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Association between Cancer and Alzheimer's Disease: Systematic Review and Meta-Analysis

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Abstract. This study examined the association between cancer and Alzheimer's disease (AD) by a quantitative meta-analysis of cohort studies. Studies were identified by searching PubMed database through 1966 to December 2013 using the terms "Alzheimer's disease", "neoplasm", and "cancer". Six studies met the inclusion criteria in the overall meta-analysis. We pooled effect sizes using fixed-effects and random-effects models. Furthermore, we also tested for heterogeneity and publication bias. The results suggested that individuals diagnosed with AD had a decreased risk for incident cancer by 42% (95% CI, 0.40–0.86; $p < 0.05$), and patients with a history of cancer had a 37% decreased risk of AD (RR = 0.63; 95% CI, 0.56–0.72; $p = 0.495$). The Egger's test for publication bias ($p = 0.280$) showed no significant evidence for bias in the data from studies on AD and cancer risk. In summary, our meta-analysis demonstrated an inverse association between cancer and AD.

Keywords: Alzheimer's disease, cancer, meta-analysis, neoplasm

INTRODUCTION

Alzheimer's disease (AD) is the most common progressive neurodegenerative disorder, affecting more than 13% of the population older than 65 years and 43% older than 85 years [1, 2]. Cancer, an age-associated condition, has become one of the most challenging health issues today [3]. A growing number of cohort and case-control studies have reported an inverse relationship between AD and cancer, such that the rate of developing cancer was significantly slower in participants with AD, while participants with a history of cancer had a slower rate of developing AD [4–10]. Indeed, an inverse association between cancer and Parkinson's disease, the second most common neurodegenerative disorder, has also been reported by more than one study [11–13]. This observation is intriguing, since AD is characterized by the premature progressive loss of neuronal cells, and cancer is a disorder resulting from inappropriate cell survival or proliferation [14]. Basic research suggests that the development of AD and many cancers may be related via one or more common molecular mechanisms [15–17]; this might be a potential explanation for the inverse association between cancer and AD.

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However, in many epidemiologic studies, variations in the design, methods, and quality of studies exploring the relationship between cancer and AD have made it difficult to ascertain the correlation of these two diseases with certainty. Therefore, we report a quantitative meta-analysis of several independent cohort studies, to determine the cancer risk among patients with AD, and AD risk among patients with cancer.

METHODS

Search method

We searched the PubMed database using search terms including "Alzheimer's disease" and "cancer" or "neoplasm" (1966 to December 2013). Studies were restricted to papers published in English and Chinese and were limited to "human studies". We placed no constraints on the region of residence or age group of study subjects. This meta-analysis aimed to include all published cohort studies that provide an estimate of the correlation between AD and cancer.

Inclusion/exclusion criteria

For inclusion in the meta-analysis, eligible studies had to present original data or a risk ratio (RR), hazard ratio (HR), or standardized incidence ratio (SIR), or enough information to quantify the association between AD and cancer. The AD diagnosis was generally made using accepted clinical criteria (NINCDS-ADRDA; DSM-IV); a partial use of the generally accepted criteria (MMSE; CDR); or by a history of use of anti-dementia drug. The studies based the definition of cancer diagnosis on hospital chart-based ICD codes. The study cohort was recruited at the population level. Mortality and autopsy studies were excluded in the overall analysis, because of selection bias inherent to the study design. In addition, studies with a quality score of less than 5 points according to the Quality assessment criteria (see Table 1) were abandoned.

Quality assessment

The quality of all included studies was appraised with checklists developed for cohort study designs according to the earlier systematic review and the guidelines for reporting meta-analyses of cohort studies [18]. These checklists include external validity (sample representatives, sample size, participation at follow-up), internal validity (duration of follow-up, outcome measurement), and descriptive issues. The authors independently evaluated each of the potentially included studies according to quality assessment, and discrepancies were resolved by discussion.

Data extraction

We extracted data from the studies, in particular concerning: 1) name of first author, 2) publication year, 3) study design, 4) follow-up time, 5) number of patients in the analysis, 6) age of patients, 7) method of AD assessment, and 8) RR of statistical analysis.

Statistical analysis

Data were entered into the Stata 12.0 Meta analysis program. In the meta-analysis of cohort studies for incidence rates of AD/cancer, RR and 95% confidence intervals (95% CI) were calculated. We estimated the heterogeneity across all eligible comparisons using the chi-square test. Heterogeneity was considered significant for $p < 0.05$. In the meta-analyses, both fixed-effects model and random-effects model were used. When the heterogeneity was non-significant, the RR from fixed-effects model was chosen. If heterogeneity was obvious, the RR from random-effects was chosen. The significance of the pooled effect size was determined through the z test. We assessed publication bias using the method of Egger's test.

