Multivitamin Use and Risk of Prostate Cancer in the National Institutes of Health–AARP Diet and Health Study

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Background Multivitamin supplements are used by millions of Americans because of their potential health benefits, but the relationship between multivitamin use and prostate cancer is unclear.

Methods We prospectively investigated the association between multivitamin use and risk of prostate cancer (localized, advanced, and fatal) in 295 344 men enrolled in the National Institutes of Health (NIH)–AARP Diet and Health Study who were cancer free at enrollment in 1995 and 1996. During 5 years of follow-up, 10 241 participants were diagnosed with incident prostate cancer, including 8765 localized and 1476 advanced cancers. In a separate mortality analysis with 6 years of follow-up, 179 cases of fatal prostate cancer were ascertained. Multivitamin use was assessed at baseline as part of a self-administered, mailed food-frequency questionnaire. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated by use of Cox proportional hazards regression, adjusted for established or suspected prostate cancer risk factors.

Results No association was observed between multivitamin use and risk of localized prostate cancer. However, we found an increased risk of advanced and fatal prostate cancers (RR = 1.32, 95% CI = 1.04 to 1.67 and RR = 1.98, 95% CI = 1.07 to 3.66, respectively) among men reporting excessive use of multivitamins (more than seven times per week) when compared with never users. The incidence rates per 100 000 person-years for advanced and fatal prostate cancers for those who took a multivitamin more than seven times per week were 143.8 and 18.9, respectively, compared with 113.4 and 11.4 in never users. The positive associations with excessive multivitamin use were strongest in men with a family history of prostate cancer or who took individual micronutrient supplements, including selenium, β-carotene, or zinc.

Conclusion These results suggest that regular multivitamin use is not associated with the risk of early or localized prostate cancer. The possibility that men taking high levels of multivitamins along with other supplements have increased risk of advanced and fatal prostate cancers is of concern and merits further evaluation.

J Natl Cancer Inst 2007;99:754–64

Multivitamin supplements constitute a major portion of vitamin intake in the United States, with 35% of adults taking some type of multivitamin–multimineral supplement (1). Supplements are used largely because of their potential health benefits (2,3), although scientific support for their efficacy for prevention of chronic disease is limited (3,4). Prostate cancer is the most commonly diagnosed cancer in men in the United States, where it accounts for the third largest number of cancer-related deaths (5). Therefore, any association between intake of multivitamin supplements and the risk or severity of prostate cancer would have important consequences for public health.

Data on the relationship of multivitamins to prostate cancer risk are sparse (6) and are derived from two analytic epidemiologic studies (7,8) and a randomized clinical trial (9). A case–control study (7) found that, compared with non use, regular multivitamin use (seven or more times per week) was not associated with prostate cancer incidence (relative risk [RR] = 0.96, 95% confidence interval [CI] = 0.73 to 1.26). However, two consecutive reports (8,10) from the Cancer Prevention Study-II suggested that multivitamin use was associated with a higher risk of fatal prostate cancer. The first report (8) found that, compared with nonusers, men consuming multivitamins for 5 or more years were at increased risk of fatal prostate cancer (RR = 1.31, 95% CI = 1.04 to 1.66). An updated analysis (10) reported that multivitamin use for 15 or more times per month was associated with a marginally increased risk of fatal prostate cancer (RR = 1.07, 95% CI = 0.99 to 1.15) compared with

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See "Notes" following "References."

DOI: 10.1093/jnci/djk177

non use. Neither analysis addressed the relationship between multivitamin use and the risk of early-stage, incident prostate cancer. Recently, the Supplementation en Vitamines et Mineraux Antioxydants trial (9) investigated the effect of nutritional doses of a mixture of antioxidant vitamins on the incidence of prostate cancer. It reported that among men with normal baseline prostate-specific antigen (PSA) levels (<3 μg/L), taking multivitamin–multimineral supplements containing a limited number of individual agents (vitamin C, β-carotene, selenium, and zinc) markedly reduced prostate cancer risk compared with placebo (RR = 0.52, 95% CI = 0.29 to 0.92). However, a reduction in risk was not seen in men with elevated baseline PSA levels (RR = 1.54, 95% CI = 0.87 to 2.72).

Overall, the available data suggest that multivitamin use may protect against the initiation of prostate cancer but may be associated with more rapid progression. To further investigate the association of multivitamin supplements and the risk of prostate cancer and prostate cancer progression, we examined whether multivitamin use was differentially associated with organ-confined versus more advanced stages of prostate cancer, in a large, prospective cohort study of US men. We also evaluated whether the relationship between multivitamin use and prostate cancer risk was modified by concomitant use of individual vitamin and mineral supplements, screening for elevated PSA, abnormal digital rectal examination results, or a family history of prostate cancer.

CONTEXT AND CAVEATS

Prior knowledge

Previous epidemiologic studies have suggested that multivitamin supplement use may be associated with more rapid prostate cancer progression.

Study design

In a prospective cohort study, demographic data and information pertaining to multivitamin and individual supplement use were obtained via questionnaire; information on prostate cancer diagnosis was accessed via certified cancer registries.

Contribution

This large study was confirmatory of previous reports of an association between multivitamin use and advanced prostate cancer. It also found potential associations of various individual vitamins and mineral supplements with prostate cancer that should be investigated further.

