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A randomized controlled Alzheimer's disease prevention trial's evolution into an exposure trial: the PREADVISE trial

Richard J. Kryscio[1,2], **Erin L. Abner**[1], **Frederick A. Schmitt**[3,4,5], **Phyllis J. Goodman**[6], **Marta Mendiondo**[1,2], **Allison Caban-Holt**[3], **Brandon C. Dennis**[4], **Eric A. Klein**[7], and **John J. Crowley**[6] **for the SELECT Investigators**

[1]Sanders-Brown Center on Aging, and Department of Biostatistics, University of Kentucky, Lexington KY, USA

[2]Department of Statistics, University of Kentucky, Lexington KY, USA

[3]Department of Behavioral Science, University of Kentucky, Lexington KY, USA

[4]Department of Neurology, University of Kentucky, Lexington KY, USA

[5]Department of Psychiatry & Psychology, University of Kentucky, Lexington KY, USA

[6]Cancer Research and Biostatistics/SWOG Statistical Center, Seattle WA, USA

[7]Cleveland Clinic, Cleveland, OH, USA

Abstract

Objectives—To summarize the ongoing Prevention of Alzheimer's Disease (AD) by Vitamin E and Selenium (PREADViSE) trial as a cooperative study to SELECT (a large prostate cancer prevention trial) and to present the blinded results of the first year as an exposure study.

Design—PREADViSE was designed as a double blind randomized controlled trial (RCT).

Setting—SELECT terminated after 5.5 years of accrual and follow-up due to a futility analysis. Both trials then converted into an exposure study.

Participants—In the randomized component PREADViSE enrolled 7,547 men age 62 or older (60 if African American). Once the trial terminated 4,246 of these men volunteered for the exposure study. Demographics were similar for both groups with exposure volunteers having baseline mean age 67.3 ± 5.2 years, 15.3 ± 2.4 years of education, 9.8% African Americans, and 22% reporting a family history of dementia.

Intervention—In the RCT men were randomly assigned to either daily doses of 400 IU of vitamin E or placebo and/or 200 μg of selenium or placebo using a 2×2 factorial structure.

Measurements—In the RCT, participants completed the brief Memory Impairment Screen (MIS) and if they failed, underwent a longer screening (based on an expanded Consortium to Establish a Registry in AD [CERAD] battery). CERAD failure resulted in visits to their clinician for medical examination with records of these examinations forwarded to the PREADViSE center for further review. In the exposure study, men are contacted by telephone and complete the MIS-T screen. If they fail the MIS-T a Modified Telephone Interview of Cognitive Status (TICS-M) exam is given. A failed TICS-M exam also leads to a visit to their clinician for an in depth examination and forwarding of records for a centralized consensus diagnosis by expert clinicians. A subgroup of the men who pass the MIS-T also take the TICS-M exam for validation purposes.

Results—While this ancillary trail was open to all 427 SELECT clinical sites, only 34% chose to participate in PREADViSE. Continual staff turnover at the sites presented challenges when training persons unfamiliar with cognitive testing procedures to conduct the memory screens. In

the RCT few participants (1.6%) failed the MIS screen and among those who passed this screen a significant practice effect was encountered.

In the exposure study 3,581 men were reached by phone in year 1, 15.7% could not be reached after 5 calls, and of those contacted 6.0% refused the screen even after consenting to the procedures at their clinical site. Most notable is that the failure rate for the MIS-T increased fourfold to 7.2%. Of the 257 men who took the TICS-M, 84% failed and were asked to contact their physicians for a more detailed memory assessment and approximately half of these had some form of dementia or cognitive impairment. Several of these dementia cases are not AD.

Conclusion—Partnering with SELECT led to an AD prevention trial conducted at a very reasonable cost by taking advantage of the experience and efficient clinical trial management found in a cancer cooperative group (SWOG). Once unblinded, the RCT and exposure study data have the potential to yield new information on long term exposure to antioxidant supplements under controlled conditions.

