

Multivitamin Use and Risk of Cancer and Cardiovascular Disease in the Women's Health Initiative Cohorts

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Background: Millions of postmenopausal women use multivitamins, often believing that supplements prevent chronic diseases such as cancer and cardiovascular disease (CVD). Therefore, we decided to examine associations between multivitamin use and risk of cancer, CVD, and mortality in postmenopausal women.

Methods: The study included 161 808 participants from the Women's Health Initiative clinical trials (N=68 132 in 3 overlapping trials of hormone therapy, dietary modification, and calcium and vitamin D supplements) or an observational study (N=93 676). Detailed data were collected on multivitamin use at baseline and follow-up time points. Study enrollment occurred between 1993 and 1998; the women were followed up for a median of 8.0 years in the clinical trials and 7.9 years in the observational study. Disease end points were collected through 2005. We documented cancers of the breast (invasive), colon/rectum, endometrium, kidney, bladder, stomach, ovary, and lung; CVD (myocardial infarction, stroke, and venous thromboembolism); and total mortality.

Results: A total of 41.5% of the participants used multivitamins. After a median of 8.0 years of follow-up in the clinical trial cohort and 7.9 years in the observational study cohort, 9619 cases of breast, colorectal, endometrial, re-

nal, bladder, stomach, lung, or ovarian cancer; 8751 CVD events; and 9865 deaths were reported. Multivariate-adjusted analyses revealed no association of multivitamin use with risk of cancer (hazard ratio [HR], 0.98, and 95% confidence interval [CI], 0.91-1.05 for breast cancer; HR, 0.99, and 95% CI, 0.88-1.11 for colorectal cancer; HR, 1.05, and 95% CI, 0.90-1.21 for endometrial cancer; HR, 1.0, and 95% CI, 0.88-1.13 for lung cancer; and HR, 1.07, and 95% CI, 0.88-1.29 for ovarian cancer); CVD (HR, 0.96, and 95% CI, 0.89-1.03 for myocardial infarction; HR, 0.99, and 95% CI, 0.91-1.07 for stroke; and HR, 1.05, and 95% CI, 0.85-1.29 for venous thromboembolism); or mortality (HR, 1.02, and 95% CI, 0.97-1.07).

Conclusion: After a median follow-up of 8.0 and 7.9 years in the clinical trial and observational study cohorts, respectively, the Women's Health Initiative study provided convincing evidence that multivitamin use has little or no influence on the risk of common cancers, CVD, or total mortality in postmenopausal women.

Trial Registration: clinicaltrials.gov Identifier: NCT00000611

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THE USE OF MULTIVITAMINS IS a common health practice in the United States.¹ Despite the availability of a diverse and relatively affordable food supply, 50% of Americans routinely use dietary supplements, annually spending more than \$20 billion on these products.² The motivations for supplement use vary, but common reasons include the belief that these preparations will prevent chronic diseases, such as cancer and cardiovascular disease (CVD).^{3,4} These views are often fueled by product health claims, consumer testimonials, and an industry that is largely unregulated owing to the 1994 Dietary Supplement and Health Education Act.^{5,6} Despite the widespread use of supplements and the strong consumer beliefs

about benefits, convincing scientific data to support efficacy are lacking.⁷⁻⁹ With the exception of recommending a folic acid-containing supplement to women of child-bearing potential^{10,11} and advising avoidance the use of high-dose beta carotene supplements by smokers,¹² current data are insufficient to formulate public health recommendations for dietary supplement use for otherwise healthy persons.²

The hypothesis that taking multivitamins might lower the risk of CVD and cancer derives from published evidence supporting a role for specific micronutrients in disease prevention. Data are consistent in stating that diets high in fruits and vegetables are associated with a lower risk of CVD and cancer. Moreover, low serum concentrations of B vitamins, carotenoids, and tocopherols have been associated with an

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increased risk of colorectal cancer and CVD.¹³⁻²⁰ Because these vitamins, minerals, and other small-molecule compounds can be effectively packaged into pill form, supplement use could ensure adequate micronutrient intake or correct low circulating concentrations, especially among persons with poor diets.²¹ Multivitamins are a potential vehicle, as they contain the micronutrients identified as essential by the Institute of Medicine.^{22,23}

Multivitamins are the most frequently used dietary supplement. However, of the numerous observational studies that have examined associations between supplement use and disease risk, few have explicitly investigated the use of multivitamins. Limited evidence from case-control and cohort studies suggests that multivitamin use is associated with a reduced risk of colon and bladder cancers but with an increased risk of non-Hodgkin lymphoma.²⁴ Other observational studies have reported no associations of multivitamin use with colorectal, gastric, or lung cancers. One study of more than 1 million Americans reported no association of multivitamin use with total mortality, coronary heart disease mortality, or cancer mortality.²⁵ One study reported no risk reduction for CVD or mortality among a cohort of men who used multivitamins compared with those who did not use multivitamins.²⁶ A prospective study of 37 920 women reported no association of multivitamin use with risk of breast cancer.²⁷

In this study, we examined the associations between multivitamin use in the Women's Health Initiative (WHI) clinical trial (CT) and observational study (OS) cohorts and the risk of site-specific solid tumors (invasive breast, renal, endometrial, ovarian, bladder, and stomach cancers)²; CVD; and total mortality.³

METHODS

OVERVIEW OF THE WHI

The WHI is a study of postmenopausal women's health and risk factors for cancer, heart disease, and skeletal health.²⁸ It was designed as a set of randomized controlled CTs and an OS. Women were eligible for participation if they were 50 to 79 years of age at screening, postmenopausal, and likely to live in close geographic proximity to 1 of 40 WHI clinical centers for at least 3 years. Women were excluded for medical conditions with a predicted survival of 3 years or less, for conditions limiting adherence or retention (eg, alcohol or drug dependency and dementia), or for active participation in any other intervention trial in which participants were individually randomized to a control or intervention group.²⁸ The CTs (N=68 132) included 3 overlapping components: the hormone therapy trials (N=27 347), the dietary modification trial (N=48 835), and the calcium and vitamin D trial (N=36 282). Eligible women could be randomized into 1, 2, or all 3 of the CTs. Trial arm assignment was randomly designated (1:1 for the hormone therapy and calcium and vitamin D trials; 40% were assigned to low-fat intervention and 60% to usual diet for the dietary modification trial).²⁸ Women who were ineligible or unwilling to join the CTs were invited to join the OS, as were those who were specifically recruited for the OS (N=93 676). The CT women attended baseline and annual clinic visits. The OS women attended baseline and 3-year clinic visits and completed all other annual study activities by mail (eg, medical history and lifestyle-exposure updates). The women were followed up for a median of 8.0 years in the CTs and 7.9 years in the OS. All WHI participants provided written informed consent, and institutional review board approval was obtained at each of

the 40 WHI clinical centers and at the Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center, Seattle, Washington. This report is based on data from 161 808 women in both the OS and the CTs; 2 women were excluded because of incomplete dietary supplement information.