Implications

Despite the perceived health benefits of multivitamin supplements, the risks associated with their use need to be explored further.

Limitations

Differences between heavy users of multivitamins and nonusers that may not be controlled for in a study of this type may obscure the true relationship between multivitamin use and prostate cancer.

Methods

Study Population

Data used in this study were obtained from men participating in the National Institutes of Health (NIH)–AARP Diet and Health Study, the design of which has been reported previously (11). Briefly, study participants were selected from 3.5 million AARP members, aged 50–71 years, who resided in one of six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). Individuals were sent a baseline questionnaire in 1995 or 1996 that captured information on usual dietary intake, vitamin supplement use, demographic factors, and health-related behaviors. Of the 567 169 surveys that were completed (11), we excluded those with duplicate representation in our database (n = 179), those from people who were later determined to have died or to had moved from the study area before their survey was received (n = 582), surveys that were not completed by the intended respondent (n = 15 760), and one from a person who withdrew from the study. In late 1996–1997, a supplemental questionnaire requesting more detailed information regarding cancer risk factors, including history of PSA and digital rectal examination testing in the 3 years before baseline, was sent to those who had completed the original questionnaire. A total of 334 910 participants responded, but response was not necessary for inclusion in the study.

For this analysis, we additionally excluded women (n = 225 471), those who reported prevalent cancers (excluding nonmelanoma skin cancer) at study enrollment (n = 27 245), and those whose calorie intake was considered to be an outlier of the population distribution (those more than two interquartile ranges above the 75th percentile or below the 25th percentile of Box–Cox log-transformed intake which corresponds to <414.8 and >6143.6 kcal/day, n = 2587), leaving 295 344 men for analysis. All participants in the NIH–AARP Diet and Health Study provided informed written consent. The study was approved by the Special Studies Institutional Review Board of the National Cancer Institute.

Cohort Follow-up and Case Ascertainment

NIH–AARP cohort participants were followed annually for changes in address via matching to the National Change of Address database (maintained by the US Postal Service) and by returned mail, other address update services, and participants' notification. Vital statistics were ascertained by annual linkage to the Social Security Administration Death Master File. Follow-up searches of the National Death Index Plus provided confirmation and supplemental information on underlying cause of death.

Men with a diagnosis of incident first primary prostate cancer (International Classification of Diseases, 9th Revision, code 185, or 10th Revision, code C61) through December 31, 2000, were ascertained via probabilistic linkage to eight state cancer registries. The cancer registries in these eight states were certified by the North American Association of Cancer Registries (12) as meeting the highest standard of quality (95% case ascertainment within 18 months of the close of the diagnosis year). For matching purposes, we had data on first and last names, address history, sex, date of birth, and Social Security number (the latter was available for 85% of the cohort). All suspected matches were subject to a review that automatically rejected potential matches unlikely to be true (approximately 4%); additional uncertain matches underwent manual review. In a validation study (12), we compared registry findings with self-reports and medical records and estimated that approximately 90% of all cancer cases in our cohort were validly identified using linkage to cancer registries. Incident prostate cancer cases

were defined as localized (organ confined) or advanced (extraprostatic) using the American Joint Committee on Cancer 1997 tumor–node–metastasis classification system (13). Men with T1, T2, and N0M0 tumors were classified as having localized disease, whereas those with T3, T4, or N1 or M1 cancers and those who died of prostate cancer on or before December 31, 2000, were considered to have advanced prostate cancer. Through December 31, 2000, 10241 participants were ascertained with incident first primary prostate cancer; 8765 were found to have localized prostate cancer and 1476 were found to have advanced cancer. Follow-up for the analysis of fatal prostate cancer was through December 31, 2001; 179 cases with prostate cancer as the underlying cause of death were ascertained using the National Death Index Plus. Ninety-one percent of these individuals were confirmed via registries to be incident cases diagnosed after baseline. A sensitivity analysis removing those individuals for whom there was no confirmed diagnosis date obtained from registries produced similar results (data not shown).

Assessment of Supplement Use

The baseline questionnaire asked participants about the frequencies with which they used three types of multivitamins ("stress-tab type", "therapeutic or theragran type", and "one-a-day type") during the preceding 12 months. For each type of multivitamin, participants were asked to report frequency of use as never, less than one time per week, one to three times per week, four to six times per week, or every day. Each frequency category was assigned a single value (never = 0, less than one time per week = 0.5, one to three times per week = 2, four to six times per week = 5, and every day = 7). Multivitamin use was defined as the sum of the values obtained for each type of multivitamin and was categorized as never use, casual use (between zero and six times per week), consistent use (seven times/wk), or heavy use (more than seven times per week). Thus, a participant who reported using a stress-tab type one to three times per week and a one-a-day type four to six times per week was considered to have been consuming multivitamins seven times/wk. Participants were also queried regarding dose and frequency of use of single supplements including vitamin A, β-carotene, vitamin C, vitamin E, and calcium. Daily dose for vitamin E supplement intake was calculated as dose × daily frequency (frequency of use options were the same as multivitamins, and dose options were <100, 100–250, 300–500, ≥600 IU, or unknown). Each category of dose was assigned as 100, 200, 400, and 800 IU, and for those answering "unknown", a value of 400 IU was assigned. For those taking a multivitamin, daily dose of supplemental vitamin E was assumed to be 30 IU. Use of iron, zinc, selenium, and folic acid was assessed by asking participants whether or not they used each of these individual supplements more than once per month in the past 12 months (yes or no).

