

DIETARY ANTIOXIDANT VITAMINS AND DEATH FROM CORONARY HEART DISEASE IN POSTMENOPAUSAL WOMEN

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Abstract Background. The role of dietary antioxidant vitamins in preventing coronary heart disease has aroused considerable interest because of the knowledge that oxidative modification of low-density lipoprotein may promote atherosclerosis.

Methods. We studied 34,486 postmenopausal women with no cardiovascular disease who in early 1986 completed a questionnaire that assessed, among other factors, their intake of vitamins A, E, and C from food sources and supplements. During approximately seven years of follow-up (ending December 31, 1992), 242 of the women died of coronary heart disease.

Results. In analyses adjusted for age and dietary energy intake, vitamin E consumption appeared to be inversely associated with the risk of death from coronary heart disease. This association was particularly striking in the subgroup of 21,809 women who did not consume vitamin supplements (relative risks from lowest to highest quintile of vitamin E intake, 1.0, 0.68, 0.71, 0.42, and 0.42;

P for trend = 0.008). After adjustment for possible confounding variables, this inverse association remained (relative risks from lowest to highest quintile, 1.0, 0.70, 0.76, 0.32, and 0.38; P for trend = 0.004). There was little evidence that the intake of vitamin E from supplements was associated with a decreased risk of death from coronary heart disease, but the effects of high-dose supplementation and the duration of supplement use could not be definitively addressed. Intake of vitamins A and C did not appear to be associated with the risk of death from coronary heart disease.

Conclusions. These results suggest that in postmenopausal women the intake of vitamin E from food is inversely associated with the risk of death from coronary heart disease and that such women can lower their risk without using vitamin supplements. By contrast, the intake of vitamins A and C was not associated with lower risks of dying from coronary disease. (N Engl J Med 1996;334:1156-62.)

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THERE is growing evidence that the oxidative modification of low-density lipoprotein (LDL) may be critical to the development of atherosclerosis.¹⁻³ Oxidized LDL is present in atherosclerotic plaques⁴; the oxidation of LDL appears to enhance the uptake of LDL by macrophages, thereby encouraging the formation of foam cells and the development of fatty streaks¹; and increased susceptibility to such oxidation is associated with greater severity of carotid atherosclerosis.⁵ The inhibition of atherosclerosis in laboratory animals by antioxidants such as probucol,⁶ butylated hydroxytoluene,⁷ and vitamin E⁸ provides further evidence of a role for oxidative processes in the development of atherosclerosis.

Epidemiologic studies also indicate that antioxidants may have a role in preventing the development of coronary heart disease. Some studies indicate an inverse association between the intake of vitamin E and coronary heart disease,^{9,10} whereas others suggest that vitamin C¹¹ or provitamin A carotenoids¹² may be protective. The Iowa Women's Health Study, a prospective cohort study of postmenopausal women, provided an opportunity to examine whether the dietary intake of antioxidants is related to mortality from coronary heart disease.

METHODS

The study participants were recruited from a random sample of 99,826 women 55 to 69 years of age who had valid Iowa driver's li-

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censes in 1985. These women were sent a 16-page questionnaire in January 1986; 41,836 women returned it, and they form the cohort under study. The mortality rates of the cohort members and those who did not respond to the mailing were similar, except that smoking-related causes of death were more common among the women who did not respond.¹³

Dietary Assessment

The base-line questionnaire included questions concerning factors pertinent to the risk of coronary heart disease. A 127-item food-frequency questionnaire similar to that used in the 1984 survey of the Nurses' Health Study¹⁴ was also included. The list of foods was augmented by questions asking the respondent to specify the type of fat used, the brand of cooking oil, the names of other regularly consumed foods, and the brand names of multivitamin preparations and breakfast cereals, all of which were potential sources of vitamins. There were also questions about the current use and dosage of supplements of specific vitamins (such as vitamins A and E).

To evaluate the reliability of the questionnaire, we compared the vitamin intake in a subgroup of 44 women with their mean intake estimated from five 24-hour dietary-recall interviews.¹⁵ With regard to the total intake of vitamins A, E, and C, the correlation coefficients for the two instruments were 0.56, 0.55, and 0.76, respectively. With regard to vitamin intake excluding that from supplements, the corresponding coefficients were 0.14, 0.79, and 0.53. The validity of estimates of vitamin intake from food-frequency questionnaires has been examined in comparison with plasma levels of beta carotene ($r = 0.30$) and alpha-tocopherol ($r = 0.41$) in the Nurses' Health Study.¹⁶

Study Design

Women were excluded from the study if they had not reached menopause (569 women); if the food-frequency questionnaire had 30 or more items left blank (2751 women); or if their reported energy intake was implausibly high or low (<600 or ≥ 5000 kcal per day) (317 women). Women were also excluded if they reported at base line that a physician had told them they had angina or heart disease or had had a heart attack (3713 women). This left 34,486 women who were eligible for follow-up.