ASSESSMENT OF DIETARY SUPPLEMENT USE

Dietary supplement data were collected during in-person clinic visits. Women brought supplement bottles to the baseline clinic visit and to annual visits thereafter in the CTs and to the baseline and 3-year visits in the OS. A standardized interviewer-administered 4-page form was used to collect information on multivitamins, other mixtures, and single supplements. For the multivitamins, separate sections were provided on the form to designate multivitamins, multivitamins with minerals, or stress supplements. Staff members directly transcribed the ingredients for each supplement. They also asked participants about frequency (pills per week) and duration (months and years) of use for each supplement.^{29,30} Only supplements used at least once a week were recorded, but there was no limit on the total number of supplements allowed. A validity study of these procedures demonstrated that correlations of interviewer-transcribed doses with data from photocopied labels ranged from 0.8 to 1.0.^{29,30}

Multivitamins were grouped into 3 classifications based on ingredients: (1) *multivitamins (alone)* were preparations with 10 or more vitamins and no minerals in which the nutrient levels were at least 100% of US Recommended Dietary Allowance (RDA); (2) *multivitamins with minerals* were preparations with 20 to 30 vitamins and minerals and nutrient levels of 100% or less of US RDA; and (3) *stress multisupplements* were preparations with higher doses (often >200% of US RDA) of several B vitamins and often including large doses of vitamin C or selected minerals, such as selenium or zinc. *Supplement mixtures* with fewer than 10 components, such as B complex or antioxidant mixtures, were not considered multivitamins.

ASCERTAINMENT OF OUTCOMES

Clinical outcomes of interest in the WHI included CVD (coronary heart disease, stroke, congestive heart failure, angina, peripheral vascular disease, carotid artery disease, and coronary revascularization), cancer (breast, colorectal, endometrial, ovarian, and other cancers), osteoporotic fractures (hip and other), and other conditions (diabetes, deep vein thrombosis, pulmonary embolism, and total mortality). Outcomes were initially ascertained by self-report using a semiannual (in the CTs) or annual (in the OS) questionnaire and documented by medical records. Charts with potential cardiovascular, cancer, fracture, and death outcomes were sent to local WHI-physician adjudicators for evaluation and classification. Locally adjudicated cases (all cancers) were then sent to the Coordinating Center for central adjudication of selected outcomes.³¹ Five major cancers (of the breast, colon, rectum, endometrium, and ovary) were centrally coded by trained tumor registry coders using standardized SEER (Surveillance, Epidemiology, and End Results) guidelines. This report includes end points reported and adjudicated through the end of the WHI closeout period of March 2005. We included 8 solid tumor cancers (invasive breast, colorectal, endometrial, stomach, ovarian, renal, lung, and bladder) and 3 CVD end points (myocardial infarction [MI], stroke, and venous thromboembolism [CTs only]).

OTHER DATA

Standard procedures used across the CTs and the OS were used to collect data on age, race/ethnicity, reproductive/gynecological history, education, physical activity, medical history, fam-

Table 1. Characteristics of 161 806 Multivitamin Supplement Users and Nonusers in the Women's Health Initiative

Characteristic	No. (%) ^a					P Value ^b
	Combination Users (n=1091)	Stress Multivitamin Users (n=3741)	Users of Multivitamins With Minerals (n=56 296)	Multivitamin Users (n=5667)	Nonusers (n=95 011)	
Age at screening, y						<.001
50-59	421 (38.6)	1414 (37.8)	16 895 (30.0)	1667 (29.4)	33 160 (34.9)	
60-69	460 (42.2)	1631 (43.6)	26 080 (46.3)	2527 (44.6)	41 887 (44.1)	
70-79	210 (19.2)	696 (18.6)	13 321 (23.7)	1473 (26.0)	19 964 (21.0)	
Years since menopause						<.001
<5	158 (15.1)	572 (15.9)	6616 (12.3)	672 (12.5)	12 489 (14.1)	
5 to <10	210 (20.1)	709 (19.7)	9342 (17.3)	919 (17.1)	16 224 (18.3)	
10 to <15	192 (18.4)	745 (20.7)	10 795 (20.0)	997 (18.6)	17 284 (19.5)	
≥15	483 (46.3)	1567 (43.6)	27 167 (50.4)	2783 (51.8)	42 422 (48.0)	
Race/ethnicity						<.001
White	953 (87.4)	3093 (82.7)	49 165 (87.3)	5048 (89.1)	75 273 (79.2)	
Black	64 (5.9)	180 (4.8)	3253 (5.8)	322 (5.7)	10 807 (11.4)	
Hispanic	20 (1.8)	88 (2.4)	1620 (2.9)	107 (1.9)	4677 (4.9)	
American Indian	5 (0.5)	7 (0.2)	194 (0.3)	10 (0.2)	499 (0.5)	
Asian/Pacific Islander	35 (3.2)	297 (7.9)	1364 (2.4)	113 (2.0)	2383 (2.5)	
Unknown	14 (1.3)	76 (2.0)	700 (1.2)	67 (1.2)	1372 (1.4)	
BMI (collapsed categories)						<.001
<25 (normal)	457 (42.4)	1579 (42.7)	21 251 (38.1)	2315 (41.3)	30 729 (32.6)	
25 to <30 (overweight)	348 (32.3)	1228 (33.2)	19 535 (35.0)	1949 (34.8)	32 606 (34.6)	
≥30 (obese)	273 (25.3)	892 (24.1)	15 020 (26.9)	1344 (24.0)	30 835 (32.7)	
Education						<.001
High school or less	175 (16.1)	605 (16.3)	11 172 (20.0)	1117 (19.8)	23 192 (24.6)	
School after high school	451 (41.6)	1433 (38.6)	21 136 (37.8)	1999 (35.5)	35 883 (38.1)	
College degree or higher	458 (42.3)	1676 (45.1)	23 616 (42.2)	2512 (44.6)	35 146 (37.3)	
Alcohol use						<.001
Nondrinker	110 (10.2)	372 (10.0)	5169 (9.2)	507 (9.0)	11 494 (12.2)	
Past drinker	202 (18.7)	718 (19.3)	10 020 (17.9)	986 (17.5)	18 221 (19.3)	
Alcoholic drinks, No./wk						
<1	353 (32.7)	1209 (32.5)	18 672 (33.4)	1843 (32.6)	30 830 (32.7)	
1-7	311 (28.8)	975 (26.2)	15 183 (27.1)	1552 (27.5)	23 179 (24.6)	
>7	104 (9.6)	446 (12.0)	6906 (12.3)	759 (13.4)	10 541 (11.2)	
Smoking						<.001
Never smoked	527 (49.1)	1808 (48.9)	28 234 (50.8)	2931 (52.3)	47 931 (51.2)	
Past smoker	486 (45.3)	1675 (45.3)	24 205 (43.5)	2357 (42.1)	38 386 (41.0)	
Current smoker	60 (5.6)	217 (5.9)	3173 (5.7)	314 (5.6)	7379 (7.9)	
General health						<.001
Excellent	205 (18.8)	732 (19.7)	9754 (17.4)	966 (17.1)	15 730 (16.7)	
Very good	463 (42.6)	1600 (43.1)	23 938 (42.7)	2418 (42.9)	37 216 (39.5)	
Good	340 (31.3)	1126 (30.4)	18 036 (32.2)	1803 (32.0)	31 736 (33.6)	
Fair/poor	80 (7.4)	252 (6.8)	4280 (7.6)	446 (7.9)	9636 (10.2)	
Prior bilateral oophorectomy	214 (20.2)	744 (20.2)	11 372 (20.6)	1081 (19.4)	18 145 (19.6)	<.001

