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Use of multivitamins and prostate cancer mortality in a large cohort of US men

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Abstract

Objective: To assess the association between the use of multivitamins and prostate cancer mortality.
Methods: A total of 5585 deaths from prostate cancer were identified during 18 years of follow-up of 475,726 men who were cancer-free and provided complete information on multivitamin use at enrollment in the Cancer Prevention Study II (CPS-II) cohort in 1982. Cox proportional hazards modeling was used to measure the association between multivitamin use at baseline and death from prostate cancer and to adjust for potential confounders.
Results: The death rate from prostate cancer was marginally higher among men who took multivitamins regularly (≥15 times/month) compared to non-users (multivariate rate ratio = 1.07, 95% CI: 0.99–1.15); this risk was statistically significant only for those multivitamin users who used no additional (vitamin A, C, or E) supplements (multivariate rate ratio = 1.15, 95% CI: 1.05–1.26). In addition, risk was greatest during the initial four years of follow-up (1982–1986, multivariate rate ratio = 1.12, 95% CI: 0.87–1.46).
Conclusions: Regular multivitamin use was associated with a small increase in prostate cancer death rates in our study, and this association was limited to a subgroup of users.

Introduction

Approximately one third of adults in the United States report taking some vitamin or mineral supplement within the previous year, according to the third National Health and Nutrition Examination Survey (NHANES III, 1989–1994) [1]. Multivitamins are effective in preventing vitamin deficiencies, but whether they are beneficial for individuals in developed countries where deficiencies are less common is unclear [2, 3]. In fact, the US Preventive Task Force recently determined that there was insufficient evidence to support a recommendation either for or against the use of multivitamins for the prevention of cancer or cardiovascular disease [4]. Thus, additional studies are needed to assess the benefit or harm of multivitamin supplements for specific chronic diseases.

Several studies have investigated the association between multivitamin use and cancers of the oesophagus, stomach, and colorectum [5–10], but little research has focused specifically on prostate cancer. Among men in the US, prostate cancer is the most commonly diagnosed invasive cancer and the second most common cause of cancer death [11]. Only two published epidemiological studies have investigated the association between multivitamins and prostate cancer. Watkins *et al.* [12] examined the association between multivitamin use and death for multiple diseases among men enrolled in the American Cancer Society (ACS) Cancer Prevention Survey II (CPS-II). In analysis of seven years of follow-up, multivitamin use for more than five years

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prior to enrollment in 1982 was associated with a moderately increased risk of death from prostate cancer (rate ratio (RR) = 1.31, 95% confidence intervals (CI) 1.04–1.66) [12]. A population-based case-control study of prostate cancer incidence found no association between incident prostate cancer and multivitamin use in 697 cases [13]. Thus, the published data are limited and inconsistent.

Several of the vitamins included in multivitamin preparations, including vitamins A, C, D, E, and folic acid, may affect the risk of other cancers [14, 15] but have no clearly established relationship with prostate cancer. The incidence and mortality rates for prostate cancer were significantly lower in men receiving vitamin E supplements (as α-tocopherol) in the Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study (ATBC Study) [16], but the inverse association was attenuated after an additional six (for incidence) or eight (for mortality) years of follow-up [17]. This attenuation could reflect either a lack of association between vitamin E use and prostate cancer, or dilution of an effect on a late stage of prostate carcinogenesis due to cessation of the treatment. No relationship was observed between use of vitamin E supplements and prostate cancer incidence in several epidemiologic studies of this association [13, 18–21], including a recent study in the CPS-II Nutrition Cohort [21]. However, two of these studies [20, 21] did not rule out a potential subgroup effect of reduced risk among current smokers. No association has been found between use of vitamin C supplements and prostate cancer [13, 18, 19].

Both vitamins A and D have been shown to inhibit the growth and induce differentiation of prostate cancer cells grown in culture [22–24]. Epidemiologic studies also provide some evidence that vitamin D can influence prostate cancer risk. Some studies investigating exposure to ultraviolet (UV) irradiation [25, 26] (which mediates subcutaneous vitamin D synthesis) or levels of circulating vitamin D metabolites [27, 28] have supported a protective effect for this vitamin in prostate cancer, whereas others have not (reviewed in [29]). In contrast, the evidence regarding vitamin A is so limited that an international review group concluded that there is no evidence to suggest this vitamin plays a role in prostate cancer prevention [30]. Only two published studies have examined the association of prostate cancer with folic acid [31, 32]. Although folic acid is critical in maintaining genetic stability and is associated with decreased risk of colorectal, cervical, and breast cancer [33, 34], no significant association was seen between serum folate levels and prostate cancer incidence in either of these studies [31, 32].

