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Inverse association for diagnosis of Alzheimer's disease subsequent to both melanoma and non-melanoma skin cancers in a large, urban, single center, Midwestern U.S. patient population

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Abstract

Background—Although literature demonstrates a decreased risk of Alzheimer's disease (AD) in individuals with various cancers, including squamous cell cancers (SCC) and basal cell cancers (BCC) comprising non-melanoma skin cancers (NMSC), there is a paucity of literature to substantiate an association between malignant melanoma (MM) and AD.

Objective—The aim of this study is to determine if an association exists between MM and AD as well as for NMSC and AD.

Methods—A large urban, Midwestern, U.S., single center, medical record (EMR) data repository was searched between Jan 2001 and Dec 2015, to identify all patients age ≥60 and <89 years with a clinic follow-up of at least 1 year and no diagnosis for AD, MM or NMSC at the time of the study entry. Data collected included age, gender, race, and duration of follow-up. MM and NMSC were detected by ICD-9 codes and ICD-10 codes. Incident diagnosis of AD was also detected by ICD 9 and 10 codes. Logistic regression analysis was utilized to obtain crude and adjusted odds ratios (ORs).

Results—Data for a total of 82,925 patients with known race, gender and were detected. After adjusting for confounding factors (race, gender, age, cerebrovascular disease, peripheral vascular disease, and diabetes), there was a significant decreased risk for subsequent AD in patients with MM (OR: 0.39; 95%CI: 0.16–0.96; p=0.042) as well as in patients with BCC (OR: 0.18; 95%CI: 0.08–0.45; p<0.0001) and for patients with SCC (OR: 0.08; 95%CI: 0.01–0.56; p=0.013).

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Conclusion—These findings add to the growing body of evidence for a decreased risk of AD in patients with various cancers, and highlight the need for ongoing research to elucidate both neurologic and biologic mechanisms that may underlie this apparent inverse association.

Introduction

The relationship between age-related neurodegenerative diseases and cancer remains an important and ongoing area of research as well as clinical interest. Abnormal cancer patterns were first described in patients with Parkinson's disease (PD) where an inverse relationship was determined for PD subsequent to diagnosis of selective types of cancer¹. This prompted investigation into other neurodegenerative conditions, and several large cohort studies have now demonstrated an inverse association between Alzheimer's disease (AD) and various types of cancer^{1–3}.

Analysis of the cognition cohort in a cardiovascular health study demonstrated that individuals with cancer had up to 43% lower risk for subsequent diagnosis of AD ($p=0.02$), and those with AD had a 69% decreased risk for subsequent diagnosis of incident cancer³. The Framingham Heart Study also demonstrated that participants with a history of cancer had a lower risk of incident AD and vice versa². The bidirectional nature of the relationship between cancer risk and AD risk additionally suggests it is unlikely that the association could be due to bias in study design or population studied.

Of interest, the relationship between AD and skin cancers remains less well-elucidated to date. Analysis of data from the Einstein Aging Study (a U.S. East Coast population-based longitudinal study) demonstrated that individuals older than 70 years with non-melanoma skin cancers (NMSC) have significantly reduced risk for subsequent diagnosis of AD compared to individuals without NMSC⁴. Another study evaluating the registry data of a large Danish patient population (16,221 NMSC patients and 1,081,097 matched controls) demonstrated NMSC to be associated with 2–10% reductions in both AD and all-cause dementia⁵. Since the relationship between MM and AD has not been well-characterized, we searched the data repository for a large, single center, urban, U.S. Midwestern patient population in order to characterize the relationship for both malignant melanoma (MM) and NMSC (squamous cell cancers (SCC) and basal cell cancers (BCC)) with a subsequent diagnosis of AD.