(continued)

ily or personal history of cancer or coronary heart disease, diabetes mellitus, current health status, and tobacco and alcohol use. The clinic staff members measured blood pressure, height, and weight using standardized protocols.

STATISTICAL ANALYSES

Descriptive statistics characterized the study population. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for any use of multivitamins as well as the categories of multivitamins, multivitamins with minerals, and stress multivitamins for each of the disease outcomes. The time metric for these models was based on the time of randomization in the CTs and time of enrollment in the OS.^{32,33} For a particular event, time accrued while the participants were still at risk for an event until the date of diagnosis of cancer or CVD, until death from any cause, until they were unavailable for follow-up, or until March 31, 2005. Proportional hazards assumptions were assessed by a 1-*df* test of the interaction between log-survival time and multivitamin use; evidence of non-proportionality did not exist. Hazard ratios were adjusted for

baseline characteristics: age; race/ethnicity; years since menopause (<5, 5-10, 10-15, and >15 years); body mass index; education; alcohol use; smoking; general health; history of bilateral oophorectomy; geographic region; physical activity; duration of prior postmenopausal estrogen therapy use (0, <5, 5-10, 10-15, and >15 years); duration of prior postmenopausal estrogen plus progesterone use (0, <5, 5-10, 10-15, and >15 years); fruit and vegetable intake; percentage of energy from fat; single supplements of vitamin C, E, or calcium and any other single supplement use and stratified according to age (5-year groups), hormone therapy trial randomization assignment or study enrollment (active conjugated equine estrogen [CEE] plus medroxyprogesterone acetate, placebo CEE and medroxyprogesterone acetate, active CEE, placebo CEE, or not randomized), dietary modification trial randomization (intervention, control, or not randomized), or OS enrollment.^{32,33} Specific to cancer analyses, a family history of cancer was an additional covariate; women were excluded if they had a history of the particular cancer. For breast cancer analyses, women without a mammogram within 2 years of baseline were excluded. Specific to CVD analysis, treated diabetes, treated hyperlipid-

Table 1. Characteristics of 161 806 Multivitamin Supplement Users and Nonusers in the Women's Health Initiative (continued)