Table 1
Quality assessment of studies

Quality parameters	Score		
	2	1	0
Sample representatives	Well-defined	Baseline response rate 50% or more	Baseline response rate less 50%
Sample size at baseline	>500	100–500	<100
Duration at follow-up	>3 years	1–3 years	<1 year
Participation follow-up	Participation rate at 70% response or more	Participation rate at follow-up 60–69·9%	Participation rate less 60%
Outcome measurement	Recognized international criteria by a central consensus committee	Active screening with ad-hoc criteria	Based on medical records

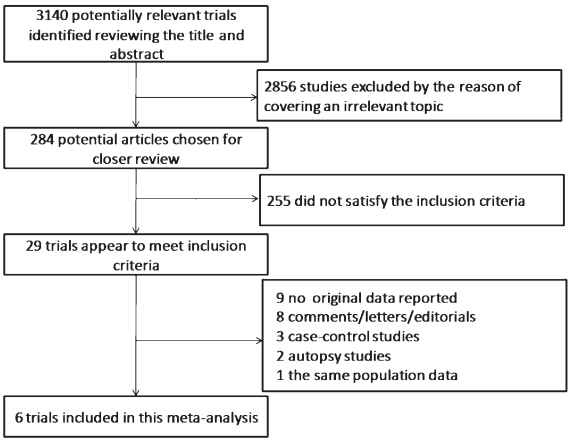

Fig. 1. The patient selection flowchart.

RESULTS

Figure 1 shows the stages in obtaining studies for inclusion in the overall review. Six studies met study eligibility criteria and were finally included in the overall meta-analysis (Fig. 1). The six studies were cohort studies, in which two studies only reported the subsequent AD incidence in cancer patients, one study only mentioned the subsequent cancer incidence following diagnosis of AD, and three studies compared the effect of above two aspects.

Half of the studies ($n = 3$) clearly defined the AD diagnosis using generally accepted clinical criteria (NINCDS-ADRDA; DSM-IV), two studies used the generally accepted criteria (MMSE; CDR), and one of these studies validated the AD diagnosis by a history of use of anti-dementia drugs. The average of study quality scores was 8.2 (the maximum possible score was 9).

AD diagnosis on cancer risk

Table 2 summarizes study-specific and pooled RRs of overall cancer in individuals with and without AD. The total sample included in the analysis was 12,956 participants (9,901 with a history of dementia of the Alzheimer type cases and 3,055 non-demented controls). 12,956 participants and 987 cancer events were available for the analysis of multiple-adjusted association between AD and incidence cancer risk. Figure 2 presents a forest plot of the individual studies of cancer as well as the pooled estimate of the RR. Combining all four studies, we found that individuals with a history of AD had a decreased risk for incident cancer by 42% (95% CI, 0.40–0.86; $p < 0.05$). Obviously heterogeneity was observed, so the result were based on the random-effects model. The Egger's test for publication bias ($p = 0.280$) showed no significant evidence for bias in the data from studies on AD and cancer risk. The funnel plot was not conducted due to the low quantity of studies.

Ou et al. discovered when the relationship between AD and overall cancer was stratified by gender; only women with AD had a significant decreased risk (SIR = 0.81, 95%CI, 0.70–0.93; $p = 0.003$), whereas men with AD did not (SIR = 0.95, 95% CI, 0.83–1.08) [8]. As for the subgroup analysis by cancer site, patients with AD had a decreased risk of colorectal cancer (RR = 0.67; 95% CI, 0.31–1.47), hematologic malignancies (RR = 0.72; 95% CI, 0.35–1.46), breast cancer (RR = 0.76; 95%CI, 0.55–1.05), and skin cancers (RR = 0.66; 95% CI, 0.38–1.07) (Fig. 4). In contrast, individuals with AD had an increased risk of prostate cancer (RR = 1.12; 95% CI, 0.84–1.48). However, none of these associations reached statistical significance. An exception was the lung cancer, for which patients with AD had a significantly decreased risk (RR = 0.72; 95%CI, 0.56–0.91).

