LESS IS MORE

B Vitamin and/or ω-3 Fatty Acid Supplementation and Cancer

Ancillary Findings From the Supplementation With Folate, Vitamins B_6 and B_{12}, and/or Omega-3 Fatty Acids (SU.FOL.OM3) Randomized Trial

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Background: To advance knowledge about the cancer-chemopreventive potential of individual nutrients, we investigated the effects of B vitamin and/or ω-3 fatty acid supplements on cancer outcomes among survivors of cardiovascular disease.

Methods: This was an ancillary study of the Supplementation With Folate, Vitamins B_6 and B_{12} and/or Omega-3 Fatty Acids (SU.FOL.OM3) secondary prevention trial (2003-2009). In all, 2501 individuals aged 45 to 80 years were randomized in a 2 × 2 factorial design to one of the following 4 daily supplementation groups: (1) 5-methyltetrahydrofolate (0.56 mg), pyridoxine hydrochloride (vitamin B_6; 3 mg) and cyanocobalamin (vitamin B_{12}; 0.02 mg); (2) eicosapentaenoic and docosahexaenoic acid (600 mg) in a 2:1 ratio; (3) B vitamins and ω-3 fatty acids; or (4) placebo. Overall and sex-specific hazard ratios (HRs) and 95% CIs regarding the cancer outcomes were estimated with Cox proportional hazards models.

Results: After 5 years of supplementation, incident cancer was validated in 7.0% of the sample (145 events in men and 29 in women), and death from cancer occurred in 2.3% of the sample. There was no association between cancer outcomes and supplementation with B vitamins (HR, 1.15 [95% CI, 0.85-1.55]) and/or ω-3 fatty acids (HR, 1.17 [95% CI, 0.87-1.58]). There was a statistically significant interaction of treatment by sex, with no effect of treatment on cancer risk among men and increased cancer risk among women for ω-3 fatty acid supplementation (HR, 3.02 [95% CI, 1.33-6.89]).

Conclusion: We found no beneficial effects of supplementation with relatively low doses of B vitamins and/or ω-3 fatty acids on cancer outcomes in individuals with prior cardiovascular disease.

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PROPER NUTRITIONAL STATUS IS considered protective against cancer; however, much is unknown regarding the roles of individual nutrients in different populations.[1,2] Cell differentiation and chromosomal stability are modulated through DNA methylation, which uses methyl groups supplied by various nutrients.[2,3] Folate deficiency, for example, is considered a potentiator because it could alter DNA methylation, thus disrupting DNA synthesis/repair.[2,4,5] The chemopreventive properties of the vitamin B group have been rigorously investigated with respect to colorectal carcinogenesis.[4-7] Reviews and meta-analyses of observational studies suggest beneficial effects regarding colorectal cancer risk[6-9]; however, inconsistencies in the findings are common.[10,11]

Evidence about cancer risk from randomized controlled trials (RCTs) is also equivocal. A small RCT involving individuals with gastritis found significant protective effects of folic acid, 20 mg/d, and vitamin B_{12}, 1 mg/mo, on gastrointestinal cancer.[12] A larger RCT in individuals with prior colorectal adenoma reported significantly higher noncolorectal cancer rates in those treated with folic acid, 1 mg/d, for at least 3 years compared with their counterparts in the placebo group, with the difference driven by prostate cancer.[13] Combined analyses of the Norwegian Vitamin Trial (NORVIT) and Western Norway B