Characteristic	No. (%) ^a					P Value ^b
	Combination Users (n=1091)	Stress Multivitamin Users (n=3741)	Users of Multivitamins With Minerals (n=56 296)	Multivitamin Users (n=5667)	Nonusers (n=95 011)	
US region						<.001
Northeast	146 (13.4)	822 (22.0)	12 872 (22.9)	1764 (31.1)	21 308 (22.4)	
South	274 (25.1)	682 (18.2)	13 312 (23.6)	993 (17.5)	26 658 (28.1)	
Midwest	200 (18.3)	531 (14.2)	12 520 (22.2)	1375 (24.3)	20 937 (22.0)	
West	471 (43.2)	1706 (45.6)	17 592 (31.2)	1535 (27.1)	26 108 (27.5)	
Physical activity, ×/wk						<.001
None or <2	520 (49.2)	1725 (47.7)	28 047 (51.5)	2852 (53.2)	53 845 (59.9)	
2-4	188 (17.8)	721 (20.0)	10 436 (19.2)	1007 (18.8)	15 098 (16.8)	
≥4	349 (33.0)	1167 (32.3)	15 969 (29.3)	1498 (28.0)	20 917 (23.3)	
Unopposed estrogen by category, y						<.001
None	652 (59.8)	2335 (62.4)	34 630 (61.5)	3651 (64.4)	62 834 (66.1)	
<5	158 (14.5)	516 (13.8)	7428 (13.2)	729 (12.9)	12 605 (13.3)	
5-<10	102 (9.3)	283 (7.6)	4224 (7.5)	414 (7.3)	6338 (6.7)	
10-<15	63 (5.8)	227 (6.1)	3474 (6.2)	320 (5.6)	4805 (5.1)	
>15	116 (10.6)	380 (10.2)	6540 (11.6)	553 (9.8)	8427 (8.9)	
Estrogen plus progesterone by category, y						<.001
None	753 (69.0)	2449 (65.5)	39 725 (70.6)	4132 (72.9)	72 656 (76.5)	
<5	162 (14.8)	644 (17.2)	7963 (14.1)	748 (13.2)	11 734 (12.4)	
5-<10	105 (9.6)	356 (9.5)	4569 (8.1)	421 (7.4)	5958 (6.3)	
10-<15	45 (4.1)	190 (5.1)	2730 (4.8)	241 (4.3)	3150 (3.3)	
>15	26 (2.4)	102 (2.7)	1309 (2.3)	125 (2.2)	1511 (1.6)	
Vitamin C as single supplement	474 (43.4)	1440 (38.5)	20 195 (35.9)	2004 (35.4)	18 578 (19.6)	<.001
Vitamin E as single supplement	512 (46.9)	1574 (42.1)	22 830 (40.6)	2206 (38.9)	21 462 (22.6)	<.001
Calcium as single supplement (including antacids)	340 (31.2)	1014 (27.1)	19 044 (33.8)	2130 (37.6)	20 306 (21.4)	<.001
Single supplement (not including vitamins C or E or calcium)	933 (85.5)	3741 (100.0)	26 528 (47.1)	2477 (43.7)	28 353 (29.8)	<.001
Treated diabetes mellitus (pills or shots)	33 (3.0)	101 (2.7)	1934 (3.4)	199 (3.5)	4900 (5.2)	<.001
History of high cholesterol levels requiring pills	111 (10.7)	476 (13.3)	7643 (14.2)	765 (14.4)	12 541 (14.2)	.01
Family history of cancer	730 (69.9)	2373 (66.1)	36 356 (67.4)	3660 (67.2)	59 587 (65.8)	<.001
Mammogram in last 2 y	911 (85.7)	3124 (86.0)	47 349 (86.3)	4818 (87.2)	74 608 (81.4)	<.001
History of breast cancer	45 (4.1)	122 (3.3)	2009 (3.6)	198 (3.5)	2649 (2.8)	<.001
History of colorectal cancer	8 (0.7)	13 (0.3)	341 (0.6)	36 (0.6)	549 (0.6)	.31
Family history of MI	518 (50.0)	1785 (50.5)	28 257 (52.9)	2832 (52.4)	46 780 (52.2)	.006
Age at screening, mean (SD), y	62.4 (7.2)	62.4 (7.2)	63.7 (7.2)	64.1 (7.3)	62.9 (7.3)	<.001
Fruit and vegetable servings, mean (SD), No./d	4.4 (2.2)	4.4 (2.2)	4.3 (2.1)	4.3 (2.1)	3.9 (2.1)	<.001
Calories from fat, mean (SD), %/d	31.0 (8.3)	31.1 (8.6)	31.7 (8.3)	31.5 (8.2)	33.4 (8.3)	<.001
Systolic BP, mean (SD), mm Hg	125.5 (17.7)	126.5 (18.1)	126.9 (17.6)	127.6 (18.0)	127.7 (17.8)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; MI, myocardial infarction.

^aPercentages may not sum to 100 because of rounding.

^bP values are from *t* tests for continuous variables and χ^2 tests for categorical variables.

emia, systolic blood pressure level, and history of the particular CVD were additional covariates.

Additional analyses tested persistent use of multivitamins (ie, use at baseline and follow-up) in relation to risk of cancer or CVD. The likelihood ratio test estimated multiplicative interaction between baseline characteristics (age, smoking, alcohol use, body mass index, and fruit and vegetable consumption) and multivitamin use in relation to the disease outcomes.

All statistical tests were 2-sided, with a *P* value of less than .05 considered statistically significant. Analyses were conducted with SAS, version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Table 1 presents demographic, health, and lifestyle data according to use of multivitamin supplements in the WHI. Of the 161 806 WHI participants with completed di-

etary supplement data collection forms, 41.5% reported multivitamin use. The most common category was multivitamins with minerals (35.0%), with fewer participants taking multivitamins (alone) (3.5%) or stress multivitamins (2.3%). Women who used any multivitamins were more likely also to use single supplements of vitamin E, vitamin C, or calcium than women who did not use multivitamins (*P* < .001). Compared with women who did not use multivitamins, multivitamin users were more likely to be white, living in the western United States, have a lower body mass index, be more physically active, and have a college degree or higher (all *P* < .001). Women who used multivitamins were more likely to consume alcohol and less likely to smoke than nonusers. Multivitamin users reported slightly higher fruit and vegetable consumption and a lower percentage of energy from fat than nonusers at baseline.

Table 2. Multivariable Adjusted^a Relative Risk of Major Cancers by Multivitamin Use in the Women's Health Initiative (CTs and OS)

Category of Multivitamin Use	Cancer Type											
	Invasive Breast ^b			Colorectal ^c			Endometrial ^d			Kidney		
	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value
Any multivitamin			.53			.84			.53			.37
No	2472 (0.44)			955 (0.13)			502 (0.07)			181 (0.02)		
Yes	1928 (0.47)	0.98 (0.91-1.05)		635 (0.12)	0.99 (0.88-1.11)		410 (0.08)	1.05 (0.90-1.21)		137 (0.03)	1.13 (0.87-1.46)	
Type of multivitamin			.69			.90			.78			.37
None	2472 (0.44)			955 (0.13)			502 (0.07)			181 (0.02)		
Multivitamin	171 (0.47)	1.05 (0.89-1.25)		60 (0.14)	1.05 (0.79-1.41)		35 (0.08)	0.99 (0.68-1.45)		10 (0.02)	0.90 (0.44-1.85)	
Multivitamin with minerals	1620 (0.47)	0.97 (0.90-1.04)		532 (0.12)	0.98 (0.86-1.11)		344 (0.08)	1.04 (0.90-1.22)		120 (0.03)	1.17 (0.90-1.54)	
Stress multivitamins	105 (0.45)	0.94 (0.75-1.17)		30 (0.10)	0.89 (0.57-1.37)		26 (0.09)	1.24 (0.80-1.91)		4 (0.01)	0.51 (0.16-1.64)	