Statistical Analysis

Age-adjusted and multivariable Cox proportional hazards models were used to estimate relative risks and 95% confidence intervals for each category of multivitamin use compared with never use for total, localized, advanced, and fatal prostate cancers. Follow-up time for each participant was calculated from the date we processed the baseline questionnaire to the date of prostate cancer diagnosis, death, December 31, 2000 (for incident prostate cancer analysis), or December 31, 2001 (for fatal prostate cancer analysis). To investigate the effect of latent disease on associations, we also conducted analyses after removing those diagnosed within the first 2 and 3 years of follow-up. Linear trend tests were based on ordered categorical variables in the model. The covariates chosen for inclusion in the multivariable models were based on previously identified risk factors for prostate cancer, as well as those that were statistically significantly associated with prostate cancer in the NIH–AARP Diet and Health Study. Multivariable models included body mass index (<25, 25–30, >30 kg/m^2), height (<1.58, 1.58–1.63, 1.64–1.68, >1.68 m); age (continuous); family history of prostate cancer (yes/no); education (<8 years, 8–11 years, 12 years or high school equivalent, some college, college graduate); race (non-Hispanic white, non-Hispanic black, Hispanic, and Asian, Pacific Islander, American Indian, and Alaskan Native combined); smoking status (never, former, current); vigorous physical activity (never, rarely, one to three times per month, one to two times per week, three to four times per week, five or more times per week); marital status (married, widowed, divorced, separated, never married); personal history of diabetes (yes/no); use of supplemental calcium (yes/no), zinc (yes/no), vitamin E (yes/no), and alcohol intake; and energy-adjusted daily dietary intakes (based on quintiles distribution) of tomato products, fish, red meat, α-linolenic acid, calcium, vitamin D, zinc, α-tocopherol. Potential confounding by screening for elevated PSA or digital rectal examination in the 3 years before baseline was investigated and found not to confound the relationship between multivitamin use and prostate cancer in a subanalysis among participants who responded to the supplementary questionnaire. Age-adjusted incidence rates were calculated as reported by Breslow and Day (14) with 5-year age bands and standardized to the entire population under study. The proportional hazards assumption was tested and upheld using a cross product term of person-years by multivitamin use as an ordered categorical variable.

We examined whether the association between multivitamin use and prostate cancer risk was modified by use of an individual supplement (iron, zinc, selenium, folic acid, vitamin A, β-carotene, vitamin C, vitamin E, and calcium; yes/no), dietary intakes of micronutrients (zinc, selenium, folic acid, vitamin A, β-carotene, vitamin C, vitamin E, vitamin D, and calcium; continuous), pyramid servings of tomato products [continuous, servings of tomato products were calculated from the questionnaire as pyramid servings based on methods developed by Subar et al. (15) using national dietary data from the US Department of Agriculture's 1994–1996 Continuing Survey of Food Intake by Individuals] (16), family history of prostate cancer (yes/no), smoking status (current, former, never), age (split at the median [62.65 years] of the sample), and history of PSA screening (yes/no) or digital rectal examination screening (yes/no). Effect modification was assessed by entering the main effects term for multivitamin use and the covariate of interest along with a term for their product (the coefficient for which was evaluated by the Wald test) into the appropriate multivariable model. For the interaction analyses, multivitamin use was coded as an ordinal variable, and in an alternative analysis it was coded as a binary variable (seven or fewer versus more than seven times per week). We also ran stratified analyses to assess

Table 1. Distribution and characteristics of study subjects according to frequency of multivitamin use in the National Institutes of Health–AARP Diet and Health Study

Characteristics	Frequency of multivitamin use, no. of times per week			
	Never	1–6	7	>7
Participants, No.	142 634	32 878	105 978	13 854
Mean age, y	62.2	61.3	62.4	61.9
Body mass index, kg/m^2	27.5	27.2	27.0	27.3
Physical activity, %*				
Never/rarely	17.0	13.2	13.2	12.5
1–2 times per wk	35.7	40.9	32.3	32.1
≥3 times per wk	46.2	45.0	53.9	54.6
Smoking status, %				
Never	29.4	31.8	28.9	30.9
Former	57.5	54.8	60.3	57.7
Current	11.2	11.8	9.3	9.7
Education, %				
<12 y	6.9	4.6	5.0	4.1
12 y	17.5	12.8	14.4	11.8
>12 y	72.9	80.1	78.1	80.6
Race, %				
White	92.3	90.6	93.5	91.5
Black	2.9	3.6	2.1	2.7
Other†	3.5	4.6	3.4	4.3
Married, %	86.2	83.9	84.1	80.9
Single supplement use, %‡				
Calcium	10.1	32.7	31.2	52.3
Zinc	6.1	18.9	19.7	40.1
Vitamin E	18.8	47.8	52.6	78.2
Vitamin A	5.3	20.3	17.9	43.6
β-Carotene	7.1	20.7	21.7	47.0
Vitamin C	20.0	56.5	56.1	81.2
Iron	3.3	14.4	13.4	27.3
Selenium	3.3	8.5	11.1	24.7
Folate	3.9	10.4	12.4	27.1
History of diabetes, %	10.9	7.7	10.0	9.9
Family history of prostate cancer, %	8.1	8.6	8.5	8.7
Screening history, %§				
Prostate-specific antigen‖	69.3	69.2	74.5	75.4
Digital rectal examination¶	81.9	82.7	85.5	85.9
Mean daily dietary intake#				
Total energy, kcal	2010	2015	2008	2096
Red meat, g	73.9	72.2	67.6	65.2
Fish, g	20.0	20.6	21.2	22.9
Tomatoes, No. pyramid servings	0.62	0.62	0.65	0.70
Alcohol, g	16.9	16.3	16.6	16.6
α-Linolenic acid, μg	1.32	1.32	1.29	1.30
Calcium, mg	750.4	764.0	791.1	796.8
Vitamin D, μg	4.7	4.7	4.9	4.8
α-Tocopherol, mg	7.3	7.3	7.4	7.5
Zinc, mg	10.8	10.9	11.0	11.0