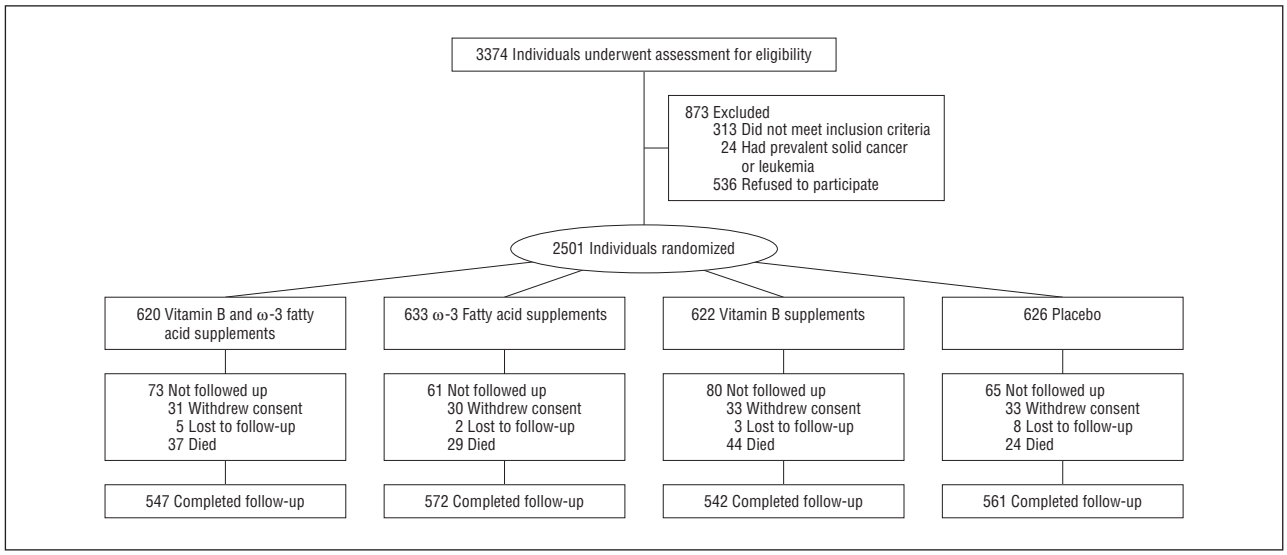

Figure. Flowchart of study participants.

Vitamin Intervention Trial (WENBIT) RCTs revealed a more than 20% higher cancer risk in survivors of ischemic heart disease treated with folic acid (0.8 mg/d) and vitamin B_{12} (0.4 mg/d) compared with those treated with vitamin B_6 (40 mg/d) or placebo.[14] However, a recent meta-analysis of large RCTs (including NORVIT and WENBIT) with participants at increased risk for cardiovascular disease (CVD) did not find an effect of folic acid supplementation on cancer incidence (and no heterogeneity by sex).[15] Overall, the chemopreventive properties of vitamin B supplementation regarding specific cancer sites and in specific populations are presently unclear.

Long-chain polyunsaturated fatty acids of the ω-3 series represent another class of nutrients that has received attention in the chemoprevention literature.[16,17] Via suppression of arachidonic acid–derived eicosanoid biosynthesis, influence on transcription factor activity, and signal transduction, ω-3 fatty acids could restrict tumor cell proliferation by increasing apoptotic potential along the crypt axis and could modulate inflammation and immunity.[2,16,17] A small RCT demonstrated protection by ω-3 fatty acids against early genotoxic markers for skin cancer.[18] However, RCTs have focused on the cancer-treating rather than cancer-preventive properties of these nutrients. Evidence from epidemiological studies is heterogeneous and their methodologic quality has been questioned.[19-22] Given the insufficient and inconclusive evidence, herein we present secondary analyses of data from the Supplementation With Folate, Vitamins B_6 and B_{12} and/or Omega-3 Fatty Acids (SU.FOL.OM3) RCT assessing the effects of several B vitamins and/or ω-3 fatty acids on cancer outcomes.

METHODS

STUDY DESIGN AND PARTICIPANTS

The SU.FOL.OM3 RCT was conducted in France from February 1, 2003, through July 1, 2009.[23,24] Individuals aged 45 to 80 years who had experienced an acute myocardial infarction, unstable angina, or ischemic stroke within the preceding 12 months were eligible for recruitment (**Figure**) via a network of 417 physicians. Individuals with a history of noncardiovascular disease (eg, solid cancer and leukemia) and with expected survival of less than 5 years were ineligible.[23] The trial's primary outcomes were recurrent myocardial infarction, stroke, and CVD mortality. The design, implementation, and principal findings of the study have been described previously.[23,24] Written informed consent was provided by all participants, and the protocol was approved by the respective ethics and information protection committees.[24]

RANDOMIZATION AND INTERVENTION

After stratification by sex, age, prior CVD, and recruitment center, the participants were randomized in a 2×2 factorial design to one of the following 4 groups, with supplements given as 2 capsules to be taken once daily: (1) B vitamins 5-methyltetrahydrofolate (0.56 mg), pyridoxine hydrochloride (vitamin B_6; 3 mg), and cyanocobalamin (vitamin B_{12}; 0.02 mg); (2) ω-3 fatty acids eicosapentaenoic and docosahexaenoic acid, 600 mg, in a ratio of 2:1; (3) B vitamins and ω-3 fatty acids; or (4) placebo. Details about the supplementation are available elsewhere.[24]

OUTCOME ASSESSMENT

All health events were reported biannually by the treating physicians and/or the participants. On notification of a suspected major health event, all relevant medical records were solicited. Regarding cancer (the main outcome in this analysis), all reported cases were confirmed by pathology reports. Cancer diagnosis was classified according to the *International Statistical Classification of Diseases, 10th Revision*. Guided by the trial's steering committee expert decision, we included cancer diagnoses within the following codes or code ranges: C00 to C78, C81 to C97, D03, D09, D45, and D46. We also investigated the effects of the supplementation on cancer mortality, which was adjudicated by 2 independent physician committees blinded to treatment allocation.[24]

