Vitamin C Intake and Mortality among a Sample of the United States Population

James E. Enstrom; Linda E. Kanim; Morton A. Klein

Epidemiology, Vol. 3, No. 3. (May, 1992), pp. 194-202.

Stable URL:
http://links.jstor.org/sici?sici=1044-3983%28199205%293%3A3%3C194%3AVCIAMA%3E2.0.CO%3B2-A

Epidemiology is currently published by Lippincott Williams & Wilkins.

Your use of the JSTOR archive indicates your acceptance of JSTOR's Terms and Conditions of Use, available at http://www.jstor.org/about/terms.html. JSTOR's Terms and Conditions of Use provides, in part, that unless you have obtained prior permission, you may not download an entire issue of a journal or multiple copies of articles, and you may use content in the JSTOR archive only for your personal, non-commercial use.

Please contact the publisher regarding any further use of this work. Publisher contact information may be obtained at http://www.jstor.org/journals/lww.html.

Each copy of any part of a JSTOR transmission must contain the same copyright notice that appears on the screen or printed page of such transmission.

JSTOR is an independent not-for-profit organization dedicated to and preserving a digital archive of scholarly journals. For more information regarding JSTOR, please contact support@jstor.org.

http://www.jstor.org
Wed Jun 13 02:12:00 2007

Vitamin C Intake and Mortality among a Sample of the United States Population

James E. Enstrom, Linda E. Kanim, and Morton A. Klein

We examined the relation between vitamin C intake and mortality in the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study cohort. This cohort is based on a representative sample of 11,348 noninstitutionalized U.S. adults age 25-74 years who were nutritionally examined during 1971-1974 and followed up for mortality (1,809 deaths) through 1984, a median of 10 years. An index of vitamin C intake has been formed from detailed dietary measurements and use of vitamin supplements. The relation of the standardized mortality ratio (SMR) for all causes of death to increasing vitamin C intake is strongly inverse for males and weakly inverse for females. Among those with the highest vitamin C intake, males have an SMR (95% confidence interval) of 0.65 (0.52-0.80) for all causes, 0.78 (0.50-1.17) for all cancers, and 0.58 (0.41-0.78) for all cardiovascular diseases; females have an SMR of 0.90 (0.74-1.09) for all causes, 0.86 (0.55-1.27) for all cancers, and 0.75 (0.55-0.99) for all cardiovascular diseases. Comparisons are made relative to all U.S. whites, for whom the SMR is defined to be 1.00. There is no clear relation for individual cancer sites, except possibly an inverse relation for esophagus and stomach cancer among males. The relation with all causes of death among males remains after adjustment for age, sex, and 10 potentially confounding variables (including cigarette smoking, education, race, and disease history). (Epidemiology 1992;3:194-202)

Keywords: vitamin C, vitamin supplements, mortality, NHEFS cohort, gender, neoplasms, cardiovascular diseases.

There has been much interest in recent years in the possible role of vitamin C (ascorbic acid) in the prevention of cancer and other diseases.[1-3] Vitamin C has been hypothesized to act as an antioxidant to prevent stomach cancer[4] and cardiovascular diseases.[5] Supporting epidemiologic data include numerous case-control studies involving cancer patients[1-3] and four cohort studies dealing with several causes of death.[6-9] Most of the existing studies, however, have dealt with only one cancer site at a time, without regard for the impact of vitamin C on overall health. Vitamin C indices of varying quality have been used; they have almost always been based on dietary sources of vitamin C alone. Many of these studies, particularly the cohort studies, have not been able to control properly for confounding variables.

It has also been hypothesized that there are benefits of vitamin C intake at levels greatly in excess of the Recommended Dietary Allowance (RDA) of 60 mg per day.[10,11] The general public has shown much interest in this notion, and several surveys indicate that about 25% of all U.S. adults now use vitamin supplements on a daily basis and up to 50% use them to some extent.[12-15] Vitamin C is the most common single vitamin among these supplements and is the one most likely to be used in quantities greatly in excess of the RDA.[15]

Unfortunately, the existing epidemiologic data on the long-term health effects of high vitamin C intake are sparse and inconclusive.[3] Enstrom and Pauling[16] found that 479 health-conscious elderly Californians consuming high daily amounts of vitamin C (~1,500 mg) and vitamin E (~500 IU) had lower than expected total mortality, especially cardiovascular disease mortality, but this benefit did not appear to be due to vitamin supplements *per se*. A study of 3,119 Alameda County, California, adults found that 10-year total mortality was similar above and below 250 mg per day, using a crude measure of vitamin C intake.[17] A large study of 1,000,000 Americans during the 1960s indicated that increased consumption of fruits and vegetables was inversely related to lung cancer mortality, but that vitamin pills of unspecified nature showed no relation.[18]

We report here the relation between vitamin C

From the School of Public Health and Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA 90024. Address correspondence to: James E. Enstrom at School of Public Health.

This research was supported primarily by the Wallace Genetic Foundation and by American Cancer Society Grant RD-278.

© 1992 Epidemiology Resources Inc.

intake and mortality in a large cohort based on a representative sample of the general U.S. population that has undergone an extensive nutritional examination, including measuring vitamin C intake from both the diet and the use of supplements.

