A REEVALUATION OF THE DURATION OF SURVIVAL AFTER THE ONSET OF DEMENTIA

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ABSTRACT

Background   Dementia shortens life expectancy; estimates of median survival after the onset of dementia have ranged from 5 to 9.3 years. Previous studies of people with existing dementia, however, may have underestimated the deleterious effects of dementia on survival by failing to consider persons with rapidly progressive illness who died before they could be included in a study (referred to as length bias).

Methods   We used data from the Canadian Study of Health and Aging to estimate survival from the onset of symptoms of dementia; the estimate was adjusted for length bias. A random sample of 10,263 subjects 65 years old or older from throughout Canada was screened for cognitive impairment. For those with dementia, we ascertained the date of onset and conducted follow-up for five years.

Results   We analyzed data on 821 subjects, of whom 396 had probable Alzheimer's disease, 252 had possible Alzheimer's disease, and 173 had vascular dementia. For the group as a whole, the unadjusted median survival was 6.6 years (95 percent confidence interval, 6.2 to 7.1). After adjustment for length bias, the estimated median survival was 3.3 years (95 percent confidence interval, 2.7 to 4.0). The median survival was 3.1 years for subjects with probable Alzheimer's disease, 3.5 years for subjects with possible Alzheimer's disease, and 3.3 years for subjects with vascular dementia.

Conclusions   Median survival after the onset of dementia is much shorter than has previously been estimated. (N Engl J Med 2001;344:1111-6.)

DEMENTIA shortens life expectancy: estimates of median survival from the onset of symptoms vary from 5 years (range, 1 to 13)[1] to 9.3 years (range, 1.8 to 16 or more).[2] These estimates are based on the follow-up of persons who had dementia at the time of the study; however, this approach can lead to an underestimation of the deleterious effects of dementia because of the failure to include persons with rapidly progressive disease who died before they could be included in the study.[3,4] This type of bias is referred to as length bias.[3,4]

Most studies of the duration of dementia have focused on survival from the time of study entry,[3,5-10] rather than on survival from the onset of disease.[1,2,11-13] However, there are numerous variables unrelated to disease that influence the time at which a person enters a study. Although the onset of dementia is gradual and cannot always be pinpointed,[14-16] it is preferable to calculate the duration of survival from a carefully ascertained date of onset. Stern et al.[8] recognize that "patients with a longer estimated duration of symptoms at their initial visit had a better prognosis." This finding has been reported in other studies.[10,17,18] What is not stated, however, is that estimates of survival based on such data result in the overestimation of survival in patients with dementia. Using data from the Canadian Study of Health and Aging (CSHA), we estimated the duration of survival from the onset of dementia, while adjusting for length bias.

METHODS

The Canadian Study of Health and Aging

The CSHA is a multicenter epidemiologic study of dementia and other health problems in elderly people in Canada.[19-21] In the first phase of the study (CSHA-1), 14,026 subjects 65 years old or older were randomly selected from throughout Canada, and 10,263 agreed to participate (a response rate of 73.2 percent). The sampling was stratified, with 9008 subjects living in the community and 1255 living in institutions. Subjects living in the community had a brief home interview during which they were assessed with the Modified Mini–Mental State Examination,[22] a screening test for cognitive impairment on which scores range from 0 to 100, with lower scores indicating greater impairment. Those who had a score of less than 78, suggesting that they had cognitive impairment, were invited to undergo a standardized clinical examination,[23] as were a random sample of those who had a score of 78 or higher. The study subjects who were living in institutions were all examined clinically. Dementia was diagnosed according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* third edition, revised (DSM-III-R),[24] and the *International Classification of Diseases,* 10th revision (ICD-10).[25]

The clinical examination had three phases. First, a nurse administered the Modified Mini–Mental State Examination again, screened the subject for hearing and vision problems, recorded the vital signs, and interviewed a relative to obtain the subject's medical and family history. Second, a physician conducted a physical and neurologic examination. Third, a neuropsychologist oversaw the administration of neuropsychological tests (Appendix 2) to subjects who had received a score of 50 or higher on the second Modified Mini–Mental State Examination. The physician and neuropsychologist, who were unaware of the subjects' scores on the screening test, made independent diagnoses using the DSM-III-R criteria. Subsequently, they arrived at a consensus diagnosis of dementia, cognitive impairment but no dementia, or no cognitive loss.

The criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association[27] were used for the diagnosis of probable and possible Alzheimer's disease. A clinical diagnosis of probable Alzheimer's disease requires an insidious onset of dementia with progression, in the absence of any other disorder that could account for the observed cognitive deficits. A clinical diagnosis of possible Alzheimer's disease applies either if there are atypical clinical features or if progressive dementia is thought to be due to Alzheimer's disease despite the presence of other disorders capable of affecting cognitive function. Possible Alzheimer's disease was most often associated with vascular disease, other coexisting diseases that might have contributed to the dementia, an atypical presentation, or Parkinson's disease.

The ICD-10 criteria[25] were used to define subcategories of vascular dementia and other dementias. Other dementias included those associated with Huntington's disease, Creutzfeldt–Jakob disease, Parkinson's disease, Pick's disease, and head injury. Dementia that did not fit into any of these categories was labeled as unclassified. Our analyses are restricted to persons who were given a diagnosis of probable Alzheimer's disease, possible Alzheimer's disease, or vascular dementia. The collection of data for CSHA-1 began in February 1991 and was completed by May 1992. All study subjects (or family members) were contacted by telephone in 1993.

In 1996, in the second phase of the CSHA (CSHA-2), the cohort was reevaluated with the use of an approach similar to that used for CSHA-1. Subjects with dementia at the time of their evaluation for CSHA-1 who were still alive at the time of CSHA-2 were invited to undergo a clinical examination. For study subjects who had died between the two phases of the study, an interview was conducted with a family member to determine the date and cause of death. Data on survival were available for all 1132 subjects with dementia. Data were collected for CSHA-2 between January 1996 and May 1997. Approval for both phases of the study was obtained from the ethics review boards of the 18 participating centers. In both phases of the study, a signed consent form was obtained from

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TABLE 1. CHARACTERISTICS OF THE SUBJECTS WHO WERE INCLUDED IN THE STUDY AND THOSE WHO WERE EXCLUDED.*

CHARACTERISTIC	SUBJECTS WHO WERE INCLUDED (N=821)	SUBJECTS WHO WERE EXCLUDED (N=134)
Female sex (%)	70.9	66.4
Age at CSHA-1 (yr)	83.8±7.03	82.3±7.05
Level of education†		
Mean (yr)	8.6±3.78	7.9±4.08
≤8 yr (%)	35.9	45.7
Diagnosis (%)		
Probable Alzheimer's disease	48.2	38.8
Possible Alzheimer's disease	30.7	35.8
Vascular dementia	21.1	25.4
Severity of dementia (%)‡		
Mild	18.8	38.7¶
Moderate	39.3	34.1
Severe	41.9	27.3
Score on Modified Mini–Mental State Examination at CSHA-1§	37.3±25.13	46.7±26.0¶

*Plus–minus values are means ±SD. Subjects were excluded if their age at the onset of dementia was unknown. CSHA-1 denotes the first phase of the Canadian Study of Health and Aging.

†Data were available for 678 subjects who were included in the study and 116 subjects who were excluded.

‡Data were available for 812 subjects who were included in the study and 132 subjects who were excluded.

§Data were available for 738 subjects who were included in the study and 120 subjects who were excluded.

¶P<0.001 for the comparison with the subjects who were included.

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all participants and, to ensure that valid consent was obtained for subjects who received a score lower than 65 on the Modified Mini–Mental State Examination, from a relative or caregiver.