Materials and Methods

The Northwestern Medicine Enterprise Data Warehouse (NMEDW), a repository of Electronic Medical Record (EMR) data for over 5 million patients, was searched. The study population consisted of patients who had a first in-clinic encounter between Jan 2001 and Dec 2015. Inclusion criteria were: age 60 and 89 years at the time of study entry (first in-clinic encounter); follow-up of at least 1 year (defined as the time between the first and last in-clinic encounter); and no diagnosis for AD, MM or NMSC at the time of the study entry. Data collected included age, gender, race, and duration of follow-up. MM and NMSC were detected by ICD-9 codes (MM:172.0–172.9, BCC: 173.01–173.91 and SCC 173.02–173.92) and ICD-10 codes (MM:C43.0–C43.9, BCC and SCC: C44.0–C44.9). Incident diagnosis of

AD was also detected by ICD 9 and 10 codes (331.0 and G30.0, G30.1, G30.9 respectively), and data were included only if the diagnosis of AD occurred at least 1 year after the index date (MM or NMSC diagnosis or in-clinic encounter). Data on cerebrovascular disease, peripheral vascular disease and diabetes were also collected as potential confounding factors for AD using ICD-9-CM and ICD-10 coding algorithms for Charlson comorbidities⁶.

Statistical analyses

Logistic regression analysis was used to determine the odds ratio (OR) for an association between MM, BCC, SCC and AD. The dependent variable was AD. Multivariable logistic regression was used to adjust analyses for potential confounders including age, gender, race, cerebrovascular disease, peripheral vascular disease and diabetes.

Results

Data for a total of 82,925 patients, age range 60–88 years, with known race, gender, and at least one year of in-clinic follow-up, were extracted and included for analysis. Of 1,147 patients who were diagnosed for MM, 5 were diagnosed with subsequent AD. Of 2,506 who were diagnosed with BCC, 5 had a subsequent AD diagnosis, and of 967 who were diagnosed with SCC, only 1 had a subsequent diagnosis for AD (Table 1). Notably, after adjusting for confounding factors (race, gender, age, cerebrovascular disease, peripheral vascular disease, and diabetes), there was a significant decreased risk for subsequent AD in patients with MM (OR: 0.39; 95% CI: 0.16–0.96; $p=0.042$) and, there was also a significant decreased risk for subsequent AD in patients with BCC (OR: 0.18; 95% CI: 0.08–0.45; $p<0.0001$) as well as for patients with SCC (OR: 0.08; 95% CI: 0.01–0.56; $p=0.013$). Additional adjusted ORs are shown in Table 2.

Discussion

The findings in this study revealed a significantly decreased risk for both a diagnosis of AD in patients with MM, as well as for a diagnosis of AD in those with NMSC. Nevertheless, these findings in MM patients are consistent with several large cohort studies reporting lower rates of AD in patients with various other cancer types^{2,3}. Moreover, the finding of decreased diagnoses of AD in those with NMSC remains consistent with prior studies that demonstrate an inverse association between the two conditions^{4,5}.

Both biological and psychosocial mechanisms have been proposed to account for the inverse association between NMSC and AD. Physical activity has been shown to provide neuroprotective effects, and physically active persons are at lower risk of developing certain types of dementia⁷. However, outdoor physical activity increases exposure to UV radiation, a well-known risk factor for NMSC. White, et al. suggested that NMSC could be a marker for other factors, such as education and socioeconomic status⁴. Lower education may result in decreased reporting of mental illness, whereas higher education may result in more frequent skin checks. As such, lifestyle and psychosocial variables conceivably could account for a relative increase in NMSC and decrease in dementia. Schmidt, et al., additionally noted the role of bias in that NMSC may be reported and/or detected less in

persons with cognitive impairment, whereas physicians may not be as likely to diagnose dementia in cancer patients given the priorities for patient management.⁵

Signaling pathways involved in cell survival have also been postulated to play a role in the relationship between AD and cancer. Pathways that promote survival (decreased regulation, increased proliferation) are a pro-cancer phenotype, whereas pathways with increased cell death may be a pro-AD phenotype (increased neuronal loss).

