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MULTIVITAMIN USE AND RISK OF CANCER AND CARDIOVASCULAR DISEASE IN THE WOMEN'S HEALTH INITIATIVE COHORTS

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Abstract

Context—Millions of postmenopausal women use multivitamins, often believing that supplements prevent chronic diseases such as cancer and cardiovascular disease.

Objective—To examine associations between multivitamin use and risk of cancer, cardiovascular disease and mortality in postmenopausal women.

Design, Setting and Participants—161,808 participants from the Women's Health Initiative Clinical Trials (n=68,132 in three overlapping trials of hormone therapy, dietary modification and calcium-vitamin D) or Observational Study (n=93,676). Detailed data were collected on multivitamin use at baseline and follow-up time points. Study enrollment occurred between 1993–

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1998; women were followed for a median of 8.0 years in the clinical trials and 7.9 years in the observational study. Disease endpoints were collected through 2005.

Outcome Measures—Cancers of the breast (invasive), colon/rectum, endometrium, kidney, bladder, stomach, ovary and lung; cardiovascular disease (myocardial infarction, stroke, venous thrombosis); and total mortality.

Results—41.5% of participants used multivitamins. After a median of 8.0 years of follow-up in the CT and 7.9 years in the OS, 9,619 cases of breast, colorectal, endometrium, kidney, bladder, stomach lung or ovary cancer; 8,751 CVD events and 9,865 deaths were reported. Multivariate-adjusted analyses revealed no association of multivitamins with risk of cancer (breast HR=0.98, 95%CI 0.91–1.05; colorectal HR = 0.99, 95% CI 0.88–1.11; endometrial HR = 1.05, 95%CI= 0.90–1.21; lung HR = 1.0, 95% CI=0.88–1.13; ovary HR = 1.07, 95%CI =0.88–1.29); CVD (MI HR= 0.96, 95%CI= 0.89–1.03; stroke HR = 0.99, 95%CI =0.91–1.07; VT HR = 1.05, 95%CI =0.85–1.29); or mortality (HR = 1.02, 95% CI=0.97–1.07).

Conclusion—After a median follow-up of 8.0 and 7.9 years in the CT and OS, respectively, the WHI cohorts provide convincing evidence that multivitamin use has little or no influence on the risk of common cancers, cardiovascular disease or total mortality in postmenopausal women.

Clinical Trial Registration—clinicaltrials.gov identifier: NCT00000611

Keywords

dietary supplements; vitamins; minerals; breast cancer; lung cancer; colon cancer; myocardial infarction; stroke

INTRODUCTION

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 over $20 billion dollars 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 (3,4). These views are often fueled by product health claims, consumer testimonials and an industry that is largely unregulated due to the 1994 Dietary Supplement and Health Education Act (DHSEA) (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 childbearing potential (10,11) and advising avoidance of high-dose β-carotene by smokers (12), current data are insufficient to formulate public health recommendations for dietary supplement use for otherwise healthy people (2).

The hypothesis that multivitamins might lower the risk of cardiovascular disease and cancer derives from published evidence supporting a role for specific micronutrients in disease prevention. Data are consistent that diets high in fruits and vegetables are associated with a lower risk of cardiovascular disease and cancer. Moreover, low vs. high serum concentrations of B-vitamins, carotenoids and tocopherols have been associated with increased risk of colorectal cancer and cardiovascular disease (13–20). Since these vitamins, minerals and other small molecule compounds can be effectively packaged into pill form, supplements could ensure adequate micronutrient intake or correct low circulating concentrations, especially among persons with poor diets (21). Multivitamins are a potential vehicle since 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 examining associations between supplement use and disease risk, few have explicitly investigated multivitamins. Limited evidence from case-control and cohort studies suggests that multivitamins are associated with reduced risk of colon and bladder cancer, but increased risk of non-Hodgkin's lymphoma (24). Other observational studies report no associations of multivitamins with colorectal, gastric, or lung cancers. One study of more than 1 million Americans reported no association of multivitamin use with total mortality, CHD mortality or cancer mortality (25). A cohort of men reported no risk reduction for cardiovascular disease or mortality for men who used multivitamins vs. those not using multivitamins (26). A prospective study of 37,920 women reported no association of multivitamin use with risk of breast cancer (27).

In this report we examined the associations between multivitamin use in the Women's Health Initiative (WHI) Clinical Trial and Observational Study cohorts with risk of site-specific solid tumors: (invasive breast, kidney, endometrium, ovary, bladder and stomach cancers); (2) cardiovascular disease; and (3) total mortality.