Study Subjects

At the time of CSHA-1, 1132 persons with dementia were identified, resulting in an estimated prevalence of 8 percent.[19] The majority had been given a diagnosis of Alzheimer's disease (448 with probable and 301 with possible Alzheimer's disease). Information on the date of onset of dementia was collected during the clinical examination for CSHA-1. The age at onset was derived, in a hierarchical fashion, from the responses to three questions from the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)[28]: "When did the subject first see a doctor about memory problems?" "When did memory problems first affect the subject's life?" "What is the duration of the memory problems?" The answer to the first question was used as the date of onset; if it was missing, the answer to the second question was used; if both of these answers were missing, the answer to the third question was used. When all three answers were missing, the date of onset was defined as missing. In a separate analysis,[29] the date of onset obtained by means of this algorithm was compared with that obtained with the use of slightly different questions posed by the physician to a relative of the subject during the clinical evaluation. The use of the two algorithms resulted in very similar ages at onset, with an intraclass correlation coefficient of 0.90. The difference between the mean ages at onset derived by the two methods was −0.24 years (95 percent confidence interval, −0.54 to 0.06). We chose to use the CAMDEX algorithm since it is a standardized instrument that has been used extensively and with which researchers are already familiar, whereas the questions used in the clinical algorithm are specific to the CSHA.

Of the original 1132 subjects, the date of onset was missing for

185 subjects. The subgroup of 175 who were considered to have other or unclassified dementia was excluded from further analyses. This subgroup included 51 of the 185 for whom the date of onset of dementia was missing. Thus, 823 subjects were eligible for the analysis. Two subjects who died 52.3 years and 50.9 years after the onset of symptoms were identified as outliers and were excluded from further analyses. Data for the remaining 821 subjects — 252 with possible Alzheimer's disease, 396 with probable Alzheimer's disease, and 173 with vascular dementia — were used in the analysis.

Predictors of Survival

Information on possible predictors of survival at the time of the onset of symptoms was abstracted from the reports on the clinical examinations performed for CSHA-1. Years of education were dichotomized at the median (eight years). The analysis focuses only on predictors of survival at the time of the onset of disease; clinical features present at the time of CSHA-1 (e.g., psychiatric symptoms and language disturbance) were not considered, since it was not known whether these features were present at the onset of disease.

Statistical Analysis

All statistical analyses were adjusted for length bias in the observed survival and censoring times.[30] The survival function of the group of subjects with dementia was estimated without the use of a priori assumptions about its form, as was the survival function of the various subgroups. We calculated 95 percent confidence intervals for the differences between the subgroups in two-year and five-year survival. To assess the effect of covariates simultaneously, we adjusted for length bias by adapting the methods of Wang[30] to accommodate covariates. This was done with the use of a parametric regression model, which used Wang's method to adjust for length bias. All P values are two-sided.