Subjects and Methods

The NHANES I Epidemiologic Follow-up Study (NHEFS) is a prospective cohort study based on the National Health and Nutrition Examination Survey (NHANES I).[19] NHANES I was conducted by the National Center for Health Statistics between 1971 and 1975 on a representative sample of the civilian noninstitutionalized population of the United States.[20] Persons estimated to be at risk of malnutrition (children, the elderly, women of child-bearing age, and the poor) were oversampled to improve estimates of nutritional status for these groups. A total of 14,407 adults age 25–74 years who were examined in 1971–1975 were included in the NHEFS, and over 90% of these persons were traced and/or reinterviewed between 1982 and 1984, with median 10-year follow-up. NHEFS was designed to investigate the association between factors measured at the baseline with subsequent disease occurrence and death. The size and scope of these data provide a unique opportunity to examine etiologic relationships in a large, heterogeneous national population.

The subjects of this report are the 11,348 persons on whom extensive diet and nutrition data were collected during 1971–1974 using food frequency and 24-hour recall questionnaires.[21] Follow-up was completed on 10,550 persons (94% of the 4,479 men and 92% of the 6,869 women) and death certificates with cause of death information were obtained for 1,728 deaths (97% of the 1,069 male deaths and 94% of the 740 female deaths). The underlying cause for each death was coded by the National Center for Health Statistics following the rules of the Ninth Revision of the International Classification of Diseases (ICD9). Because of the oversampling of elderly, 37% of the men and 26% of the women were age 65–74 years at entry, and 80% of all deaths occurred among persons age 65–86 years at death. Analysis in this paper is limited to mortality.

We created one master file for the cohort of 11,348 nutritionally examined NHEFS subjects by linking together 1971–1974 nutrition and medical history data, specially coded 1971–1974 vitamin supplement data, 1982–1984 follow-up interview data, and 1971–1984 death data described elsewhere.[14,19] Cigarette smoking data in 1971–1974 were obtained on only 3,854 persons in the cohort. Lifetime cigarette smoking histories were obtained for 9,602 persons (91% of the 10,550 persons traced) in the 1982–1984 follow-up interview, including a proxy interview with a spouse or other informant for most of those who had died. Using both the 1971–1974 and 1982–1984 data, cigarette smoking histories, including average number of cigarettes smoked, were available on 10,128 persons (90% of the cohort).

NHANES I collected extensive dietary data through personal interviews.[21] These included 24-hour dietary recall data (all foods consumed during the midnight to midnight period preceding the interview) and 3-month food frequency data (frequency of food intake for the preceding 3 months). The National Center for Health Statistics processed food recall data for nutrient contents using a computer program that was adapted from one used in the Ten-State Nutrition Survey and was originally developed at Tulane University.[21] The vitamin C content of each food consumed during the 24-hour period was determined using the nutritive values of food items appearing in the U.S. Department of Agriculture Handbook No. 8, as well as information from food industry sources and other databases. These values were summed by the National Center for Health Statistics to yield total dietary vitamin C intake in milligrams. Some food items had missing values for vitamin C and were not included in the total. The major food items containing vitamin C are oranges, grapefruits, tomatoes, and their juices. The food frequency question most relevant to vitamin C regarded intake of fruits and vegetables rich in vitamin C. There are some limitations to NHANES I, but basically it represents one of the most comprehensive nutritional surveys conducted on a national sample.[19–21]

NHANES I also collected 1971–1974 information on type (but not quantity) of vitamin supplements used and frequency of vitamin supplement usage: never, irregular (defined as at least weekly but less than daily), and regular (defined as daily). These data have been described and tabulated in detail elsewhere.[14] Supplements containing vitamin C (multivitamin pills and/or vitamin C pills) were used regularly by 16% of the men, 20% of the women, and about 85% of those using any type of supplement regularly. The most common type of supplement used was multivitamin pills. The only information on quantity or length of vitamin supplement usage was obtained in the 1982–1984 follow-up interview on about 8,000 survivors (70% of the original cohort). We have combined the 1971–1974 data on dietary intake based on 24-hour recall with the 1971–1974 data on regular use of supplements containing vitamin C (defined as regular supplements) to construct a simple index of three distinct levels of vitamin C intake: 0–49 mg, 50+ mg and no regular supplements, and 50+ mg and regular supplements. The first category includes a small portion (about 15%) of persons using regular supplements. Further subdivision has not been done because of fluctuations in dietary intake from that measured during the 24-hour period, the limited data on the quantity of vitamin C intake from supplements, changes in supplement usage over time, and the relatively small number of deaths in some subgroups.

Dietary intake based on one 24-hour recall period may be a somewhat variable measure of average long-term vitamin C intake for each individual. Thus, we have used the 1971–1974 data on the frequency of consumption of fruits and vegetables rich in vitamin C during the preceding 3 months (defined as frequency) to construct a vitamin C frequency index. The four levels of the vitamin C frequency index are: frequency of less than one time per week; frequency of one to six times per week; frequency of at least one time per day and no regular supplements; and frequency of at least one time per day and regular supplements. This index does not include all sources of vitamin C, but clearly vitamin C intake increases with more frequent consumption of fruits and vegetables rich in vitamin C, as indicated in Tables 1 and 2.