METHODS

Overview of The Women's Health Initiative

The WHI is a study of postmenopausal women's health investigating risk factors for cancer, heart disease, and skeletal health (28). WHI was designed as a set of randomized controlled Clinical Trials and an Observational Study. Women were eligible for WHI participation if they were 50–79 years of age at screening, postmenopausal, and likely to live in close geographic proximity to one of 40 WHI Clinical Centers for at least three years. Women were excluded for medical conditions with a predicted survival of three years of less, conditions limiting adherence or retention (i.e., alcohol or drug dependency, dementia), or active participation in any other intervention trial where participants were individually randomized to a control or intervention group (28). The Clinical Trials (CT) (N=68,132) included three overlapping components: the Hormone Therapy (HT) Trials (n=27,347), Dietary Modification (DM) Trial (n=48,835), and Calcium and Vitamin D (CaD) Trial (n=36,282). Eligible women could be randomized into one, two, or all three of the CTs. Trial arm assignment was randomly designated (1:1 for the HT and CaD trials; for the DM, 40% were assigned to the low-fat intervention and 60% to usual diet) (28). Women who were ineligible or unwilling to join the CT were invited to join the Observational Study (OS), as were those who were specifically recruited for the OS (n=93,676). CT women attended baseline and annual clinic visits. OS women attended baseline and year 3 clinic visits and completed all other annual study activities by mail (i.e., medical history and lifestyle-exposure updates). Women were followed for a median of 8.0 years in the CT 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. This report is based on data from 161,808 women from both the Observational Study and the Clinical Trials; two 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 CT, and to the baseline and 3-year visit in the OS. A standardized interviewer-administered four-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 directly transcribed the ingredients for each supplement. Staff also queried 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 0.8–1.0 (29,30).

Multivitamins were grouped into three classifications based on ingredients: (i) 'multivitamins (alone)' were preparations with 10 or more vitamins and no minerals where the nutrient levels were at least 100% of US RDA; (ii) 'multivitamins with minerals' were preparations with 20–30 vitamins and minerals and nutrient levels ≤ 100% of US RDA; (iii) 'stress multi-supplements' 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.

Outcomes Ascertainment

Clinical outcomes of interest in WHI included cardiovascular disease (coronary heart disease, stroke, congestive heart failure, angina, peripheral vascular disease, carotid artery disease and coronary revascularization) cancer (breast, colorectal, endometrial, ovarian, 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 semi-annual (in the CT) 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 (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 endpoints reported and adjudicated through the end of the WHI close-out period of March, 2005. We included eight solid tumor cancers (invasive breast, colorectal, endometrial, stomach, ovary, kidney, lung, and bladder) and three CVD endpoints (myocardial infarction, stroke and venous thrombosis (CT only)).

Other Data

Standard procedures used across the CT and OS were employed to collect data on age, race/ethnicity, reproductive/gynecological history, education, physical activity, medical history, family or personal history of cancer or coronary heart disease, diabetes, current health status, and tobacco and alcohol use. Clinic staff measured blood pressure, height and weight using standardized protocols

Statistical Analyses

Descriptive statistics characterized the study population. Cox proportional hazard models estimated hazard ratios and 95% confidence intervals 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 CT and time of enrollment in the OS (32,33). For a particular event, time accrued while a participant was still at risk for an event until date of diagnosis for cancer or cardiovascular disease, death from any cause, loss to follow-up, or March 31, 2005. Proportional hazards assumptions were assessed by a one-degree of freedom 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,>15), BMI, education, alcohol use, smoking, general health, history of bilateral oophorectomy, geographic region, physical activity, duration of prior postmenopausal estrogen therapy use (none,<5, 5–10,10–15, >15 years), duration of prior postmenopausal estrogen+progesterone use (none,<5, 5–10,10–15, >15 years), fruit and vegetable intake, percent energy from fat, single supplements of vitamin C, E or calcium, any other single supplement, and stratified on age (5 year groups), HT trial randomization assignment/study enrollment [active conjugated equine estrogen + medroxyprogesterone acetate, (hereafter called CEE and MPA), placebo CEE+MPA, active CEE, placebo CEE, not randomized], DM trial randomization (intervention, control, not randomized) or OS enrollment (32,33). Specific to cancer analyses, family history of cancer was an additional covariate; women were excluded if they had a prior history of the particular cancer. For breast cancer analyses, women without a mammogram within two years of baseline were excluded. Specific to CVD analysis, treated diabetes, treated hyperlipidemia, systolic blood pressure, and prior history of the particular cardiovascular disease were additional covariates.

