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The Effects of Personal and Family History of Cancer on the Development of Dementia in Japanese Americans: The KAME Project

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The Effects of Personal and Family History of Cancer on the Development of Dementia in

Japanese Americans: The KAME Project

by

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A thesis submitted in partial fulfillment
of the requirements for the degree of
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DEDICATION

To my mom, Debra, for her unconditional love.

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ABSTRACT

An increasing number of studies have shown an inverse association between a personal history of cancer (PHC) and dementia/Alzheimer's disease (AD), both in those using dementia/AD as the outcome or cancer as the outcome. This is the first study to examine this potential association in Japanese Americans; and to examine family history of cancer and its association with incident dementia. Also, the association between these two diseases in the parents of participants were analyzed.

The *Kame* Project, conducted from 1992 through 2001 in King County, Washington was a population-based, prospective cohort study of older Japanese Americans. Conversion to incident dementia was observed throughout the follow-up period and diagnosed by standard criteria in a consensus conference.

A PHC did not have a significant association with the development of dementia. Differences between this study and those conducted previously showing an inverse association between cancer and dementia or AD included a lower age of the present cohort, race/ethnicity, focus on all-cause dementia vs. AD and adjustment for the competing risk of death. A family history of cancer was inversely associated with the development of dementia. There were statistically significant trends for a dose-response association between the numbers of affected relatives with cancer and risk for dementia. The findings are most likely explained by an inverse genetic association between cancer and dementia. Older Japanese Americans (the parents) with a history of cancer were nearly 2.5 times less likely to have a history of dementia than those without a cancer history.

CHAPTER ONE:

THE ASSOCIATION BETWEEN A PERSONAL HISTORY OF CANCER AND

INCIDENT DEMENTIA IN JAPANESE AMERICANS: THE *KAME* PROJECT

Introduction

There is a growing body of epidemiologic evidence supporting a protective effect for cancer survivors in the development of AD.[1-3] The three cited, recently conducted meta-analyses all show approximately a one-third reduced risk for the development of AD.

The evidence for an inverse association among all-cause dementia is less robust. A nested-case control study in Sweden showed an inverse association among all cancer types and dementia.[4] However, two prospective studies (the Framingham Heart Study and Einstein Aging Study) reported hazard ratios (HR) below one, but their findings were not statistically significant.[5, 6]

The current study is the first to investigate the relationship between cancer and dementia among Japanese Americans. Our *a priori* hypothesis was that there would be an inverse association between a personal history of cancer (PHC) and incident dementia in this population.

Methods

    Study Population

    The *Kame* Project was a prospective cohort study of older Japanese Americans in King County, Washington from 1992 through 2001. The baseline examination was completed by 1,985 of 3,045 cohort eligible participants (65.2%) who were at least 65 years old (Figure 1.1). The number of prevalent dementia cases was 150, and 190 participants were lost to follow-up. The baseline questionnaire, given by an interviewer and completed by either the participant or their proxy, included a section on personal medical history. This section included information on various diseases, including cancer and stroke. The methods, prevalence and incidence have been described in detail previously.[7, 8] For the current analyses, only participants who were dementia-free at baseline were included. There were insufficient data on history of cancer for 100 participants and on a history of stroke for 5 participants. Furthermore, 22 participants were missing data on history of smoking in the sub-analysis. All participants gave written informed consent, and the study was approved by the University of Washington and University of South Florida Institutional Review Boards.

    Dementia Case Ascertainment

    Participant follow-up continued throughout four biennial waves.[8] Incident dementia cases were assessed through repeated screenings of the Cognitive Abilities Screening Instrument (CASI). When a participant scored 86 of 100 or less on the CASI, they were asked to return with a proxy informant. At that time, the potential case underwent detailed neuropsychological testing and received a workup by study clinicians, including laboratory testing and imaging if deemed necessary. Diagnoses were made by a consensus conference using DSM-IV criteria for

dementia.[9] Each case was also sub-classified as vascular dementia (VaD) or Alzheimer's disease (AD) if they met the criteria.[10, 11] If they did not meet DSM-IV criteria for dementia, they were placed back in the non-demented cohort and followed biennially. The current analysis investigates all-cause dementia as the outcome.

Covariate Ascertainment

The personal history questionnaire asked participants if they had been diagnosed with cancer other than skin cancer. Previous and current cancers were combined into one composite cancer variable. All covariates were dichotomized, History of cancer and history of stroke were coded either yes or no; Education was divided into those with 12 years of education or less and those with more than 12 years of education. Smoking was dichotomized into ever (currently or in the past) versus never smoking. The investigation of comorbidities (including histories of Type II diabetes, coronary heart disease and hypertension, which were not associated with dementia and excluded from the final models)[6, 12-14] and smoking[5, 13, 14] is consistent with previous cancer-dementia studies.

Statistical Analyses

All independent variables analyzed were assessed at baseline. Baseline characteristics (sex, education, history of smoking, history of stroke and survival status) were compared by PHC status using the chi-square test. The Student's t-test was used for baseline age. A p-value below 0.05 was considered statistically significant for both tests. Age was used as the time scale in survival analyses. For non-demented participants, the difference between their baseline age (left-truncation) and their age at loss to follow-up, death or study end (right-censoring) was used

to determine their contribution to person-years. For demented participants, their dementia age was calculated as the midpoint between their previous examination and the one at which their diagnosis occurred.

We used Fine-Gray proportional hazard regression models[15] to obtain hazard ratios and 95% confidence intervals for PHC adjusted for age at baseline, sex, education and history of stroke in model 1, and additionally for history of smoking in model 2. Both models took into account the competing risk of death (survival status). The models used the left-truncation of baseline age. The data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Written informed consent was obtained from all of the *Kame* cohort participants included in the current study. The *Kame* Project was approved by the University of Washington and University of South Florida Institutional Review Boards.