We calculated the standardized mortality ratio (SMR) for the subgroups defined by sex, vitamin C index, and other selected variables. The outcomes we examined were all causes of death, all cancers (ICD9 140–208), all cardiovascular diseases (ICD9 390–459), and selected major cancer sites. The SMR for each subgroup is the number of observed deaths divided by the number of expected deaths, expressed as a percentage. The total number of expected deaths is the sum of the expected deaths for each 5-year age group starting at age 25. The number of expected deaths for one 5-year age group is the number of person-years of risk multiplied by the age-specific mortality rate for that age group of U.S. whites. Each person's period of risk began on the date of his or her initial examination during 1971–1974 and ended on the date of death, on the date of follow-up interview during 1982–1984, or on the date the subject was lost to follow-up, whichever came first.

We calculated each SMR and its 95% confidence interval (CI) using a computer program developed by Monson,[22] with expected deaths based on person-years of observation and concurrent death rates among all U.S. whites. By this definition, the SMR for all U.S. whites is 1.00. U.S. whites have been chosen as the referent group for comparison because detailed data on them are widely available and because the NHEFS cohort is based on a nationally representative sample which is 82% white. The observed mortality among the NHEFS cohort has been shown to agree with expected mortality based on U.S. death rates.[23]

Because of the small number of deaths, especially for cancer, in some subgroups, we have calculated SMRs, which use a different standard for each comparison, instead of direct age standardization with a common standard. The age distribution of the cohort is similar for all levels of vitamin C index, however, so the changing standard does not introduce any serious distortion. The male age distribution at the time of original interview is: 17.8% for ages 25–34, 14.9% for ages 35–44, 17.1% for ages 45–54, 13.2% for ages 55–64, and 37.0% for ages 65–74. The female age distribution is: 27.6% for ages 25–34, 24.2% for ages 35–44, 12.1% for ages 45–54, 9.7% for ages 55–64, and 26.4% for ages 65–74.

The sample weights associated with the oversampling of certain NHANES I subjects have not been used in our analysis. The SMRs are based primarily on deaths among persons at least 65 years of age. The cause of death was not obtained for 3% of the male deaths and 6% of the female deaths, and thus cause-specific SMRs are correspondingly lower than they should be. We also conducted analyses using the Cox proportional hazards model to investigate the relation of the vitamin C index to mortality while controlling for several potentially confounding variables.[24,25]

Results

Key 1971–1974 demographic and nutritional characteristics for the NHEFS cohort as a function of the three-level vitamin C index are shown in Table 1 for males and in Table 2 for females. Several of the characteristics vary substantially by vitamin C intake, but the differences are slight between the two upper categories. It is useful to note the strong correlation between increasing vitamin C index and more frequent consumption of fruits and vegetables rich in vitamin C. This correlation indicates that the 24-hour recall data are consistent with the 3-month food frequency data, even though food intake fluctuates somewhat from day to day for each individual. Thus, individuals at the lower end of the index consume substantially less dietary vitamin C as a group than individuals at the upper end, whether measured by 24-hour recall or 3-month food frequency.

While the precise level of vitamin C intake from supplement use in 1971–1974 is not known, an indi-

TABLE 1. Key Demographic Characteristics and Nutrient Intake for NHEFS Males as a Function of Vitamin C Index, Based on 24-Hour Recall of Dietary Intake and Regular Use of Supplements Containing Vitamin C (Reg Supps)

	1971-1974 Vitamin C Index			
1971-1974 Characteristic	0-49 mg	50+ mg and No Reg Supps	50+ mg and Reg Supps	Total
Number of subjects	1,997	2,031	451	4,479
Age				
Mean in years	53	53	54	53
% ≥ 65 years	37	37	38	37
Race (% white)	80	84	92	83
Marital status (% married)	80	84	84	82
Education (% < 12 years)	61	47	32	52
Height (mean in cm)	173	174	174	174
Weight (mean in kg)	76	78	76	77
History of serious diseases (% yes)	12	13	11	12
Cigarette smoking history* (% never)	23	29	29	26
Follow-up cigarette smoking*				
% never	26	31	32	28
% current	34	26	24	29
Follow-up cigarettes per day* (mean)	18	16	14	16
Alcohol consumption (% never)	25	22	22	23
Recreational exercise (% much)	20	22	27	22
Other physical activity (% much)	45	47	44	46
Calories (mean)	1,947	2,322	2,334	2,156
Fat (mean in gm)	82	95	95	89
Serum cholesterol (mean in mg per dl)	220	221	225	221
Dietary vitamin A (mean in IU)	3,222	7,022	7,438	5,370
Dietary vitamin C (mean in mg)	22	130	145	83
Frequency of consumption of fruits and vegetables rich in vitamin C				
% ≥ 1 time per day	16	46	53	34
% < 1 time per week	30	10	7	19
Vitamin C supplement use (% regular)	13	0	100	16
1982-1984 follow-up vitamin C supplement use* (% current)	26	25	66	30

* Variable based on a portion of the subjects, as explained in text.