* Physical activity was defined to be at least 20 minutes in duration and causing increased breathing or heart rate or working up a sweat.

† Includes Hispanics, Asians, Pacific Islanders, and American Indians/Alaskan natives.

‡ Use was defined as taking single supplement at least once per month in each of the past 12 months.

§ Available for individuals who returned the supplemental questionnaire (n = 176 876).

‖ Prostate-specific antigen test at least once in the last 3 years.

¶ Digital rectal examination test at least once in the last 3 years.

All dietary variables, with the exception of alcohol, were adjusted for total energy intake using residual adjustment.

effect modification. All statistical tests were two-sided, and *P* values of less than .05 were considered to be statistically significant. SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC), was used for all analyses.

Results

Among men in this analysis (n = 295 344), 122 111 (41%), 34 828 (12%), and 16 576 (6%) reported use of a one-a-day, theragran, and stress-tab type of multivitamin, respectively (some participants

Table 2. Relative risks and 95% confidence intervals for prostate cancer according to frequency of multivitamin use in the National Institutes of Health–AARP Diet and Health Study*

Prostate cancer	Frequency of multivitamin use, no. of times per week				P_{trend}
	Never	1–6	7	>7	
Total†					
No. of cases/person-years	4931/11 895	1050/2547	3768/8952	492/1139	
Age-adjusted RR (95% CI)	1.00 (ref)	0.98 (0.92 to 1.05)	1.02 (0.97 to 1.06)	1.05 (0.96 to 1.16)	.30
Multivariable RR‡ (95% CI)	1.00 (ref)	0.97 (0.91 to 1.04)	1.02 (0.98 to 1.07)	1.06 (0.97 to 1.17)	.20
Localized†					
No. of cases/person-years	4231/10 357	887/2201	3240/7818	407/971	
Age-adjusted RR (95% CI)	1.00 (ref)	0.97 (0.90 to 1.05)	1.02 (0.97 to 1.06)	1.02 (0.92 to 1.13)	.49
Multivariable RR‡ (95% CI)	1.00 (ref)	0.96 (0.89 to 1.03)	1.02 (0.97 to 1.07)	1.02 (0.92 to 1.14)	.39
Advanced†					
No. of cases/person-years	700/1538	163/346	528/1134	85/168	
Age-adjusted RR (95% CI)	1.00 (ref)	1.05 (0.89 to 1.25)	1.01 (0.90 to 1.13)	1.27 (1.02 to 1.59)	.30
Multivariable RR‡ (95% CI)	1.00 (ref)	1.05 (0.88 to 1.25)	1.03 (0.91 to 1.16)	1.32 (1.04 to 1.67)	.21
Fatal§					
No. of deaths/person-years	90/331	20/67	55/218	14/58	
Age-adjusted RR (95% CI)	1.00 (ref)	1.07 (0.66 to 1.73)	0.80 (0.57 to 1.12)	1.65 (0.94 to 2.91)	.84
Multivariable RR‡ (95% CI)	1.00 (ref)	1.18 (0.71 to 1.94)	0.90 (0.63 to 1.29)	1.98 (1.07 to 3.66)	.65

* RR = relative risk; CI = confidence interval; ref = referent category.

† Based on up to 5 years of follow-up time (1995–2000).

‡ Adjusted for body mass index; height; age; family history of prostate cancer; education; race; smoking status; physical activity; marital status; intakes of tomato and tomato products, fish, red meat, α-linolenic acid, dietary calcium, individual calcium supplement, dietary vitamin D, dietary zinc, individual zinc supplement, dietary vitamin E, individual vitamin E supplement, and alcohol; and personal history of diabetes.

§ Based on up to 6 years of follow-up time (1995–2001).

reported using more than one type); consistent daily (seven times per week) intake of some type of multivitamin was reported by 105 978 men (36%; Table 1). Five percent of the men included in the analysis (n = 13 854) were heavy users of multivitamins (intake more than seven times per week). Of the supplements queried, multivitamins were the most commonly used (51%), followed by vitamin C (40%), vitamin E (37%), and calcium (22%).