Keywords

Alzheimer's disease; prevention; telephone screening; cognitive assessments; case ascertainment

Introduction

There is a need to develop prevention strategies for Alzheimer's disease (AD) and other forms of dementia because treatment trials for these diseases have only provided modest symptomatic success and because there is an anticipated rise in the incidence of these diseases over the next few decades primarily due to the aging populations worldwide[1]. Several prevention trials have been recently completed, all with equally null/inconclusive results[2–6]. The purpose of this manuscript is to describe how a trial investigating the use of vitamins to prevent dementia had to be prematurely terminated for futility unrelated to cognition and converted into an exposure study. The term "exposure" refers to a follow-up on the cognitive status of individuals who have been exposed in blinded fashion to nutritional supplements or placebo for an average of 5 years.

The rationale for the Prevention of Alzheimer's Disease (AD) by Vitamin E and Selenium (PREADViSE) trial is based on numerous animal models, human autopsy studies, several large observational studies, and at least one human AD clinical trial of vitamin E that investigating the role of antioxidants in the disease process[7–9]. Oxidative stress has been shown to be important in the pathophysiology of neuron degeneration and death in AD[10,11].

The PREADViSE trial was leveraged as a cooperative study of a large multi-center prostate cancer prevention trial for healthy older men (SELECT) directed by SWOG, a federally funded cancer research cooperative group. This 2×2 factorial randomized clinical trial (RCT) was terminated after 5.5 years of exposure due to a futility analysis (prostate cancer outcome)[12]. It is now an exposure study of approximately half of its men who volunteered for centralized follow-up. Recent data based on 7–10 years of follow-up showed that men randomized in the Vitamin E only arm had a significant 17% increase in the incidence of prostate cancer compared to the placebo arm. However, men randomized in the selenium only or selenium plus vitamin E arms did not incur significant increases in prostate cancer[13].

The specific aims of PREADViSE were to determine the effect of selenium and vitamin E used in combination or alone on the incidence of Alzheimer's disease (AD) primarily and on the incidence of other neurodegenerative diseases secondarily. A third aim was to investigate the features of normal cognitive aging in a validation subsample. This manuscript describes PREADViSE in the context of an AD prevention trial as an ancillary

study to a cancer prevention trial and presents the blinded results of the first year of its exposure study.

Materials and Methods

SELECT enrolled 35,533 men in 34 months who were aged 55 or older (50 if African American) at 427 sites throughout the United States, Canada, and Puerto Rico. Men were randomly assigned to either 1 capsule containing 400 IU of vitamin E or placebo and 1 capsule containing 200 μg of selenium or placebo per day utilizing a 2×2 factorial double blind RCT design[14].

PREADViSE enrolled 7,547 of SELECT's oldest men (age 62 or older; over age 60 if African American) at 128 of these sites. To be eligible for this cooperative study these men had to be enrolled at a SELECT site willing to participate in PREADViSE, sign a consent form specific to this study, and be free from dementia at baseline on the Memory Impairment Screen (MIS), Men with active neurologic conditions affecting cognition or with a history of major psychiatric disorder or substance abuse, and men on memory enhancement drugs were ineligible for this substudy[15].

PREADViSE used the following two-tiered screening system administered annually by trained clinical research assistants at SELECT study sites for identifying incident cases of dementia:

Tier 1: Memory Impairment Screen[16]: a two-minute, four-item delayed free and cued recall memory test with controlled learning. A cut-score of four was suggested by the creators of the measure because it provided a high level of sensitivity (0.80), specificity (0.96), and positive predictive value (>0.69) for most base rates of dementia. It was administered to all PREADViSE participants at baseline, then annually during follow-up. Participant falling below the cut score also completed the second-tier evaluation.

Tier 2: An expanded Consortium to Establish a Registry for Alzheimer's Disease (CERAD[17,18]): a protocol comprising the CERAD battery of verbal fluency (Animal Naming), Boston Naming Test, Constructional Praxis, Mini-Mental State Exam, 10-item word list with immediate and delayed recall and recognition trials that was supplemented by the NYU paragraph recall test, clock drawing, Geriatric Depression Scale, and the Short Blessed Test. This is the expanded CERAD battery (CERADe).