cation is available from the 1982-1984 follow-up interview, which determined that the average user of vitamin C pills consumed about 800 mg per day, the average user of vitamin E pills consumed about 500 IU per day, and the average user of vitamin A pills consumed about 10,000 IU per day. The consumption levels of these vitamins from multivitamin pills were not determined, but typical multivitamin pills usually contain levels of vitamins C, E, and A at least equal to the RDA, defined in 1980 to be 60 mg per day for vitamin C, 10-15 IU per day for vitamin E, and 5,000 IU per day for vitamin A.[26] It is reasonable to assume that those persons regularly using supplements containing vitamin C ingested an average of several hundred milligrams of vitamin C per day, as well as some supplemental vitamin E, vitamin A, and/or other nutrients. The 1982-1984 data indicate changes since 1971-1974 in the regular use of supplements containing vitamin C.

Table 3 shows the SMR and 95% CI as a function of the vitamin C index for major causes of death. Strong inverse trends are evident as a function of increasing vitamin C intake for all causes and all cardiovascular diseases, for males alone and for both sexes combined. There are weaker inverse trends for all cancers and for females.

Table 4 shows the SMR as a function of the vitamin C frequency index for major causes of death. Again, strong inverse trends are evident as a function of this second measure of vitamin C intake. Compared with the cohort as a whole, the SMRs for the persons with the highest vitamin C intake are substantially reduced for all causes and all cardiovascular diseases among males, females, and both sexes combined. The SMRs for the highest level of the vitamin C frequency index are in good agreement with the corresponding SMRs for the vitamin C index even though these indices are based on different measures of vitamin C intake.

TABLE 2. Key Demographic Characteristics and Nutrient Intake for NHEFS Females as a Function of Vitamin C Index Based on 24-Hour Recall of Dietary Intake and Regular Use of Supplements Containing Vitamin C (Reg Supps)

	1971–1974 Vitamin C Index			
1971-1974 Characteristic	0–49 mg	50+ mg and No Reg Supps	50+ mg and Reg Supps	Total
Number of subjects	3,145	2,840	884	6,869
Age				
Mean in years	46	49	50	48
% ≥ 65 years	23	28	32	26
Race (% white)	79	81	91	81
Marital status (% married)	67	70	66	68
Education (% < 12 years)	51	43	32	45
Height (mean in cm)	161	161	162	161
Weight (mean in kg)	67	67	63	67
History of serious diseases (% yes)	7	9	9	8
Cigarette smoking history* (% never)	54	61	57	57
Follow-up cigarette smoking*				
% never	54	61	58	57
% current	31	22	20	25
Follow-up cigarettes per day* (mean)	8	6	6	7
Alcohol consumption (% never)	37	36	29	35
Recreational exercise (% much)	12	15	17	14
Other physical activity (% much)	43	43	42	43
Calories (mean)	1,339	1,568	1,623	1,470
Fat (mean in gm)	56	62	64	60
Serum cholesterol (mean in mg per dl)	219	222	225	221
Dietary vitamin A (mean in IU)	2,913	6,053	7,251	4,769
Dietary vitamin C (mean in mg)	21	129	140	81
Frequency of consumption of fruits and vegetables rich in vitamin C				
% ≥ 1 time per day	22	54	64	41
% < 1 time per week	23	7	7	14
Vitamin C supplement use (% regular)	16	0	100	20
1982–1984 follow-up vitamin C supplement use* (% current)	35	35	66	39

* Variable based on a portion of the subjects, as explained in text.

TABLE 3. SMR and 95% CI during 1971–1984 among NHEFS Cohort for Major Causes of Death as a Function of 1971–1974 Vitamin C Index. Comparisons Made Relative to U.S. Whites (with SMR = 1.00)

	All Causes		All Cancers (ICD9 140–208)		All Cardiovascular Diseases (ICD9 390–459)	
1971-1974 Vitamin C Index	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)
Males	1,069	0.97 (0.91–1.03)	228	0.91 (0.80–1.04)	558	0.94 (0.86–1.02)
0–49 mg	520	1.11 (1.01–1.21)	106	0.99 (0.81–1.20)	266	1.05 (0.93–1.18)
50+ mg and no reg supps*	464	0.93 (0.84–1.02)	99	0.87 (0.71–1.06)	251	0.93 (0.82–1.05)
50+ mg and reg supps	85	0.65 (0.52–0.80)	23	0.78 (0.50–1.17)	41	0.58 (0.41–0.78)
Females	740	0.95 (0.88–1.02)	169	0.88 (0.75–1.02)	371	0.90 (0.81–0.99)
0–49 mg	323	1.00 (0.89–1.11)	73	0.91 (0.71–1.14)	171	1.00 (0.86–1.16)
50+ mg and no reg supps	311	0.93 (0.83–1.03)	72	0.86 (0.67–1.08)	152	0.85 (0.72–1.00)
50+ mg and reg supps	106	0.90 (0.74–1.09)	24	0.85 (0.55–1.27)	48	0.75 (0.55–0.99)
Both sexes	1,809	0.96 (0.91–1.01)	397	0.90 (0.81–0.99)	929	0.92 (0.86–0.98)
0–49 mg	843	1.06 (0.99–1.13)	179	0.96 (0.83–1.11)	437	1.03 (0.94–1.13)
50+ mg and no reg supps	775	0.93 (0.87–1.00)	171	0.87 (0.75–1.01)	403	0.90 (0.82–0.99)
50+ mg and reg supps	191	0.77 (0.67–0.89)	47	0.82 (0.60–1.09)	89	0.66 (0.53–0.82)

* reg supps = regular supplements.