We followed the women annually by consulting the State Health Registry of Iowa, which collects information on deaths in Iowa. Deaths were also reported in response to follow-up questionnaires mailed in 1988, 1990, and 1992, and were identified by linking women who did not respond with the National Death Index. Women were

considered to have died of coronary heart disease if the cause of death was assigned to codes 410 through 414 or 429.2 of the *International Classification of Diseases, 9th Revision*. Although we did not validate this coding, other studies have found that the validity of death certificates listing coronary heart disease as the cause of death is relatively high.^{17,18} Many known risk factors for coronary heart disease were also evident in this cohort.¹⁹

The study design was approved by the Committee on the Use of Human Subjects in Research of the University of Minnesota.

Statistical Analysis

The length of follow-up for each woman was calculated as the number of days from the completion of the base-line questionnaire to the date of death or December 31, 1992, whichever came first. Among the women eligible for follow-up, 242 died of coronary heart disease.

We studied the association of vitamin intake with mortality from coronary heart disease. Dietary intake of vitamin A as retinol or provitamin A carotenoids was also assessed, because carotenoids have antioxidant properties but retinol does not. Because vitamins can be ingested from both foods and supplements, exposure to each vitamin was studied in three ways. First, the total intake of the vitamin from both food and supplements was determined. Second, intake of the vitamin from food alone was determined; this analysis was limited to women who had no supplemental intake of that vitamin. Finally, analyses of supplemental intake were conducted. Because in early 1986 supplemental vitamin A was derived almost exclusively from retinol, the analyses of supplemental vitamin A intake were not partitioned according to whether the vitamin was derived from retinol or carotene.

The association of vitamins A, E, and C with death from coronary heart disease was examined primarily by proportional-hazards regression analysis. Values for vitamin intake were categorized in quintiles or other categories as appropriate, and the mortality rate from coronary heart disease in each category was compared with that in the lowest intake category. The initial analyses examined associations adjusted for age. The analyses were also adjusted for other factors that were significant predictors of death from coronary heart disease or that substantially altered the risk estimates associated with vitamin intake. These included total energy intake, history of hypertension, history of diabetes mellitus, body-mass index (calculated as the weight in kilograms divided by the square of the height in meters), waist-to-hip ratio, history of cigarette smoking, level of physical activity, estrogen-replacement therapy, and alcohol intake.

The relative risk associated with a given category of vitamin intake was estimated by calculating the exponent of the proportional-hazards regression coefficient for that level of intake. P values for trend were determined, with each level of exposure weighted according to its median value.

RESULTS

As reported previously,¹⁹ recognized risk factors for coronary heart disease were evident in this cohort. Women who reported the following risk factors on the base-line questionnaire had higher age-adjusted risks of death from coronary heart disease than women without the risk factors: hypertension (relative risk, 2.21; 95 percent confidence interval, 1.70 to 2.86), diabetes mellitus (relative risk, 4.72; 95 percent confidence interval, 3.47 to 6.42), and current smoking (relative risk, 3.16; 95 percent confidence interval, 2.37 to 4.21). Women were at decreased risk if they reported a high degree of physical activity (relative risk as compared with women with a low degree of physical activity, 0.49; 95 percent confidence interval, 0.35 to 0.71) or the use of estrogen-replacement therapy (relative risk as compared with nonusers, 0.72; 95 percent confidence interval, 0.55 to 0.95). Higher body-mass indexes and higher waist-to-hip ratios were also associated with higher

age-adjusted risks of death from coronary heart disease (P<0.001 for both).

Table 1 shows the distribution of these risk factors according to the intake of vitamins E and C, both overall and from food only; the patterns observed for vitamin A were similar to those for vitamin E and are not shown. The quintiles with greater overall intake of vitamins were associated with lower mean waist-to-hip ratios, smaller proportions of current smokers, and larger proportions of women who were physically active or used estrogen-replacement therapy. Similar patterns were seen with regard to the intake of vitamins E and

Table 1. Association of Various Base-Line Factors with the Risk of Coronary Heart Disease in Postmenopausal Women, According to Intake of Vitamins E and C.*