Previous cancer on AD risk

Table 3 summarizes study-specific and pooled RRs of overall AD in individuals with and without cancer. The total sample included in the analysis was 27,100 participants (22,555 with a history of cancer and 4,545 controls with no cancer). 27,100 participants and more than 860 cancer events were available for the analysis of multiple-adjusted association between cancer and incidence AD risk. Figure 3 presents a forest plot of the individual studies of cancer as well as the pooled estimate of the RR. Combining all five studies, we found a 37% decreased risk of AD among patients with a history of cancer (RR = 0.63; 95% CI, 0.56–0.72; $p = 0.495$). No heterogeneity was observed, so the result are based on the fixed-effects model.

We discovered the lower AD risk was greatest among survivors of lung (HR = 0.85, 95% CI, 0.49–1.39), breast (HR = 0.68, 95% CI, 0.45–1.00), and colorectal (HR = 0.44, 95% CI, 0.23–0.75) cancer in Musicco's study [7]. Moreover, we also found a lower AD risk with non-melanoma skin (HR = 0.21, 95% CI, 0.051–0.87) in White's study [9]. In addition, Driver and colleagues found that survivors of smoking related cancer had a substantially lower risk of probable AD (HR = 0.26, 95%CI, 0.08–0.82) than survivors of non-smoking related cancer (HR = 0.82, 95%CI, 0.57–1.19) excluding non-melanoma cancer

Table 2
Characteristics of the 4 cohort studies comparing the incidence rates of cancer in subjects with Alzheimer's disease

Reference	Country	Age	Patient base	Cancer patient	Methods of AD diagnosis	Follow-up	Adjustment	Quality score	RR(95%CI)
[4]	USA	>65	594	45	CDR	11	gender, age at study entry, and education	8	HR 0.391 (0.207–0.739)
[5]	USA	>65	3020	376	NINCDS-ADRDA 3MSE	8.3	age, gender, obesity, physical activity, smoking	9	HR 0.31 (0.12–0.86)
[8]	Taipei	>70	6960	405	MMSE;CDR	10	gender, age, comorbidities, medications	8	SIR 0.88 (0.80–0.97)
[7]	Northern Italy	>60	2382	161	CDR	5	age, gender, calendar year–specific incidence rates	7	RR 0.57 (0.49–0.67)

3MSE, modified Mini-Mental State Examination; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; HR, hazard ratio; SIR, standardized incidence ratio; CI, confidence interval; RR, risk ratio.

Table 3
Characteristics of the five cohort studies comparing the incidence rates of Alzheimer's disease (AD) in subjects with cancer

Reference	Country	Age	Patient base	AD patient	Methods of AD diagnosis	Follow-up	Adjustment	Quality score	RR(95%CI)
[4]	USA	>65	249	NA	CDR	11	gender, age at study entry, education,	8	HR 0.400 (0.122–1.132)
[5]	USA	>65	3020	478	NINCDS-ADRDA 3MSE	5.4	age, gender, obesity, physical activity, smoking	9	HR 0.57 (0.36 –0.90)
[6]	USA	>65	1278	221	NINCDS-ADRDA	22	age, gender, smoking, educational level, APOEε4 status, plasma homocysteine level	9	HR 0.67 (0.47–0.97)
[7]	Northern Italy	>60	21451	161	Anti-dementia drug	5	age, gender, calendar year–specific incidence rates	7	RR 0.65 (0.56–0.76)
[9]	USA	>70	1102	100	NINCDS-ADRDA; DSM-IV	3.7	hypertension, diabetes, and coronary heart disease	8	HR 0.21 (0.051–0.87)

NA, not available; 3MSE, modified Mini-Mental State Examination; CDR, Clinical Dementia Rating; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; HR, hazard ratio; CI, confidence interval; RR, risk ratio; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders.