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

All statistical tests were two-sided with a p-value<0.05 considered statistically significant. Analyses were conducted with SAS, version 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Table 1 presents demographic, health and lifestyle data according to use of multivitamin supplements in WHI. Of the 161,806 WHI participants with completed dietary supplement data collection forms, 41.5% reported multivitamin use. The most common category was ‘multivitamins with minerals’ (35.0%), with fewer taking ‘multivitamins (alone)’ (3.5%) or ‘stress-multivitamins’ (2.3%). Those who used any multivitamins were more likely to also use single supplements of vitamin E, vitamin C or calcium, compared to women who did not use multivitamins ($p< 0.001$). Compared to women not using multivitamins, multivitamin users were more likely to be white, living in the western United States, have a lower BMI, be more physically active and have a college degree or higher (all $p< 0.001$). Women who used multivitamins were more likely to consume alcohol and less likely to smoke than were non-users. Multivitamin users reported slightly higher fruit and vegetable consumption and lower percent energy from fat than non-users at baseline.

There was no evidence that multivitamin use either increased or decreased risk of cancer (Table 2). Overall, there was no association of any multivitamin use with risk for cancers of the breast, colon/rectum, endometrium, ovary, kidney, bladder, stomach or lung. When we examined risk by the three classes of multivitamins, there was also no apparent association and the null value of 1.0 was included in the 95% confidence intervals of all multivariate-adjusted hazard ratio estimates. We observed a non-significant 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 hazard ratio estimates.

We next examined the association of multivitamin use with risk of cardiovascular disease (MI, stroke, venous thrombosis) (Table 3). The annualized percentages of cardiovascular

disease events were non-significantly lower among women using multivitamins compared to those not taking multivitamins and the overall hazard ratios ranged from 0.96 (95% CI, 0.89–1.03) to 1.05 (95% CI, 0.85, 1.29). Stress-multivitamins were the only supplements for which a cardiovascular protective association was suggested; for MI the adjusted-HR was 0.75 (95%CI, 0.56–0.99).

To investigate variation in risk by total duration of use, we categorized duration into four groups: (i) less than one year; (ii) 1–5 years; (iii) 6–10 years; and (iv) > 10 years. Of the 1,928 invasive breast cancer cases who used multivitamins, 685 (35.5%) reported multivitamin use for at least 10 years (Table 4). While the annualized percent of breast cancer events was slightly higher among those with at least 10 years of use (0.50), compared to non-users of multivitamins (0.44), the adjusted HR was 1.03 (95%CI 0.94, 1.14). Five to ten years and more than 10 years of multivitamin use were associated with small but statistically non-significant increased risks for endometrial cancer (HR= 1.19, 95%CI, 0.91–1.56 and HR = 1.09, 95%CI, 0.89–1.35, respectively) kidney cancer (HR = 1.32, 95% CI, 0.82–2.13 for 5–10 years of use) and stomach cancer (HR= 1.36, 95%CI 0.73, 2.56 for > 10 years of use).

Duration of multivitamin use had no apparent association with cardiovascular disease risk. There was a slightly higher annualized percentage of MI cases for multivitamin non-users than users. However, the adjusted hazard ratios for nearly all outcomes in Table 5 were close to 1.0 and all 95% confidence intervals 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 persistent multivitamin compared to any use in relation to any of the cancer or CVD outcomes are approximately equal (Table 6).

The associations of multivitamin use with cancer and cardiovascular disease risk were weakly modified by demographic, health and lifestyle characteristics. Analyses by age suggested older multivitamin users (≥70 years at baseline) had a reduced risk of endometrial cancer (HR=0.73, 95% CI=0.55–0.97, p, interaction <0.01) and multivitamin users who were obese had a reduced risk of invasive breast cancer (HR=0.84, 95%CI= 0.74–0.95, p, interaction <0.01). However, younger women using multivitamins were at a slightly higher risk of death (HR=1.07, 95%CI, 1.01–1.14, p, interaction <0.05). Multivitamin users who were current smokers or consumers of more than one alcohol drink per day had non significant increased risks of mortality and myocardial infarction, respectively (p, interaction <0.05). There was a non-significant increased risk of myocardial infarction and ovarian cancer among women who used multivitamins (p, interaction = 0.04 and 0.05, respectively). Fruit and vegetable intake did not modify the associations of multivitamin use with disease outcomes (data not shown).