Category of Multivitamin Use	Cancer Type											
	Bladder ^f			Stomach ^g			Lung ^h			Ovarian ⁱ		
	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value
Any multivitamin			.13			.85			.95			.50
No	236 (0.03)			61 (0.01)			795 (0.11)			315 (0.04)		
Yes	143 (0.03)	0.83 (0.65-1.06)		40 (0.01)	0.96 (0.60-1.53)		545 (0.11)	1.00 (0.88-1.13)		264 (0.05)	1.07 (0.88-1.29)	
Type of multivitamin			.44			.68			.57			.74
None	236 (0.03)			61 (0.01)			795 (0.11)			315 (0.04)		
Multivitamin	12 (0.03)	0.84 (0.46-1.55)		1 (<0.01)	0.33 (0.05-2.40)		54 (0.12)	1.19 (0.88-1.61)		23 (0.05)	1.06 (0.66-1.72)	
Multivitamin with minerals	120 (0.03)	0.82 (0.63-1.05)		36 (0.01)	1.00 (0.61-1.62)		452 (0.10)	0.97 (0.85-1.11)		216 (0.05)	1.04 (0.85-1.27)	
Stress multivitamin	9 (0.03)	1.05 (0.51-2.17)		1 (<0.01)	0.56 (0.07-4.20)		28 (0.10)	0.88 (0.56-1.37)		16 (0.05)	1.35 (0.79-2.32)	

Abbreviations: CI, confidence interval; CTs, clinical trials; HR, hazard ratio; OS, observational study.

^aAll HRs from a proportional hazards model adjusted for the characteristics listed in Table 1 and stratified according to age (5-year groups), hormone therapy trial randomization assignment or study enrollment (active conjugated equine estrogen [CEE] plus medroxyprogesterone acetate [MPA]), placebo CEE plus MPA, active CEE, placebo CEE, not randomized), dietary modification trial randomization (intervention, control, not randomized), or OS enrollment.

^bIn addition to the adjustments listed in footnote a, the models were adjusted for Gail score (tertiles, linear). Women who did not have a mammogram within 2 years of baseline and/or a history of breast cancer were excluded.

^cWomen with a history of colorectal cancer were excluded.

^dWomen with a history of endometrial cancer were excluded.

^eAnnualized percentage of cases.

^fWomen with a history of bladder cancer were excluded.

^gWomen with a history of stomach cancer were excluded.

^hWomen with a history of lung cancer were excluded.

ⁱWomen with a history of ovarian cancer were excluded.

There was no evidence that multivitamin use either increased or decreased the risk of cancer (**Table 2**). Overall, there was no association of any multivitamin use with the risk of cancers of the breast, colon/rectum, endometrium, ovary, kidney, bladder, stomach, or lung. When we examined risk according to the 3 classes of multivitamins, there was also no apparent association, and the null value of 1.0 was included in the 95% CIs of all multivariate-adjusted HR estimates. We observed a modest inverse association between use of stress-type multivitamins and stomach and kidney cancer and an inverse association of multivitamins without minerals and stomach cancer, but the numbers of cases were far too small to provide stable or meaningful HR estimates.

Next, we examined the association of multivitamin use with risk of CVD (MI, stroke, and venous thromboembolism) (**Table 3**). The annualized percentages of CVD events were nonsignificantly lower among women taking multivitamins than among those not taking multivitamins, and the overall HRs ranged from 0.96 (95% CI, 0.89-1.03) to 1.05 (95% CI, 0.85-1.29). Stress multivi-

tamins were the only supplements for which a cardiovascular protective association was suggested; the adjusted HR was 0.75 (95% CI, 0.56-0.99) for MI.

To investigate variation in risk by total duration of use, we categorized duration into 4 groups: (1) less than 1 year, (2) 1 through 5 years, (3) 6 through 10 years, and (4) more than 10 years. Of the 1928 women with invasive breast cancer who used multivitamins, 685 (35.5%) reported multivitamin use for at least 10 years (**Table 4**). While the annualized percentage of breast cancer events was slightly higher among those with at least 10 years of use (0.50) compared with non-users of multivitamins (0.44), the adjusted HR was 1.03 (95% CI, 0.94-1.14). Five to 10 years and more than 10 years of multivitamin use were associated with small but statistically nonsignificant increased risks for endometrial cancer (HR, 1.19, and 95% CI, 0.91-1.56; and HR, 1.09, and 95% CI, 0.89-1.35, respectively), kidney cancer (HR, 1.32, and 95% CI, 0.82-2.13 for 5-10 years of use), and stomach cancer (HR, 1.36, and 95% CI, 0.73-2.56 for >10 years of use).

Table 3. Events, Annualized Percentages, and Multivariable Adjusted^a Relative Risks of Cardiovascular Disease (CVD) by Multivitamin Use in the Women's Health Initiative (CTs and OS)

Category of Multivitamin Use	CVD Events											
	MI ^b			Stroke ^c			Venous Thromboembolism ^d			Total Mortality		
	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value
Any multivitamin			.27			.75			.64			.48
No	2828 (0.39)			2173 (0.30)			354 (0.10)			5911 (0.80)		
Yes	1765 (0.35)	0.96 (0.89-1.03)		1427 (0.28)	0.99 (0.91-1.07)		204 (0.10)	1.05 (0.85-1.29)		3954 (0.77)	1.02 (0.97-1.07)	
Type of multivitamin			.10			.68			.85			.69
None	2828 (0.39)			2173 (0.30)			354 (0.10)			5911 (0.80)		
Multivitamin	176 (0.40)	1.08 (0.91-1.28)		140 (0.32)	1.10 (0.91-1.33)		21 (0.12)	0.91 (0.52-1.60)		372 (0.83)	1.03 (0.92-1.16)	
Multivitamin with minerals	1497 (0.35)	0.96 (0.89-1.03)		1201 (0.28)	0.98 (0.90-1.06)		173 (0.10)	1.07 (0.86-1.32)		3335 (0.77)	1.02 (0.97-1.07)	
Stress multivitamins	64 (0.22)	0.75 (0.56-0.99)		65 (0.22)	0.97 (0.73-1.29)		6 (0.05)	0.80 (0.33-1.99)		181 (0.61)	0.94 (0.80-1.10)	

Abbreviations: CI, confidence interval; CTs, clinical trials; HR, hazard ratio; MI, myocardial infarction; OS, observational study.

^aAll HRs from a proportional hazards model adjusted for the characteristics listed in Table 1 and stratified according to age (5-year groups), hormone therapy trial randomization assignment or study enrollment (active conjugated equine estrogen [CEE] plus medroxyprogesterone acetate [MPA]), placebo CEE plus MPA, active CEE, placebo CEE, not randomized), dietary modification trial randomization (intervention, control, not randomized), or OS enrollment.