This report updates and expands the previous analysis [12] of multivitamin use and prostate cancer mortality among men in the CPS-II cohort. The current analyses are based on 18 years of follow-up (1982–2000) and include five times as many prostate cancer deaths as previously considered [12].

Methods

Study cohort and follow-up

Men were drawn from 508,318 male participants enrolled in CPS-II, a prospective study of cancer mortality of approximately 1.2 million Americans begun in 1982. The cohort participants, who were enrolled by more than 77,000 ACS volunteers, came from all 50 states, the District of Columbia, and Puerto Rico [35, 36]. The median age of the male participants in 1982 was 57 with the majority being between 47 and 70 years of age. Participants completed a self-administered questionnaire upon enrollment that included questions on demographic, medical, lifestyle, environmental, and dietary characteristics.

Follow-up for vital status was done through personal inquiries by volunteers in 1984, 1986, and 1988 to determine whether participants were alive and to ascertain the date and place of death. After 1988, automated linkage using the National Death Index (NDI) was used to determine this information and to identify deaths among 8485 men lost to follow-up between 1982 and 1988 [37]. After 18 years of follow-up (through 31 December, 2000), 331,360 (65.2%) of the men were still living, 176,140 (34.6%) men had died, and 818 (0.2%) men had follow-up truncated on 31 December, 1988 due to insufficient data for linkage with the NDI. Death certificates or multiple cause-of-death codes were obtained for 98.7% of known deaths in CPS-II. Follow-up ended at the date of death or 31 December, 2000, depending on which came first.

Cases in the analysis are men who were cancer-free at enrollment and who died during the follow-up period with prostate cancer as their primary cause of death. The International Classification of Diseases, ninth revision (ICD-9) code 185 was used for deaths between 1982 and 1998 [38]; the ICD-10 code C61 was used for deaths in 1999 and 2000 [39]. Of the 508,318 men enrolled in 1982, we excluded 25,238 who reported prevalent cancer (other than nonmelanoma skin cancer) at baseline and 7,354 for whom information on use of any vitamin supplement was incomplete or uninterpretable. Responses were classified as incomplete or uninterpretable if any of the following were observed: the

entire section dealing with vitamin use was left blank; times/month was reported as zero or missing but a valid value was entered for years of use; times/month was reported to be greater than 90; the response for times/month could not be understood; or the times/month box was marked but no quantity was indicated. After exclusions, the analytic cohort consisted of 475,726 men. Of these, 5,585 died from prostate cancer during the 18-year follow-up period.

Assessment of vitamin use

All information on vitamin use was obtained from the 1982 baseline questionnaire which included a section asking about duration and frequency of current use of four vitamin supplements (multivitamins, vitamins A, C, and E) as well as several medications. Participants were asked to report the number of times in the last month and for how many years they had used each vitamin supplement. Non-users of a given vitamin were categorized as those who reported "zero" for that supplement as well as those who gave valid responses for other vitamins or medications but left the answers for the given vitamin missing. As noted above, men who left the entire section of the questionnaire blank were excluded from the analysis. Users who reported taking the supplement ≥15 times/month at baseline were defined as "regular users". Approximately 90% of participants meeting this definition of regular use reported use at least 25 times per month, a frequency that we classified as daily use. Occasional multivitamin use was defined as any use of the supplement less than 15 times/month. No information was collected on the dose or brand of vitamin supplements, use of any other dietary supplements, or past vitamin use that had stopped before study enrollment. Among regular users, duration of use prior to baseline was categorized into 0 to <5 years, 5 to <10 years, 10 to <15 years, and ≥15 years.

Statistical analysis

Cox proportional hazards modeling [40] was used to calculate hazard rate ratios (RR) and corresponding 95% confidence intervals (CI) for the relationship between multivitamin use and prostate cancer mortality. The reference group was men who reported no use of multivitamin supplements at baseline.

All Cox models were stratified on the exact year of age of the men at enrollment and adjusted for race (white, black, other). Information on potential confounders was collected at baseline in 1982. Variables included in the fully adjusted models were education (less than high school, high school graduate, some college, college graduate, graduate school, missing), smoking status (never, current, former, unclassifiable), family history of prostate cancer (yes, no), physical activity (none, slight, moderate, heavy, missing), body mass index (BMI) at enrollment (<25, 25 to <30, 30+, missing), alcohol use (none, any, missing), vegetable consumption (quartiles, incomplete diet information), vitamin A use (yes, no), vitamin C use (yes, no) and vitamin E use (yes, no).