To assess the potential for confounding, we evaluated multivitamin use in relation to prostate cancer risk factors including age, body mass index, physical activity, smoking status, education, race, marital status, supplement use, history of diabetes, history of cancer screening, and dietary intakes of red meat, fish, tomato products, alcohol, α-linolenic acid, calcium, vitamin D, α-tocopherol, and zinc (Table 1). Frequency of multivitamin use was positively associated with elements of a healthy lifestyle, including less current smoking; greater physical activity; more frequent prostate cancer screening; increased dietary intakes of tomato products, fish, calcium, vitamin E, and zinc; and decreased consumption of red meat. Use of individual supplements of calcium, zinc, vitamin E, vitamin A, β-carotene, vitamin C, iron, selenium, and folate were all associated with increased multivitamin use.

We next examined the association of multivitamin use with prostate cancer risk (Table 2) using never users of multivitamin supplements as the reference group. The age-adjusted relative risks of total, localized, advanced, and fatal prostate cancers for heavy use of multivitamin supplements (more than seven times per week) were 1.05 (95% CI = 0.96 to 1.16), 1.02 (95% CI = 0.92 to 1.13), 1.27 (95% CI = 1.02 to 1.59), and 1.65 (95% CI = 0.94 to 2.91), respectively. In multivariable analyses, controlling for dietary, anthropometric, and lifestyle factors potentially related to prostate cancer (listed in Table 2), the corresponding relative risks for total, organ-confined, advanced, and fatal prostate cancers were 1.06 (95% CI = 0.97 to 1.17), 1.02 (95% CI = 0.92 to 1.14), 1.32 (95% CI = 1.04 to 1.67), and 1.98 (95% CI = 1.07 to 3.66), respectively. The incidence rates per 100 000 person-years for advanced prostate cancer for those who took more than seven multivitamins per week was 143.8 (95% CI = 113.2 to 174.4), compared with 113.4 (95% CI = 105.0 to 121.8) in never users. The incidence rates per 100 000 person-years for fatal prostate cancer for those who took more than seven multivitamins per week was 18.9 (95% CI = 9.0 to 28.7), compared with 11.4 (95% CI = 9.0 to 13.8) in never users.

Because latent prostate cancer symptoms could have led to increased multivitamin use, thereby biasing our results, we repeated our analysis excluding men diagnosed with prostate cancer within the initial 2 years of follow-up. The relative risk of advanced prostate cancer with heavy multivitamin use was attenuated after excluding these individuals (RR = 1.06, 95% CI = 0.74 to 1.50), but the association with prostate cancer mortality was essentially the same as that observed with the total study population (RR = 1.96, 95% CI = 1.03 to 3.71), and it became stronger after excluding those diagnosed within the first 3 years of follow-up (RR = 2.42, 95% CI = 1.25 to 4.68).

We investigated whether the association of multivitamin use to prostate cancer risk varied according to individual supplement use (Table 3). Among men who reported using a selenium supplement, heavy multivitamin use (versus never use) was associated with a statistically significant 37% increased risk of localized prostate cancer, whereas no association was apparent among those who did not report using selenium (*P* value for test of interaction = .008). Similar effect modification was noted for use of supplemental folate and vitamin E (*P* values for tests of interaction = .012 and .028, respectively). There was also a statistically significant

Table 3. Relative risks and 95% confidence intervals for the association between frequency of multivitamin use and prostate cancer risk, stratified by intake of selected single nutrient supplements in the National Institutes of Health–AARP Diet and Health Study*

Prostate cancer by single nutrient supplement	Frequency of multivitamin use, no. of times per week				P_{trend}
	Never	1–6	7	>7	
Selenium use					
Total†					
Cases, No.	138	78	419	130	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.01 (0.76 to 1.34)	1.23 (1.02 to 1.50)	1.39 (1.09 to 1.77)	.003
Localized†					
Cases, No.	118	65	369	109	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.98 (0.72 to 1.33)	1.27 (1.03 to 1.56)	1.37 (1.05 to 1.78)	.004
Advanced†					
Cases, No.	20	13	50	21	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.21 (0.60 to 2.45)	1.03 (0.61 to 1.74)	1.53 (0.82 to 2.85)	.36
Fatal§					
Deaths, No.	2	2	6	8	
Multivariable RR‡ (95% CI)	1.00 (ref)	2.31 (0.31 to 17.40)	1.23 (0.24 to 6.37)	5.80 (1.16 to 29.12)	.054
No selenium use					
Total†					
Cases, No.	4793	972	3349	362	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.97 (0.90 to 1.04)	1.01 (0.96 to 1.06)	1.02 (0.91 to 1.14)	.67
Localized†					
Cases, No.	4113	822	2871	298	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.96 (0.89 to 1.03)	1.00 (0.95 to 1.06)	0.98 (0.87 to 1.11)	1.00
Advanced†					
Cases, No.	680	150	478	64	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.04 (0.87 to 1.25)	1.03 (0.91 to 1.17)	1.28 (0.98 to 1.67)	.28
Fatal§					
Deaths, No.	88	18	49	6	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.17 (0.69 to 1.97)	0.91 (0.63 to 1.32)	1.20 (0.51 to 2.84)	.79
Vitamin E use					
Total†					
Cases, No.	908	521	1994	396	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.04 (0.94 to 1.16)	1.08 (1.00 to 1.16)	1.15 (1.02 to 1.30)	.015
Localized†					
Cases, No.	772	444	1734	327	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.05 (0.93 to 1.18)	1.10 (1.01 to 1.20)	1.12 (0.99 to 1.28)	.016
Advanced†					
Cases, No.	136	77	260	69	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.02 (0.77 to 1.35)	0.93 (0.75 to 1.14)	1.32 (0.98 to 1.77)	.55
Fatal§					
Deaths, No.	14	9	23	11	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.23 (0.53 to 2.87)	0.78 (0.40 to 1.53)	1.93 (0.86 to 4.34)	.62
No vitamin E use					
Total†					
Cases, No.	4023	529	1774	96	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.93 (0.84 to 1.01)	0.99 (0.94 to 1.05)	0.93 (0.75 to 1.14)	.58
Localized†					
Cases, No.	3459	443	1506	80	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.91 (0.82 to 1.00)	0.98 (0.92 to 1.04)	0.90 (0.72 to 1.12)	.31
Advanced†					
Cases, No.	564	86	268	16	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.03 (0.82 to 1.30)	1.08 (0.93 to 1.26)	1.09 (0.66 to 1.81)	.30
Fatal§					
Deaths, No.	76	11	32	3	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.15 (0.60 to 2.19)	0.98 (0.64 to 1.51)	1.67 (0.52 to 5.43)	.83
Folate use					
Total†					
Cases, No.	173	98	453	144	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.97 (0.75 to 1.24)	1.14 (0.95 to 1.36)	1.32 (1.06 to 1.65)	.010
Localized†					
Cases, No.	141	87	392	121	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.06 (0.81 to 1.39)	1.20 (0.99 to 1.46)	1.35 (1.06 to 1.73)	.010