^bIncludes fatal and nonfatal MI. In addition to the adjustments listed in footnote a, the models were adjusted for a family history of MI and a personal history of MI.

^cIncludes fatal and nonfatal stroke. In addition to the adjustments listed in footnote a, the models were adjusted for a family history of stroke and a personal history of stroke.

^dClinical trials only: includes venous thromboembolism and pulmonary embolism; the outcomes were not adjudicated for the OS. In addition to the adjustments listed in footnote a, the models were adjusted for a history of venous thromboembolism and a history of pulmonary embolism.

^eAnnualized percentage of cases.

Table 4. Multivariable Adjusted^a Relative Risk of Major Cancers by Duration of Multivitamin Use in the Women's Health Initiative (CTs and OS)

Category of Multivitamin Use	Cancer Type											
	Invasive Breast ^b			Colorectal ^c			Endometrial ^d			Kidney		
	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value
Duration of multivitamin use, y			.17			.56			.36			.63
0	2472 (0.44)			955 (0.13)			502 (0.07)			181 (0.02)		
<1	283 (0.44)	0.93 (0.81-1.06)		114 (0.14)	1.09 (0.87-1.36)		61 (0.07)	1.01 (0.75-1.35)		24 (0.03)	1.12 (0.68-1.84)	
1-5	677 (0.46)	0.97 (0.88-1.07)		218 (0.12)	0.97 (0.82-1.15)		133 (0.07)	0.97 (0.78-1.19)		49 (0.03)	1.16 (0.81-1.65)	
6-10	283 (0.44)	0.93 (0.81-1.07)		98 (0.13)	0.92 (0.72-1.17)		66 (0.09)	1.19 (0.91-1.56)		23 (0.03)	1.32 (0.82-2.13)	
>10	685 (0.50)	1.03 (0.94-1.14)		205 (0.12)	0.98 (0.83-1.17)		150 (0.09)	1.09 (0.89-1.35)		41 (0.02)	0.99 (0.66-1.48)	

Category of Multivitamin Use	Cancer Type											
	Bladder ^f			Stomach ^g			Lung ^h			Ovarian ⁱ		
	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value
Duration of multivitamin use, y			.28			.35			.08			.06
0	236 (0.03)			61 (0.01)			795 (0.11)			315 (0.04)		
<1	19 (0.02)	0.62 (0.35-1.09)		7 (0.01)	0.90 (0.36-2.27)		94 (0.11)	1.16 (0.91-1.48)		34 (0.04)	0.87 (0.58-1.30)	
1-5	53 (0.03)	0.91 (0.66-1.27)		12 (0.01)	0.87 (0.44-1.73)		188 (0.10)	1.01 (0.84-1.21)		84 (0.05)	0.93 (0.71-1.23)	
6-10	17 (0.02)	0.51 (0.27-0.93)		5 (0.01)	0.41 (0.10-1.72)		86 (0.11)	1.03 (0.80-1.32)		51 (0.07)	1.32 (0.95-1.85)	
>10	54 (0.03)	0.99 (0.72-1.38)		16 (0.01)	1.36 (0.73-2.56)		177 (0.10)	0.89 (0.73-1.08)		95 (0.06)	1.20 (0.93-1.56)	

Abbreviations: CI, confidence interval; CTs, clinical trials; HR, hazard ratio; OS, observational study.

^aAll HRs from a proportional hazards model adjusted for the characteristics listed in Table 1 and stratified according to age (5-year groups), hormone therapy trial randomization assignment or study enrollment (active conjugated equine estrogen [CEE] plus medroxyprogesterone acetate [MPA]), placebo CEE plus MPA, active CEE, placebo CEE, not randomized), dietary modification trial randomization (intervention, control, not randomized), or OS enrollment.

^bIn addition to the adjustments listed in footnote a, the models were adjusted for Gail score (tertiles, linear). Women who did not have a mammogram within 2 years of baseline and/or a history of breast cancer were excluded.

^cWomen with a history of colorectal cancer were excluded.

^dWomen with a history of endometrial cancer were excluded.

^eAnnualized percentage of cases.

^fWomen with a history of bladder cancer were excluded.

^gWomen with a history of stomach cancer were excluded.

^hWomen with a history of lung cancer were excluded.

ⁱWomen with a history of ovarian cancer were excluded.

Table 5. Events, Annualized Percentages, and Multivariable Adjusted^a Relative Risks of Cardiovascular Disease (CVD) by Multivitamin Use^a in the Women's Health Initiative (CTs and OS)

Category of Multivitamin Use	CVD Events											
	MI ^b			Stroke ^c			Venous Thromboembolism ^d			Total Mortality		
	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value	No. (%) ^e	HR (95% CI)	P Value
Duration of multivitamin use, y												
0	2828 (0.39)		.72	2173 (0.30)		.36	354 (0.10)		.81	5911 (0.80)		.52
<1	262 (0.32)	0.93 (0.80-1.07)		221 (0.27)	0.99 (0.84-1.16)		35 (0.09)	0.95 (0.64-1.40)		609 (0.73)	1.00 (0.91-1.10)	
1-5	645 (0.35)	0.97 (0.88-1.07)		482 (0.26)	0.94 (0.84-1.06)		74 (0.10)	1.08 (0.81-1.43)		1374 (0.75)	1.01 (0.95-1.08)	
6-10	270 (0.35)	0.97 (0.84-1.11)		224 (0.29)	1.00 (0.85-1.17)		32 (0.11)	1.17 (0.77-1.79)		608 (0.77)	1.01 (0.92-1.11)	
>10	588 (0.35)	0.97 (0.87-1.07)		500 (0.30)	1.03 (0.92-1.16)		63 (0.10)	1.03 (0.74-1.43)		1363 (0.80)	1.03 (0.97-1.11)	

Abbreviations: CI, confidence interval; CTs, clinical trials; HR, hazard ratio; MI, myocardial infarction; OS, observational study.

^aAll HRs from a proportional hazards model adjusted for the characteristics listed in Table 1 and stratified according to age (5-year groups), hormone therapy trial randomization assignment or study enrollment (active conjugated equine estrogen [CEE] plus medroxyprogesterone acetate [MPA]), placebo CEE plus MPA, active CEE, placebo CEE, not randomized), dietary modification trial randomization (intervention, control, not randomized), or OS enrollment.

