scenario). In this cohort, by the end of follow-up (30 years, age 95), 98.8% of the cohort had died. Over this follow-up time and prior to death, 20.2% of the cohort experienced dementia, and 12.5% (62% of dementia cases) received a dementia diagnosis, indicating that just over one third of dementia cases died before their dementia was diagnosed. These dementia cases would not be seen in an empirical study and are therefore not included in the IRRs in the following results; as described previously, only observed (diagnosed) dementia cases are included.

Results for bias observed in the cancer–dementia association in simulations in the Nondifferential Delay Scenario varied by cancer type due to differences in cancer type-specific mortality rates. The observed IRR for the effect of cancer on diagnosed dementia was close to null (0.98) for all cancer types combined. For breast and prostate cancers, which have excellent average survival, IRRs were slightly positive (1.02 and 1.01, respectively). The observed IRR for the effect of lung cancer on dementia showed a protective association (IRR = 0.78), as expected given that lung cancer has a high fatality rate.

Figure 3 shows results for analyses of the impact of differential delay on observed bias for each cancer type. Moving from left to right along the x-axis corresponds to increasingly delayed dementia diagnosis among those with cancer history versus without (ie, slower rate of dementia diagnosis). As expected, an increasing delay in dementia diagnosis in those with cancer resulted in increasingly negative bias. Importantly, regardless of the magnitude of effect of cancer on the timing of dementia diagnosis (delays along the x-axis), cancers with worse survival had more protective observed IRRs. For example, nearly all lung cancer simulations produced observed IRRs for dementia that were protective (<1.0), while the breast cancer simulations produced observed positive IRRs (>1.0) even when dementia diagnoses were very slightly delayed in breast cancer patients.

Figure 4 shows the simulation model results overlaid with results from a recent systematic review and meta-analysis (Ospina-Romero et al. (4)) and an analysis of Danish registry data (Ording et al. (33)) for each cancer type. The Nondifferential Delay Scenario results were slightly more positive than point estimates in empirical data for all cancer types combined (eg, IRR 0.98 vs 0.81–0.96 in empirical data), breast cancer (IRR 1.02 vs 0.93–1.00), or prostate cancer (IRR 1.01 vs 0.96–0.99); however, the simulated lung cancer estimate appeared slightly more protective than the literature estimates IRR (0.78 vs 0.84–1.12). The best-match Differential Delay Scenario for all cancer types (defined by weighted LMSE) occurred when the rate of dementia diagnosis was

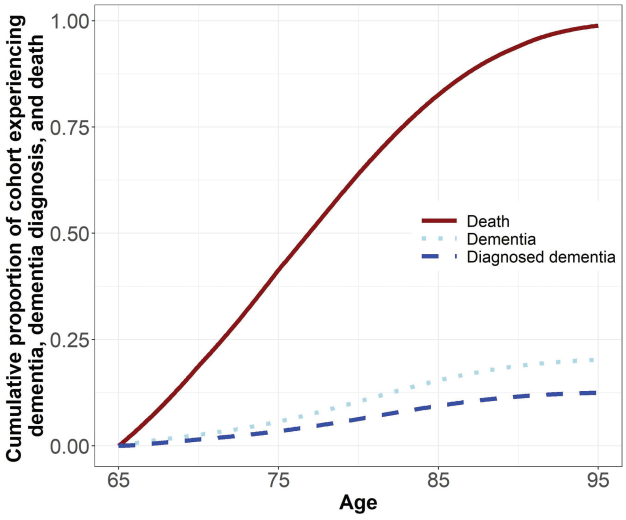

Figure 2. Overview of cumulative proportion of cohort experiencing dementia, dementia diagnosis, and death in example simulated cohort (all cancers, Nondifferential Delay Scenario). Full color version is available within the online issue.

20% slower in those with cancer than those without cancer history, corresponding to an additional 4.5-month delay in Figure 3 (or 18 months in those without cancer, and 22.5 months in those with cancer). In this scenario, the observed IRR was 0.87, between the estimates from Ospina-Romero et al. (4) and Ording et al. (33) for the association of all types of cancer with dementia. Simulated observed IRR estimates for breast and prostate cancers were most consistent with reported literature estimates when the dementia diagnosis rates were 10% smaller (an additional 2-month delay) in people with cancer history than without. In contrast, due to the qualitative differences in the literature estimates for Alzheimer's dementia and all-cause dementia, the best match for the lung cancer model, which weighed both literature estimates equally, required a 40% increase in dementia diagnosis rate (over 5-month reduction in delay) among those with lung cancer history.