Polymorphisms in the p53 tumor suppressor gene are one specific example; inactivation results in higher rates of cancer, whereas mice expressing a constitutively activated p53 have been shown to have accelerated aging and shorter lifespan, but also low to non-existent rates of cancer^{8,9}. Another possible mechanism involves Pin1, an enzyme involved in protein folding and cell-cycle control. Pin1 is over-expressed in many tumors, but has low function in the brain tissue of those with AD. Inhibition of Pin1 can cause tumor regression and decreased risk of cancer, but with an increased risk of AD. Conversely, upregulation in mouse models reverses neurodegeneration^{2, 9,10}.

Limitations of this study include inability for verification of diagnostic coding and documentation of diagnosis beyond original medical record data entry. Additionally, MM risk factor data such as that for other malignancies, chronic inflammatory diseases, immunosuppression, as well as co-morbidities and concurrent drugs, were not evaluated in this population. Moreover, although both skin cancer and AD have their peak incidence around 60 years of age, it should be noted that the association between skin cancer and AD has not been well-assessed in the adult population.

Although this study adds to the body of supporting evidence for a decreased risk of AD in those with NMSC, it importantly further expands our knowledge with the finding of a decreased risk for Alzheimer's disease in individuals with melanoma. Further exploration of these relationships may help elucidate complex biological and psychosocial interactions between Alzheimer's disease, melanoma and non-melanoma skin cancer.

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Table 1

Patient characteristics

	MM		No MM		BCC		NO BCC		SCC		NO SCC	
	AD	No AD	AD	No AD	AD	No AD	AD	No AD	AD	No AD	AD	No AD
Total	5	1142	856	80922	5	2501	856	79563	1	966	860	81098
Age in years: (mean $\pm$ SD)	67.4 (3.28)	67.48 (5.64)	71.26 (5.9)	67.46 (5.84)	70.2 (6.53)	67.7 (5.95)	71.25 (5.89)	67.45 (5.83)	71	67.89 (5.75)	71.24 (5.9)	67.46 (5.84)
Sex:												
Males	5	616	334	35071	2	1335	337	34352	1	558	338	35129
Females	0	526	522	45851	3	1166	522	46377	0	408	522	45969
Race:												
White	5	1222	669	66827	5	2474	669	65475	1	954	673	66995
Black-AA	0	13	160	10690	0	4	160	10699	0	6	160	10697
Other	0	4	26	3319	0	19	26	3304	0	2	26	3321
CD	5	267	477	16599	3	555	479	16311	0	707	481	16607
PVD	1	921	187	11928	1	416	187	11704	0	188	188	11932
DM	-	-	1	71	-	-	1	71	1	0	1	70

Abbreviations: MM= malignant melanoma; BCC= basal cell carcinoma; SCC= squamous cell carcinoma; AD=Alzheimer's disease; SD= standard deviation; AA= African-American; CD = Cardiovascular Disease; PVD= Peripheral Vascular Disease; DM= Diabetes Mellitus

Table 2

Odds Ratios (ORs) and 95% CI for skin cancer with Alzheimer's disease (AD) and variables used in the adjusted analyses: age, gender, race, cerebrovascular disease (CD), peripheral vascular disease (PVD) and diabetes mellitus (DM).

ORs (95%CI)	
	AD
Malignant Melanoma	0.39 (0.16–0.97)
Gender	1.22 (1.07–1.41)
Race	1.37 (0.18–10.47)
Age	1.12 (1.11–1.14)
CD	3.68 (3.19–4.25)
PVD	0.74 (0.62–0.88)
DM	0.59 (0.08–4.37)
Basal Cell Carcinoma	0.18 (0.07–0.45)
Gender	1.22 (1.06–1.40)
Race	1.43(0.19–10.91)
Age	1.12 (1.11–1.14)
CD	3.69 (3.19–4.26)
PVD	0.74 (0.62–0.88)
DM	0.59 (0.08–4.33)
Squamous Cell Carcinoma	0.08 (0.01–0.59)
Gender	1.22 (1.06–1.40)
Race	1.4 (0.18–10.64)
Age	1.12 (1.11–1.14)
CD	3.68 (3.19–4.26)
PVD	0.74 (0.62–0.88)
DM	0.60 (0.08–4.38)