DISCUSSION

In this large cohort of postmenopausal women, we observed no overall associations between multivitamin use and risk of several common cancers or cardiovascular disease. 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 cardiovascular disease 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 increased risk of endometrial, stomach and kidney cancer, but decreased risk for bladder cancer; however, the variation in risk was not dose-dependent. Long term multivitamin use had no association with any cardiovascular event or total mortality. These results suggest that multivitamin use does not confer meaningful benefit or harm in relation to cancer or cardiovascular disease risk in postmenopausal women.

This report is 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 (RR= 0.71, 95% CI 0.57,0.89) (37,38). This same cohort reported no association of multivitamin use with stomach cancer or fatal non-Hodgkin's lymphoma (24,39). A pooled analysis of eight cohort studies from North America and Europe found no overall association of multivitamin use with lung cancer risk, but a RR of 1.17 (95% CI 1.04,1.32) when only women were considered (40). In the Nurses' Health Study, multivitamins were associated with lower colon cancer incidence, but only when used for 15 years or more (15). The Nurses' Health Study also reported a weak, non-significant protective association for breast cancer for 5–9 years of use multivitamins (41), but an increased risk for fatal non-Hodgkin's 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 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 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 multivitamins and risk of MI or any CHD death, but the analysis was focused on 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).

NIH'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 U.S. Preventive Services Task Force stating that data were insufficient to either support or oppose dietary supplements, including multivitamins, for prevention of cardiovascular disease and cancer (43). The American Heart Association's Nutrition Committee recommends against the use of antioxidant supplements for cardiovascular disease prevention, but their statement refers to single supplements or mixtures of five 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 multivitamins (46). The World Cancer Research Fund's report on nutrition and cancer prevention made no evaluation about multivitamins (47). In contrast, a report by Fletcher and Fairfield advised all adults to take a daily multivitamin due to concerns about diet quality in Americans (48).

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 since 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 (AI)) for particular nutrients, consumers will still exceed the tolerable upper intake level (UL) if they use more than one supplement, eat fortified foods, or use multivitamins exceeding 100% of the RDA (50,51). The risks associated with exceeding the UL are just beginning to be understood (51,52).

The gold standard approach to resolving whether a heath practice offers benefit or harm to the public is through the conduct of a well-designed randomized controlled trial. Few large scale RCTs 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 Trial II is a randomized, double-blind placebo controlled trial testing whether a standard multivitamin (Centrum Silver®) will reduce the incidence of cancer, cardiovascular disease, eye disease and cognitive decline among U.S. male physicians aged 50 years and older (54). Trial results are expected in 2012, but since 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 been either single agents or a mixture of two to three ingredients, also in high doses that would not typically be classified as a standard multivitamin (54–57). While RCTs 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 routine use of multivitamins.

This study has several strengths. WHI is one of the largest studies on 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 covariates in these analyses (58). Second, WHI procedures to assess dietary supplement use collected more data that other concurrent cohorts; 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 assure that there is no residual confounding. For example, there may be residual confounding from risk factors that were not assessed in WHI, such as workplace or environmental exposures. Further, 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, WHI only included postmenopausal women; results may not be generalizeable to other populations.

In conclusion, the WHI Clinical Trial and Observational Study cohorts provide convincing evidence that multivitamin use has little or no influence on the risk of cancer or cardiovascular disease 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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Table 1

Characteristics of Multivitamin Supplement Users and Non-Users in the Women's Health Initiative (CT+OS, n=161806)