CERADe failures, defined as a CERAD T-score below 35, were advised to visit their physician for medical examination with records of these examinations forwarded to the PREADViSE coordinating center for further review. All participants were asked to donate a blood sample at baseline and 5 years post baseline; these samples were processed and stored at the SWOG biospecimen bank for the National Cancer Institute in Frederick, Maryland. In addition, a subset of the participants (n = 563) who passed the MIS underwent the CERADe test to form a longitudinal validation study of normal aging and the MIS.

Exposure Study

To qualify for the exposure study a participant had to visit their SELECT site (which also had to agree to consent subjects for centralized follow-up) during the close out year, complete the final in-person screen, and consent to telephone follow-up. Consenters are telephoned from the PREADViSE site during their birth month and complete the MIS-T screen[16] as well as the animal naming test and COWAT. If they fail the MIS-T screen[19], as well as category and phonemic verbal fluency tests. If they fails the MIS-T, a TICS-M exam is given (20–22). A man who fails both procedures and who has a current medication list suggestive of cognitive impairment and/or past memory complaint is considered to be a

suspected mild cognitive impairment in this study. He is then sent a packet of forms: an AD8[23] (to evaluate changes in daily living skills), Geriatric Depression Scale[24] (to evaluate depression), a medical records release form, t, a reimbursement form for $300 to help cover the participant's cost of a medical exam, and a form that requests the date of this exam and contact information for the doctor completing this workup. As with the RCT phase of the study, men with suspected or confirmed cases are encouraged to remain in the study.

Results

While this ancillary trail was open to all SELECT sites, only 30% participated in PREADViSE. This illustrates some reluctance from the cancer community to become involved in an area of research remote to their main interests, particularly when the site lacked personnel with expertise in neuropsychology. Subject reimbursement issues, securing local IRB approval for the ancillary study, as well the presence of competing ancillary studies presented barriers to PREADViSE participation. This impacted study enrollment which peaked at 7,547 (representing 45.4% of eligible participants) well shy of the 10,400 sample that was desired to achieve adequate statistical power based on the original study design, planned 7 year treatment interval, and enrollment timetable of 3 years[25]. For cooperating sites, personnel unfamiliar with dementia research were trained at the semi-annual meetings of the SELECT group to administer both the MIS as well as the CERAD battery. Staff turnover at both the local principal investigator as well as the certified research nurse levels presented challenges to quality assurance and required ongoing semiannual staff training sessions.

Table 1 presents the baseline characteristics of the men enrolled in the RCT portion of PREADVISE and the subset enrolled in the exposure study. Characteristics were similar in both groups indicating little evidence of selection bias in those men who later volunteered for telephone participation in the exposure study. In the RCT portion of PREADViSE few participants (1.6%) failed the initial MIS screen. We noted modest but significant practice effects from year to year even if we alternated equivalent versions of the MIS; hence, after four years the cut off score for failure was raised with some success in capturing additional cases. Examination of the CERAD results for a subset of those participants who passed the MIS indicated the failure to identify some cases, especially those of borderline memory impaired subjects. During the RCT 909 (12.0%) of the participants either dropped out or died while on PREADViSE and 48 sites with 330 participants refused to participate in the exposure study. The participation rate at the eligible exposure sites was 65.6%.

In the exposure study 3,581 men were reached by phone in year one, but 15.7% of those who volunteered for the exposure study could not be reached after at least 5 calls. Of those contacted, 6.0% refused to participate. Most notable is that of the men who were successfully contacted and participated, the failure rate for the MIS-T increased substantially to 7.2% compared to failure rates consistently near but below 2.0% for in person screening. This is examined further in Table 2. This increase was hypothesized to be due to was older age for the men, more uniform training of the telephone screeners, and a more homogenous educational background of these screeners related to mental status examinations. Of the 257 men who took the TICS-M after failing the MIS T, 84% failed and were asked to contact their physicians for a more detailed memory assessment. In 60 suspected MCI cases who visited their doctors and then forwarded their medical records to our center, consensus review found that 78.3% had a true MCI or dementia diagnosis.