(Table continues)

Table 3 (continued).

Prostate cancer by single nutrient supplement	Frequency of multivitamin use, no. of times per week				P_{trend}
	Never	1–6	7	>7	
Advanced†					
Cases, No.	32	11	61	23	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.56 (0.28 to 1.11)	0.86 (0.56 to 1.32)	1.19 (0.69 to 2.05)	.63
Fatal§					
Deaths, No.	4	0	6	7	
Multivariable RR‡ (95% CI)	1.00 (ref)	—‖	0.63 (0.17 to 2.35)	2.89 (0.78 to 10.60)	.14
No folate use					
Total†					
Cases, No.	4758	952	3315	348	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.97 (0.90 to 1.04)	1.00 (0.96 to 1.06)	1.01 (0.90 to 1.13)	.69
Localized†					
Cases, No.	4090	800	2848	286	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.95 (0.88 to 1.03)	1.01 (0.96 to 1.06)	0.97 (0.85 to 1.09)	.98
Advanced†					
Cases, No.	668	152	467	62	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.09 (0.91 to 1.31)	1.03 (0.91 to 1.17)	1.29 (0.98 to 1.70)	.27
Fatal§					
Deaths, No.	86	20	49	7	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.37 (0.83 to 2.27)	0.95 (0.66 to 1.38)	1.48 (0.66 to 3.32)	.89

* RR = relative risk; CI = confidence interval; ref = referent category.

† Based on up to 5 years of follow-up time (1995–2000).

‡ Adjusted for body mass index; height; age; family history of prostate cancer; education; race; smoking status; physical activity; marital status; intakes of tomato and tomato products, fish, red meat, α-linolenic acid, dietary calcium, individual calcium supplement, dietary vitamin D, dietary zinc, individual zinc supplement, dietary vitamin E, individual vitamin E supplement, and alcohol; and personal history of diabetes. Models stratified by individual supplement use were adjusted for the other two individual supplements. Models stratified by vitamin E use did not adjust for individual vitamin E supplementation.

§ Based on up to 6 years of follow-up time (1995–2001).

‖ Cell contains no cases.

interaction between daily dose of supplemental vitamin E and multivitamin use for localized prostate cancer (*P* value for test of interaction = .019), with those reporting the highest daily dose of vitamin E supplement intake (≥800 IU) having the highest risk of localized prostate cancer associated with multivitamin use (Table 4). Thus, despite the overall lack of association between multivitamin use and risk of localized prostate cancer, we found a statistically significant increased risk of localized prostate cancer among heavy multivitamin users who consumed a selenium, folate, or vitamin E supplement. Use of selenium, vitamin E, or folate as individual supplements was not associated with prostate cancer (data not shown).

The statistically significant positive association between heavy multivitamin use (more than seven times per week) and advanced prostate cancer was somewhat modified by β-carotene supplement use (*P* value for test of interaction = .074), with an association apparent only among those concomitantly taking a β-carotene supplement (RR for increasing categories of multivitamin use among β-carotene users = 1.00 [referent], 1.21 [95% CI = 0.74 to 1.97], 1.29 [95% CI = 0.89 to 1.87], and 1.66 [95% CI = 1.06 to 2.61]; *P* value for test of trend = .036). Despite the small number of participants, heavy multivitamin users who were also taking a selenium supplement had a statistically significant 5.8-fold increased risk of fatal prostate cancer, whereas among nonusers of a selenium supplement, there was no association between fatal prostate cancer and multivitamin use (*P* value for test of interaction = .037). Heavy multivitamin use versus never use was associated with an increased risk of both advanced prostate cancer (RR = 2.48, 95% CI = 1.45 to 4.23) and fatal prostate cancer (RR = 16.41, 95% CI = 2.62 to 102.68) among men with a positive family history of prostate cancer, whereas no association was apparent among those without a family history (RR = 0.97, 95% CI = 0.70 to 1.34; RR = 1.07, 95% CI = 0.44 to 2.58) (Table 5).