COVARIATES

We assessed sociodemographic, behavioral, and clinical characteristics and concentrations of folate, vitamin B_{12}, vitamin B_6, homocysteine, cholesterol, triglycerides, creatinine, and fasting glu-

Table 1. Baseline Characteristics by Supplementation Group

Characteristic	Supplementation Group[a]					
	Vitamin B			ω-3 Fatty Acids		
	Yes (n = 1242)	No (n = 1259)	*P* Value[b]	Yes (n = 1253)	No (n = 1248)	*P* Value[b]
Demographic						
Age, mean (SD), y	61.4 (9.0)	61.3 (9.1)	.90	61.3 (9.3)	61.4 (8.8)	.80
Female	252 (20.3)	262 (20.8)	.75	259 (20.7)	255 (20.4)	.88
Married	889 (71.6)	906 (72.0)	.91	893 (71.3)	902 (72.3)	.78
Education <high school diploma	745 (60.0)	740 (58.8)	.49	739 (59.0)	746 (59.8)	.83
Employed	437 (35.2)	453 (36.0)	.77	454 (36.2)	436 (34.9)	.41
Foreign born	154 (12.4)	150 (11.9)	.71	152 (12.1)	152 (12.2)	.97
Behavioral						
Current smoker	136 (11.0)	133 (10.6)	.75	139 (11.1)	130 (10.4)	.52
Former smoker	752 (60.5)	765 (60.8)	.94	742 (59.2)	775 (62.1)	.25
Current alcohol use	288 (23.2)	325 (25.8)	.11	307 (24.5)	306 (24.5)	.82
Current aspirin use	1153 (92.8)	1183 (94.0)	.26	1164 (92.9)	1172 (93.9)	.31
Clinical, mean (SD)						
BMI	27.7 (4.2)	27.5 (3.9)	.28	27.6 (4.2)	27.6 (3.9)	.91
Systolic BP, mm Hg	133.3 (21.7)	133.4 (21.0)	.87	133.7 (21.7)	133.1 (21.1)	.49
Diastolic BP, mm Hg	83.2 (12.5)	83.1 (12.1)	.80	83.5 (12.3)	82.9 (12.3)	.25
Biological, median (IQR)						
Serum folate level, ng/mL	6.7 (3.4)	6.8 (3.6)	.54	6.7 (3.6)	6.8 (3.5)	.32
Plasma vitamin B_6 level, ng/mL	9.3 (5.8)	9.4 (6.3)	.66	9.3 (6.1)	9.3 (5.9)	.37
Serum vitamin B_{12} level, pg/mL	360.0 (161.0)	372.0 (174.0)	.09	363.0 (170.0)	367.0 (164.0)	.29
Plasma EPA level, %	1.1 (0.9)	1.2 (0.9)	.01	1.1 (0.9)	1.2 (0.9)	.98
Plasma DHA level, %	2.5 (1.2)	2.6 (1.2)	.12	2.5 (1.2)	2.6 (1.2)	.40
Plasma homocysteine level, mg/L	1.8 (0.7)	1.7 (0.7)	.06	1.7 (0.7)	1.7 (0.7)	.25
Plasma creatinine level, mg/dL	0.9 (0.2)	0.9 (0.2)	.30	0.9 (0.2)	0.9 (0.2)	.39
Plasma fasting glucose level, mg/dL	99.1 (18.0)	97.3 (18.0)	.12	99.1 (18.0)	97.3 (18.0)	.95
Plasma TC level, mg/dL	173.7 (54.1)	173.7 (54.1)	.27	173.7 (54.1)	173.7 (54.1)	.80
Plasma HDL-C level, mg/dL	46.3 (15.4)	42.5 (15.4)	.37	46.3 (11.6)	42.5 (15.4)	.49
Plasma LDL-C level, mg/dL	104.2 (42.5)	104.2 (42.5)	.60	104.2 (42.5)	104.2 (42.5)	.49
Plasma triglyceride level, mg/dL	115.0 (70.8)	106.2 (70.8)	.05	106.2 (70.8)	106.2 (70.8)	.09
CVD history						
Myocardial infarction	568 (45.7)	582 (46.2)	.80	580 (46.3)	570 (45.7)	76
Unstable angina	344 (27.7)	369 (29.3)	.37	361 (28.8)	352 (28.2)	.74
Ischemic stroke	330 (26.6)	308 (24.5)	.23	312 (24.9)	326 (26.1)	.48

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

SI conversion factors: To convert TC, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; creatinine to micromoles per liter, multiply by 88.4; folate to nanomoles per liter, multiply by 2.266; glucose to millimoles per liter, multiply by 0.0555; homocysteine to micromoles per liter, multiply by 7.397; triglycerides to millimoles per liter, multiply by 0.0113; vitamin B_6 to nanomoles per liter, multiply by 4.046; and vitamin B_{12} to picomoles per liter, multiply by 0.7378.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Based on χ^2 tests, unpaired *t* tests, or Wilcoxon rank sum test as appropriate.