RESULTS

The characteristics of the 821 study subjects are summarized in Table 1. The majority were women, and most subjects were given a diagnosis of possible or probable Alzheimer's disease; the average age of the subjects was 83.8 years at the time of CSHA-1. Only 21.9 percent of these subjects (180) survived until CSHA-2. In general, the subjects who were excluded because of missing information about their age at the onset of dementia were similar, with respect to diagnosis, educational level, age, and sex, to the subjects who were included. However, they were less cognitively impaired, as measured by their mean score on the Modified Mini–Mental State Examination (46.7 vs. 37.3, P<0.001), and their dementia was deemed less severe (38.7 percent with mild dementia, vs. 18.8 percent in the group included; P<0.001).
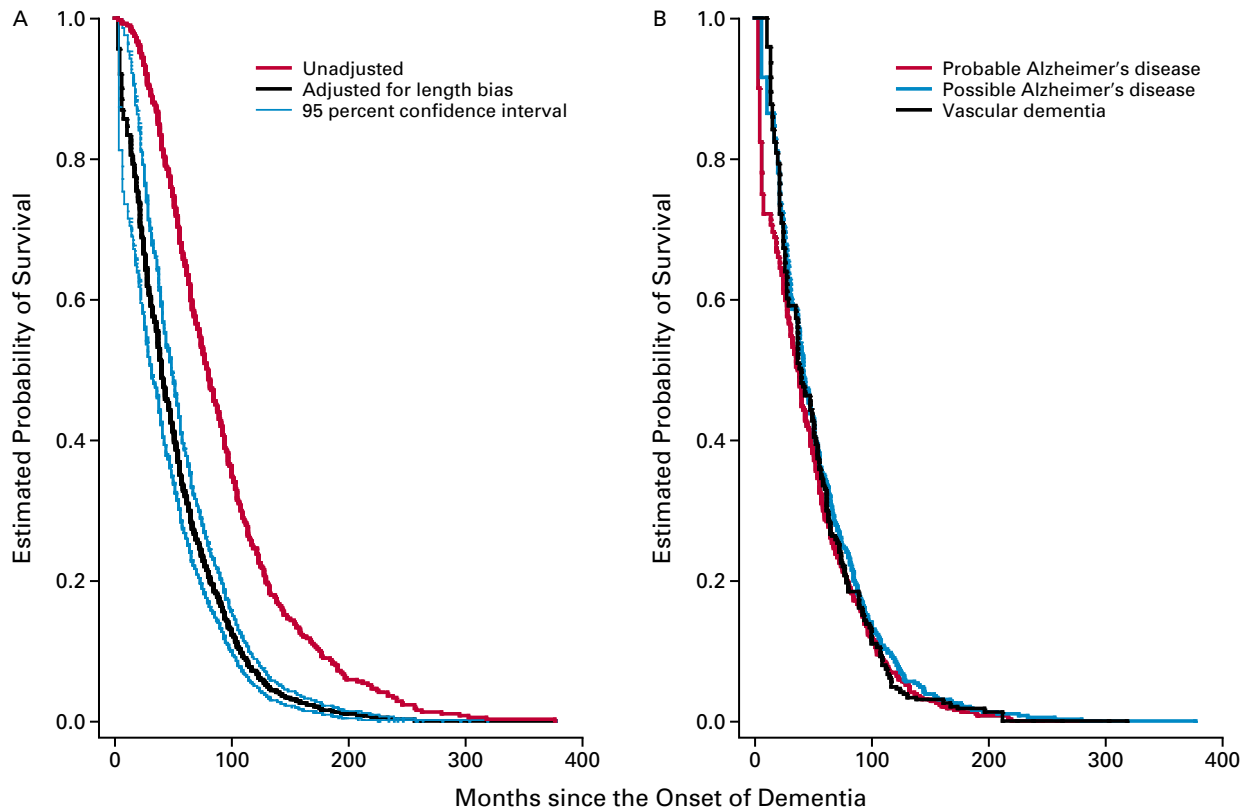
Figure 1. Estimated Probability of Survival among All Study Subjects, with and without Adjustment for Length Bias (Panel A), and Estimated Probability of Survival According to Diagnosis, after Adjustment for Length Bias (Panel B).

TABLE 2. SURVIVAL AFTER ADJUSTMENT FOR LENGTH BIAS, ACCORDING TO SEX, LEVEL OF EDUCATION, DIAGNOSIS, AND AGE AT ONSET OF DEMENTIA.*

VARIABLE	ADJUSTED MEDIAN SURVIVAL (95% CI)	ESTIMATED HAZARD RATIO FOR DEATH† (95% CI)
	yr	
All subjects	3.33 (2.66–4.00)	—
Sex		
Male	3.17 (2.57–3.78)	1.52 (1.3–1.72)
Female	3.36 (2.19–4.54)	1.0‡
Education		
≤8 yr	3.33 (1.98–4.68)	1.0‡
>8 yr	3.59 (2.58–4.59)	1.07 (0.95–1.22)
Data missing	2.74 (1.74–3.75)	—
Diagnosis		
Probable Alzheimer's disease	3.14 (1.45–4.83)	1.0‡
Possible Alzheimer's disease	3.49 (2.37–4.61)	0.87 (0.76–1.02)
Vascular dementia	3.31 (2.32–4.31)	1.16 (0.97–1.38)
Age at onset of dementia		
<65 yr	—§	1.0‡
65–74 yr	5.70 (4.54–6.86)	2.36 (1.36–4.06)
75–84 yr	4.18 (3.26–5.10)	4.26 (2.51–7.17)
≥85 yr	2.76 (1.80–3.72)	8.08 (4.39–12.94)

*CI denotes confidence interval.

†A total of 134 subjects with missing data on level of education were excluded from the simultaneous covariate analysis. A hazard ratio of less than 1.00 represents a decreased likelihood of death, whereas a hazard ratio greater than 1.00 represents an increased likelihood of death.