Our main effects analysis had revealed a positive association of multivitamin use with advanced and fatal prostate cancers that was limited to heavy use of multivitamins (more than seven times per week) but was not seen for nonheavy use (less than or equal to seven times per week). Thus, we tested whether such a pattern, of increased risk seen only in one group of users, could be confirmed in subgroup analyses by conducting tests for interaction that were based on a two-level multivitamin variable (seven or fewer versus more than seven times per week). The subgroup-specific findings were consistent with those observed in the main analysis for the interaction between heavy multivitamin use and positive family history of prostate cancer. Multivitamin use at more than seven versus seven or fewer times per week was related to increased risk of advanced and fatal prostate cancers but only among men with a positive family history of prostate cancer, with *P* values for the tests of interaction for advanced and fatal prostate cancers of .002 and .043, respectively. Among men who reported taking a zinc supplement, multivitamin use at more than seven versus seven or fewer times per week was associated with an increased risk of fatal prostate cancer (RR = 4.36, 95% CI = 1.83 to 10.39), whereas no association with multivitamins was observed for men not taking a zinc supplement (RR = 1.13, 95%CI = 0.46 to 2.80; *P* value for test of interaction = .042). Thus, the apparent adverse effect of

Table 4. Relative risks and 95% confidence intervals for the association between frequency of multivitamin use and prostate cancer risk, stratified by daily dose of vitamin E supplementation in the National Institutes of Health–AARP Diet and Health Study*

Prostate cancer by supplemental vitamin E level	Frequency of multivitamin use, no. of times per week				P_{trend}
	Never	1–6	7	>7	
Vitamin E ≥ 800 IU/day					
Total†					
Cases, No.	121	21	302	79	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.59 (1.00 to 2.52)	1.26 (1.02 to 1.56)	1.38 (1.03 to 1.84)	.019
Localized†					
Cases, No.	104	21	263	62	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.86 (1.16 to 2.97)	1.28 (1.02 to 1.61)	1.27 (0.92 to 1.74)	.069
Vitamin E 400–799 IU/day					
Total†					
Cases, No.	482	85	1180	203	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.07 (0.85 to 1.35)	1.06 (0.95 to 1.17)	1.08 (0.92 to 1.28)	.273
Localized†					
Cases, No.	413	75	1020	172	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.10 (0.86 to 1.41)	1.07 (0.95 to 1.19)	1.08 (0.90 to 1.29)	.300
Vitamin E 200–399 IU/day					
Total†					
Cases, No.	143	126	282	71	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.06 (0.83 to 1.35)	1.03 (0.84 to 1.26)	1.17 (0.88 to 1.57)	.474
Localized†					
Cases, No.	116	105	246	60	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.08 (0.82 to 1.40)	1.10 (0.88 to 1.38)	1.21 (0.88 to 1.66)	.250
Vitamin E 100–199 IU/day					
Total†					
Cases, No.	74	110	155	41	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.95 (0.70 to 1.28)	0.99 (0.74 to 1.31)	1.26 (0.85 to 1.86)	.413
Localized†					
Cases, No.	60	89	139	31	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.95 (0.69 to 1.33)	1.10 (0.81 to 1.50)	1.19 (0.76 to 1.84)	.304
Vitamin E ≤ 99 IU/day					
Total†					
Cases, No.	88	708	1849	98	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.03 (0.82 to 1.29)	1.11 (0.89 to 1.37)	0.98 (0.73 to 1.30)	.28
Localized†					
Cases, No.	79	597	1572	82	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.97 (0.77 to 1.23)	1.04 (0.83 to 1.31)	0.91 (0.67 to 1.24)	.48

* RR = relative risk; CI = confidence interval; ref = referent category.

† Based on up to 5 years of follow-up time (1995–2000).

‡ Adjusted for body mass index; height; age; family history of prostate cancer; education; race; smoking status; physical activity; marital status; intakes of tomato and tomato products, fish, red meat, α-linolenic acid, dietary calcium, and alcohol; and personal history of diabetes.

multivitamin use on prostate cancer seen among the subgroup of men defined by a positive family history of prostate cancer and zinc supplement use was stronger in heavy versus nonheavy use of multivitamins.

The level of specific dietary micronutrients or foods (with the exception of tomato products) consumed did not modify the association between multivitamin use and prostate cancer risk. An increased risk of advanced prostate cancer was observed for heavy multivitamin users with intakes of tomato products above the population mean (P value for test of interaction = .043). Age; smoking status; history of PSA screening or digital rectal examinations; use of supplements other than selenium, folate, vitamin E, β-carotene, and zinc; and intake of dietary nutrients or foods other than tomato products did not substantially modify the associations between multivitamin use and total, localized, or advanced prostate cancer, or prostate cancer mortality (data not shown).