TABLE 4. SMR and 95% CI during 1971–1984 among NHEFS Cohort for Major Causes of Death as a Function of 1971–1974 Vitamin C Frequency Index. This Index Is Based on the Frequency of Usage of Fruits and Vegetables Rich in Vitamin C (FFV) and Regular Usage of Supplements Containing Vitamin C (Reg Supps)

	Cause of Death					
	All Causes		All Cancers (ICD9 140–208)		All Cardiovascular Diseases (ICD9 390–459)	
1971-1974 Vitamin C Frequency Index	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)
Males						
FFV < 1 time per week	242	1.13 (0.99–1.28)	44	0.90 (0.66–1.21)	133	1.14 (0.96–1.35)
FFV = 1–6 times per week	422	0.94 (0.85–1.03)	96	0.93 (0.76–1.14)	207	0.86 (0.75–0.98)
FFV ≥ 1 time per day and no reg supps	297	0.92 (0.81–1.03)	59	0.81 (0.61–1.04)	165	0.94 (0.80–1.09)
FFV ≥ 1 time per day and reg supps	66	0.74 (0.57–0.94)	22	1.11 (0.69–1.67)	30	0.61 (0.41–0.87)
Females						
FFV < 1 time per week	118	0.96 (0.79–1.15)	30	1.03 (0.69–1.47)	58	0.88 (0.66–1.12)
FFV = 1–6 times per week	282	0.98 (0.87–1.10)	59	0.81 (0.62–1.04)	149	1.00 (0.84–1.17)
FFV ≥ 1 time per day and no reg supps	232	0.93 (0.82–1.06)	56	0.90 (0.68–1.16)	119	0.90 (0.75–1.08)
FFV ≥ 1 time per day and reg supps	68	0.73 (0.57–0.93)	22	0.99 (0.62–1.49)	22	0.44 (0.27–0.66)
Both sexes						
FFV < 1 time per week	360	1.07 (0.96–1.19)	74	0.95 (0.75–1.20)	191	1.04 (0.90–1.20)
FFV = 1–6 times per week	704	0.95 (0.88–1.02)	155	0.88 (0.75–1.03)	356	0.91 (0.82–1.01)
FFV ≥ 1 time per day and no reg supps	529	0.92 (0.84–1.00)	115	0.84 (0.70–1.02)	284	0.92 (0.82–1.03)
FFV ≥ 1 time per day and reg supps	134	0.74 (0.62–0.88)	44	1.04 (0.76–1.39)	52	0.52 (0.39–0.69)

Table 5 shows SMRs for major cancer sites as a function of the vitamin C index. The SMRs for esophagus and stomach cancer mortality among males consuming at least 50 mg per day of vitamin C (1.15 and 0.0) appear to be substantially lower than the SMR for males consuming less than 50 mg per day (1.99). The large confidence intervals, however, preclude any conclusion that high vitamin C intake has a protective effect. No similar trend is found for esophagus and stomach cancer among females. The small differences in the SMRs for lung cancer are consistent with the minimal differences in smoking habits seen in Tables 1 and 2. Taken as a whole, the cancer data show no consistent relation to vitamin C intake, but they do not rule out the possibility of a small protective effect.

Table 6 shows the persistence of the relation of vitamin C index to total mortality during two follow-up periods (up to 5 years and beyond 5 years), in spite of changes in vitamin C intake over time. The relation is stronger during the first 5 years for both males and females, as might be expected, inasmuch as changes in dietary and supplement intake would be less during a shorter follow-up period. Also shown is the relation of vitamin C intake and mortality, omitting the first 2 years of follow-up, because precursor states of illness at the time of initial examination could have influenced the intake of vitamin C. Note that omitting these 2 years changes the relation only slightly, indicating that any such effect is not large.

We used the Cox proportional hazards linear model to fit length of survival up to 5 years or until the end of follow-up to key independent variables.[24,25] The independent variables in this analysis are those indicated from Table 1 or 2 or from previous studies to be related to vitamin C intake or mortality. The results are presented in Table 7 in pairs for four models based on sex and length of follow-up. Shown are the coefficient, standard error, and relative risk comparing highest vitamin C index to lowest vitamin C index. The first of each pair includes only the variables of age, sex, and vitamin C index. The second of each pair includes age, sex, vitamin C index, and the following 10 poten-

TABLE 5. SMR and 95% CI during 1971–1984 among NHEFS Cohort for Major Cancer Sites as a Function of 1971–1974 Vitamin C Index