The trend test for the duration of multivitamin use was applied using the median number of years for each duration interval and included non-vitamin users as a zero time point. Potential effect modification of the association between multivitamin use and prostate cancer mortality was assessed by modeling multiplicative interaction terms between multivitamin use and each covariate. The statistical significance of the interaction terms was assessed at the $p<0.05$ level using the Likelihood Ratio Test [41].

Results

Approximately 29% (n = 137,671) of men in our study reported some use of multivitamins at enrollment. Of these, 63% (18% of the total, n = 86,089) took multivitamins regularly (defined as ≥15 times/month). Slightly more than half of the multivitamin users (n = 69,667) took at least one additional vitamin supplement. Of the additional supplements, vitamin C use was the most common (22% of total cohort, n = 105,504), followed by vitamin E (16% of total cohort, n = 74,489), and vitamin A (7% of total cohort, n = 35,283).

Baseline characteristics of non-users, occasional users, and regular users of multivitamin supplements are shown in Table 1. Men who took multivitamins regularly were more educated, less likely to be current smokers, leaner, reported greater consumption of vegetables, and greater usage of vitamin A, C, or E supplements than those who reported no multivitamin use. Many of the characteristics of the occasional multivitamin users were intermediate between those of the non-users and regular users. Men who reported occasional use of multivitamins reported similar use of vitamins A, C, and E as the regular multivitamin users.

Occasional use of multivitamins was not associated with risk of prostate cancer mortality (multivariate RR = 1.00, 95% CI: 0.92–1.10). Regular use of multivitamins was associated with marginally higher risk (RR = 1.07, 95% CI: 0.99–1.15) (Table 2). Stratified according to use or non-use of additional vitamin supplements, the association was confined to men who regularly used multivitamins but did not use additional vitamin supplements (multivariate RR = 1.15, 95% CI:

Table 1. Age-standardized frequencies of selected characteristics by multivitamin use (results are in percents unless otherwise noted)[a]

Variable	Non-multivitamin user n = 338,055	Occasional[b] multivitamin user n = 51,582	Regular[c] multivitamin user n = 86,089
Race			
White	93.5	93.4	96.5
Black	4.2	3.8	1.8
Other/missing	2.3	2.8	1.8
Mean Age in 1982	57.3	56.5	57.4
Education			
< High school	17.4	13.5	9.9
High school grad	21.3	17.1	15.8
Some college	26.2	29.0	27.8
College grad	16.5	18.6	21.7
Graduate school	16.8	20.6	24.0
Missing	1.7	1.1	0.8
Smoking			
Never	24.7	25.6	26.5
Current	21.7	20.8	18.0
Former	29.1	28.9	30.4
Unclassifiable	24.4	24.7	25.1
Family history of prostate cancer			
No history	97.1	97.0	96.8
History	2.9	3.0	3.2
Physical activity			
None	2.3	1.9	1.8
Slight	21.5	22.1	22.8
Moderate	62.9	63.6	63.1
Heavy	12.1	11.6	11.4
Missing	1.3	0.9	0.8
Body mass index (BMI)			
< 25	36.9	41.9	44.8
25 to < 30	49.6	47.4	45.9
30 +	11.1	8.8	7.6
Missing	2.4	1.9	1.8
Mean BMI (kg/m^2)	26.1	25.7	25.5
Alcohol use			
None	11.9	11.4	12.6
Any	37.2	42.0	44.4
Missing	51.0	46.6	43.0
Vegetable consumption[d]			
< 6.5	20.7	18.7	13.7
6.5 to < 11.5	23.9	22.8	22.3
11.5 to < 17.25	24.1	24.9	26.6
17.25 +	22.9	27.1	32.2
Incomplete info	8.4	6.4	5.2
Vitamin A use			
Non-user	97.1	81.0	81.6
Any use	2.9	19.0	18.4
Vitamin C use			
Non-user	87.1	56.6	54.1
Any use	12.9	43.4	45.9
Vitamin E use			
Non-user	91.9	68.1	64.5
Any use	8.1	31.9	35.5

[a] Age-adjusted among men used in this analysis.
[b] Less that 15 times per month
[c] ≥15 times per month.
[d] Consumption of green leafy vegetables, tomatoes, cabbage, raw vegetables, carrots and squash, reported as the sum of the number of days/week each was eaten.