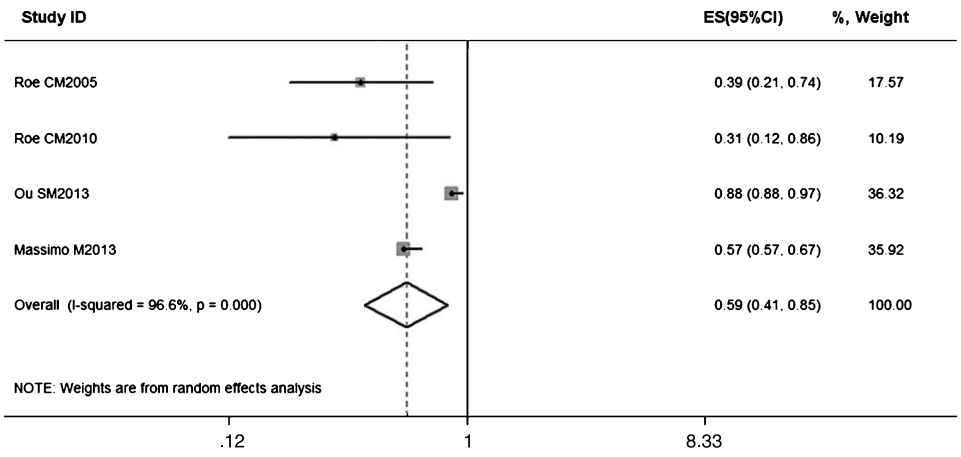

Fig. 2. The forest plot of RR from four studies comparing the incidence rates of cancer in subjects with AD.

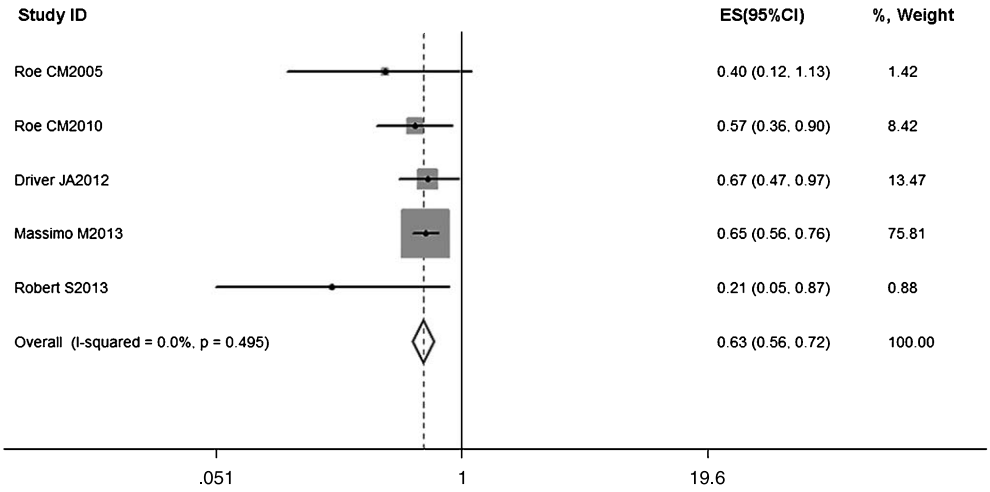

Fig. 3. The forest plot of RR from five studies comparing the incidence rates of AD in subjects with cancer.

when adjusted for age, gender, smoking, and incident cancer [6].

DISCUSSION

Our meta-analysis demonstrated an inverse correlation between cancer and AD; the diagnosis of AD was associated with an overall 42% decreased risk of cancer, and patients with a history of cancer with an overall 37% reduced risk of subsequent AD.

The results of decreased risk of cancer patients with AD from four cohort studies were consistent regardless of study design, length of follow-up, or study setting [4, 5, 7, 8]. Patients with AD tended to be diagnosed with cancer at a later stage, since their poor condition made it less convenient and comfortable to undergo cancer screening; moreover, they might not be hospitalized as frequently as those without dementia. This might result in the appearance of a decreased cancer risk after the diagnosis of AD in cohort studies. Besides, Ou et al. found a smaller risk reduction of cancer in women with AD compared to men in their cohort study [8]; this could be partially due to the fact that estrogen has antioxidant, anti-apoptotic, neurotrophic, and anti-amyloidogenic properties [19–21], and laboratory studies have discovered that low concentrations of estrogen might cause apoptosis of tumor cells [22]. Manly et al. conducted a case-control study and found postmenopausal women had lower estradiol levels than normal subjects; however, the risk of AD among postmenopausal women can be significantly decreased by using hormone replacement therapy [23].