‡This group served as the reference category.

§Median survival for subjects younger than 65 years old is not reported, because there were too few subjects for a nonparametric analysis.

Stratified Analyses

Before adjustment for the length bias in the data, the median survival for the 821 subjects was estimated to be 6.60 years (95 percent confidence interval, 6.22 to 7.09) (Fig. 1A). After adjustment for length bias, the estimated median survival for all subjects was 3.33 years (95 percent confidence interval, 2.66 to 4.00) (Fig. 1A). The bias-adjusted survival curves for the subjects with probable Alzheimer's disease, possible Alzheimer's disease, and vascular dementia are shown in Figure 1B. Not surprisingly, survival decreased as the age at the onset of dementia increased (Table 2). In keeping with other studies, we found a slightly shorter duration of survival among men than among women, but no significant differences according to diagnosis (Table 2).

We also compared the subgroups in terms of the estimated probability of survival two years and five years after the onset of dementia (Table 3). We found no significant differences between men and women in survival two years or five years after the onset of dementia. Similarly, we found no significant differences when we made pairwise comparisons between sub-groups defined by diagnosis. There was no significant difference in survival between the subjects with more than eight years of education and those with eight or fewer years of education.

Simultaneous Covariate Analyses

All the potential predictors were entered simultaneously into a survival model, which was adjusted for length bias (Table 2). Both female sex and a younger age at the onset of dementia were significant predictors of longer survival. There was also a trend toward shorter survival among patients with vascular dementia than among those with probable Alzheimer's disease.

DISCUSSION

In 1994, Beard et al.[31] reported on the rate of survival among 960 retrospectively identified patients in whom the onset of Alzheimer's disease occurred between 1960 and 1984. The authors concluded that those with an onset in more recent years survived longer. For the most part, however, the diagnosis of Alzheimer's disease was based on a review of medical charts before the development of the criteria for Alzheimer's disease of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[27] Hence, the results should be interpreted cautiously. Other studies of survival have been limited to persons with existing dementia, which can lead to artificially high estimates of survival. Our results indicate that when adjustments are made for this bias, the median survival is found to be markedly reduced.

When examining the potential predictors of survival individually (Table 2), we found that, as in other studies, a younger age at the onset of dementia was associated with longer survival.[1,12] Subjects with a diagnosis of possible Alzheimer's disease survived slightly longer than those with a diagnosis of probable Alzheimer's disease. This difference could be due to the heterogeneity of causes in cases classified as possible Alzheimer's disease, as well as to the possible inclusion in this category of cases in which Alzheimer's disease was later ruled out. Survival among subjects with vascular dementia was intermediate between those for the two categories of Alzheimer's disease. The level of education was not associated with survival, in contrast to the findings of two studies,[32,33] although the goal of those studies was to assess the effect of educational level on the duration of survival from the time of diagnosis.

These findings are supported by the 95 percent confidence intervals for the differences in survival between various subgroups two years and five years after the onset of dementia in the stratified (nonparametric) analysis (Table 3). These intervals provide estimates of the magnitude of the differences in the probability of survival, arrived at with few a priori assumptions about the form of the model.

TABLE 3. DIFFERENCES IN THE PROBABILITY OF SURVIVAL TWO AND FIVE YEARS AFTER THE ONSET OF DEMENTIA ACCORDING TO SEX, DIAGNOSIS, AGE AT ONSET, AND LEVEL OF EDUCATION.*