Table 2. Rate ratios (RR) and 95% confidence intervals for prostate cancer mortality associated with multivitamin supplement use

	n/Person years	Deaths	RR[a]	RR[b]
Any multivitamin use				
Non-users	338,055/5,253,930	3949	1.00	1.00
Occasional users	51,582/814,455	571	1.00 (0.91–1.09)	1.00 (0.92–1.10)
Regular users	86,089/1,357,499	1065	1.05 (0.98–1.12)	1.07 (0.99–1.15)
Multivitamin use only				
Non-users	284,770/4,428,759	3246	1.00	1.00
Occasional users	26,407/412,109	279	0.95 (0.84–1.08)	0.96 (0.85–1.09)
Regular users	41,597/645,042	556	1.13 (1.03–1.23)	1.15 (1.05–1.26)
Multivitamin use with other supplements[c]				
Non-users	53,285/825,171	703	1.00	1.00
Occasional users	25,175/402,346	292	1.04 (0.90–1.19)	1.04 (0.91–1.19)
Regular users	44,492/712,457	509	0.97 (0.87–1.09)	0.99 (0.88–1.11)

[a] Age- and race-adjusted RR and corresponding 95% CI.
[b] Fully-adjusted RR and corresponding 95% CI adjusted for: age, race, education, smoking, family history of prostate cancer, exercise, BMI, alcohol use, vegetable consumption, vitamin A use, vitamin C use, and vitamin E use.
[c] Multivitamin use among men using vitamin A, C, or E alone or in any combination.

1.05–1.26) (Table 2). No association was seen between regular multivitamin use and prostate cancer mortality among men with any use of vitamins A, C, or E (multivariate RR = 0.99, 95% CI: 0.88–1.11). The *p*-value for the multiplicative interaction between the risk associated with regular multivitamin use only and that for users who also took any other vitamin supplement was 0.05. Use of multivitamins in combination

Table 3. Rate ratios (RR) and 95% confidence intervals for prostate cancer mortality associated with multivitamin supplement use

	n/Person years	Deaths	RR[a]
Vitamin A supplement use			
Non-users	440,443/6,870,800	5136	1.00
Occasional users	16,285/255,145	203	0.94 (0.79–1.11)
Regular users	18,998/299,939	246	1.03 (0.88–1.21)
Vitamin C supplement use			
Non-users	370,222/5,750,331	4308	1.00
Occasional users	46,271/734,595	552	1.02 (0.91–1.13)
Regular users	59,233/940,958	725	0.97 (0.87–1.08)
Vitamin E supplement use			
Non-users	401,237/6,259,600	4598	1.00
Occasional users	30,223/470,614	405	1.07 (0.94–1.22)
Regular users	44,266/695,670	582	1.02 (0.90–1.15)

[a] Fullyadjusted RR and corresponding 95% CI adjusted for: age, race, education, smoking, family history of prostate cancer, exercise, BMI, alcohol use, vegetable consumption, multivitamin use, vitamin A use, vitamin C use, and vitamin E use.

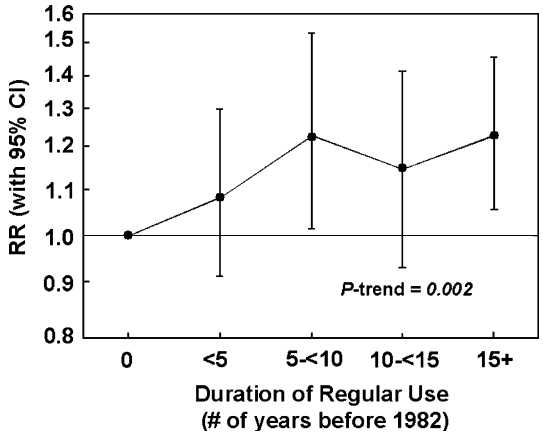

Fig. 1. Association between regular multivitamin use before 1982 and prostate cancer mortality. The multivariate RR for years of multivitamin use in men who regularly used multivitamins without any individual supplements is indicated on the *x*-axis. This RR has been adjusted for age, race, education, smoking, family history of prostate cancer, exercise, BMI, alcohol use, vegetable consumption, vitamin A use, vitamin C use, and vitamin E use. The vertical lines indicate the 95% CI for each RR.

with a single individual supplement also was not associated with prostate cancer mortality: for vitamin A, multivariate RR = 0.97 (95% CI: 0.78–1.20); for vitamin C, RR = 0.96 (95% CI: 0.85–1.09) for vitamin E, RR = 0.99 (95% CI: 0.86–1.15). Finally, as shown in Table 3, no association was found for men who used individual vitamin A, C, or E supplements (either occasional or regular use). Stratification of the individual supplement users into those who took multivitamins and those who did not yielded the same results (data not shown).