^bIncludes fatal and nonfatal MI. In addition to the adjustments listed in footnote a, the models were adjusted for a family history of MI and a personal history of MI.

^cIncludes fatal and nonfatal stroke. In addition to the adjustments listed in footnote a, the models were adjusted for a family history of stroke and a personal history of stroke.

^dClinical trials only: includes venous thromboembolism and pulmonary embolism; the outcomes were not adjudicated for the OS. In addition to the adjustments listed in footnote a, the models were adjusted for a history of venous thromboembolism and a history of pulmonary embolism.

^eAnnualized percentage of cases.

Table 6. Comparison of Multivariable^a Adjusted Relative Risks Between Multivitamin Users and Persistent^b Users of Multivitamins (CTs and OS)

Event	Hazard Ratio (95% Confidence Interval)	
	Multivitamin Users	Persistent Multivitamin Users
Invasive breast cancer	0.98 (0.91-1.05)	1.00 (0.92-1.09)
Colorectal cancer	0.99 (0.88-1.11)	1.09 (0.88-1.36)
Endometrial cancer	1.05 (0.90-1.21)	1.11 (0.91-1.34)
Kidney cancer	1.13 (0.87-1.46)	1.06 (0.76-1.46)
Bladder cancer	0.83 (0.65-1.06)	0.65 (0.47-0.89)
Stomach cancer	0.96 (0.60-1.53)	0.85 (0.47-1.54)
Lung cancer	1.00 (0.88-1.13)	1.11 (0.95-1.31)
Ovarian cancer	1.07 (0.88-1.29)	0.92 (0.72-1.18)
MI	0.96 (0.89-1.03)	0.99 (0.91-1.09)
Stroke	0.99 (0.91-1.07)	0.98 (0.88-1.08)
VTE	1.05 (0.85-1.29)	1.07 (0.84-1.37)
Death	1.02 (0.97-1.07)	0.98 (0.92-1.04)

Abbreviations: CTs, clinical trials; MI, myocardial infarction; OS, observational study; VTE, venous thromboembolism.

^aPersistent-use models had the same multivariable adjustment as the corresponding multivitamin-use model (see Table 2 for details).

^bPersistent users are defined as participants who were using any multivitamins at baseline and at their first collection of any multivitamin information during follow-up (year 1 for the CTs and year 3 for the OS).

Duration of multivitamin use had no apparent association with CVD risk. There was a slightly higher annualized percentage of MI cases among multivitamin non-users than among users. However, the adjusted HRs for nearly all outcomes in **Table 5** were close to 1.0, and all 95% CIs contained the null value of 1.0. There was no association of duration of multivitamin use with total mortality.

As with overall multivitamin use (Table 2), there was no association of persistent multivitamin use with risk of cancer or CVD. We see that the influence of persis-

tent multivitamin compared with any multivitamin use in relation to any of the cancer or CVD outcomes is approximately equal (**Table 6**).

The associations of multivitamin use with cancer and CVD risk were weakly modified by demographic, health, and lifestyle characteristics. Analyses by age suggested that older multivitamin users (≥ 70 years at baseline) had a reduced risk of endometrial cancer (HR, 0.73, and 95% CI, 0.55-0.97; interaction P , $<.01$), and multivitamin users who were obese had a reduced risk of invasive breast cancer (HR, 0.84, and 95% CI, 0.74-0.95; interaction P , $<.01$). However, younger women using multivitamins were at a slightly higher risk of death (HR, 1.07, and 95% CI, 1.01-1.14; interaction P , $<.05$). Multivitamin users who were current smokers or consumers of more than 1 alcoholic drink per day had nonsignificant increased risks of mortality and MI, respectively (interaction P , $<.05$). There was a nonsignificant increased risk of MI and ovarian cancer among women who used multivitamins (interaction P , .04 and .05, respectively). Fruit and vegetable intake did not modify the associations of multivitamin use with disease outcomes (data not shown).

COMMENT

In this large cohort of postmenopausal women, we observed no overall associations between multivitamin use and risk of several common cancers or CVD. There were also no associations between multivitamin use and total mortality. Risk estimates did not materially change when stratified by class of multivitamins, with the exception of a possible lower risk of MI among users of stress-type supplements. Many stress supplements include high doses of folic acid and other B vitamins; previous studies have supported a protective role for folic acid in relation to CVD and its antecedent risk

factors.^{26,34-36} Alternatively, many statistical tests were conducted as part of this investigation, and it is quite possible that this observation for lower MI risk occurred by chance. For long-term use of multivitamins, there was suggestive evidence for an increased risk of endometrial, stomach, and kidney cancer but a decreased risk of bladder cancer; however, the variation in risk was not dose dependent. Long-term multivitamin use had no association with any CVD event or total mortality. These results suggest that multivitamin use does not confer meaningful benefit or harm in relation to cancer or CVD risk in postmenopausal women.

Our findings are consistent with most previously published results. The Cancer Prevention II Cohort reported no association of baseline multivitamin use with colorectal cancer, but long-term use (>10 years) was associated with significantly reduced risk (relative risk, 0.71, and 95% CI, 0.57-0.89).^{37,38} This same cohort reported no association of multivitamin use with stomach cancer or fatal non-Hodgkin lymphoma.^{24,39} A pooled analysis of 8 cohort studies from North America and Europe found no overall association of multivitamin use with lung cancer risk but a relative risk of 1.17 (95% CI, 1.04-1.32) when only women were considered.⁴⁰ In the Nurses' Health Study, multivitamin use was associated with lower colon cancer incidence but only when such use lasted for 15 years or more.¹³ The Nurses' Health Study also reported a weak, nonsignificant protective association for breast cancer with 5 to 9 years of multivitamin use⁴¹ but an increased risk for fatal non-Hodgkin lymphoma with long-term (>10 years) use.²⁴ The Women's Health Study was a randomized, placebo-controlled trial of vitamin E and aspirin in 39 876 female health professionals.⁴² Since the end of the trial in 2004, participants have been followed up as a cohort.⁴² The investigators recently reported no association of baseline multivitamin use with subsequent breast cancer risk after an average follow-up of 10 years, nor association by duration of use, but they did report a modest suggestion of effect modification of breast cancer risk by alcohol intake.²⁷ Fewer cohorts have published data on the association with CVD risk. The Nurses' Health Study reported an inverse association between multivitamin use and risk of MI or any coronary heart disease death, but the analysis was focused on the use of B vitamins, including folic acid.³⁶ Results from other cohorts with CVD outcomes have not demonstrated any appreciable association of these events with multivitamin use.²⁵