| FACTOR† | QUINTILE OF VITAMIN INTAKE | | | | |
|--|----------------------------|-------|-------|-------|-------------|
| | 1 (LOWEST) | 2 | 3 | 4 | 5 (HIGHEST) |
| Vitamin E | | | | | |
| From food and supplements (n = 34,486) | | | | | |
| Age (yr) | 61.4 | 61.4 | 61.5 | 61.6 | 61.6 |
| Body-mass index | 27.2 | 27.1 | 27.2 | 26.6 | 26.6 |
| Waist-to-hip ratio | 0.843 | 0.838 | 0.836 | 0.835 | 0.831 |
| Current smoker (%) | 18.7 | 15.2 | 13.5 | 14.5 | 14.1 |
| Hypertension (%) | 38.8 | 37.0 | 35.9 | 35.4 | 34.0 |
| Diabetes mellitus (%) | 6.7 | 5.6 | 5.8 | 5.6 | 5.0 |
| Any estrogen-replacement therapy (%) | 34.0 | 35.6 | 35.7 | 40.2 | 45.0 |
| High level of physical activity (%) | 18.7 | 22.3 | 25.6 | 28.1 | 29.9 |
| From food only (n = 21,809) | | | | | |
| Age (yr) | 61.3 | 61.4 | 61.5 | 61.5 | 61.6 |
| Body-mass index | 27.2 | 26.2 | 27.0 | 27.2 | 27.2 |
| Waist-to-hip ratio | 0.844 | 0.840 | 0.837 | 0.836 | 0.839 |
| Current smoker (%) | 19.8 | 16.4 | 15.0 | 13.3 | 14.0 |
| Hypertension (%) | 39.0 | 38.1 | 36.9 | 36.3 | 35.2 |
| Diabetes mellitus (%) | 6.2 | 6.8 | 5.5 | 5.5 | 6.2 |
| Any estrogen-replacement therapy (%) | 33.6 | 34.8 | 36.0 | 35.6 | 35.5 |
| High level of physical activity (%) | 17.4 | 20.7 | 22.8 | 25.2 | 26.4 |
| Vitamin C | | | | | |
| From food and supplements (n = 34,486) | | | | | |
| Age (yr) | 61.1 | 61.5 | 61.6 | 61.7 | 61.6 |
| Body-mass index | 26.9 | 27.1 | 27.1 | 26.9 | 26.6 |
| Waist-to-hip ratio | 0.842 | 0.838 | 0.838 | 0.836 | 0.829 |
| Current smoker (%) | 22.0 | 13.9 | 12.9 | 12.4 | 14.9 |
| Hypertension (%) | 33.9 | 36.7 | 37.9 | 37.5 | 35.1 |
| Diabetes mellitus (%) | 4.9 | 6.3 | 6.2 | 6.0 | 5.3 |
| Any estrogen-replacement therapy (%) | 34.4 | 35.8 | 36.2 | 38.8 | 45.4 |
| High level of physical activity (%) | 16.7 | 22.2 | 26.0 | 28.7 | 31.0 |
| From food only (n = 18,905) | | | | | |
| Age (yr) | 61.0 | 61.3 | 61.6 | 61.7 | 61.7 |
| Body-mass index | 26.9 | 27.1 | 27.2 | 27.4 | 27.5 |
| Waist-to-hip ratio | 0.844 | 0.840 | 0.837 | 0.838 | 0.840 |
| Current smoker (%) | 25.6 | 16.2 | 13.3 | 11.6 | 11.0 |
| Hypertension (%) | 33.2 | 35.8 | 36.7 | 38.4 | 41.5 |
| Diabetes mellitus (%) | 4.3 | 5.7 | 6.6 | 6.7 | 8.2 |
| Any estrogen-replacement therapy (%) | 33.5 | 35.0 | 35.8 | 33.8 | 33.6 |
| High level of physical activity (%) | 14.7 | 19.8 | 22.2 | 25.1 | 28.8 |

*There were approximately equal numbers of women in each quintile in each analysis. The analyses of vitamin intake from food alone do not include women who used supplements containing the vitamin specified.

†Values shown for age, body-mass index, and waist-to-hip ratio are mean values for the women in the quintile. Percentages indicate the proportion of the women in the quintile who had the indicated factor.

Table 2. Relative Risks and 95 Percent Confidence Intervals (CI) of Death from Coronary Heart Disease (CHD), According to Quintile of Antioxidant Intake from Food and Supplements, among 34,486 Postmenopausal Women, 1986–1992.