Results

Cancer prevalence among the cohort was 9.9% ($n = 153$), with the remaining 1,387 participants cancer-free at baseline (Table 1.1). There were 172 cases of all-cause incident dementia in the original *Kame* cohort,[8] but due to missing data for history of cancer and history of stroke, there were 145 cases (9.4%) in the current analysis. Of these 145 cases, there were 115 cases of AD and 45 cases of VaD. These subtypes are not mutually exclusive, as an individual can have more than one subtype. The sample consisted of 863 (56.0%) women; 538 (38.8%) of the participants had more than 12 years of education; 44 participants (3.2%) had had a stroke; and 749 (48.6%) were ever smokers. The overall average age at baseline was 71.9 years (SD = 5.5) for participants without a history of cancer and 72.8 years (SD = 5.2) for those with a history of cancer. There were no statistically significant differences between participants with and

without a history of cancer for any of these variables. There was a statistically significant difference (P <0.01) for survival status at the end of the study period.

Table 1.2 shows the univariate analysis and final multivariate models (Model 1 and 2). The univariate hazard ratio for dementia associated with a PHC was 1.07 (95% CI = 0.65-1.76). Covariates that statistically significantly associated with the development of dementia in the crude analysis included education (HR = 0.62, 95% CI = 0.42-0.90) and history of stroke (HR = 2.18, 95% CI = 1.09-4.37). In Model 1, the association between PHC and incident dementia was HR = 1.13 (95% CI = 0.69-1.86). Education (HR = 0.63, 95% CI = 0.42-0.94) and history of stroke (HR = 2.14, 95% CI = 1.05-4.32) were independently associated with dementia. The addition of history of smoking to the second model attenuated the potential association with dementia (HR = 1.06, 95% CI = 0.63-1.79). In this model, education and history of stroke were no longer statistically significant.

Age-specific risks for dementia are shown in Table 1.3. Participants who were age 70 or younger at baseline showed a higher point estimate (HR = 3.01) in Model 1 and (HR = 2.02) in Model 2 than those older than 70 (HR = 0.96) and (HR = 0.94), respectively. However, differences between age-specific HRs were not statistically significant. We also tested whether those who survived to the end of the study had a different adjusted hazard ratio from those who died during the study and did not find significant differences between these groups.

Discussion

The results from this population-based, prospective cohort study did not show that having had cancer was inversely associated with the development of dementia. Although there was a tendency for younger participants to show an increased positive association between PHC and

incident dementia than older participants, neither of the point estimates was statistically

significant and the test for interaction between age group and personal cancer history did not

reveal a significant difference. Furthermore, we did not see a significant difference between the

hazard ratios in those who survived to the end of the study and those who died.

Our findings of no protective effect of personal cancer history on the risk of dementia

need to be interpreted in the context of a substantial number of studies that showed significant

inverse associations between cancer history and dementia or AD risk.[5, 6, 13, 14, 16] Because

dementia and death from cancer represent competing risks, apparent protective associations can

occur if individuals who are destined to develop AD die of cancer before manifesting dementia,

while those without cancer are not selected in the same manner. In the present analyses, we used

Fine-Gray proportional hazards regression to address the issue of competing risk of death.

Previous studies have not addressed the competing risk of death. However, Driver et al.[5]

restricted their sample to individuals who survived to at least 80 and did not see a significant

difference between the HR obtained in that sample and the entire sample that included people

with earlier mortality. We also did not find a significantly different hazard ratio in participants

who were younger versus those who were older at baseline, as might be expected if differential

survival of those with cancer was playing an important role. The point estimate for younger

participants, however, was lower than that for older participants. Other studies also have shown

stronger inverse associations for older participants.[4, 16]

Two significant differences between our cohort and those of studies showing significant

protective effects are age and race. The mean age in the *Kame* Project was 71.9 years. The

Framingham Heart Study cohort[5] had the same minimum age, but mean age at baseline for those

without cancer was 76 years and with cancer, 77 years. The Bronx Aging Study[6] reported a

mean age at baseline of 78.6 for dementia-free participants and 80.7 years for all-cause dementia, with study entry also set at 65. Given that participants in the *Kame* Project were younger, the higher mean age in the other studies' may have led to a greater chance of finding an inverse association between a PHC and incident dementia due to a stronger competing risk of mortality at higher ages.

The increased point estimate observed in the *Kame* Project is similar to a previous study that included African Americans. The Cardiovascular Health Study-Cognition Sub-study of participants from California, North Carolina, Maryland and Pennsylvania separately analyzed data on minorities ($n = 232$), of whom most were African American.[6] In this sub-sample, the HR between cancer and incident VaD and AD was 2.57 (95% CI = 1.27-5.23). Most previous studies have focused on European or European American populations. The results from the present study of Japanese Americans, when taken into account with the results from African Americans, may indicate a difference between ethnic groups, particularly in the US.