cose. All blood samples were treated and stored and all biomarkers measured according to strict protocol guidelines.[24]

STATISTICAL ANALYSIS

Whereas synergism between the ω-3 fatty acids and B vitamins was not expected,[25] the factorial design necessitated the assessment of interaction. Because these tests did not reveal any effect modification ($P = .35$), we evaluated the effect of B vitamins (comparing individuals receiving B vitamins alone or combined with ω-3 fatty acids with individuals not receiving B vitamins) and the effect of ω-3 fatty acids (comparing individuals receiving ω-3 fatty acids alone or combined with B vitamins with individuals not receiving ω-3 fatty acids) regarding cancer outcomes (significance level, .05, 2 sided). Baseline characteristics and group comparability were explored with χ^2 tests, unpaired *t* tests, and Wilcoxon rank sum test. We strove to specify our models well, adjusting for the most pertinent covariates to minimize the potential for type I error. Consistent with knowledge about sex differences in cancer incidence, we performed tests for interaction between sex and each supplement type. Because time from the detrimental exposure to a clinically detectable tumor (carcinogenesis) could be measured in decades,[1,2] any potential role of the supplements would pertain to cancer progression, not initiation.

For the statistical models, the participants contributed time-at-risk (in years) up to the date of the initial cancer diagnosis, the date of the last returned questionnaire, or July 1, 2009 (the scheduled end of the trial), whichever occurred first. The hazard ratios (HRs) and 95% CIs associated with the effect of group assignment on cancer outcomes were estimated with Cox proportional hazards models. The participants' ages were the time scale; thus, all HR estimates are age adjusted. The model's proportionality assumption was evaluated graphically and was met for assignment to B vitamins (yes/no) and ω-3 fatty acids (yes/no). We conducted analyses using commercially available software (SAS, version 9.1; SAS Institute, Inc) according to the intent-to-treat principle.

Table 2. Baseline Characteristics by Sex and Supplementation Group

Characteristic	Supplementation Group[a]					
	Men					
	Vitamin B			ω-3 Fatty Acids		
	Yes (n = 990)	No (n = 997)	*P* Value[b]	Yes (n = 994)	No (n = 993)	*P* Value[b]
Demographic						
Age, mean (SD), y	60.9 (8.8)	60.8 (8.8)	.78	60.8 (8.9)	60.9 (8.6)	.72
Married	746 (75.4)	756 (75.8)	.93	749 (75.4)	753 (75.8)	.99
Education <high school diploma	554 (56.0)	558 (56.0)	.99	550 (55.3)	562 (56.6)	.60
Employed	383 (38.7)	395 (39.6)	.82	396 (39.8)	382 (38.5)	.49
Foreign born	130 (13.1)	122 (12.2)	.55	123 (12.4)	129 (13.0)	.68
Behavioral						
Current smoker	120 (12.1)	107 (10.7)	.32	119 (12.0)	108 (10.9)	.40
Former smoker	652 (65.9)	670 (67.2)	.59	654 (65.8)	668 (67.3)	.68
Current alcohol use	269 (27.2)	309 (31.0)	.03	289 (29.1)	289 (29.1)	.93
Current aspirin use	930 (93.9)	945 (94.8)	.41	932 (93.8)	943 (95.0)	.25
Clinical, mean (SD)						
BMI	27.6 (3.8)	27.5 (3.5)	.78	27.5 (3.8)	27.6 (3.5)	.36
Systolic BP, mm Hg	133.1 (21.5)	133.2 (20.6)	.96	133.3 (21.4)	133.0 (20.8)	.76
Diastolic BP, mm Hg	83.2 (12.4)	83.1 (11.8)	.84	83.3 (12.0)	83.1 (12.2)	.69
Biological, median (IQR)						
Serum folate level, ng/mL	6.5 (3.2)	6.7 (3.6)	.48	6.6 (3.4)	6.7 (3.5)	.67
Plasma vitamin B_6 level, ng/mL	9.3 (5.9)	9.7 (6.6)	.38	9.6 (6.2)	9.5 (6.2)	.43
Serum vitamin B_{12} level, pg/mL	360.0 (159.0)	367.0 (165.0)	.23	359.0 (163.0)	366.0 (159.0)	.20
Plasma EPA level, %	1.1 (0.9)	1.2 (1.0)	.02	1.2 (0.9)	1.2 (0.9)	.41
Plasma DHA level, %	2.6 (1.2)	2.6 (1.3)	.29	2.6 (1.3)	2.7 (1.2)	.52
Plasma homocysteine level, mg/L	1.8 (0.7)	1.8 (0.7)	.74	1.8 (0.7)	1.8 (0.7)	.23
Plasma creatinine level, mg/dL	0.9 (0.2)	0.9 (0.2)	.92	0.9 (0.2)	0.9 (0.2)	.44
Plasma fasting glucose level, mg/dL	99.1 (18.0)	99.1 (18.0)	.18	99.1 (18.0)	99.1 (16.2)	.86
Plasma TC level, mg/dL	173.7 (54.1)	169.9 (54.1)	.27	169.9 (54.1)	169.9 (54.1)	.89
Plasma HDL-C level, mg/dL	42.5 (11.6)	42.5 (11.6)	.52	42.5 (11.6)	42.5 (11.6)	.48
Plasma LDL-C level, mg/dL	104.2 (42.5)	100.4 (42.5)	.40	100.4 (42.5)	104.2 (42.5)	.80
Plasma triglyceride level, mg/dL	115.0 (88.5)	106.2 (88.5)	.12	106.2 (88.5)	106.2 (88.5)	.17
CVD history						
Myocardial infarction	474 (47.9)	488 (48.9)	.63	494 (49.7)	468 (47.1)	.25
Unstable angina	290 (29.3)	289 (29.0)	.88	289 (29.1)	290 (29.2)	.95
Ischemic stroke	226 (22.8)	220 (22.1)	.68	211 (21.2)	235 (23.7)	.19