| VARIABLE | QUINTILE OF VITAMIN INTAKE* | | | | | P VALUE FOR TREND |
|----------------------------|-----------------------------|------------------|------------------|------------------|------------------|-------------------|
| | 1 (LOWEST) | 2 | 3 | 4 | 5 (HIGHEST) | |
| Vitamin A | | | | | | |
| No. of deaths from CHD | 44 | 70 | 40 | 36 | 52 | |
| Vitamin A intake (IU/day) | <7264 | 7265–10,748 | 10,749–14,572 | 14,573–20,332 | ≥20,333 | |
| Relative risk (95% CI) | | | | | | |
| Age- and energy-adjusted | 1.0 | 1.46 (1.00–2.13) | 0.80 (0.52–1.24) | 0.68 (0.43–1.07) | 0.92 (0.60–1.41) | 0.12 |
| Multivariate adjusted† | 1.0 | 1.49 (0.98–2.28) | 0.89 (0.55–1.44) | 0.95 (0.59–1.54) | 1.22 (0.76–1.96) | 0.89 |
| Retinol | | | | | | |
| No. of deaths from CHD | 49 | 46 | 58 | 50 | 39 | |
| Retinol intake (IU/day) | ≤1244 | 1245–3026 | 3027–4899 | 4900–7539 | ≥7540 | |
| Relative risk (95% CI) | | | | | | |
| Age- and energy-adjusted | 1.0 | 0.82 (0.54–1.24) | 1.07 (0.72–1.57) | 0.89 (0.59–1.33) | 0.68 (0.44–1.05) | 0.11 |
| Multivariate adjusted† | 1.0 | 0.90 (0.57–1.41) | 1.13 (0.74–1.73) | 0.98 (0.62–1.53) | 0.80 (0.50–1.28) | 0.37 |
| Carotenoids | | | | | | |
| No. of deaths from CHD | 43 | 59 | 55 | 39 | 46 | |
| Carotenoid intake (IU/day) | ≤4421 | 4422–6087 | 6088–8856 | 8857–13,464 | ≥13,465 | |
| Relative risk (95% CI) | | | | | | |
| Age- and energy-adjusted | 1.0 | 1.29 (0.87–1.91) | 1.11 (0.74–1.66) | 0.77 (0.49–1.20) | 0.83 (0.53–1.29) | 0.06 |
| Multivariate adjusted† | 1.0 | 1.26 (0.81–1.95) | 1.18 (0.65–1.68) | 1.04 (0.65–1.68) | 1.03 (0.63–1.70) | 0.71 |
| Vitamin E | | | | | | |
| No. of deaths from CHD | 52 | 58 | 38 | 43 | 51 | |
| Vitamin E intake (IU/day) | <5.68 | 5.69–7.82 | 7.83–12.18 | 12.19–35.58 | ≥35.59 | |
| Relative risk (95% CI) | | | | | | |
| Age- and energy-adjusted | 1.0 | 0.95 (0.65–1.40) | 0.53 (0.34–0.84) | 0.61 (0.39–0.95) | 0.78 (0.52–1.18) | 0.88 |
| Multivariate adjusted† | 1.0 | 1.05 (0.69–1.69) | 0.52 (0.31–0.87) | 0.68 (0.41–1.10) | 0.96 (0.62–1.51) | 0.27 |
| Vitamin C | | | | | | |
| No. of deaths from CHD | 44 | 48 | 38 | 51 | 61 | |
| Vitamin C intake (mg/day) | ≤112.3 | 112.4–161.3 | 161.4–226.7 | 226.8–391.2 | ≥391.3 | |
| Relative risk (95% CI) | | | | | | |
| Age- and energy-adjusted | 1.0 | 1.00 (0.66–1.51) | 0.76 (0.49–1.18) | 1.00 (0.66–1.51) | 1.22 (0.82–1.82) | 0.11 |
| Multivariate adjusted† | 1.0 | 1.08 (0.69–1.69) | 0.85 (0.53–1.37) | 0.99 (0.61–1.59) | 1.49 (0.96–2.30) | 0.02 |

*There were approximately equal numbers of women in each quintile in each analysis.

†This analysis was adjusted for age, total energy intake, body-mass index, waist-to-hip ratio, pack-years of cigarette smoking (none, 1 to 19, 20 to 39, or 40 or more), hypertension (yes or no), diabetes mellitus (yes or no), oral-contraceptive use (ever or never), estrogen-replacement therapy (current, former, or never), physical activity (low, moderate, or high level), alcohol intake (none, <4 g per day, from 4 to <10 g per day, or ≥10 g per day), marital status (currently married, never married, separated or divorced, or widowed), and level of educational attainment (no high-school diploma, high-school diploma, college or vocational school but no degree, or college degree).

A from food sources alone. With regard to vitamin C derived from food, higher intake was associated with smaller proportions of current smokers and greater physical activity but also with larger proportions of women with hypertension and diabetes mellitus.

Table 2 shows age- and energy-adjusted relative risks of death from coronary heart disease according to overall vitamin intake. With regard to the intake of vitamin A, retinol, and carotenoids, there were suggestions of inverse associations. In the case of vitamin A, the association showed an inconsistent dose response, with an elevated risk in the second quintile of intake (relative risk as compared with the lowest quintile, 1.46) and a decreased risk in the fourth quintile (relative risk, 0.68). Overall vitamin E intake also appeared to be inversely associated with the risk of death from coronary heart disease; there were significantly decreased risks in the third (relative risk, 0.53) and fourth (relative risk, 0.61) quintiles of intake, but the overall trend was not statistically significant. Overall intake of vitamin C was not associated with the risk of death from coronary heart disease.

Associations of overall vitamin intake with the risk of

death from coronary heart disease after adjustment for potential confounders are also shown in Table 2. The suggested inverse associations with the intake of vitamins A and E, retinol, and carotenoid were weakened after multivariate adjustment. There was a suggestion of a positive association between overall vitamin C intake and the risk of death from coronary heart disease (relative risk in highest vs. lowest quintile, 1.49; 95 percent confidence interval, 0.96 to 2.30).