Another possible reason that we did not observe an inverse association is that we did not ascertain the presence of skin cancer. The questionnaire asked about the presence of cancer, excluding skin cancer. Skin cancer is often subdivided into melanoma and non-melanoma skin cancer (NMSC). NMSC is the most common form of cancer, of which the most commonly occurring types are basal-cell carcinoma and squamous-cell carcinoma.[17] Some of the previous studies on cancer and incident dementia included or excluded melanoma and/or NMSCs. The Einstein Aging Study in the Bronx, reported a null association between all cancers and any dementia (HR = 0.85, 95% CI = 0.56-1.29), while a separate model consisting exclusively of NMSC cancers yielded a more inverse result that was also not statistically significant (HR = 0.68, 95% CI = 0.35-1.31).[6] The Swedish nested-case control study of registry data ($N =$

167,080; 19,756 cases) included multiple types of cancers, and treated melanoma and NMSCs separately.[4] Their findings for all cancers (HR = 0.60, 95% CI = 0.52-0.69) fell in between that of melanoma (HR = 0.44, 95% CI = 0.20-0.97) and NMSCs (HR = 0.77, 95% CI = 0.58-1.04). We also relied on self-reporting of cancers which is consistent with previous epidemiologic studies investigating cancer and incident dementia and AD.[6, 18, 19]

A final possible limitation of our findings was the inclusion of vascular and Alzheimer cases in the outcome of all-cause dementia. Other studies have reported stronger inverse associations in Alzheimer's versus other types of dementia.[5, 6, 13] However, given that two-thirds of cases carried a diagnosis of AD, the inclusion of vascular dementia cases is unlikely to have completely eliminated an inverse association.

An additional strength of our study was the prospective and uniform identification of dementia cases. Some previous studies relied on the use of clinical or registry data.[4, 16] The clinical diagnosis of dementia and its subtypes was made by a consensus committee consisting of a neurologist, geriatrician, internist, neuropsychologist and epidemiologist using standardized research criteria.[20]

Table 1.1. Baseline statistics by cancer status.

N = 1,540	No Cancer (n = 1,387)		Cancer (n = 153)		
	No. or mean	% or (SD)	No. or mean	% or (SD)	P
Age at baseline, y	71.9	(5.5)	72.8	(5.2)	0.45
Sex					0.70
Male	612	44.1	65	42.5	
Female	775	55.9	88	57.5	
Education					0.92
≤12 years	849	61.2	93	60.8	
>12 years	538	38.8	60	39.2	
Smoking					0.39
Never	688	50.3	81	54.0	
Ever	680	49.7	69	46.0	
Stroke					0.20
No	1,343	96.8	151	98.7	
Yes	44	3.2	2	1.3	
Survival status					<0.01
Survivors	1,183	85.3	117	76.5	
Nonsurvivors	204	14.7	36	23.5	

Table 1.2. Results of Fine-Gray Cox proportional hazards models testing unadjusted covariates with dementia outcome and testing the final model.

N = 1,540 Predictor	No dementia (n)	Dementia diagnosis (n)	Univariate HR (95% CI)	Model 1* HR (95% CI)	Model 2* HR (95% CI)
Cancer				*N = 1,540*	*N = 1,518*
No	1,260	127	1.00	1.00	1.00
Yes	135	18	1.07 (0.65-1.76)	1.13 (0.69-1.86)	1.06 (0.63-1.79)
Sex					
Male	620	57	1.00	1.00	1.00
Female	775	88	1.17 (0.84-1.64)	1.09 (0.77-1.55)	1.10 (0.70-1.73)
Education					
≤12 years	833	109	1.00	1.00	1.00
>12 years	562	36	0.62 (0.42-0.90)†	0.63 (0.42-0.94)†	0.67 (0.45-1.01)
Smoking					
Never	697	72	1.00	***	1.00
Ever	687	62	1.06 (0.76-1.49)	***	1.12 (0.73-1.73)
Stroke					
No	1,359	135	1.00	1.00	1.00
Yes	36	10	2.18 (1.09-4.37)†	2.14 (1.05-4.32)†	2.06 (0.99-4.30)

*Model 1 adjusted for age at baseline, cancer, sex, education and stroke. Model 2 additionally controls for smoking. †P < 0.05

Table 1.3. Age-specific risks by baseline age group.

	Model 1		Model 2
n	HR (95% CI)	n	HR (95% CI)
655	3.01 (0.80-11.3)	652	2.02 (0.41-10.1)
885	0.96 (0.57-1.64)	866	0.94 (0.54-1.64)
1,518	1.13 (0.69-1.86)	1,518	1.06 (0.63-1.79)

Abbreviations: HR = hazard ratio; CI = confidence interval
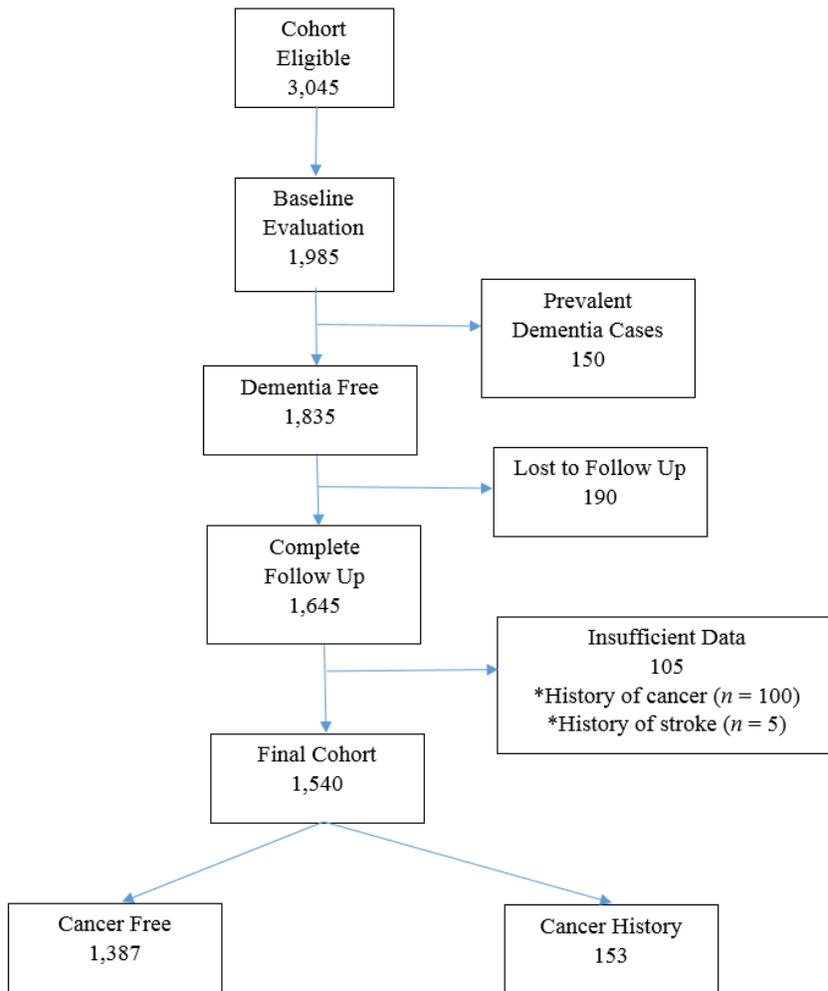
Figure 1.1. Participant flow chart.