The relative risk of death from prostate cancer increased with the duration of regular multivitamin use prior to 1982 among men who did not take additional vitamin supplements. These results for men are shown in Figure 1. Regular use for less than five years before baseline was not associated with significant risk (RR = 1.09, 95% CI: 0.91–1.30) whereas longer use was (RR = 1.24, 95% CI: 1.05–1.46 for 15+ years, p-trend = 0.002). There was no association for any length of use among men who took other supplements with their regular multivitamin (RR = 0.95, 95% CI: 0.76–1.18 for less than five years and RR = 0.99, 95% CI: 0.82–1.19 for 15+ years, data not shown). The p value for the multiplicative interaction of these two groups was 0.22.

Misclassification of vitamin supplement use would be expected to increase with longer follow-up time and to bias risk estimates toward the null. To investigate this potential bias, we examined the risks associated with multivitamin use stratified by intervals of follow-up time (Table 4). The relative risk estimate was highest during the first four years of follow-up (RR = 1.12, 95% CI: 0.87–1.46) and decreased towards the null over successive follow-up intervals (p-trend = 0.28). Among men who took no other supplements, regular multivitamin use was more strongly associated with prostate cancer mortality during the first four years of follow-up (RR = 1.41, 95% CI: 1.03–1.92 for 1982–1986), and again, the risk decreased with longer follow-up time (p-trend = 0.18).

No statistically significant interactions were found between regular multivitamin use and any covariate, including smoking status and age of death.

Discussion

The small positive association that we observed between regular use of multivitamins and death rates from

Table 4. Rate ratios (RR) and 95% confidence intervals (CI) for prostate cancer mortality associated with regular multivitamin use[a] during early and later follow-up periods

Follow-up period	Deaths	RR[b]	RR[c]
Any multivitamin use			
1982–1986			
Non-multivitamin users	317	1.00	1.00
Regular users	81	1.07 (0.84–1.37)	1.12 (0.87–1.46)
1987–1990			
Non-multivitamin users	762	1.00	1.00
Regular users	205	1.07 (0.92–1.25)	1.07 (0.91–1.26)
1991–1995			
Non-multivitamin users	1,409	1.00	1.00
Regular users	386	1.07 (0.95–1.19)	1.09 (0.97–1.23)
1996–2000			
Non-multivitamin users	1,461	1.00	1.00
Regular users	393	1.02 (0.91–1.14)	1.03 (0.92–1.16)
p-trend		0.29	0.28
Multivitamin use only			
1982–1986			
Non-multivitamin users	253	1.00	1.00
Regular users	50	1.31 (0.96–1.77)	1.41 (1.03–1.92)
1987–1993			
Non-multivitamin users	619	1.00	1.00
Regular users	111	1.18 (0.96–1.44)	1.20 (0.98–1.47)
1991–1995			
Non-multivitamin users	1,177	1.00	1.00
Regular users	199	1.12 (0.96–1.30)	1.12 (0.97–1.31)
1996–2000			
Non-multivitamin users	1,197	1.00	1.00
Regular users	196	1.08 (0.93–1.25)	1.10 (0.94–1.28)
p-trend		0.19	0.18

[a] Defined as use of multivitamin use$^{\circ}$15 times/month.
[b] Age- and race-adjusted RR and corresponding 95% CI.
[c] Multivariate-adjusted RR and corresponding 95% CI adjusted for: age, race, education, smoking, family history of prostate cancer, exercise, BMI, alcohol use, and vegetable consumption.

prostate cancer is provocative, but must be interpreted carefully. The widespread use of PSA testing has substantially increased the early detection of this cancer and significantly decreased the incidence of advanced or metastatic disease [42]. The follow-up period of this study begins before the introduction of prostate specific antigen (PSA) screening in the late 1980s and continues after this. The association that we observed between regular multivitamin use and prostate cancer mortality was strongest during the initial four years of follow-up (1982–1986, Table 4), prior to the introduction of PSA screening. The association was attenuated in the later follow-up intervals, when use of PSA screening was more widespread. This result could be explained if one or more of the ingredients of multivitamins promoted the growth of preexisting tumors. Because there was more undetected prostate cancer prior to the introduction of PSA screening, the risk associated with regular multivitamin use would be expected to be the strongest during that period, which corresponds to the first follow-up interval.