The National Institutes of Health's Office of Dietary Supplements and Office of Medical Applications sponsored a 2006 conference to evaluate the evidence for multivitamin efficacy in relation to chronic disease prevention. An executive summary concluded that there was insufficient evidence to either promote or discourage the use of multivitamins for chronic disease prevention.² This declaration is similar to a 2003 report from the US Preventive Services Task Force stating that data were insufficient to either support or oppose the use of dietary supplements, including multivitamins, for the prevention of CVD and cancer.⁴³ The American Heart Association's Nutrition Committee recommends against the use of antioxidant supplements for CVD prevention, but their

statement refers to single supplements or mixtures of 5 or fewer ingredients. No specific statement about standard multivitamins has been issued.^{44,45} The American Cancer Society's "Guidelines on Nutrition and Physical Activity for Cancer Prevention" do not recommend dietary supplements for cancer prevention; they only suggest that subgroups, such as pregnant women, may benefit from taking multivitamins.⁴⁶ The World Cancer Research Fund's report on nutrition and cancer prevention made no evaluation about the use of multivitamins.⁴⁷ In contrast, a report by Fletcher and Fairfield⁴⁸ advised all adults to take a daily multivitamin because of concerns about diet quality in Americans.

An important question is, "Why do millions of Americans use a daily multivitamin for chronic disease prevention when the supporting scientific data are weak?" One reason may be the varied health messages received by the public. The position statements from the scientific and medical community that multivitamins are not effective for disease prevention are juxtaposed with messages to "use a multivitamin if dietary intake is inadequate."⁴⁸ These conflicting messages leave the public confused, especially because multivitamins are often regarded as safe, over-the-counter preparations.⁴⁹ However, while many multivitamins contain less than 100% of the RDA (or adequate intake) for particular nutrients, consumers will still exceed the tolerable upper intake level if they use more than 1 supplement, eat fortified foods, or use multivitamins exceeding 100% of the RDA.^{50,51} The risks associated with exceeding the upper intake level are just beginning to be understood.^{51,52}

The "gold standard" approach to resolving whether a health practice offers benefit or harm to the public is through the conduct of a well-designed randomized controlled trial. Few large-scale randomized controlled trials have been conducted to test the efficacy of multivitamins. The Linxian, China, intervention and the SUVIMAX study in France tested high-dose, limited-ingredient antioxidant vitamins.^{21,53} The Physicians' Health Study II is a randomized, double-blind, placebo-controlled trial testing whether a standard multivitamin (Centrum Silver) will reduce the incidence of cancer, CVD, eye disease, or cognitive decline among US male physicians aged 50 years and older.⁵⁴ Trial results are expected in 2012, but because the study is limited to male physicians, many questions will remain about the efficacy of multivitamin use in women. The remaining US-based supplement trials have involved either single agents or a mixture of 2 to 3 ingredients, also in high doses, that would not typically be classified as standard multivitamins.⁵⁴⁻⁵⁷ While randomized controlled trials are a considerable investment of resources, they are the only study design for which causal inference can be established. The scientific community might consider whether a randomized controlled trial of multivitamins in women could definitively resolve whether benefit or harm ensues from the routine use of multivitamins.

This study has several strengths. The WHI is one of the largest studies of postmenopausal women's health. Detailed data were collected on numerous exposures using standardized protocols. The reliability of many of these measures has been assessed, including those used as co-

variates in these analyses.⁵⁸ Second, WHI procedures to assess dietary supplement use collected more data than other concurrent cohorts; the WHI captured detailed data on dose, frequency, and duration of supplements. The direct transcription of information from the participants' supplement bottles did not rely on participants' recall, thereby minimizing misclassification of exposure. Finally, WHI outcomes were physician adjudicated, minimizing misclassification that might result from self-report alone.

There are also limitations. Despite the state-of-the-art methods used in WHI, dietary supplement use is difficult to assess. Manufacturers frequently change formulations, and label ingredient information may not reflect content.^{8,51} Moreover, persons who use supplements frequently engage in other preventive health behaviors, and disentangling highly correlated exposures is difficult.⁵⁹ In this study, we controlled for other health behaviors; however, it is not possible in observational studies to ensure that there is no residual confounding. For example, there may be residual confounding from risk factors that were not assessed in the WHI, such as workplace or environmental exposures. Furthermore, the WHI may be underpowered for rare cancers with few cases. Moreover, the follow-up time may not have been sufficient for cancers that take many years to develop. Finally, the WHI only included postmenopausal women; the results may not be generalizable to other populations.

In conclusion, the WHI CT and OS cohorts provide convincing evidence that multivitamin use has little or no influence on the risk of cancer or CVD in postmenopausal women. Nutritional efforts should remain a principal focus of chronic disease prevention, but without definitive results from a randomized controlled trial, multivitamin supplements will not likely play a major role in such prevention efforts.

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Correction

Error in Financial Disclosure. In the Original Investigation by Engler et al titled "Half- vs Full-Dose Trivalent Inactivated Influenza Vaccine (2004-2005): Age, Dose, and Sex Effects on Immune Responses" published in the December 8/22, 2008 issue of the *Archives* (2008;168(22):2405-2414), an error occurred in the Financial Disclosure on page 2413. The Financial Disclosure should have read as follows:

"Financial Disclosure: Dr Keitel has received research support from Protein Sciences Inc and Novartis Vaccines. Dr Nichol has served as a consultant for the influenza vaccine manufacturers sanofi pasteur, GlaxoSmithKline Biologicals, CSL Biotherapies, Novartis, and MedImmune and has received research funding from sanofi pasteur and GlaxoSmithKline Biologicals. Dr Treanor has received research support from Protein Sciences, Merck, Wyeth, GlaxoSmithKline, Antigen Express, Mercia Pharma, VaxInnate, Ligocyte, Sanofi, and CSL Biotherapies; has served as a consultant/scientific advisory board member for AlphaVax, Epimmune, Dynavax, Immune Targeting Systems, Pulmatrix, Powdermed, PaxVax, and Toyama; and has served as a Data Safety Monitoring Board member for Medimmune and Novavax."