(continued)

RESULTS

SAMPLE CHARACTERISTICS

Baseline characteristics of the 514 women (20.6%) and 1987 men (79.4%) randomized in the trial are summarized in **Table 1** (by supplementation type) and **Table 2** (by sex and supplementation type). Treatment groups were balanced except for some variability between the vitamin B supplement groups (yes/no) regarding median eicosapentaenoic acid ($P = .01$) and triglyceride concentrations ($P = .05$). Mean (SD) baseline age was 61.3 (9.0) years (mean, 60.9 years among men and 63.2 years among women); at cancer diagnosis, 65.6 (9.0) years (65.1 years among men and 67.4 years among women). The median time between the acute CVD event and randomization was 101 days,[24] and median follow-up was 4.7 (interquartile range, 1.5) years.

CANCER INCIDENCE AND MORTALITY

In total, 174 participants (7.0%) presented with incident primary cancer (not including 14 cases of basal cell carcinoma). Of these events, 145 occurred in men (7.3%) and 29 in women (5.6%). The rates per 1000 observation-years were 13.2 among women and 17.2 among men. Approximately 70% of the cancer incidence occurred in the second half of the trial, and only 2 events occurred during the first year of follow-up. Among men, the distribution of the affected anatomical locations was 50 in the prostate, 22 in the lung/bronchus, 16 in the bladder, 13 in the colon/rectum, and 44 in all other locations. Among women, the respective distribution was 9 in the breast, 4 in the lung, 3 in the colon/rectum, and 13 in all other locations. Cancer mortality occurred in 2.3% of the sample. There were 47 deaths among men (2.4%) and 11 among women (2.1%). **Table 3** summarizes the characteristics distribution by cancer status. Compared with

Table 2. Baseline Characteristics by Sex and Supplementation Group (continued)