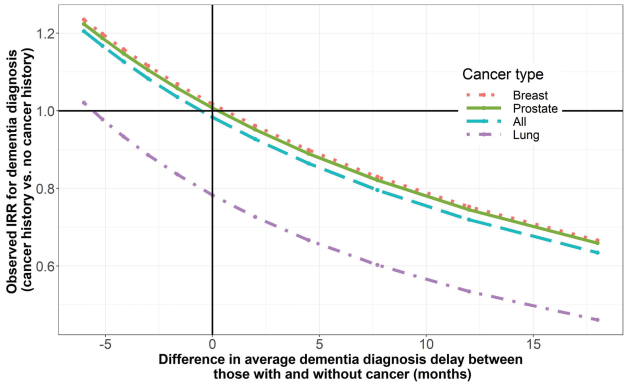

Figure 3. Observed cancer–dementia incidence rate ratios (IRRs) in Differential Delay Scenario models varying effect of cancer on dementia diagnostic delay. *Note*: Negative delay indicates faster dementia diagnosis among those with cancer history than without; positive delay indicates slower dementia diagnosis among those with cancer history than without. Full color version is available within the online issue.

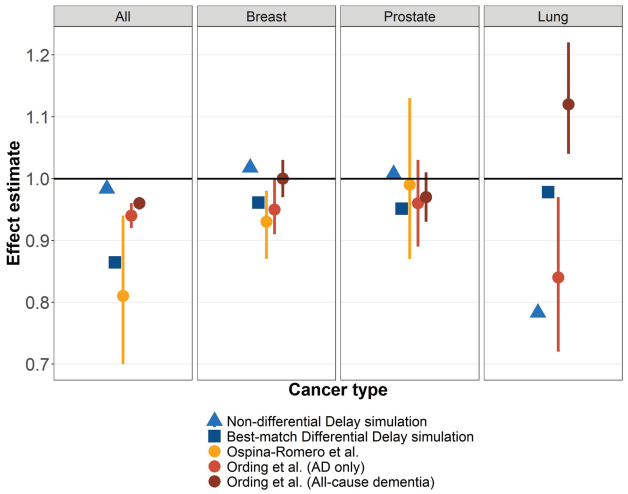

Figure 4. Nondifferential Delay Scenario simulation results and Differential Delay Scenario simulation results best-matched to empirical findings, overlaid with empirical findings, by cancer type. Triangles and squares represent simulation results, and circles represent empirical findings from the literature. The best-match Differential Delay Scenario simulations (triangles) included the following relative rates for dementia diagnosis among those with cancer history versus without: all cancer types: 0.8; breast cancer: 0.9; prostate cancer: 0.9; lung cancer 1.4. AD = Alzheimer's dementia. Full color version is available within the online issue.

In sensitivity analyses, we examined the impact of both average time to dementia diagnosis and assumptions about the combined effects of cancer and dementia on mortality (ie, mortality rates in States E and F in Figure 1) in the all cancer types model. Figure 5 shows the results for this model in the Nondifferential Delay (5A) and best-match Differential Delay (5B) Scenarios (net 20% decrease in dementia diagnosis rate in those with cancer history). In each panel, longer delays in dementia diagnosis (moving left to right on x-axis) yielded greater bias in the observed IRR; indeed, when there was minimal delay (0.05 years, or approximately 2.5 weeks in those without cancer), there was essentially no bias observed. In addition, the greater the combined effects of cancer and dementia on mortality (moving from light to dark lines), the greater the negative bias in the observed IRR; with larger combined effects, the mortality rate increases for those with cancer and dementia, making them more likely than counterparts without cancer to die before a dementia diagnosis.