CHAPTER TWO:

FAMILY HISTORY OF CANCER IS INVERSELY ASSOCIATED WITH DEMENTIA.

THE *KAME* PROJECT

Introduction

A personal history of cancer has been shown in some studies to be inversely associated with incident dementia[4-6, 13] as well as Alzheimer's disease (AD).[1-3] Because people with a personal history of cancer may have a higher risk of dying before manifesting dementia than those without such a history, inverse associations could be the result of survival bias. Furthermore, individuals with impending dementia may be less likely to have their cancer diagnosed promptly.[21] If the association is real and is genetically-determined, individuals with dementia would be less likely to have a family history of cancer in close blood relatives. To address this issue, we assessed whether a family history of cancer is associated with risk of incident dementia. To our knowledge, this is the first time this question has been addressed.

Methods

Study Population

Participants were from the *Kame* Project, a population-based prospective cohort study of Japanese Americans aged 65 and older residing in King County, Washington between 1992 and the end of 2001.[7, 8] The baseline questionnaire was completed by 1,835 dementia-free

participants. Participants were asked to complete a family tree diagram of first-degree relatives before arriving for their first visit at the study site. Each diagram was transposed by the interviewer into the questionnaire. Data were collected on each family member concerning whether or not each family member had cancer or experienced memory problems. Of those who completed the baseline examination, 190 (10.4%) were lost to follow-up and 160 (8.7%) were excluded from the analysis due to insufficient data (100 for personal history of cancer, 55 for family history of cancer and 5 for personal history of stroke) (Figure 2.1). The sample size for the current analysis was 1,481.

Each family member from the questionnaire was uniquely identified. Relatives for whom data on family history of cancer and dementia were collected included parents, full- and half-siblings. Children were excluded from the analysis as few had reached high risk ages for cancer and dementia.

Written informed consent was obtained from all of the *Kame* cohort participants included in the current study. The *Kame* Project was approved by the University of Washington and University of South Florida Institutional Review Boards.

Dementia Case Ascertainment

Participant follow-up continued throughout four biennial waves. Methods for diagnosis are detailed elsewhere.[7, 8] Briefly, incident cases were assessed through repeated screenings of the Cognitive Abilities Screening Instrument (CASI). When a participant scored 86 of 100 or less on the CASI, they were asked to return for a second examination with a proxy informant. At this time, the potential case underwent detailed neuropsychological testing and was worked up by a study clinician. A consensus diagnosis was later performed. If the potential case met DSM-

IV criteria for dementia, they became an incident dementia case.[9] Each case was also sub-classified Alzheimer's disease,[11] vascular dementia (VaD)[10] or other dementias. If a potential case did not meet DSM-IV criteria for dementia, they were placed back in the non-demented cohort and followed biennially. This study investigated all-cause dementia as the outcome.

Cancer Case Ascertainment

The personal history questionnaire asked *Kame* participants if they had been diagnosed with cancer, with the exception of skin cancer. Previous and prevalent cancers were combined into one composite cancer variable. *Kame* Project participants were asked for each first degree relative, whether or not they had been diagnosed with cancer, leukemia and Hodgkin's disease. These three questions were combined into one derived variable for analyses. The family cancer history variable was classified three different ways: 1) 0 vs. ≥1; 2) 0 vs. 1 vs. ≥2; 3) 0 vs. 1 vs. 2 vs. ≥3.

Covariate Ascertainment

The baseline questionnaire collected data on personal characteristics, including family size, sex, age (years), education (years), personal history of smoking and personal health history of stroke. Age at baseline and family size (excluding the participant) were treated as continuous variables. Education was dichotomized into 12 years or less and more than 12 years. Personal history of smoking was defined as ever (current or past) or never. A personal history of stroke was diagnosed by a physician were endorsed as Yes or No.

Statistical Analyses

Baseline variables were compared by family history of cancer status (yes or no). Comparisons used the chi-square test for dichotomous variables and the Student's t-test for continuous variables. These same covariates were analyzed separately to determine their crude association with the outcome using Fine-Gray proportional hazard regressions.

All Fine-Gray regression models used age as the time scale.[15] For non-demented participants, the difference between their baseline age (left-truncation) and their age at loss to follow-up, death or study end (right-censoring) was used to determine their person-years contribution. For demented participants, their dementia age was calculated as the midpoint between their previous examination and the one at which their diagnosis occurred. Univariate and multivariate statistics presented in the tables include the hazard ratio (HR) point estimate and 95% confidence interval. For disease status, the absence of the condition is the reference category. Men formed the reference group for sex and 12 years or less for education. Covariates in the final models included family history of cancer, age, sex, education, family size, personal history of cancer, personal history of smoking and personal history of stroke. A separate final model was run for each classification of family history of cancer and a P value for trend was obtained. The data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

There were 680 participants with no family history of cancer versus 805 participants with at least one affected FDR (Table 2.1). Women represented a majority of the sample, with a significant difference (P = 0.03) between the cancer groups in chi-square testing. Participants with a family history of cancer had a larger family size (mean = 6.67, SD = 2.36) versus those

without, mean = 6.02, SD = 2.14, P = <0.01); women represented a higher proportion among this group (P <0.05).