VARIABLE	2 YR AFTER ONSET		5 YR AFTER ONSET	
	PROPORTION SURVIVING	ABSOLUTE DIFFERENCE (95% CI)	PROPORTION SURVIVING	ABSOLUTE DIFFERENCE (95% CI)
	percent			
Sex				
Female	65.1		33.3	
Male	74.2	−9.1 (−27.7 to 9.6)	28.4	4.9 (−6.4 to 16.0)
Diagnosis				
Possible Alzheimer's disease	71.5		34.2	
Probable Alzheimer's disease	62.3	9.2 (−18.5 to 36.8)	29.3	4.9 (−10.4 to 20.1)
Possible Alzheimer's disease	71.5		34.2	
Vascular dementia	69.6	1.9 (−19.2 to 23.0)	32.5	1.7 (−12.0 to 15.2)
Probable Alzheimer's disease	62.3		29.3	
Vascular dementia	69.6	−7.3 (−17.5 to 32.2)	32.5	−3.2 (−17.5 to 10.7)
Age at onset				
65–74 yr	92.1		57.8	
75–84 yr	75.1	17.0 (1.8 to 32.1)	40.2	17.6 (2.2 to 33.0)
65–74 yr	92.1		57.8	
≥85 yr	60.6	31.5 (13.3 to 49.8)	21.5	36.3 (21.4 to 51.1)
75–84 yr	75.1		40.2	
≥85 yr	60.6	14.5 (−4.4 to 33.5)	21.5	18.7 (8.3 to 29.0)
Education				
>8 yr	71.4		35.1	
≤8 yr	66.2	5.2 (−17.8 to 28.2)	33.4	1.7 (−11.6 to 15.1)
≤8 yr	66.2		33.4	
missing data	64.3	1.9 (−16.9 to 20.7)	20.7	12.7 (2.1 to 23.1)
>8 yr	71.4		35.1	
missing data	64.3	7.1 (−7.1 to 21.3)	20.7	14.4 (5.7 to 23.0)

*CI denotes confidence interval. Differences are between the values in the indented rows and the values in the rows immediately above them.

In the regression model, there was a trend toward an increased likelihood of death among subjects with vascular dementia as compared with those with probable Alzheimer's disease. There was no effect of the level of education on survival. The age at the onset of dementia was the strongest predictor of survival, both alone and in combination with other variables. Therefore, real differences in survival among the other subgroups — if any — are small.

One must be careful when comparing the statistical inferences from the confidence intervals for the differences between groups with those obtained from the parametric model of simultaneous covariates, since the latter requires stronger assumptions. In addition, whereas the stratified analyses included all 821 study subjects, the 134 subjects with missing data on educational level were excluded from the parametric regression model, which we had decided, a priori, should include the number of years of education as a covariate. A subsidiary analysis showed that the subjects with missing data on education had more severe cognitive impairment than the remainder of the cohort and had shorter survival. Thus, their exclusion from the regression analysis explains, in part, the small discrepancies between some of the results.

We estimated that the unadjusted overall median survival was 6.60 years, which is within the range obtained by others. Therefore, our finding of an adjusted median survival of 3.33 years after the onset of dementia (95 percent confidence interval, 2.66 to 4.00) cannot be explained by a discrepant sample. This adjusted median survival is similar to that for other serious diseases that may develop in older persons. For example, median survival among patients with congestive heart failure is reported to be three to five years.[34]

APPENDIX 1

The following persons also participated in the Clinical Progression of Dementia Study Group: H. Bergman, J. Correa, E. Elby, S. Gauthier, I. McDowell, M. Panisset, A. Perrault, F. Rouah, and R. Steenhuis.

APPENDIX 2. NEUROPSYCHOLOGICAL TESTS ADMINISTERED TO PERSONS 65 YEARS OF AGE OR OLDER AS PART OF A CLINICAL EXAMINATION FOR DEMENTIA.*

VARIABLE	TESTS
Memory	Buschke Cued Recall
	Wechsler Memory Scale: Information Subtest
	Rey Auditory Verbal Learning Test
	Benton Visual Retention Test (revised)
	WAIS-R Digit Span
	Working Memory Test
Abstract thinking	WAIS-R Similarities (Short Form)
Judgment	WAIS-R Comprehension (Short Form)
Aphasia	Token Test (11 items)
	Lexical Fluency (words)
	Semantic Fluency (animals)
Apraxia	WAIS-R Digit Symbol Test
Agnosia	Buschke Visual Component
Construction	WAIS-R Block Design (short form)
	Clock Test (optional)

*Dementia was diagnosed according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* third edition, revised.[24] WAIS-R denotes the Wechsler Adult Intelligence Scale–Revised. The tests and the reasons for their inclusion in CSHA have been described previously.[26]

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