Vitamin E intake was inversely associated with the risk of death from coronary heart disease among women who did not take vitamin E supplements (relative risks from lowest to highest quintile of intake, 1.0, 0.68, 0.71, 0.42, and 0.42; P for trend = 0.008) (Table 3). In contrast, no association was observed for vitamin A, retinol, carotenoids, or vitamin C derived from food. After adjustment for potential confounders, the inverse association with vitamin E derived from food remained (relative risks from lowest to highest quintile of intake, 1.0, 0.70, 0.76, 0.32, and 0.38; P for trend = 0.004).

Table 4 shows the association of supplemental vitamin intake with the risk of death from coronary heart disease. A relatively low intake (1 to 5000 IU per day)

Table 3. Relative Risks and 95 Percent Confidence Intervals (CI) of Death from Coronary Heart Disease (CHD), According to Quintile of Antioxidant Intake from Food among Postmenopausal Women Who Did Not Take Supplemental Vitamins, 1986–1992.

| VARIABLE | QUINTILE OF VITAMIN INTAKE FROM FOOD* | | | | | P VALUE FOR TREND |
|----------------------------|---------------------------------------|------------------|------------------|------------------|------------------|-------------------|
| | 1 (LOWEST) | 2 | 3 | 4 | 5 (HIGHEST) | |
| Vitamin A† | | | | | | |
| No. of deaths from CHD | 25 | 40 | 50 | 24 | 35 | |
| Vitamin A intake (IU/day) | ≤6207 | 6208–8774 | 8775–11,965 | 11,966–16,755 | ≥16,756 | |
| Relative risk (95% CI) | | | | | | |
| Age- and energy-adjusted | 1.0 | 1.44 (0.87–2.38) | 1.70 (1.04–2.77) | 0.77 (0.43–1.38) | 0.99 (0.57–1.74) | 0.25 |
| Multivariate adjusted‡ | 1.0 | 1.59 (0.92–2.75) | 1.76 (1.02–3.04) | 0.94 (0.50–1.77) | 1.25 (0.68–2.31) | 0.83 |
| Retinol† | | | | | | |
| No. of deaths from CHD | 36 | 24 | 33 | 50 | 31 | |
| Retinol intake (IU/day) | ≤925 | 926–1676 | 1677–3324 | 3325–4576 | ≥4577 | |
| Relative risk (95% CI) | | | | | | |
| Age- and energy-adjusted | 1.0 | 0.57 (0.33–0.96) | 0.73 (0.44–1.19) | 1.16 (0.74–1.80) | 0.63 (0.37–1.06) | 0.87 |
| Multivariate adjusted‡ | 1.0 | 0.51 (0.28–0.92) | 0.81 (0.47–1.38) | 1.12 (0.69–1.82) | 0.60 (0.34–1.07) | 0.91 |
| Carotenoids† | | | | | | |
| No. of deaths from CHD | 28 | 38 | 43 | 29 | 36 | |
| Carotenoid intake (IU/day) | ≤4349 | 4350–5959 | 5960–8455 | 8456–13,026 | ≥13,027 | |
| Relative risk (95% CI) | | | | | | |
| Age- and energy-adjusted | 1.0 | 1.26 (0.77–2.06) | 1.32 (0.81–2.15) | 0.87 (0.51–1.48) | 0.96 (0.56–1.63) | 0.34 |
| Multivariate adjusted‡ | 1.0 | 1.21 (0.71–2.06) | 1.33 (0.78–2.25) | 1.00 (0.56–1.78) | 1.19 (0.67–2.12) | 0.89 |
| Vitamin E§ | | | | | | |
| No. of deaths from CHD | 36 | 30 | 36 | 25 | 35 | |
| Vitamin E intake (IU/day) | ≤4.91 | 4.92–6.24 | 6.25–7.62 | 7.63–9.63 | ≥9.64 | |
| Relative risk (95% CI) | | | | | | |
| Age- and energy-adjusted | 1.0 | 0.68 (0.42–1.12) | 0.71 (0.43–1.17) | 0.42 (0.24–0.75) | 0.42 (0.22–0.82) | 0.008 |
| Multivariate adjusted‡ | 1.0 | 0.70 (0.41–1.18) | 0.76 (0.44–1.29) | 0.32 (0.17–0.63) | 0.38 (0.18–0.80) | 0.004 |
| Vitamin C¶ | | | | | | |
| No. of deaths from CHD | 23 | 28 | 26 | 24 | 40 | |
| Vitamin C intake (mg/day) | ≤87.3 | 87.4–120.5 | 120.6–151.7 | 151.8–196.2 | ≥196.3 | |
| Relative risk (95% CI) | | | | | | |
| Age- and energy-adjusted | 1.0 | 1.11 (0.64–1.93) | 0.96 (0.55–1.70) | 0.84 (0.47–1.51) | 1.27 (0.72–2.23) | 0.60 |
| Multivariate adjusted‡ | 1.0 | 1.25 (0.68–2.30) | 1.15 (0.61–2.15) | 0.92 (0.48–1.78) | 1.43 (0.75–2.70) | 0.47 |

*There were approximately equal numbers of women in each quintile in each analysis.