Of participants with a family history of cancer, 7.1% developed dementia versus 10.3% without a family history of cancer (Table 2.2). Demented and non-demented participants differed by family history of cancer, education and personal history of stroke (P <0.05) in Model 1. The first model only dichotomized (two classification levels) family history of cancer.

Table 2.3 shows the results of the final models for risk of all-cause dementia for each family history of cancer classification. In Model 1, compared to participants without a family history of cancer, those with at least one affected first degree relative had a reduced likelihood of developing dementia (HR = 0.63, 95% CI = 0.44-0.91, P = 0.01). Participants with two or more affected first degree relatives in Model 2 also had a reduced likelihood for dementia (HR = 0.54, 95% CI = 0.31-0.91) (P trend=0.04). Model 3 also showed a significant trend toward reduced dementia risk with increasing numbers of first-degree relatives with cancer (P trend = 0.04), particularly among participants with three or more affected first degree relatives (HR = 0.28, 95% CI = 0.09-0.83).

Across all multivariate models, the inverse association with education weakened slightly as more family history of cancer classifications were added. Family history of dementia, personal history of coronary heart disease and hypertension, family history of stroke, Type II diabetes, coronary heart disease and hypertension did not improve the fit of the model. We conducted an additional analysis using data on Apolipoprotein (APOE), the major known polymorphism associated with increased risk for Alzheimer's disease, which was available for a majority of participants. Adjusting for APOE, there was no change in the model, indicating that it was neither a confounder nor an effect modifier. Therefore, it was excluded from the final model.

Discussion

We found that a family history of cancer reduced the risk for incident dementia by about one-third among Japanese Americans age 65 and over. There was also a significant trend for a dose-response effect when family history of cancer was analyzed by the number of affected first-degree relatives. The statistical significance of the trend was strongest when the family history of cancer variable was dichotomized, weakening slightly as the study's ability to detect differences due to lower power was limited. To our knowledge, this is the first evidence that family history of cancer is inversely associated with an individual's risk of developing dementia.

Previous studies addressing *personal* history of cancer and all-cause incident dementia found inverse associations.[4-6, 12, 13, 16, 19, 22] Published meta-analyses based on these studies showed that personal history of cancer was associated with a marked reduction in risk of AD.[2, 3, 23] In a second paper and in the present analyses, we found that personal history of cancer was not associated with dementia risk.

No definitive biologic mechanism has been identified in the cancer-dementia association. Recent research has postulated that cell cycle deregulation may cause cells to exhibit a preference for either cell proliferation or cell degeneration (apoptosis).[24-27] The three genetic factors garnering the most intensive research interest are the peptidyl-prolyl cis-trans isomerase nima-interacting 1 (PIN1) tumor suppressor, the tumor protein p53 (p53) enzyme and the wingless-type murine-mammary tumor virus integration site (Wnt) signaling pathway.[24-27] The up-regulation/over-expression of PIN1, the up-regulation of Wnt and/or the down-regulation of p53 can cause cell proliferation and lead to cancer, with the reverse being true for cell apoptosis and AD.[25-28] All are associated with τ protein and Aβ plaques. Stressors cause Aβ accumulation, leading to the activation of p53, followed by τP aggregation and finally neuronal death.[27, 28] PIN1

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is involved in τP dephosphorylation and Aβ accumulation.[28] The under-expression of PIN1 sets off two progressions: the overproduction of Aβ-42 causes the accumulation of plaques leading to the development of AD; and τP aggregation creates NFT leading to the development of AD.[29] The inactivation of the Wnt pathway causes Aβ induced neurotoxicity.[28] These cell cycle alterations leading to AD pathogenesis or oncogenesis are indicative of shared genetic pathways between cancer and dementia/AD.

Both cancer and AD pathogenesis can be modified by epigenetic mechanisms such as aging, environmental toxins, diet and exercise.[30, 31] All of these are known to be risk factors associated with cancer and dementia. Epigenetic mechanisms affect changes in the cell's biology, interfering with the normal cell cycle.[27] Additionally, both DNA damage and oxidative stress are biological factors inherent to aging, and thus factors relevant to the development of cancer and dementia.[25] For example, oxidative stress from the aging process causes a down-regulation of PIN1 leading to the buildup of AD pathology.[29]

It is of interest that family history of cancer and not personal history of cancer was associated inversely with dementia risk in this study. Associations of personal history of cancer with genes known to regulate both oncogenesis and apoptosis may be weak in comparison with specific oncogenes with a more direct connection with the cancer but without an effect on apoptosis. On the other hand, specific genes know to regulate both oncogenesis and apoptosis, such as PIN1, p53 and GSK-3, may have inverse effects in AD and cancer. Polymorphisms for each of these genes have been shown to be related to both cancer and AD.