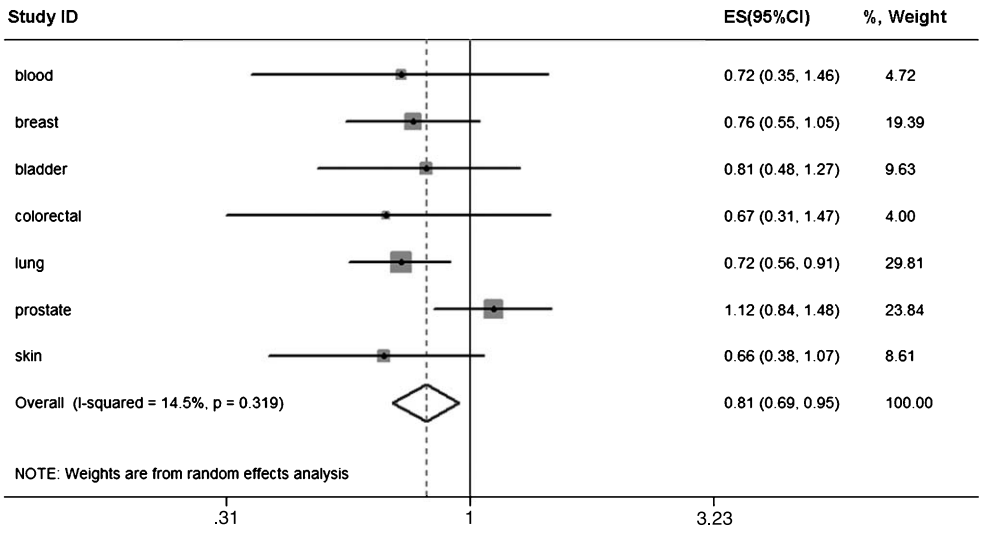

Fig. 4. The forest plot of RR(s) of the incidence rates of cancer in subjects with AD from the subgroup analysis by cancer site.

Nevertheless, whether a lower estrogen level promotes early tumor cell death and protects women with AD against cancers has not been determined and requires further investigation.

The protective effect of a baseline cancer history on subsequent AD diagnosis also was observed in five studies [4–7, 9]. Previous observations on a decreased risk of AD in patients with cancer gave rise to the thought that it was related to chemotherapy use. In a large population-based cohort conducted by Du et al. the risk of developing AD was significantly lower in older breast cancer patients who received chemotherapy compared with those who did not [24]. Similarly, Laura et al. discovered that among veterans with a cancer history, treatment with chemotherapy but not radiation reduced AD risk by 20 to 45%, depending on cancer type [25]. Together, these findings indicate that the protective relationship between cancer and AD could partially be explained by the use of chemotherapy among cancer patients. This could potentially open new therapeutic strategies for AD prevention and treatment.

Notable, Driver and colleagues examined the relationship that survivors of smoking-related malignancies had an obviously lower risk of AD than non-smoking-related malignancies; a similar discovery has been found in Parkinson's disease [26]. In our analysis, a lower rate of smoking-related cancers in patients with AD was seen due to its well established negative association with smoking [27]. Additionally, genetic studies indicate that Pin1 (protein interacting with NIMA 1) might play a central role in the cell survival of cancer and AD [16]. A prevalent overexpression of Pin1 has been shown in most human cancers including prostate, breast, lung, colon, and liver [28–30]. Also, a role of Pin1 in promoting the mitochondrial apoptotic machinery has been described in neurons [31, 32]. Patients with less active Pin1 would be at a greater risk of developing AD. Conversely, those with an active Pin1 would be more prone to develop cancer. Overall, this proposed gene-environment interaction pattern could explain an inverse association between cancer and AD.

The present study was the first meta-analysis to summarize the association between cancer and AD. The findings of our study were valid because their comprehensive literatures search, strict diagnostic criteria, the sub-analyses on site-specific cancers.

The current meta-analysis also had several limitations which should be noted. First, we only searched studies in Pubmed database and the language was limited to articles published in English and Chinese; moreover, publication bias was not avoidable, as positive results were much more likely to be published. Therefore, some studies may have been missed. Finally, only six studies were included in our study, and the sample size for analysis might be limited and statistical tests might be generally of limited power when tested. Further, our estimates for site-specific cancer risks are based on a small number of studies, making it difficult to draw definite conclusions. Second, the phenomenon of survival bias is likely to exist, such that cancer patients died before they had the chance to develop dementia, and their removal could result in the

spurious finding that cancer survivors have a reduced statistical probability of dementia. On the other hand, if cancer incidence was computed from national statistics or collected retrospectively, then all cancers, despite survival, could be included, and would introduce a bias. Third, it is well-known that caregivers of a cancer survivor will often mask symptoms of dementia and hinder the diagnosis due to cognitive decline. However, this tendency is dependent upon the extent of caring, and it may be possible that it is magnified for a caregiver who has faced the potential of losing their partner to cancer. Since no primary citations for this information available, this possibility may have an influence on our outcome.

In summary, we generally observed the lower risk of AD in patients with cancer, and vice versa, even when considering different cancer sites. Further research to study potential biological mechanisms between AD and cancer are warranted, as they may provide more data to confirm our findings and aid in the prevention and treatment of both diseases.

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