†In the age- and energy-adjusted analyses, this cohort included 22,790 women, with 174 deaths from coronary heart disease; in the multivariate analyses, the cohort included 20,572 women, with 149 deaths from coronary heart disease.

‡Adjusted for the covariates listed in the second footnote to Table 2.

§In the age- and energy-adjusted analyses, this cohort included 21,809 women, with 162 deaths from coronary heart disease; in the multivariate analyses, the cohort included 19,687 women, with 138 deaths from coronary heart disease.

¶In the age- and energy-adjusted analyses, this cohort included 18,905 women, with 141 deaths from coronary heart disease; in the multivariate analyses, the cohort included 17,107 women, with 122 deaths from coronary heart disease.

of supplemental vitamin A was associated with a decreased risk of death from coronary heart disease (age-adjusted relative risk, 0.67; 95 percent confidence interval, 0.47 to 0.95), but higher intake was not. Nor were the data on vitamin E and C supplements consistent with an inverse association. Multivariate analyses also suggested no association of supplemental vitamin intake with the risk of death from coronary heart disease.

That the intake of vitamin E derived from food, but not from supplements, was inversely associated with mortality from coronary heart disease suggested that vitamin E consumed in food may be a marker for other dietary factors associated with the risk of coronary heart disease. We conducted further analyses with adjustment for various factors, including the intake of carotenoids, folic acid, dietary fiber, linoleic acid, linolenic acid, total polyunsaturated fatty acids, meat, and other foods and food groups. Adjusting for these factors did not substantially alter the inverse association observed with vitamin E. For example, after adjustment for linoleic acid intake, the relative risks of death from coronary

heart disease associated with levels of vitamin E derived from food, from the lowest to the highest quintile of intake, were 1.0, 0.71, 0.79, 0.35, and 0.44 (P for trend=0.019). This was the largest attenuation of the association observed after adjustment for any of the factors examined.

Table 5 shows a multivariate analysis of the association of the risk of death from coronary heart disease with the intake of specific foods that are dietary sources of vitamin E. Intake of the following was inversely associated with the risk of death from coronary heart disease: margarine (P for trend=0.048), nuts and seeds (P for trend=0.016), and mayonnaise or creamy salad dressings (P for trend=0.069). Additional adjustment for vitamin E weakened the associations, suggesting that they could be attributed in part to the intake of vitamin E.

We investigated the weak positive association of vitamin C with coronary heart disease further by excluding deaths during the first two years of follow-up, since women who were ill early in the study may have taken

Table 4. Relative Risks and 95 Percent Confidence Intervals (CI) of Death from Coronary Heart Disease (CHD), According to Category of Antioxidant Intake from Supplements, among 34,486 Postmenopausal Women, 1986–1992.

| VARIABLE | CATEGORY OF VITAMIN INTAKE FROM SUPPLEMENTS | | | | | P VALUE FOR TREND |
|---------------------------------|---|------------------|------------------|------------------|------------------|-------------------|
| | 1 (LOWEST) | 2 | 3 | 4 (HIGHEST) | | |
| Vitamin A | | | | | | |
| Dose (IU/day) | 0 | 1–5000 | 5001–10,000 | >10,000 | | |
| Women in category (% of cohort) | 66.1 | 20.9 | 8.6 | 4.5 | | |
| No. of deaths from CHD | 174 | 37 | 19 | 12 | | |
| Person-yr of follow-up | 153,933 | 48,640 | 20,002 | 10,319 | | |
| Relative risk (95% CI) | | | | | | |
| Age-adjusted | 1.0 | 0.67 (0.47–0.95) | 0.82 (0.51–1.31) | 1.01 (0.56–1.81) | | 0.81 |
| Multivariate adjusted* | 1.0 | 0.66 (0.44–1.00) | 1.02 (0.62–1.67) | 1.29 (0.70–2.39) | | 0.22 |
| Vitamin E | | | | | | |
| Dose (IU/day) | 0 | 1–25 | 26–100 | 101–250 | >250 | |
| Women in category (% of cohort) | 63.2 | 15.2 | 8.7 | 3.1 | 9.8 | |
| No. of deaths from CHD | 162 | 30 | 21 | 8 | 21 | |
| Person-yr of follow-up | 147,277 | 35,326 | 20,218 | 7,307 | 22,766 | |
| Relative risk (95% CI) | | | | | | |
| Age-adjusted | 1.0 | 0.76 (0.51–1.12) | 0.95 (0.60–1.50) | 0.97 (0.48–1.97) | 0.82 (0.52–1.29) | 0.78 |
| Multivariate adjusted* | 1.0 | 0.83 (0.54–1.28) | 0.95 (0.56–1.59) | 1.25 (0.58–2.68) | 1.09 (0.67–1.77) | 0.39 |
| Vitamin C | | | | | | |
| Dose (mg/day) | 0 | 1–200 | 201–500 | 501–1000 | >1,000 | |
| Women in category (% of cohort) | 54.8 | 25.5 | 8.7 | 7.6 | 3.5 | |
| No. of deaths from CHD | 141 | 51 | 27 | 15 | 8 | |
| Person-yr of follow-up | 127,695 | 59,436 | 20,062 | 17,632 | 8,069 | |
| Relative risk (95% CI) | | | | | | |
| Age-adjusted | 1.0 | 0.77 (0.56–1.05) | 1.20 (0.79–1.80) | 0.76 (0.45–1.30) | 0.91 (0.45–1.86) | 0.90 |
| Multivariate adjusted* | 1.0 | 0.81 (0.56–1.16) | 1.37 (0.87–2.14) | 0.99 (0.57–1.74) | 0.74 (0.30–1.83) | 0.60 |