Family history of a condition can be a protective or a risk factor for a disease, and has important public health significance.[32] It is possible that our results reflect a genetic biomarker or biologic mechanism that confers protection against dementia for people from a cancer-prone

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family. The up- or down-regulation of PIN1, p53 and Wnt cause an individual's cells to begin oncogenesis (cancer) or apoptosis (AD). All three play a role in the accumulation of beta-amyloid, the aggregation of tau protein and neuronal death.[27, 28] Both disease pathologies are modifiable by epigenetic mechanisms, including those integral to the aging process.[29, 33, 34]

The current study has important limitations. The derived cancer variable for FDRs included all forms of cancer while the personal cancer history excluded skin cancers. One previous study found a statistically significant inverse association between melanoma and incident dementia (HR = 0.44, 95% CI = 0.20-0.97)[4] while previous studies of non-melanoma skin cancers and incident dementia found insignificant results.[4, 6] However, the incidence of skin cancer among Japanese and Japanese Americans is lower than that of Americans.[35] This study relied on the self-report of cancer, but previous epidemiologic studies investigating cancer and incident dementia and AD also did.[6, 18, 19] We adjusted for family size to account for the tendency of larger families to have more members who develop cancer, but did not adjust for age of the relatives at baseline or age of death of the parents, both of which could be related to incidence of cancer and AD.

The greatest contribution of this research is that our study marks the first time that family history of cancer has been investigated in relation to incident dementia. Family history of disease is indicative of shared genetic, environmental or behavioral risk factors, and has important implications for public health research. Family history can be considered as a surrogate for a potential biomarker or set of biomarkers.

Table 2.1. Baseline comparison between family history of cancer groups, the Kame project.

Baseline Statistics (N = 1,485)	No Family History of Cancer (n = 680)	Family History of Cancer (n = 805)	P-Value
Age at Baseline in years (mean [SD])	71.98 ± 5.25	71.47 ± 4.87	0.06
Sex (% female)	52.5	58.1	0.03
Percent with >12 years of education	42.0	37.7	0.09
Family Size (mean [SD])*	6.02 ± 2.14	6.67 ± 2.36	<0.01
Percent of ever smokers	49.9	48.9	0.70
Percent with history of cancer	9.1	10.6	0.35
Percent with history of stroke	3.2	2.5	0.38
Percent of survivors	16.5	13.7	0.13

*Family size excludes the participant

Table 2.2. Univariate & multivariate hazard ratios (HR) and 95% confidence intervals for covariates in Model 1.

N = 1,485	n	Dementia (%*)	Univariate N = 1,485	Multivariate N = 1,470
Family history of cancer				
0	680	71 (10.4)	1 (referent)	1 (referent)
≥1	805	57 (7.1)	0.68 (0.48-0.97)	0.63 (0.44-0.91)
Sex				
Male	660	53 (8.0)	1 (referent)	1 (referent)
Female	825	75 (9.1)	1.11 (0.78-1.58)	1.11 (0.71-1.75)
Education				
≤12 years	897	95 (10.6)	1 (referent)	1 (referent)
>12 years	588	33 (5.6)	0.60 (0.40-0.89)	0.68 (0.44-1.04)
Family size	1,485	128 (8.6)	1.15 (1.07-1.23)	1.17 (1.09-1.25)
Personal history of smoking				
Never	746	65 (8.7)	1 (referent)	1 (referent)
Ever	728	59 (8.1)	1.11 (0.78-1.58)	1.20 (0.78-1.85)
Personal history of cancer				
No	1,338	111 (8.3)	1 (referent)	1 (referent)
Yes	147	17 (11.6)	1.14 (0.69-1.90)	1.13 (0.67-1.89)
Personal history of stroke				
No	1,443	120 (8.3)	1 (referent)	1 (referent)
Yes	42	8 (19.1)	2.28 (1.08-4.83)	2.45 (1.12-5.36)

* Row percentages

Table 2.3. Hazard ratios and 95% confidence intervals for family history of cancer using 3 different classifications.

Model 1* (N = 1,470)		Model 2* (N = 1,470)		Model 3* (N = 1,470)	
Number	*P = 0.01*	Number	*Ptrend = 0.04*	Number	*Ptrend = 0.04*
0	1 (referent)	0	1 (referent)	0	1 (referent)
≥1	0.63 (0.44-0.91)	1	0.69 (0.46-1.04)	1	0.69 (0.46-1.04)
		≥2	0.54 (0.31-0.91)	2	0.64 (0.36-1.13)
				≥3	0.28 (0.09-0.83)

*Adjusted for age, death, sex, education, family size, personal cancer history, personal smoking history and personal stroke history
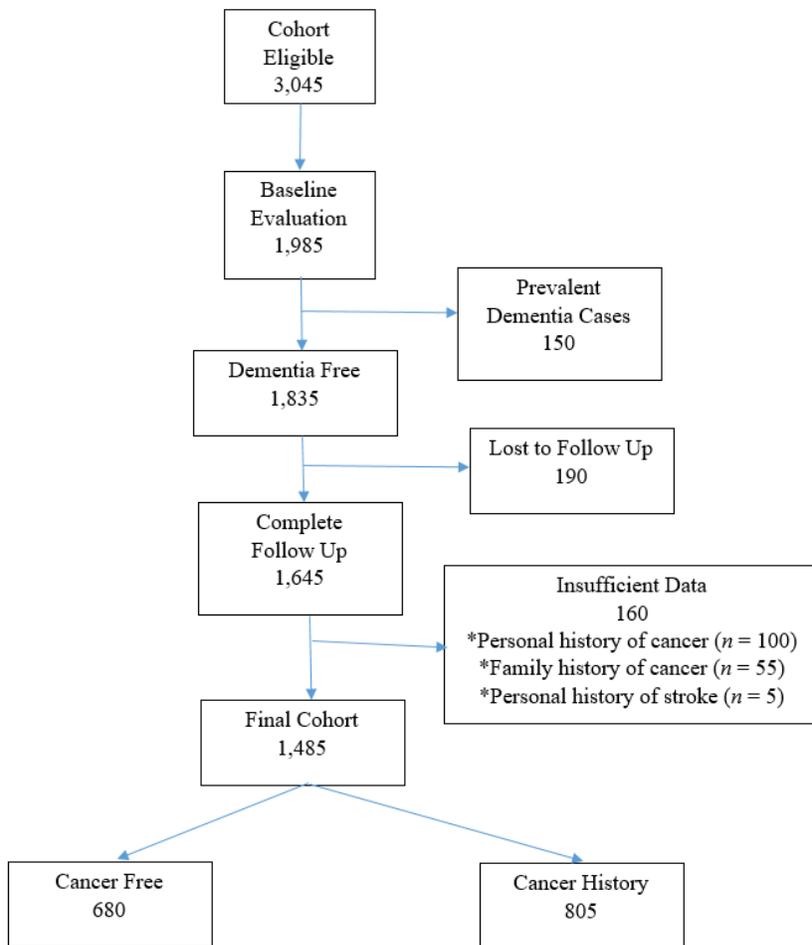

Figure 2.1. Participant flow chart.