	1971–1974 Vitamin C Index					
	0–49 mg		50+ mg and No Reg Supps*		50+ mg and Reg Supps	
Cancer Site (ICD9)	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)
Males						
All sites (140–208)	106	0.99 (0.81–1.20)	99	0.87 (0.71–1.06)	23	0.78 (0.50–1.17)
Esophagus and stomach (150–151)	10	1.99 (1.06–1.28)	8	1.15 (0.50–2.27)	0	0.0 (0.0–1.68)
Colon and rectum (153–154)	11	0.82 (0.41–1.56)	13	0.91 (0.48–1.56)	2	0.54 (0.07–1.95)
Pancreas (157)	7	1.24 (0.50–2.56)	7	1.17 (0.47–2.41)	2	1.29 (0.15–4.67)
Lung (162)	30	0.84 (0.56–1.19)	30	0.79 (0.53–1.12)	6	0.62 (0.23–1.34)
Prostate (185)	13	1.18 (0.63–2.02)	10	0.84 (0.40–1.55)	2	0.62 (0.07–2.24)
Bladder and kidney (188–189)	8	1.29 (0.56–2.54)	8	1.21 (0.52–2.38)	2	1.16 (0.14–4.19)
Leukemia (204–208)	5	1.27 (0.41–2.96)	5	1.19 (0.38–2.78)	1	0.91 (0.01–5.09)
All other sites	19	0.79 (0.48–1.23)	18	0.70 (0.42–1.11)	8	1.21 (0.52–2.38)
Females						
All sites (140–208)	73	0.91 (0.71–1.14)	72	0.86 (0.67–1.08)	24	0.85 (0.55–1.27)
Esophagus and stomach (150–151)	0	0.0 (0.0–0.93)	4	1.18 (0.32–3.02)	1	0.85 (0.02–4.73)
Colon and rectum (153–154)	12	1.01 (0.52–1.77)	14	1.12 (0.61–1.88)	4	0.92 (0.25–2.36)
Pancreas (157)	6	1.35 (0.49–2.95)	3	0.64 (0.13–1.86)	2	1.23 (0.14–4.45)
Lung (162)	11	1.00 (0.50–1.80)	4	0.35 (0.09–0.89)	7	1.35 (0.54–2.79)
Breast (174)	11	0.70 (0.35–1.26)	17	1.07 (0.62–1.71)	7	1.35 (0.54–2.79)
Uterus (180–182)	2	0.43 (0.05–1.55)	6	1.25 (0.46–2.73)	0	0.0 (0.0–2.32)
Bladder and kidney (188–189)	5	1.95 (0.63–4.54)	2	0.73 (0.09–2.64)	1	1.06 (0.03–5.90)
Leukemia (204–208)	3	1.06 (0.21–3.10)	2	0.69 (0.08–2.49)	1	1.01 (0.01–5.61)
All other sites	23	0.94 (0.60–1.41)	20	0.79 (0.48–1.22)	5	0.59 (0.19–1.37)

* reg supps = regular supplements.

TABLE 6. SMR and 95% CI for NHEFS for All Causes of Death by Different Follow-up Periods as a Function of Vitamin C Index

	Persons Followed up to 5 Years		Persons Followed beyond 5 Years		Persons Followed beyond 2 Years	
1971–1974 Vitamin C Index	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)
Males						
0–49 mg	237	1.08 (0.95–1.23)	283	1.13 (1.00–1.27)	436	1.14 (1.04–1.25)
50+ mg and no reg supps*	204	0.89 (0.77–1.02)	260	0.96 (0.85–1.09)	389	0.95 (0.86–1.05)
50+ mg and reg supps	32	0.56 (0.38–0.79)	53	0.72 (0.54–0.94)	72	0.66 (0.52–0.84)
Females						
0–49 mg	124	0.94 (0.79–1.12)	199	1.04 (0.90–1.20)	282	1.03 (0.92–1.16)
50+ mg and no reg supps	117	0.86 (0.71–1.03)	194	0.97 (0.84–1.12)	267	1.01 (0.90–1.14)
50+ mg and reg supps	35	0.72 (0.50–1.00)	71	1.03 (0.81–1.31)	91	0.91 (0.74–1.13)
Both sexes						
0–49 mg	361	1.03 (0.93–1.14)	482	1.09 (1.00–1.19)	718	1.09 (1.01–1.17)
50+ mg and no reg supps	321	0.88 (0.79–0.98)	454	0.97 (0.88–1.07)	656	0.97 (0.90–1.05)
50+ mg and reg supps	67	0.63 (0.49–0.81)	124	0.87 (0.73–1.04)	163	0.78 (0.67–0.91)

* reg supps = regular supplements.