	Combination (N=1091)		Stress Multi-Vitamins. (N=3741)		Multi-Vitamin w/minerals (N=56296)		Multi-Vitamin (N=5667)		None (N=95011)		
	N	%	N	%	N	%	N	%	N	%	P-Value*
Age group at screening, years											<0.001
50–59	421	38.6	1414	37.8	16895	30.0	1667	29.4	33160	34.9	
60–69	460	42.2	1631	43.6	26080	46.3	2527	44.6	41887	44.1	
70–79	210	19.2	696	18.6	13321	23.7	1473	26.0	19964	21.0	
Years since menopause											<0.001
< 5 yrs	158	15.1	572	15.9	6616	12.3	672	12.5	12489	14.1	
5 – <10 yrs	210	20.1	709	19.7	9342	17.3	919	17.1	16224	18.3	
10 – <15 yrs	192	18.4	745	20.7	10795	20.0	997	18.6	17284	19.5	
>= 15 yrs	483	46.3	1567	43.6	27167	50.4	2783	51.8	42422	48.0	
Ethnicity											<0.001
White	953	87.4	3093	82.7	49165	87.3	5048	89.1	75273	79.2	
Black	64	5.9	180	4.8	3253	5.8	322	5.7	10807	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	
Body mass index (BMI), kg/ m2 (collapsed categories)											<0.001
<25 (normal)	457	42.4	1579	42.7	21251	38.1	2315	41.3	30729	32.6	
25 – <30 (overweight)	348	32.3	1228	33.2	19535	35.0	1949	34.8	32606	34.6	
>=30 (obese)	273	25.3	892	24.1	15020	26.9	1344	24.0	30835	32.7	
Education											<0.001
High school or less	175	16.1	605	16.3	11172	20.0	1117	19.8	23192	24.6	
School after high school	451	41.6	1433	38.6	21136	37.8	1999	35.5	35883	38.1	
College degree or higher	458	42.3	1676	45.1	23616	42.2	2512	44.6	35146	37.3	
Alcohol											<0.001

	Combination (N=1091)		Stress Multi-Vitamins. (N=3741)		Multi-Vitamin w/minerals (N=56296)		Multi-Vitamin (N=5667)		None (N=95011)		
	N	%	N	%	N	%	N	%	N	%	P-Value*
Non drinker	110	10.2	372	10.0	5169	9.2	507	9.0	11494	12.2	
Past drinker	202	18.7	718	19.3	10020	17.9	986	17.5	18221	19.3	
<1/wk	353	32.7	1209	32.5	18672	33.4	1843	32.6	30830	32.7	
1–7/wk	311	28.8	975	26.2	15183	27.1	1552	27.5	23179	24.6	
>7/wk	104	9.6	446	12.0	6906	12.3	759	13.4	10541	11.2	
Smoking											<0.001
Never smoked	527	49.1	1808	48.9	28234	50.8	2931	52.3	47931	51.2	
Past smoker	486	45.3	1675	45.3	24205	43.5	2357	42.1	38386	41.0	
Current smoker	60	5.6	217	5.9	3173	5.7	314	5.6	7379	7.9	
General health											<0.001
Excellent	205	18.8	732	19.7	9754	17.4	966	17.1	15730	16.7	
Very Good	463	42.6	1600	43.1	23938	42.7	2418	42.9	37216	39.5	
Good	340	31.3	1126	30.4	18036	32.2	1803	32.0	31736	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	11372	20.6	1081	19.4	18145	19.6	<0.001
U.S. region											<0.001
Northeast	146	13.4	822	22.0	12872	22.9	1764	31.1	21308	22.4	
South	274	25.1	682	18.2	13312	23.6	993	17.5	26658	28.1	
Midwest	200	18.3	531	14.2	12520	22.2	1375	24.3	20937	22.0	
West	471	43.2	1706	45.6	17592	31.2	1535	27.1	26108	27.5	
Physical activity											<0.001
None or <2x/week	520	49.2	1725	47.7	28047	51.5	2852	53.2	53845	59.9	
2–4x/week	188	17.8	721	20.0	10436	19.2	1007	18.8	15098	16.8	
>=4x/week	349	33.0	1167	32.3	15969	29.3	1498	28.0	20917	23.3	
Unopposed Estrogen Duration by Category											<0.001
None	652	59.8	2335	62.4	34630	61.5	3651	64.4	62834	66.1	
< 5 Years	158	14.5	516	13.8	7428	13.2	729	12.9	12605	13.3	