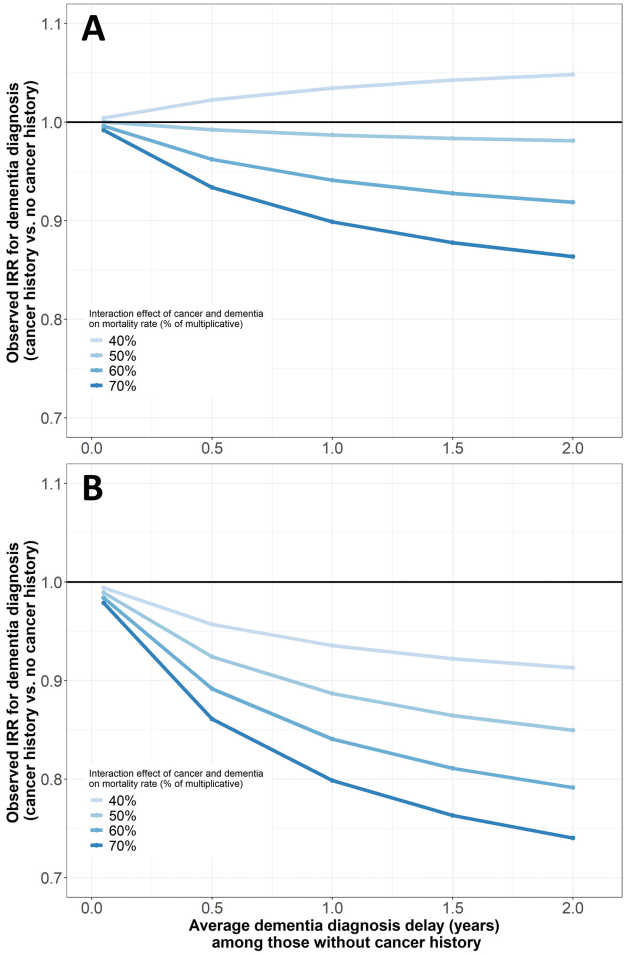

Figure 5. Sensitivity of results for all cancer types models to diagnostic delay and combined effect of cancer and dementia on mortality in (A) Nondifferential Delay Scenario and (B) Differential Delay Scenario with 80% slower dementia diagnosis rate in those with cancer. The x-axis shows the specified average time from onset of meeting clinical criteria to dementia diagnosis among those with dementia, and the y-axis shows the observed incidence rate ratio (IRR) for cancer history on dementia diagnosis. The color of the lines corresponds to the interaction effect of cancer and dementia on mortality. The lightest is 40% of fully multiplicative, darkest is 70% of fully multiplicative. For example, at a given age, if cancer increases mortality rates by 3-fold, and dementia increases mortality rates by 4-fold, 40% of multiplicative would be a 3 * 4 * 0.4 = 4.8-fold increase in mortality rates among those with both cancer and dementia versus neither, while 70% would be 3 * 4 * 0.7 = 8.4-fold increase. Full color version is available within the online issue.

The final sensitivity analysis including prevalent cancer cases yielded nearly identical results as the main analysis; because of this, results are provided in section 6 of the Supplementary Material.

Discussion

This study examined the role of dementia diagnosis, including diagnostic delays both nondifferential and differential by cancer history, in explaining the inverse cancer–dementia association. After calibrating to real-world data on cancer and dementia incidence, mortality, and dementia diagnosis rates, we found that delays in dementia diagnosis that are nondifferential by cancer status induced small biases, but empirical estimates were more protective than our estimates from these models for most cancer types. Only when dementia diagnosis rates were at least 20% slower (ie, delayed by at least 4.5 months) among people with cancer were IRRs sufficiently biased to correspond with the reported literature for all cancer types combined. These results held when allowing for prevalent cancer at baseline.

Although our findings are not conclusive, they suggest that diagnostic delays are unlikely to fully explain the inverse cancer–dementia link. Importantly, they clarify the critical assumptions necessary to quantify the impact of diagnostic delay. More fatal cancers are likely subject to greater bias because those with cancer and undiagnosed dementia are more likely to die before they are diagnosed with dementia. In our simulation results, negative bias was strongest in the lung cancer model, followed by all cancers combined, while breast and prostate cancer models produced more positive bias. We note that the positive bias in breast and prostate models in some scenarios was unexpected, but occurred because the mortality in those with breast or prostate cancer and dementia was only minimally higher than in the larger group with dementia but cancer-free, meaning more dementia diagnoses were missed in those without cancer relative to person-time accrued (simplified proof in section 7 of the Supplementary Material). Our findings across cancer types are broadly consistent with the empirical literature, where all cancer types combined show more protective effects than breast and prostate cancers (4,33,34). There is less evidence on lung cancer (and no meta-analytic results available), but some estimates do show larger protective effects, especially for Alzheimer's dementia (33,34).