CHAPTER THREE:

ASSOCIATION IN PARENTS BETWEEN TWO DEADLY DISEASES: CANCER AND DEMENTIA. THE *KAME* PROJECT

Introduction

Both cancer and dementia are leading killers of the elderly. A growing number of epidemiologic studies demonstrate an inverse association between these two conditions. Cancer, a disease of cell proliferation, and dementia, a disease of cell degeneration, appear to share common biological mechanisms.

The earliest reported results exploring the relationship between cancer and incident dementia/AD was carried out in Japan.[22] This prospective study of 2,222 Hiroshima and Nagasaki atomic bomb survivors, a methodologically standardized sister study to the *Kame* Project, for which data are analyzed here, sought to determine risk factors for dementia and its subtypes. The investigators reported an unadjusted odds ratio (OR) for AD only (OR = 0.3, 95% CI = 0.05-0.98), presenting cancer as a protective factor for AD. However, they did not control for any of the other variables they reported on (e.g., sex and age).

There have been several other studies investigating cancer and incident dementia and/or AD. One prospective cohort study drawing on data from the Washington University Alzheimer's Disease Research Center and another in the Bronx, New York both reported an inverse association between cancer history and incident dementia in their full models, but neither achieved statistical significance.[6, 19] A Swedish nested case-control study reported similar

results.[4] There have been a similar number of studies examining the association between dementia/AD history and incident cancer. However, in comparison with the incident dementia studies, these achieved statistical significance. A nested-case control study within the Framingham Heart Study matched on sex and age reported an inverse relationship, excluding non-melanoma skin cancers.[5] A Taiwanese retrospective cohort study reported a similar inverse association for all cancers.[36]

In the *Kame* Project, another population of Japanese, living in King County, WA was examined with the hypothesis that an inverse association exists between histories of cancer and dementia in the parents of participants. The associations between a personal history of cancer in the participant with incident dementia, and that between a family history of cancer in relation to incident dementia, are presented elsewhere.

Methods

Study Design

The *Kame* Project was a prospective cohort study of Japanese Americans over age 65 in King County, Washington from 1992 through 2001. Eighteen-hundred and thirty-five dementia-free participants, or probands, completed the baseline questionnaire. Before coming to the study site, participants were asked to fill out a family tree of first-degree relatives. This was transposed by the interviewer into the questionnaire, where each family member was indicated separately. Cases of dementia discovered at the prevalence phase of the study were excluded from this analysis.[7] Data were gathered for each family member from the non-demented participant on whether or not the family member experienced memory problems or had cancer. Further

information on the *Kame* Project's prevalence and incidence phases have been published in detail elsewhere.[7, 8]

Study Population

This is a cross-sectional analysis examining the parents of *Kame* participants who were reported to have cancer and dementia histories. Parents with missing information on cancer status and/or dementia status ($n = 155$) and age at death ($n = 436$) were excluded from analyses. Further excluded were those who did not reach the age of 65 ($n = 747$), which is when late-onset AD/dementia begins. The final sample size included 2,332 parents.

Cancer Case Ascertainment

The family history question on cancer subdivided the disease into three categories: cancer, leukemia and Hodgkin's disease. These three questions were combined into one derived cancer variable for analysis. Previous cancer-dementia studies also relied on cancer self-report.[6, 18, 19]

Dementia Case Ascertainment

Kame participants who indicated that a parent had a memory problem were asked to complete a separate memory grid. Specific questions were asked in order for the investigators to try to derive DSM criteria from their responses. We used four of these questions to determine if each parent was likely to have developed dementia: 1) whether the memory problem lasted for 6 months or longer; 2) if the symptoms began gradually or suddenly; 3) how it progressed (give major response categories here); and 4) whether the symptoms interfered with work or social

functions. Three raters (ALS, ARB, JAM) independently assessed patterns of the four questions to determine if each parent had dementia. Agreement to divergent coding decisions were adjudicated by the three raters.

All *Kame* cohort participants from whom the current study's sample is drawn gave written informed consent. The *Kame* Project was approved by the University of Washington and University of South Florida Institutional Review Boards.

Statistical Analyses

Sex and cancer status were compared between those parents judged to have had dementia and those judged not to have had dementia. using the chi-square test. Student's t-test was used to assess the difference in age at death between these groups. A p-value below 0.05 was considered statistically significant for both tests. Logistic regression analyses were performed to assess crude associations of cancer, sex and age at death with dementia status. A multivariate logistic model with dementia status in the parent as the dependent variable examined cancer status, with sex and age at death as covariates in the model. Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

There were 1,213 (52.0%) mothers and 1,119 (48.0%) fathers in the study ($N = 2,332$) (Table 3.1). Fathers were more likely to be reported to have had a history of cancer, 53.4% versus 46.6% for mothers (P = 0.0001). The mean age at death was 82.5 (84.3 for mothers and 80.6 for fathers). The mean age at death was higher for those who did not have a reported history

of cancer (83.2 versus 79.8) (P = 0.02). The cancer prevalence for the entire sample was 459 (19.7%) and the dementia prevalence was 251 (10.8%).