	Combination (N=1091)		Stress Multi-Vitamins. (N=3741)		Multi-Vitamin w/minerals (N=56296)		Multi-Vitamin (N=5667)		None (N=95011)		
	N	%	N	%	N	%	N	%	N	%	P-Value*
5 – < 10 Years	102	9.3	283	7.6	4224	7.5	414	7.3	6338	6.7	
10 – < 15 Years	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 + Progesterone Duration by Category											<0.001
None	753	69.0	2449	65.5	39725	70.6	4132	72.9	72656	76.5	
< 5 Years	162	14.8	644	17.2	7963	14.1	748	13.2	11734	12.4	
5 – < 10 Years	105	9.6	356	9.5	4569	8.1	421	7.4	5958	6.3	
10 – < 15 Years	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	20195	35.9	2004	35.4	18578	19.6	<0.001
Vitamin E as SINGLE supplement	512	46.9	1574	42.1	22830	40.6	2206	38.9	21462	22.6	<0.001
Calcium as single supp (including antacids)	340	31.2	1014	27.1	19044	33.8	2130	37.6	20306	21.4	<0.001
Single Supplement (not Vitamins C, E or Ca)	933	85.5	3741	100.0	26528	47.1	2477	43.7	28353	29.8	<0.001
Treated diabetes (pills or shots)	33	3.0	101	2.7	1934	3.4	199	3.5	4900	5.2	<0.001
History of high cholesterol requiring pills	111	10.7	476	13.3	7643	14.2	765	14.4	12541	14.2	0.01
Family history of cancer	730	69.9	2373	66.1	36356	67.4	3660	67.2	59587	65.8	<0.001
Mammogram in last 2 yrs	911	85.7	3124	86.0	47349	86.3	4818	87.2	74608	81.4	<0.001
History of breast cancer	45	4.1	122	3.3	2009	3.6	198	3.5	2649	2.8	<0.001
History of colorectal cancer	8	0.7	13	0.3	341	0.6	36	0.6	549	0.6	0.31
Family history of myocardial infarction (MI)	518	50.0	1785	50.5	28257	52.9	2832	52.4	46780	52.2	0.006

	Combination (N=1091)		Stress Multi-Vitamins. (N=3741)		Multi-Vitamin w/minerals (N=56296)		Multi-Vitamin (N=5667)		None (N=95011)		
	N	%	N	%	N	%	N	%	N	%	P-Value*
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	P-Value
Age at screening, years	62.4	(7.2)	62.4	(7.2)	63.7	(7.2)	64.1	(7.3)	62.9	(7.3)	<0.001
Fruit and vegetable servings/ day	4.4	(2.2)	4.4	(2.2)	4.3	(2.1)	4.3	(2.1)	3.9	(2.1)	<0.001
Percent Calories from Fat/day	31.0	(8.3)	31.1	(8.6)	31.7	(8.3)	31.5	(8.2)	33.4	(8.3)	<0.001
Systolic BP	125.5	(17.7)	126.5	(18.1)	126.9	(17.6)	127.6	(18.0)	127.7	(17.8)	<0.001

* P values are from t-tests for continuous variables and chi-squared test for categorical variables.

Table 2

Multivariable adjusted[1] Relative Risk of Major Cancers by Multivitamin Use in the Women's Health Initiative (CT+OS)

	Cancer Site																			
	Invasive Breast[2]					Colorectal[3]					Endometrium[4]					Kidney				
Category of Multivitamin	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***
Any Multivitamin					0.53					0.84					0.53					0.37
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					0.69					0.90					0.78					0.37
None	2472	(0.44)				955	(0.13)				502	(0.07)				181	(0.02)			
Multi-vitamin	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)	
Multi-vitamin w/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 Multi-vitamins	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)	

	Cancer Site																			
	Bladder[5]					Stomach[6]					Lung[7]					Ovary[8]				
Category of Multivitamin	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***
Any Multivitamin					0.13					0.85					0.95					0.50
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					0.44					0.68					0.57					0.74
None	236	(0.03)				61	(0.01)				795	(0.11)				315	(0.04%)			
Multi-vitamin	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)	
Multi-vitamin w/ 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 Multi-vitamins	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)	

[1] All hazard ratios from a proportional hazards model adjusted for age(linear), race/ethnicity, years since menopause (<5,5–10,10–15,>15, linear), BMI (<25,25–30,>30, linear), education(<=high school, some college, college grad), alcohol use (non, past,<1/wk,1–7wk,>7wk), smoking(non, past, current), general health (fair/poor, good, very good, excellent), history of bilateral oophorectomy(yes, no), region(northeast, south, midwest, west), physical activity(none/<2,2–4 episodes,>4 episodes), duration of prior E alone use (none,<5,5–10,10–15,>15years), duration of E+P use(none,<5,5–10,10–15,>15years), fruit and vegetable intake (tertiles, linear) and percent energy from fat (tertiles, linear), use of Vitamin C as a single supplement, use of Vitamin E as a single supplement, use of Calcium as a single supplement, use of any other single supplement, family history of cancer and stratified on age (5yr groups), HT trial randomization assignment/study enrollment (active CEE+MPA, placebo CEE+MPA, active CEE, placebo CEE, not randomized), DM trial randomization (intervention, control, not randomized) or OS enrollment.