TABLE 7. Proportional Hazards Linear Models for NHEFS Cohort by Sex and Years of Follow-up*

Model	Coefficient (β)	Standard Error	RR (95% CI)
1) 4,216 males followed 5 years, 473 deaths			
Vitamin C index age-adjusted	−0.270	0.073	0.46 (0.17–0.75)
Vitamin C index fully adjusted	−0.247	0.088	0.51 (0.17–0.85)
2) 4,216 males followed until 1984, 1,069 deaths			
Vitamin C index age-adjusted	−0.229	0.048	0.54 (0.35–0.73)
Vitamin C index fully adjusted	−0.126	0.056	0.75 (0.53–0.97)
3) 10,550 persons followed 5 years, 749 deaths			
Vitamin C index age-sex adjusted	−0.208	0.056	0.58 (0.36–0.80)
Vitamin C index fully adjusted	−0.191	0.067	0.62 (0.36–0.88)
4) 10,550 persons followed until 1984, 1,809 deaths			
Vitamin C index age-sex adjusted	−0.152	0.035	0.70 (0.56–0.84)
Vitamin C index fully adjusted	−0.074	0.042	0.85 (0.69–1.01)

* Vitamin C index, age, sex, and 10 potentially confounding variables defined in 1971–1974 were related to subsequent survival. The variables and ordered subgroups within each variable (in parentheses) are as follows: vitamin C index (<50 mg, 50+ mg and no regular supplements, 50+ mg and regular supplements), age (25–74 years), sex (male, female), race (white, nonwhite), history of serious diseases (no, yes), education (0–8, 9–11, 12, 12+ years), cigarette smoking history (never, ever), recreational exercise (little or no, moderate, much), alcohol consumption (never, <1 time per month, 1–4 times per month, 2+ times per week), calories (<1,000, 1,000–1,499, 1,500–1,999, 2,000+), fat (<40, 40–59, 60–79, 80–99, 100+ mg), serum cholesterol (<200, 200–239, 240+ mg per dl), and dietary vitamin A (<1,000, 1,000–2,999, 3,000–4,999, 5,000+ IU). The model results are presented for the vitamin C index after adjusting for age and sex only and after adjusting for age, sex, and the 10 potentially confounding variables. Negative coefficient (β) indicates an inverse relation to mortality; β is for each of the two increments in the vitamin C index. Relative risk (RR) compares persons with highest *vs* lowest vitamin C intake. The 95% CI is based on standard error of β.

tially confounding variables: race, history of serious diseases, education, cigarette smoking, recreational exercise, alcohol consumption, calories, fat, serum cholesterol, and dietary vitamin A. The definition of each variable is given in Table 7. The vitamin C index is a strong predictor of total mortality in each model after controlling for age and sex, consistent with the results in Tables 3 and 6. After adjustment for age, sex, and the 10 variables, the relation of vitamin C index to total mortality still remains strong in all but the last model. The relation is strongest during the first 5 years, as might be expected because of less change in vitamin C intake. During the first 5 years, the 10 variables have very little effect on the strength of the relation: they reduce the coefficient by less than 10%.

Discussion

The NHEFS findings are fairly consistent with the results for the earlier cohort studies in which reduced mortality (total, cardiovascular disease, or stomach cancer) is associated with increased dietary intake of vitamin C.[6–9] In particular, these results are quite similar to those of the 1948 survey of elderly residents of San Mateo County, California.[6] This early study showed that after 7-year mortality follow-up, 377 individuals consuming more than 50 mg per day of vitamin C had a total death rate only one-half that of 130 individuals consuming less than 50 mg per day. Because of relatively few cancer deaths, it is difficult to compare results here with the case-control studies for cancer sites where vitamin C has been shown to have a preventive effect.

Because of these NHEFS findings, we have re-analyzed the data for the 3,119 adults from Alameda County, California, who were followed for 10 years.[18] There were no material differences in mortality between the individuals consuming above and below 250 mg per day of vitamin C, using a crude vitamin C index based on a few dietary sources and vitamin C pills. We have subsequently found, however, that the 227 individuals consuming over 750 mg per day of vitamin C experienced only 7 deaths, which is only about 40% of the total cohort death rate during the 10 years. Thus, the results for the Alameda and NHEFS cohorts agree to a certain extent.

The NHEFS findings are consistent with the hypothesis that high levels of antioxidant vitamins (such as vitamins C, E, and A) increase the body's defense system against free radicals and reduce the risk of arteriosclerosis.[5] Furthermore, the NHEFS findings are plausible in the sense that they are consistent with the secular trends during the last 20 years of large increases in the consumption of supplements containing vitamin C[3] and large declines in age-adjusted death rates (total, cardiovascular disease, and stomach cancer) in the general population that are only partially explained by established risk factors.[27,28] Obviously, we cannot conclude that vitamin C is responsible for the time trends, but it could have contributed to some extent. Also, because of oversampling of the elderly and the poor, the results have occurred primarily among segments of the American population that may experience poor nutrition and could reasonably be expected to benefit from increased vitamin C intake.

Even if increased vitamin C intake *per se* has only a small beneficial effect, the population impact could still be substantial because of the large variations in dietary vitamin C intake and the widespread use of vitamin C supplements. Based on our regression analyses, the inverse relation of total mortality to vitamin C intake is stronger and more consistent in this population than the relation of total mortality to serum cholesterol and dietary fat intake, two variables on which strong public health guidelines have been issued over the years. Furthermore, the inverse relation between vitamin C and mortality in this cohort has been observed in spite of difficulties with dietary measurement and variability, which would tend to weaken an effect.

Acknowledgment

The authors express their appreciation to the National Center for Health Statistics for conducting the NHEFS and making the data available for analysis. The authors are responsible for the results and conclusions presented.