*Adjusted for the covariates listed in the second footnote to Table 2.

vitamin C. However, this exclusion did not substantially alter the association (multivariate adjusted relative risks from lowest to highest quintile of intake, 1.0, 1.20, 0.95, 1.09, and 1.69; P for trend = 0.017). The findings for vitamins A and E were also unaffected by the exclusion of early deaths.

DISCUSSION

This prospective study of postmenopausal women provides evidence of an inverse association of coronary heart disease with the intake of vitamin E from food. Women in the highest quintile of vitamin E intake had less than half the risk of death from coronary heart disease of women in the lowest quintile. This inverse association was not seen for the intake of vitamin E from supplements. There was also a suggestion of an inverse association between mortality from coronary heart disease and overall vitamin A intake, but this association was no longer apparent after adjustment for other risk factors. Vitamin C appeared, if anything, to be positively associated with the risk of death from coronary heart disease.

The inverse association of vitamin E intake with the risk of death from coronary heart disease is generally consistent with the findings of a growing number of epidemiologic studies. Prospective studies of 39,910 male health professionals⁹ and 87,245 female nurses¹⁰ demonstrated that the risk of incident coronary disease was approximately 40 percent lower in those who consumed vitamin E supplements than in those who did not. In

the study of male health professionals, no association was observed between vitamin E derived from food and coronary heart disease.⁹ A nonsignificant inverse association with vitamin E from food sources was suggested in the study of nurses.¹⁰ In a cohort of 2226 middle-aged men, Meyer et al.²⁰ also reported a substantially reduced risk of death from coronary disease among users of vitamin E supplements.

In support of an inverse association of vitamin E intake from food with mortality from coronary heart disease, we have previously reported²¹ that nut consumption is inversely associated with coronary mortality in this cohort, a finding confirmed by these updated analyses; nuts are among the more concentrated food sources of vitamin E. An inverse association of nut consumption with mortality from coronary heart disease was also reported in a prospective study of Seventh-Day Adventists.²² The intake of other foods that provide vitamin E, including margarine and mayonnaise, also appeared to be inversely associated with coronary mortality in the present study. Although these foods are sources of vitamin E (and fat) in the diet, they are distinct in other respects. For example, nuts and seeds also contain protein and carbohydrates, whereas margarine does not, and mayonnaise and creamy salad dressings may contain cholesterol. Adjustment for vitamin E intake weakened these associations, suggesting they were due in part to the vitamin E content of the foods. The inverse association seen in the case of margarine contrasts with observations in the Nurses' Health Study,²³

Table 5. Multivariate Adjusted Relative Risks and 95 Percent Confidence Intervals (CI) of Death from Coronary Heart Disease (CHD), According to Quartile of Intake of Certain Foods Containing Vitamin E, among 19,411 Postmenopausal Women Who Did Not Take Vitamin Supplements, 1986–1992.*