Table 3.2 shows the univariate and multivariate statistics for the association between history of cancer and history of dementia. When the variables were examined one at a time, we found a highly statistically significant inverse association between cancer in the parents and dementia in the parents. This association became somewhat weaker, but remained highly statistically significant (OR = 0.41, 95% CI = 0.25-0.66) when the model was adjusted for sex and age at death of the parents.

Discussion

Our results confirmed our *a priori* hypothesis that there is an inverse association between cancer status and dementia status. Our findings are consistent with the preexisting literature on dementia and cancer. Notably, the crude OR of 0.32 is almost identical to the 0.3 reported by Yamada et al.[22] The main difference between that study and this one is that our confidence interval is much narrower. More importantly, the multivariate results revealed that participants with a history of cancer were 2.44 times less likely to have a history of dementia. The results were consistent when stratified by sex, although the association was stronger among men than women (P value significant, data not shown).

The biological mechanism(s) for the cancer-dementia association have not been definitively identified. There appears to be changes in the cell cycle that cause cells to show a preference for either cell proliferation or cell death.[24-27] The three genetic factors garnering the most intensive research interest are the PIN1 tumor suppressor, the tumor protein p53 enzyme and genes in the Wnt signaling pathway.[24-27] Changes in the up- or down-regulation of PIN1, p53

and/or Wnt lead to differing consequences, including cell proliferation (cancer) or cell apoptosis (AD).[25-28] These potential modifiers are associated with phosphorylated tau protein and Aβ plaques. Accumulation of Aβ and phophorylated tau aggregation eventually lead to neuronal death.[27, 28] Both cancer and AD pathogenesis can be modified by epigenetic mechanisms such as aging, environmental toxins, diet and exercise.[30, 31] All of these are known to be risk factors associated with cancer and dementia.

The strengths of our study include a large sample size, reporting of family history of cancer and dementia by initially non-demented participants and a representative population of Japanese Americans living in King County, WA.[7, 8] In our methodologically-standardized sister study in Japan,[22] no adjustments were made for potential confounders. In our study, age at death and sex were adjusted in the multivariate models. The use of a memory grid in the *Kame* study was an additional strength, since it allowed us to get closer to a definition of dementia by DSM criteria. This study also had a more balanced proportion of parental sex than the previous study.

However, the study has several limitations. Because there was a statistically significant difference between the age at which those with a history of cancer died (those with a parental history of cancer died younger), it is possible that there is differential survival based on age at death. This has been previously suggested in the literature.[13, 37] Also, parents who became afflicted with cancer in previous decades would have had more limited treatment options. If this bias were present, we would expect that the inverse association we observed may be over-estimated. However, there only appears to have been a small effect from such potential survival bias, as we controlled for age at death. Therefore, survival bias likely was not present to a great extent. Reporting bias is a limitation arising from the potential difficulty of *Kame* probands to accurately recall their parents' medical history. One possibility is that probands may be more

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concerned with their parents dying from cancer, such that they under-recalled the presence of memory complaints. This would weaken the observed association if this were the case. A further limitation is the absence of a temporal sequence, arising from the inability to differentiate which disease occurred first in this cross-sectional analysis.

An additional explanation for our findings could be the presence of lead time bias. All participants in the *Kame* cohort were at least 65 years of age at baseline, and an incipient *Kame* dementia patient may have early signs of memory loss that are not diagnosable but still have an impact on their reporting of their family's medical history. We performed a stratified analysis of *Kame* probands to investigate this possibility. The probands were stratified by incident dementia status. No differences were observed between these groups (data not shown).

This study's results lend some of the strongest evidence for an inverse association between cancer and dementia. Epidemiologic studies in the United States, Sweden, Taiwan and Japan show consistent findings for this association. Our study, being focused on older Japanese Americans, suggests that the association holds for other ethnic groups in the United States. All studies to date have utilized data from pre-existing studies, which were not designed to assess the association between family history of cancer and dementia. Future longitudinal studies should specifically address the competing risks of these two diseases, and how their consequences affect the elderly. Environmental and lifestyle changes that currently increase risk for negative health outcomes through gene-environment interactions will need to be implemented on a community public health level, as well as with each individual in order to help prevent these increasingly prevalent and interrelated diseases.

Table 3.1. Baseline statistics of the Kame project parents.

Kame Parents BASELINE STATISTICS N = 2,332	n (%*)	No History of Cancer (n = 1,873) n (%*)	History of Cancer (n = 459) n (%*)	P-Value
Sex				**0.0001**
Male	1,119 (48.0)	874 (46.7)	245 (53.4)	
Female	1,213 (52.0)	999 (53.3)	214 (46.6)	
Age at death†				**0.02**
	82.5 ± 9.2	83.2 ± 9.2	79.8 ± 8.5	

* Column percentages

† The statistics for age: mean ± standard deviation

Table 3.2. Univariate & multivariate odds ratios (OR) and 95% confidence intervals for covariates in the model.

Kame Parents N = 2,332	n (%*)	Dementia (%*)	Univariate Statistics OR (95% CI)	Multivariate Model OR (95% CI)
Cancer				
No	1,873	231 (12.3)	1 (referent)	1 (referent)
Yes	459	20 (4.4)	**0.32 (0.20-0.52)**	**0.41 (0.25-0.66)**
Sex				
Male	1,119	66 (5.9)	1 (referent)	1 (referent)
Female	1,213	185 (15.3)	**2.87 (2.14-3.85)**	**2.34 (1.73-3.16)**
Age at death				
			1.07 (1.05-1.09)	**1.05 (1.04-1.07)**

* Row percentages

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