References

1. Committee on Diet, Nutrition, and Cancer. Diet, Nutrition, and Cancer. Washington DC: National Research Council, National Academy Press, 1982.
2. Committee on Diet and Health. Diet and Health: Implications for Reducing Chronic Disease Risks. Washington DC: National Record Council, National Academy Press, 1989.
3. Block G. Vitamin C and cancer prevention: the epidemiologic evidence. Am J Clin Nutr 1991;53:270S–282S.
4. Weisburger JH, Marquardt H, Mower JF, Hirota N, Mori H, Williams G. Inhibition of carcinogenesis: vitamin C and the prevention of gastric cancer. Prev Med 1980;9:352–371.
5. Gey KF. On the antioxidant hypothesis with regard to arteriosclerosis. Bibl Nutr Dieta 1986;37:53–91.
6. Chope H, Breslow L. Nutritional status of the aging. Am J Public Health 1956;46:61–67.
7. Bjelke E. The recession of stomach cancer: selected aspects. In: Magnus K, ed. Trends in Cancer Incidence. Washington DC: Hemisphere, 1982;165–181.
8. Gey KF, Brubacher GB, Staehelin HB. Plasma levels of antioxidant vitamins in relation to ischemic heart disease and cancer. Am J Clin Nutr 1987;45:1368–1377.
9. Kromhout D. Essential micronutrients in relation to carcinogenesis. Am J Clin Nutr 1987;45:1361–1367.
10. Cameron E, Pauling L. Cancer and Vitamin C. Menlo Park: Linus Pauling Institute of Science and Medicine, 1979.
11. Pauling L. How to Live Longer and Feel Better. New York: Avon Books, 1986.
12. Stewart ML, McDonald JT, Levy AS, Schucker RE, Henderson DP. Vitamin/mineral supplement use: a telephone survey of adults in the United States. J Am Diet Assoc 1985;12:1585–1590.
13. Moss AJ, Levy AS, Kim I, Park YK. Use of vitamin and mineral supplements in the United States: current users, types of products, and nutrients. Advance Data from Health and Vital Statistics. No. 174. Hyattsville, MD: National Center for Health Statistics, 1989.
14. Block G, Cox C, Medars G, Schreiber GB, Licitra L, Melia N. Vitamin supplement use, by demographic characteristics. Am J Epidemiol 1988;127:287–309.
15. Subar AF, Block G. Use of vitamin and mineral supplements: demographics and amounts of nutrients consumed: The 1987 Health Interview Survey. Am J Epidemiol 1990;132:1091–1101.
16. Enstrom JE, Pauling L. Mortality among health-conscious elderly Californians. Proc Natl Acad Sci USA 1982;79:6023–6027.
17. Enstrom JE, Kanim LE, Breslow L. The relationship between vitamin C intake, general health practices, and mortality in Alameda County, California. Am J Public Health 1986;76:1124–1130.
18. Long-de W, Hammond EC. Lung cancer, fruit, green salad and vitamin pills. Chin Med J 1985;98:206–210.
19. National Center for Health Statistics. Plan and Operation of the NHANES I Epidemiologic Follow-up Study, 1982–84. Vital and Health Statistics, Series 1, No. 22. DHHS Pub. No. (PHS) 87-1324. Hyattsville, MD: National Center for Health Statistics, 1987.
20. National Center for Health Statistics. Plan and Operation of the Health and Nutrition Examination Survey, United States, 1971–73. Vital and Health Statistics, Series 1, Nos. 10a and 10b. DHEW Pub. No. (HSM) 73-1310. Washington DC, U.S. Government Printing Office, 1973.
21. National Center for Health Statistics. Caloric and Selected Nutrient Values for Persons 1–74 Years of Age: First Health Nutrition Examination Survey, United States, 1971–1974. Vital and Health Statistics, Series 11, No. 209. DHEW Pub. No. (PHS) 79-1657. Washington DC: U.S. Government Printing Office, 1979.
22. Monson RR. Analysis of relative survival and proportional mortality. Comput Biomed Res 1974;7:325–332.
23. Madans JH, Cox CS, Kleinman JC, Makuc D, Feldman JJ, Finucane FF, Barbano HE, Cornoni-Huntley J. 10 years after NHANES I: mortality experience at initial follow-up, 1982–84. Public Health Rep 1986;101:474–481.
24. Cox DR, Oakes D. Analysis of Survival Data. London: Chapman & Hall, 1984.
25. Harrell F. The PHGLM Procedure and the LOGIST Procedure. In: SUGI Supplemental Library User's Guide. 1983 ed. Cary, NC: SAS Institute, Inc., 1983.
26. Food and Nutrition Board, National Academy of Sciences. Recommended Dietary Allowances. 9th ed. Washington DC: National Academy of Sciences, 1980.
27. National Center for Health Statistics. Advance Report of Final Mortality Statistics, 1987; Monthly Vital Statistics Report, vol. 38, No. 5, Supplement. DHHS Publication No. (PHS) 89-1120. Hyattsville, MD: U.S. Public Health Service, 1989.
28. Kaplan GA, Cohn BA, Cohen RD, Guralnik J. The decline in ischemic heart disease mortality: prospective evidence from the Alameda County Study. Am J Epidemiol 1988;127:1131–1142.