Characteristic	Supplementation Group[a]					
	Women					
	Vitamin B			ω-3 Fatty Acids		
	Yes (n = 252)	No (n = 262)	*P* Value[b]	Yes (n = 259)	No (n = 255)	*P* Value[b]
Demographic						
Age, mean (SD), y	63.1 (9.7)	63.2 (9.8)	.87	63.2 (10.1)	63.1 (9.3)	.92
Married	143 (56.7)	150 (57.3)	.87	144 (55.6)	149 (58.4)	.62
Education <high school diploma	191 (75.8)	182 (69.5)	.07	189 (73.0)	184 (72.2)	.51
Employed	54 (21.4)	58 (22.1)	.79	58 (22.4)	54 (21.2)	.62
Foreign born	24 (9.5)	28 (10.7)	.66	29 (11.2)	23 (9.0)	.41
Behavioral						
Current smoker	16 (6.3)	26 (9.9)	.13	20 (7.7)	22 (8.6)	.75
Former smoker	100 (39.7)	95 (36.3)	.46	88 (34.0)	107 (42.0)	.08
Current alcohol use	19 (7.5)	16 (6.1)	.47	18 (6.9)	17 (6.7)	.77
Current aspirin use	223 (88.5)	238 (90.8)	.38	232 (89.6)	229 (89.8)	.93
Clinical, mean (SD)						
BMI	27.9 (5.6)	27.2 (5.2)	.15	27.8 (5.6)	27.3 (5.2)	.31
Systolic BP, mm Hg	133.9 (22.6)	134.4 (22.6)	.82	135.1 (22.7)	133.3 (22.4)	.37
Diastolic BP, mm Hg	83.2 (12.7)	83.1 (13.1)	.87	84.1 (13.1)	82.2 (12.6)	.09
Biological, median (IQR)						
Serum folate level, ng/mL	7.2 (3.9)	7.1 (3.8)	.85	7.1 (4.0)	7.2 (3.5)	.21
Plasma vitamin B_6 level, ng/mL	9.2 (5.1)	8.8 (5.2)	.50	8.8 (5.2)	8.9 (5.0)	.62
Serum vitamin B_{12} level, pg/mL	362.0 (173.0)	386.0 (207.0)	.18	381.0 (199.0)	369.0 (200.0)	.97
Plasma EPA level, %	1.1 (0.9)	1.1 (0.8)	.26	1.1 (0.7)	1.2 (1.0)	.08
Plasma DHA level, %	2.4 (1.2)	2.6 (1.0)	.13	2.5 (1.0)	2.5 (1.2)	.58
Plasma homocysteine level, mg/L	1.7 (0.7)	1.6 (0.5)	<.001	1.6 (0.6)	1.6 (6.4)	.94
Plasma creatinine level, mg/dL	0.8 (0.2)	0.8 (0.2)	.01	0.8 (0.2)	0.8 (0.2)	.57
Plasma fasting glucose level, mg/dL	97.3 (19.8)	95.5 (18.0)	.45	97.3 (16.2)	95.5 (18.0)	.62
Plasma TC level, mg/dL	185.3 (50.2)	181.5 (50.2)	.75	185.3 (54.1)	185.3 (50.2)	.35
Plasma HDL-C level, mg/dL	50.2 (15.4)	50.2 (19.3)	.41	50.2 (15.4)	50.2 (19.3)	.90
Plasma LDL-C level, mg/dL	108.1 (42.5)	108.1 (38.6)	.61	112.0 (42.5)	104.2 (38.6)	.02
Plasma triglyceride level, mg/dL	106.2 (88.5)	97.3 (88.5)	.19	106.2 (61.9)	106.2 (79.6)	.33
CVD history						
Myocardial infarction	94 (37.3)	94 (35.9)	.74	86 (33.2)	102 (40.0)	.11
Unstable angina	54 (21.4)	80 (30.5)	.02	72 (27.8)	62 (24.3)	.37
Ischemic stroke	104 (41.3)	88 (33.6)	.07	101 (39.0)	91 (35.7)	.44

Abbreviations: See Table 1.
SI conversion factors: See Table 1.
[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.
[b] Based on χ^2 tests, unpaired *t* tests, or Wilcoxon rank sum test as appropriate.

noncases, individuals with incident cancer were older ($P<.001$) and had somewhat lower median vitamin B_6 concentrations (9.4 vs 8.9 ng/mL [$P=.05$]; to convert to nanomoles per liter, multiply by 4.046) and somewhat higher median homocysteine concentrations (1.7 vs 1.9 mg/L [$P<.001$]; to convert to micromoles per liter, multiply by 7.397).

SUPPLEMENTATION WITH B VITAMINS AND CANCER OUTCOMES

Results with the full sample and by sex ($P=.054$ for interaction) are summarized in **Table 4**. The sex- and age-adjusted full-sample models revealed a lack of effect of the B vitamins on cancer incidence (HR, 1.15 [95% CI, 0.85-1.55]) or cancer mortality (HR, 1.30 [95% CI, 0.77-2.18]). Because randomization to B vitamins (yes/no) had resulted in slight variability between the groups regarding eicosapentaenoic acid and triglyceride concentrations, we conducted sensitivity analyses that further adjusted for these variables and noted that the results remained unchanged (data not tabulated).

Among men, there were 74 cancer cases in the B vitamins group and 71 cases in the comparison group. Among women, there were 20 cases in the B vitamins group and 9 cases in the comparison group. Overall, allocation to B vitamins did not have an effect on cancer incidence or cancer mortality in men or women, although the incidence model in women (adjusted for age, homocysteine and creatinine concentrations, and prior unstable angina) reached borderline significance (HR, 2.18 [95% CI, 0.98-4.85]; $P=.06$).