[2] In addition to the adjustments listed in 1, models were adjusted for Gail score (tertiles, linear). Women who did not have a mammogram within two years of baseline and/or **prior history of breast cancer** were excluded.

[3] Women with a **prior history of colorectal cancer** were excluded.

[4] Women with a **prior history of endometrial cancer** were excluded.

[5] Women with a **prior history of bladder cancer** were excluded.

[6] Women with a **prior history of stomach cancer** were excluded.

[7] Women with a **prior history of lung cancer** were excluded.

[8] Women with a **prior history of ovarian cancer** were excluded.

[*] Number of cases.

[£] Annualized percent of cases.

Table 3

Events, Annualized Percentages and Multivariable adjusted[1] Relative Risk of Cardiovascular Disease by Multivitamin Use in the Women's Health Initiative (CT+OS)

	CVD Events																			
	M.I.[2]					Stroke[3]					Venous Thrombosis[4]					Total Mortality				
Category of Multivitamin	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***
Any Multivitamin					0.27					0.75					0.64					0.48
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					0.10					0.68					0.85					0.69
None	2828	(0.39)				2173	(0.30)				354	(0.10)				5911	(0.80)			
Multi-vitamin	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)	
Multi-vitamin w/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 Multi-vitamins	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)	

[1] All hazard ratios from a proportional hazards model adjusted for age(linear), race/ethnicity, years since menopause (<5,5–10,10–15,>15, linear), BMI (<25,25–30,>30, linear), education(<=high school, some college, college grad), alcohol use (non, past,<1/wk,1–7wk,>7wk), smoking(non, past, current), general health (fair/poor, good, very good, excellent), history of bilateral oophorectomy(yes, no), region(northeast, south, midwest, west), physical activity(none/<2,2–4 episodes,>4 episodes), duration of prior E alone use (none,<5,5–10,10–15,>15years), duration of E+P use(none,<5,5–10,10–15,>15years), fruit and vegetable intake (tertiles, linear) and percent energy from fat (tertiles, linear), use of Vitamin C as a single supplement, use of Vitamin E as a single supplement, use of Calcium as a single supplement, use of any other single supplement**, treated diabetes, treated hyperlipidemia, systolic blood pressure (tertiles, linear),** and stratified on age (5yr groups), HT trial randomization assignment/study enrollment (active CEE+MPA, placebo CEE+MPA, active CEE, placebo CEE, not randomized), DM trial randomization (intervention, control, not randomized) or OS enrollment.

[2] Includes fatal and nonfatal MI. In addition to the adjustments listed in 1, models were adjusted for **family history of MI** and **prior history of MI**.

[3] Includes fatal and nonfatal stroke. In addition to the adjustments listed in 1, models were adjusted for **family history of stroke** and **prior history of stroke**.

[4] **CT only**, includes DVT and PE; outcomes not adjudicated for OS. In addition to the adjustments listed in 1, models were adjusted for **prior history of DVT** and **prior history of PE**.

* Number of cases.

£ Annualized percent of cases

Table 4

Multivariable adjusted[1] Relative Risk of Major Cancers by Multivitamin Duration in the Women's Health Initiative (CT+OS)

	Cancer Site																			
	Invasive Breast[2]					Colorectal[3]					Endometrium[4]					Kidney				
Category of Multivitamin	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***
Duration of Multivitamin					0.17					0.56					0.36					0.63
None	2472	(0.44)				955	(0.13)				502	(0.07)				181	(0.02)			
<1 yr	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 to 5 yrs	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 to 10 yrs	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)	

	Cancer Site																			
	Bladder[5]					Stomach[6]					Lung[7]					Ovary[8]				
Category of Multivitamin	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***	**N***	**(%)£**	**HR**	**(CI)**	***p***
Duration of Multivitamin					0.28					0.35					0.08					0.06
None	236	(0.03)				61	(0.01)				795	(0.11)				315	(0.04%)			
<1 yr	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 to 5 yrs	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 to 10 yrs	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)	