There are several noncausal explanations that also could account for our findings. The difference seen between the follow-up intervals could result from the marginally significant association in the first period being a chance observation. Alternatively, increased misclassification of both the reference and multivitamin user groups with longer follow-up time could be responsible for the attenuation in the risk estimates toward the null. In this case, the rate ratio found for the initial follow-up period (RR = 1.15) would be the best estimate of the association between recent multivitamin use and prostate cancer mortality. Finally, the men who died during the first follow-up interval could have increased their use of multivitamins because they were experiencing symptoms of advanced but undiagnosed (because of lack of PSA screening) prostate cancer.

If either of the explanations related to PSA screening does account for the attenuation in the risk we observed, future studies of multivitamin use and prostate cancer in which the majority of the tumors are identified early with PSA screening will not replicate our findings. In fact, this could have contributed to the lack of association between these supplements and prostate cancer incidence found by Kristal *et al*. [13]. In that study, 70% of the cases had PSA screening at least once in the five years prior to diagnosis, suggesting that the cancer in these men had not been present for long before being detected.

The study by Kristal *et al*. [13], which is one of two other epidemiologic studies of the association between multivitamin use and prostate cancer, differed from the present study in several other ways that could also account for the disparate findings. In that case-control study, prostate cancer incidence was examined rather than mortality, regular users who had taken multivitamins for longer durations were not separated from those who took them for shorter times, and the age distribution of the study population (40–64 years old) was considerably younger than in the CPS-II cohort. Our results are similar to those found in the other previous epidemiologic study of this association, which was an earlier analysis in this cohort with seven years follow-up and considerably fewer prostate cancer deaths (12).

The magnitude of the association between regular multivitamin use and prostate cancer mortality increased with increasing duration of regular multivitamin use among men not using additional supplements such that use for 15 or more years was associated with an approximately 24% increased risk. Stratification of

regular multivitamin users based on their use of additional vitamin supplements indicated that the association with increased risk of prostate cancer mortality was only found among men who did not use individual vitamin A, C, or E supplements. The use of individual vitamin A, C, or E supplements was not associated with prostate cancer mortality in this study. However, it is conceivable that the high doses of specific vitamins contained in individual supplements could nullify adverse effects of other multivitamin components. Alternatively, it is possible that differences in unmeasured confounding factors (such as health care utilization), between men who used only multivitamins and those who used both multivitamins and individual supplements, could account for the differing results observed in analyses of these groups. Finally, the observed difference in results by use of other vitamin supplements could be a result of chance.

Among the components of multivitamins, vitamin D and folic acid have been suggested to influence cancer risk [14, 15]. Because vitamin D is expected to inhibit growth and induce differentiation of tumor cells [43], it seems unlikely that it would be contributing to the increased mortality we observed among regular multivitamin users. However, because folic acid facilitates cell growth, it is possible that higher levels of this vitamin might enhance the growth of preexisting prostate tumors. Such an effect could contribute to the increased mortality we observed. While there are no studies of folate nutrition in prostate cancer to address this, a common polymorphism in the folate-metabolizing enzyme methylenetetrahydrofolate reductase (MTHFR) has been associated with increased risk of prostate cancer incidence in one [44] of three studies of this [44–46]. Two studies found no association with this polymorphism [45, 46]. How these findings would relate to our observations is not clear.

Strengths of this study are its prospective design and large size, which allowed us to detect small associations and to examine the supplement users according to duration of use. Information on known covariates made it possible to control for potential confounders, including race, BMI and physical activity. Although we have adjusted for these factors, it is possible that residual confounding could have influenced our findings. However, regular multivitamin users in our study displayed more characteristics consistent with the maintenance of good health, such as having lower BMI, exercising more, and eating more vegetables. Therefore, we would expect any residual confounding by these factors to have resulted in an underestimate of any increase in risk associated with multivitamin use.

An important limitation of the study was our single measure of vitamin use at baseline, which would be expected to result in increasing misclassification over time. Additional limitations included the lack of information on the brands of multivitamin used and dose of component vitamins within the mixed supplements.

In summary, the results of this study indicate that men who took multivitamins regularly had a slightly higher risk of death from prostate cancer than did non-users. This risk increased with the duration of multivitamin use and was limited to the early years of follow-up, which was before the introduction of PSA screening for the early detection of prostate cancer.

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