SUPPLEMENTATION WITH ω-3 FATTY ACIDS AND CANCER OUTCOMES

Results with the full sample and by sex ($P=.02$ for interaction) are summarized in Table 4. The sex- and age-adjusted full-sample models revealed a lack of effect of the ω-3 fatty acids on cancer incidence (HR,

Table 3. Baseline Characteristics by Cancer Status[a]

Characteristic	Cancer Cases (n = 174)[b]	Noncases (n = 2327)	*P* Value[c]
Supplementation group allocation			
Vitamin B	94 (54.0)	1148 (49.3)	.23
ω-3 Fatty acids	93 (53.4)	1160 (49.8)	.36
Demographic			
Age, mean (SD), y	64.8 (7.4)	61.1 (9.1)	<.001
Female	29 (16.7)	485 (20.8)	.19
Married	131 (75.3)	1664 (71.5)	.36
Education <high school diploma	105 (60.3)	1380 (59.3)	.85
Employed	35 (20.1)	855 (36.7)	<.001
Foreign born	21 (12.1)	283 (12.2)	.97
Behavioral			
Current smoker	26 (14.9)	243 (10.4)	.06
Former smoker	102 (58.6)	1415 (60.8)	.60
Current alcohol use	47 (27.0)	566 (24.3)	.14
Current aspirin use	152 (87.4)	2184 (93.9)	<.001
Clinical, mean (SD)			
BMI	27.6 (4.0)	27.6 (4.1)	.94
Systolic BP, mm Hg	140.1 (21.7)	132.9 (21.3)	<.001
Diastolic BP, mm Hg	85.3 (12.9)	83.0 (12.2)	.02
Biological, median (IQR)			
Serum folate level, ng/mL	7.0 (3.6)	6.7 (3.5)	.74
Plasma vitamin B_6 level, ng/mL	8.9 (5.7)	9.4 (6.1)	.05
Serum vitamin B_{12} level, pg/mL	355.0 (149.0)	366.0 (167.0)	.64
Plasma EPA level, %	1.2 (0.9)	1.2 (0.9)	.99
Plasma DHA level, %	2.5 (1.2)	2.6 (1.2)	.61
Plasma homocysteine level, mg/L	1.9 (0.7)	1.7 (0.7)	<.001
Plasma creatinine level, mg/dL	0.9 (0.2)	0.9 (0.2)	.40
Plasma fasting glucose level, mg/dL	99.1 (19.8)	99.1 (18.0)	.85
Plasma TC level, mg/dL	177.6 (61.8)	173.7 (54.1)	.05
Plasma HDL-C level, mg/dL	46.3 (11.6)	42.5 (15.4)	.11
Plasma LDL-C level, mg/dL	108.1 (50.2)	104.2 (42.5)	.17
Plasma triglyceride level, mg/dL	115.0 (79.6)	106.2 (70.8)	.36
CVD history			
Myocardial infarction	73 (42.0)	1077 (46.3)	.27
Unstable angina	46 (26.4)	667 (28.7)	.53
Ischemic stroke	55 (31.6)	583 (25.1)	.06

Abbreviations: See Table 1.
SI conversion factors: See Table 1.
[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.
[b] Excludes 14 cases of basal cell carcinoma.
[c] Based on χ^2 tests, paired *t* tests, or Wilcoxon rank sum test as appropriate.

1.17 [95% CI, 0.87-1.58]) or cancer mortality (HR, 1.47 [95% CI, 0.87-2.48]). Among men, there were 72 cancer cases in the ω-3 fatty acids group and 73 cases in the comparison group. Allocation to ω-3 fatty acids did not have an effect on overall cancer incidence or cancer mortality in men. Among women, there were 21 cases in the ω-3 fatty acids group and 8 cases in the comparison group. Positive associations were noted between ω-3 fatty acid supplementation and cancer incidence (HR, 3.02 [95% CI, 1.33-6.89]) and mortality (HR, 5.49 [95% CI, 1.18-25.97]).

COMMENT

These ancillary results from the SU.FOL.OM3 trial do not provide evidence of beneficial effects of supplementation with B vitamins and/or ω-3 fatty acids in relatively low doses for 5 years on cancer incidence or mortality among CVD survivors. Our results are consistent with those of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial, in which daily supplementation with substantially larger doses did not have any effects on cancer incidence after 6.7 years of follow-up.[26] That trial used 2 mg/d of folic acid and 1 mg/d of vitamin B_{12}, whereas our doses were 0.56 mg of 5-methyltetrahydrofolate and 0.02 mg of cyanocobalamin. The lack of effects of vitamin B supplementation on cancer incidence is in line with a meta-analysis of large RCTs involving individuals at increased CVD risk who received folic acid supplementation in daily doses ranging from 0.8 to 40.0 mg during a median of 5 years.[15] Regarding the lack of beneficial effects of the ω-3 fatty acids on cancer incidence, an argument has been extended that the critical period for dietary exposure to these nutrients may be during childhood or early adulthood.[16]

In total, 83.3% of the cancer incidence and 81.0% of the cancer mortality occurred in men (who represented

Table 4. Cox Proportional Hazards Analysis of Cancer Incidence and Mortality After 5 Years of Supplementation With B Vitamins and/or ω-3 Fatty Acids