[1] All hazard ratios from a proportional hazards model adjusted for age(linear), race/ethnicity, years since menopause (<5,5–10,10–15,>15, linear), BMI (<25,25–30,>30, linear), education(<=high school, some college, college grad), alcohol use (non, past,<1/wk,1–7wk,>7wk), smoking(non, past, current), general health (fair/poor, good, very good, excellent), history of bilateral oophorectomy(yes, no), region(northeast, south, midwest, west), physical activity(none/<2,2–4 episodes,>4 episodes), duration of prior E alone use (none,<5,5–10,10–15,>15years), duration of E+P use(none,<5,5–10,10–15,>15years), fruit and vegetable intake (tertiles, linear) and percent energy from fat (tertiles, linear), use of Vitamin C as a single supplement, use of Vitamin E as a single supplement, use of Calcium as a single supplement, use of any other single supplement, family history of cancer and stratified on age (5yr groups), HT trial randomization assignment/study enrollment (active CEE+MPA, placebo CEE+MPA, active CEE, placebo CEE, not randomized), DM trial randomization (intervention, control, not randomized) or OS enrollment.

[2] In addition to the adjustments listed in 1, models were adjusted for Gail score (tertiles, linear). Women who did not have a mammogram within two years of baseline and/or **prior history of breast cancer** were excluded.

[3] Women with a **prior history of colorectal cancer** were excluded.

[4] Women with a **prior history of endometrial cancer** were excluded.

[5] Women with a **prior history of bladder cancer** were excluded.

[6] Women with a **prior history of stomach cancer** were excluded.

[7] Women with a **prior history of lung cancer** were excluded.

[8] Women with a **prior history of ovarian cancer** were excluded.

[*] Number of cases.

[£] Annualized percent of cases

Table 5

Events, Annualized Percentages and Multivariable adjusted[1] Relative Risk of Cardiovascular Disease by Multivitamin Use* in the Women's Health Initiative (CT+OS)

Category of Multivitamin	CVD Events																	
	M.I.[2]					Stroke[3]					Venous Thrombosis[4]					Total Mortality				
	N*	(%)£	HR	(CI)	*p*	N*	(%)£	HR	(CI)	*p*	N*	(%)£	HR	(CI)	*p*	N*	(%)£	HR	(CI)	*p*
Duration of Multivitamin					0.72					0.36					0.81					0.52
None	2828	(0.39)				2173	(0.30)				354	(0.10)				5911	(0.80)			
<1 yr	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 to 5 yrs	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 to 10 yrs	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)	

[1] All hazard ratios from a proportional hazards model adjusted for age(linear), race/ethnicity, years since menopause (<5,5–10,10–15,>15, linear), BMI (<25,25–30,>30, linear), education(<=high school, some college, college grad), alcohol use (non, past,<1/wk,1–7wk,>7wk), smoking(non, past, current), general health (fair/poor, good, very good, excellent), history of bilateral oophorectomy(yes, no), region(northeast, south, midwest, west), physical activity(none/<2,2–4 episodes,>4 episodes), duration of prior E alone use (none,<5,5–10,10–15,>15years), duration of E+P use(none,<5,5–10,10–15,>15years), fruit and vegetable intake (tertiles, linear) and percent energy from fat (tertiles, linear), use of Vitamin C as a single supplement, use of Vitamin E as a single supplement, use of Calcium as a single supplement, use of any other single supplement, treated diabetes, treated hyperlipidemia, systolic blood pressure (tertiles, linear), and stratified on age (5yr groups), HT trial randomization assignment/study enrollment (active CEE+MPA, placebo CEE+MPA, active CEE, placebo CEE, not randomized), DM trial randomization (intervention, control, not randomized) or OS enrollment.

[2] Includes fatal and nonfatal MI. In addition to the adjustments listed in 1, models were adjusted for **family history of MI** and **prior history of MI**.

[3] Includes fatal and nonfatal stroke. In addition to the adjustments listed in 1, models were adjusted for **family history of stroke** and **prior history of stroke**.

[4] **CT only**, includes DVT and PE; outcomes not adjudicated for OS. In addition to the adjustments listed in 1, models were adjusted for **prior history of DVT** and **prior history of PE**.

* Number of cases.

£ Annualized percent of cases

Table 6

Comparison of Multivariable[1] Adjusted Relative Risk between multivitamin users and persistent[2] users of multivitamins (CT+OS)

Event	HR(95%CI) of multivitamin use	HR(95%CI) of persistent use
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)
Ovary 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)

[1] Persistent use models had the same multivariable adjustment as the corresponding multivitamin use model (see Table 2 for details).

[2] Persistent 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 CT and Year 3 for the OS).