| VARIABLE | CATEGORY OF INTAKE | | | | P VALUE FOR TREND |
|--|--------------------|------------------|------------------|------------------|-------------------|
| | 1 (LOWEST) | 2 | 3 | 4 (HIGHEST) | |
| Margarine | | | | | |
| No. of times eaten per week | 0 | 0.5–3 | 4–7 | >7 | |
| Relative risk (95% CI) | | | | | |
| Multivariate adjusted | 1.0 | 0.73 (0.41–1.30) | 0.60 (0.36–1.02) | 0.59 (0.36–0.97) | 0.048 |
| Also adjusted for vitamin E | 1.0 | 0.75 (0.42–1.33) | 0.64 (0.38–1.08) | 0.65 (0.39–1.07) | 0.12 |
| Nuts and seeds | | | | | |
| No. of times eaten per month | 0 | 1 or 2 | 3 or 4 | >4 | |
| Relative risk (95% CI) | | | | | |
| Multivariate adjusted | 1.0 | 0.98 (0.57–1.68) | 0.96 (0.56–1.64) | 0.60 (0.36–1.01) | 0.016 |
| Also adjusted for vitamin E | 1.0 | 1.02 (0.59–1.75) | 1.04 (0.60–1.78) | 0.72 (0.42–1.23) | 0.11 |
| Mayonnaise or creamy salad dressing | | | | | |
| No. of times eaten per week | 0 | 0.5–1 | 2 or 3 | >3 | |
| Relative risk (95% CI) | | | | | |
| Multivariate adjusted | 1.0 | 0.71 (0.46–1.11) | 0.46 (0.26–0.82) | 0.52 (0.25–1.09) | 0.069 |
| Also adjusted for vitamin E | 1.0 | 0.73 (0.48–1.18) | 0.56 (0.31–1.04) | 0.70 (0.31–1.57) | 0.40 |

*These analyses are adjusted for the covariates listed in the footnote to Table 2.

which attributed a positive association with coronary disease to the intake of trans fatty acids.

In a prospective study in Finland, Knekt et al.²⁴ also reported a substantial inverse association (relative risk in highest vs. lowest third of intake, 0.35) between vitamin E derived from food and coronary mortality among 2385 women; a similar inverse association was reported among the 2748 men in their cohort. They also reported a nonsignificant inverse association between margarine intake and coronary mortality among men, but not among women. As in our study, this association was diminished after adjustment for the intake of antioxidant vitamins.

Although we cannot eliminate the possibility that vitamin E derived from food is a marker for other dietary factors related to the risk of coronary heart disease, we could not identify any such factor. It is clear from the analyses presented here, for example, that provitamin carotenoids and vitamin C are not associated with a decreased risk. The intake of folate, another vitamin concentrated in vegetables that may decrease the risk of atherosclerosis,^{25–27} was also not inversely associated with mortality from coronary heart disease in this cohort (data not shown). Other dietary factors that are associated with vitamin E include linoleic acid, linolenic acid, total polyunsaturated fatty acids, and dietary fiber. However, the inverse association between the risk of death from coronary heart disease and the intake of vitamin E derived from food remained after we adjusted the analysis for these and other dietary factors.

Vitamin E intake is also associated with a more healthful cardiovascular risk profile (Table 1). Although

the inverse association remained after adjustment for several risk factors, the levels of risk factors were reported by the patients, and there may be some residual confounding. We also could not take into account potential confounders such as blood lipid levels or the use of nonsteroidal antiinflammatory medications. However, vitamin E intake is unlikely to be associated with blood lipid levels.⁹

As for our failure to observe an inverse association between supplemental intake of vitamin E and coronary mortality, we had no information on the duration of supplement intake. In other studies,^{9,10} an inverse association was found among persons who had been taking supplemental vitamin E for at least two years. Including recent, short-term users among long-term users would weaken the overall effect of supplemental vitamin E intake if such an effect were limited to long-term users. In addition, relatively few women in our cohort consumed high doses

of supplemental vitamin E. This would compromise the ability of our study to detect associations with mortality from coronary heart disease if such an effect is most apparent at high doses. Although the results of a Finnish trial of supplementation with beta carotene (20 mg per day) and alpha-tocopherol (50 mg per day) among smokers also do not support an effect of these supplements on the risk of death from coronary heart disease,²⁸ the dosages may have been too low to affect mortality.

As with many epidemiologic studies of diet, inaccuracies of measurement are a limitation. The random misclassification of dietary habits generally decreases the ability to detect associations between diet and disease.²⁹ Thus, the observed inverse associations of coronary mortality with vitamin E derived from food are all the more striking. The effect of changes in diet during follow-up also creates difficulties in interpreting these findings definitively. In the case of carotenoids, there has been increased awareness of the potential of beta carotene to prevent cancer and the greater availability of supplements containing beta carotene.

Given these caveats, the findings presented here do not constitute definitive evidence of an inverse association between vitamin E intake and mortality from coronary heart disease. Clarification of the effects of supplemental vitamin E in an older population appears warranted, given our findings and those of the Finnish trial.²⁸ More definitive evidence of an effect of supplemental vitamin E must await the results of clinical trials such as the Women's Health Study,³⁰ which is testing this association in younger women. However, that study

was not designed to test the association of either vitamin E intake from food or dietary changes with the risk of coronary heart disease. Our findings suggest that modifying dietary habits to increase vitamin E intake may also be worthwhile in preventing coronary heart disease. This study of older women provides information that is important in planning intervention trials in the elderly. The observations with regard to vitamins A and C are similarly not definitive, but they suggest that increased intake of these vitamins is not likely to lower the risk of death from coronary heart disease.

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