Additionally, the simulation results showed that meaningfully (at least 20%) slower rates of dementia diagnosis, corresponding to at least 4.5-month additional delays in those with cancer history, were needed to obtain sufficient bias to match results from empirical studies for all cancer types combined. Dementia has insidious onset and diagnosis may be delayed even for patients without cancer history; our findings suggest that an *additional* 4.5-month delay for patients with cancer is needed to explain empirical results. Slightly slower rates (at least 10% slower, 2-month delays) were needed to explain the small inverse associations reported in the literature for breast and prostate cancers. Individuals with cancer or cancer history are in greater contact with the medical system, which may increase their rate of diagnosis, suggesting that a net reduction of 20% (all cancers combined) would require those with cancer history to be substantially less likely to be referred or diagnosed with dementia at a given level of cognitive functioning. Of course, estimates from empirical studies may be subject to multiple sources of bias, potentially in competing directions. If there are other positive sources of bias (eg, confounding) in empirical estimates, even greater differences in dementia diagnosis patterns (or other sources of negative bias) would be needed to explain reported estimates. Although more research is needed on the plausibility of this magnitude of underdiagnosis, our simulations showed that even smaller differences in diagnostic practices produced some bias, and may contribute to the reported inverse association.

Finally, the results of the sensitivity analyses show that longer lapses between individuals meeting clinical criteria and receiving a dementia diagnosis, regardless of cancer history, are likely to increase bias in the observed cancer–dementia association. Dementia diagnosis delays occur in both routinely collected electronic medical record (EMR) data and data from cohort studies; studies using EMRs typically report associations closer to the null than studies with dementia assessments at regular intervals (4). Our simulations suggest that this could be partially or fully explained if delays in diagnosis are shorter in clinical settings than in cohort studies, where participants are assessed for dementia only at follow-up waves (eg, every 2 years). However, studies using EMRs are subject to potential differential delays by cancer status, whereas cohort studies with protocolized dementia assessments avoid such bias; our results suggest that faster dementia diagnosis rates in those with cancer would be needed to explain why effect estimates from EMR versus cohort studies are closer to the null.

The primary limitations of this work are the simplifications required for the multistate simulation models, and the availability of data to parameterize the models. For example, we modeled dementia as a binary variable, rather than a trajectory of cognitive decline. Data were not available to separately model Alzheimer's, vascular, and mixed pathologies, which may be of particular interest for lung cancer, because of qualitative differences in the association between lung cancer and Alzheimer's dementia versus all-cause dementia in some empirical studies (33,34). We also assumed that mortality rates remained elevated indefinitely following a cancer diagnosis (12). If elevated mortality due to cancer did not persist, we would expect to see more positive IRRs (ie, less inverse associations) in both the Nondifferential and Differential Delay Scenarios, as reduced cancer mortality would lead to fewer deaths among those with dementia and cancer prior to dementia diagnosis; if our assumption is incorrect, our simulation results are pessimistic (observed bias from our simulations would be overly negative). No single cohort contained data needed for all input parameters, so our inputs came from multiple sources with different sample compositions. For example, dementia incidence and diagnosis rates came from a predominantly white cohort; incidence rates may be higher and diagnostic delays longer in some racial/ethnic groups (35,36). As shown in the sensitivity analyses, longer delays can result in more missed diagnoses, which could result in greater observed bias in estimates of the effect of cancer on dementia.

In conclusion, our simulations showed that delays in dementia diagnosis may play a role in explaining the inverse relationship between cancer and dementia, especially for more fatal cancers, but a moderately slower diagnosis rate (at least 20% slower; extra 4.5-month delay) in those with cancer would be required to fully explain the IRRs reported in the literature. To date, there is no evidence that cancer diagnosis delays dementia diagnosis, and increased interaction with the health care system among cancer patients may even hasten dementia diagnosis, increasing our confidence that other causal explanations for the inverse association, such as shared biological basis, may be important. However, future research that examines mortality and delays in diagnosis among individuals with cancer history, especially in cohort studies linked to EMR, may help inform the plausibility of slower rates of dementia diagnosis in those with cancer required in our simulations to match cancer–dementia associations reported in the literature.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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