	HR (95% CI)		
	Full Sample (N = 2501)[a]	Men (n = 1987)[b]	Women (n = 514)[c]
Received B vitamins (yes/no)			
Cancer incidence	1.15 (0.85-1.55)	1.21 (0.83-1.77)	2.18 (0.98-4.85)
Cancer mortality	1.30 (0.77-2.18)	1.48 (0.74-2.98)	1.66 (0.47-5.81)
Received ω-3 fatty acids (yes/no)			
Cancer incidence	1.17 (0.87-1.58)	0.99 (0.71-1.37)	3.02 (1.33-6.89)
Cancer mortality	1.47 (0.87-2.48)	1.16 (0.65-2.06)	5.49 (1.18-25.97)

Abbreviation: HR, hazard ratio.
[a]Models were adjusted for sex and age, based on 145 incident cancer cases and 47 deaths from cancer in men and 29 incident cancer cases and 11 deaths from cancer in women.
[b]Models for the effect of B vitamins were adjusted for age, current alcohol use, and eicosapentaenoic acid concentrations at baseline; models for the effect of ω-3 fatty acids were adjusted for age.
[c]Models for the effect of B vitamins were adjusted for age, baseline homocysteine and creatinine concentrations, and history of unstable angina; models for the effect of ω-3 fatty acids were adjusted for age and baseline low-density lipoprotein cholesterol concentrations.

79.4% of the sample); however, neither type of supplementation produced any effects. Among women (about 83% of the women were menopausal), both types of supplementation had a tendency to increase cancer risk; however, these results were derived from very few cases and should be regarded as preliminary. Indeed, the supplements might have acted as potentiators of subclinical dysplasia rather than as cancer initiators. Potential biological mechanisms of the sex-specific effects of B vitamins might be linked to homocysteine concentrations because it has been reported that folate and vitamin B_{12} explained a higher percentage of the total homocysteine variance in women than in men.[27] Sex-specific modulation of tumorigenesis by folic acid has been seen in animal models in which female mice fed diets with normal levels of folic acid had more and larger tumors compared with folic acid–depleted female mice and male mice with depleted and adequate levels of folic acid.[28] A crucial period of vulnerability to folic acid supply might occur after tumor initiation, especially in female subjects.[28] B vitamins play a role in cell cycle progression[2] and might have dual modulatory effects depending on the dose and timing of the supplementation.[2,29]

In turn, our findings are consistent with a large epidemiological study with postmenopausal women in which fish intake was positively associated with breast cancer risk.[30] These associations held only for estrogen receptor–positive breast cancer. Indeed, high intake of polyunsaturated fatty acids might stimulate carcinogenesis by increasing oxidative DNA damage.[31] Sex-specific effects of polyunsaturated fatty acids were suggested by a case-control study reporting trends of increased colorectal cancer risk in women and a decreased risk in men (although neither attained statistical significance) associated with intake of total polyunsaturated fatty acids (and to a lesser extent, ω-3 fatty acids).[32] Whereas mechanisms underlying the potential sex-specific effects of these nutrients are unclear, they appear to modulate estrogen metabolism.[16]

The performance of ancillary data analyses of a secondary outcome is a major limitation of the present study. The SU.FOL.OM3 RCT was designed as a secondary CVD prevention trial, and its main results showed that allocation to B vitamin or to ω-3 fatty acid supplementation had no effects on major vascular events.[24] In this trial, the 5-year duration revealed some, but likely not all, progression of subclinical dysplasia possibly present at enrollment. Also, our analyses might have been insufficiently powered. Another limitation pertains to the small number of cancer cases, which prevented site-specific analyses and, regarding women, resulted in unstable and equivocal risk estimates. Furthermore, the available data on dietary supplement use outside the trial did not permit an accurate account for such covariates. However, the randomization was successful in balancing the treatment groups. Finally, although data on cancer screening were not collected, we do not have a reason to suspect that the intensity of follow-up varied by sex.

Supplementation-based RCTs with results concerning cancer incidence typically do not combine B vitamins and ω-3 fatty acids. Another distinctive feature of this trial was the relatively low supplementation doses. Another strength pertains to the use of 5-methyltetrahydrofolate, which is the most abundant natural form of folate. Unlike folic acid, 5-methyltetrahydrofolate supplementation is not likely to lead to circulating unmetabolized folic acid, which could mask vitamin B_{12} deficiency. Furthermore, treatment adherence (defined as taking ≥80% of the assigned supplements) was high, evidenced by self-reports and increased blood concentrations of vitamin B analytes or ω-3 fatty acids at follow-up.[24] The lack of folic acid fortification in France bears on the generalizability of our findings. Overall, a replication of the models with larger cohorts of men and women is necessary. In summary, this study does not support dietary use of B vitamins or ω-3 fatty acids for cancer prevention. The preliminary evidence of adverse effects among women necessitates confirmation before firm conclusions could be drawn.

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