Since the participants in PREADViSE are well educated (Table 1), case ascertainment was likely to lag behind expectation[26]. By 2010, when the RCT was officially closed, we were expecting to observe 150 AD incident cases. In contrast, Table 3 lists the suspected and

confirmed dementia (all forms) and MCI cases cumulatively by year of study. There is a clear defivit of dementia cases. There is excellent agreement between suspected and confirmed MCI cases after accounting for the fact that men typically need 6–18 months to follow-up on the advice to complete a medical work-up and to have their records reach our offices for clinical consensus diagnosis.

Discussion

PREADViSE's rationale is based on sound research on the role of oxidative stress in AD. Partnering with a large cancer prevention trial led to a well-structured RCT at a very reasonable cost by taking advantage of the experience and efficient clinical trial management found in a cancer cooperative group. However, due to the premature termination of the parent trial, poor compliance with study entry, difficulties in verifying suspected cases, and the effect of enrolling a healthy cohort, it is doubtful that PREADViSE will achieve its primary aim of determining if the supplements decrease the incidence of AD and secondarily other dementias. PREADViSE has transformed into an exposure study with a subset of its participants who resemble those who participated in the full RCT cohort and investigators who remain blinded to partipant exposure. It has the potential to yield valuable information on long term exposure (5.5 year median) to vitamin supplements under controlled conditions

The implementation of this cooperative study on memory and dementia incidence in a cancer prevention setting shows that with appropriate infrastructure, conducting a large dementia prevention trial is feasible. Recruitment, adherence, and retention in the RCT were matters that required cooperation between the parent and ancillary personnel. Success in a future trial will be maximized by coordinating the initiation of the parent and ancillary trial, especially with regard to committees associated with the parent trial. The exposure study based on those who volunteered for centralized follow-up went smoothly and appears to have increased the yield of incident cases partly due to aging of the cohort and partly due to the use of more motivated interviewers in monitoring the mental status of the participants.

The trial offered several additional lessons including the surprising reluctance of participants who failed the in-person screens or the telephone screens to seek further cognitive evaluation from their physicians. In some cases (between annual assessments), a family physician began to treat the participant for cognitive problems based on a subjective complaint of memory dysfunction. The cohort itself is healthy and well educated compared of the general population, something that often threatens the validity of screening trials. Finally, while conducting the trial negative publicity on the use of vitamin E[27] had to be addressed. We conducted a large meta-analysis of RCTs the confirmed that use of vitamin E does not increase mortality rates[28,29].

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Table 1

Baseline Demographics and MIS Performance of All Participants (n = 7,547) and Participants Consenting to Centralized Follow-up (n=4,246)

	All Participants (Baseline)	Centralized Follow-up (Baseline)	Centralized Follow-up (Current)
Age	67.5 (5.3)	67.3 (5.2)	73.9 (5.7)
Education	15.0 (2.7)	15.3 (2.4)	15.3 (2.4)
MIS	7.6 (0.7)	7.6 (0.7)	7.4 (1.0)
Race			
White	83.8%	86.1%	86.1%
African-American	10.0%	9.8%	9.8%
Other	2.4%	3.0%	3.0%
Unknown	3.8%	1.1%	1.1%
Ethnicity			
Hispanic	6.7%	3.0%	3.0%
Family History of Dementia	21.2%	22.0%	22.0%
Years on Study	4.8 (2.1)	5.0 (1.9)	6.6 (1.9)

Table 2

Results of the last two in person MIS screens versus the first telephone screen and last in person screen

Last 2 in person MIS	Pass-Pass	Fail-Fail	Pass-Fail	Fail-Pass
Pass-Pass	3,171	NA	**142**	NA
Fail-Fail	NA	2	NA	0
Pass-Fail	NA	7	NA	8
Fail-Pass	8	NA	6	NA

Table 3

Cumulative number of suspected and confirmed cases of dementia and MCI by year of study

	Dementia Cases		MCI cases	
Year	**Suspected**	**Confirmed**	**Suspected**	**Confirmed**
2003	0	0	1	1
2004	1	0	5	5
2005	6	2	13	13
2006	16	8	25	25
2007	26	12	37	37
2008	34	17	51	51
2009	42	17	70	70
2010	50	21	108	88
2011	56	26	300	94