Discussion

In this large prospective study, we found that multivitamin use was unrelated to overall risk of total and organ-confined prostate cancer. However, we found an increased risk of advanced and fatal prostate cancer among those who took multivitamins more than seven times per week compared with never users. The risk of advanced prostate cancer and prostate cancer mortality associated with heavy multivitamin use was highest in men who reported concomitant use of selenium, β-carotene, or zinc supplements, or who had a positive family history of prostate cancer. Although there was no main effect of multivitamin use on localized prostate cancer, we found an increased risk of localized prostate cancer among those who took multivitamins more than seven times per week versus never use, in men also taking vitamin E, selenium, or folate supplements.

We considered several possible biases that could be responsible for the observed associations. Early-stage or localized prostate

Table 5. Relative risks and 95% confidence intervals for the association between multivitamin use and prostate cancer risk, stratified by family history of prostate cancer in the National Institutes of Health–AARP Diet and Health Study*

Prostate cancer by family history	Frequency of multivitamin use, no. of times per week				P_{trend}
	Never	1–6	7	>7	
Positive family history of prostate cancer					
Total†					
Cases, No.	628	151	476	76	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.02 (0.85 to 1.22)	0.97 (0.85 to 1.10)	1.24 (0.96 to 1.59)	.81
Localized†					
Cases, No.	539	124	418	56	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.97 (0.79 to 1.18)	0.97 (0.85 to 1.12)	1.05 (0.79 to 1.40)	.86
Advanced†					
Cases, No.	89	27	58	20	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.37 (0.87 to 2.13)	0.90 (0.64 to 1.28)	2.48 (1.45 to 4.23)	.30
Fatal§					
Deaths, No.	8	1	3	3	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.96 (0.10 to 9.10)	0.89 (0.21 to 3.70)	16.41 (2.62 to 102.68)	.17
No family history of prostate cancer					
Total†					
Cases, No.	3324	697	2547	295	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.97 (0.89 to 1.06)	1.03 (0.98 to 1.09)	0.97 (0.86 to 1.10)	.45
Localized†					
Cases, No.	2833	589	2178	251	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.97 (0.88 to 1.06)	1.04 (0.98 to 1.10)	0.97 (0.85 to 1.12)	.42
Advanced†					
Cases, No.	491	108	369	44	
Multivariable RR‡ (95% CI)	1.00 (ref)	0.98 (0.79 to 1.22)	1.01 (0.87 to 1.17)	0.97 (0.70 to 1.34)	.98
Fatal§					
Deaths, No.	63	14	43	6	
Multivariable RR‡ (95% CI)	1.00 (ref)	1.11 (0.61 to 2.02)	0.92 (0.61 to 1.39)	1.07 (0.44 to 2.58)	.78

* RR = relative risk; CI = confidence interval; ref = referent category.

† Based on up to 5 years of follow-up time (1995–2000).

‡ Adjusted for body mass index; height; age; education; race; smoking status; physical activity; marital status; intakes of tomato and tomato products, fish, red meat, α-linolenic acids, dietary calcium, individual calcium supplement use, dietary vitamin D, dietary zinc, individual zinc supplement use, dietary vitamin E, individual vitamin E supplement use, and alcohol; and personal history of diabetes.

§ Based on up to 6 years of follow-up time (1995–2001).

cancers are particularly prone to detection bias with current PSA-screening practices (17). The increased risk of localized prostate cancer with heavy multivitamin use among men concomitantly using a vitamin E, selenium, or folate supplement could be due to detection bias if supplement users were more likely to undergo PSA screening. In our study, prostate cancer PSA screening was most frequent among heavy users of multivitamins, consistent with survey data (18) showing men who used supplements were more likely to have PSA examinations than nonusers. Thus, it is possible that the positive association with heavy use of multivitamins along with certain supplements was spurious because more intensive screening led to increased diagnosis of localized prostate cancer in groups that used the supplements. In support of this possibility, the risk of localized prostate cancer tended to increase with increasing supplemental vitamin E intake among smokers in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial study (19), despite the findings in the Alpha-Tocopherol, Beta-Carotene (ATBC) trial (20) of decreased prostate cancer incidence in male smokers who were given vitamin E supplements. Thus, there could be increased prostate cancer detection among a subpopulation of men who both smoke and use vitamin E and are more likely to seek health care. Indeed, this interpretation is supported by the Health Professionals Follow-up Study, which showed that current smokers were more likely to undergo screening for prostate cancer than nonsmokers (21,22). The increased risk of localized prostate cancer among men with heavy multivitamin use and concomitant use of a selenium or folate supplement in our study may be due to similar diagnostic bias, although potential toxicity with high selenium intake is also possible (23), and high plasma or dietary folate levels have been associated with increased risk of prostate cancer (24–26).

Although advanced prostate cancers are not typically prone to detection bias, the observed relationship between multivitamin use and advanced prostate cancer in our study may have been due to increased multivitamin use among men with early symptoms related to prostate cancer because the association with advanced prostate cancer disappeared when those diagnosed in the initial years of follow-up were excluded. However, increased multivitamin use due to early symptoms of prostate cancer cannot account for the increased risk of fatal prostate cancer among heavy multivitamin users because the association persisted and even strengthened when we disregarded those diagnosed in the initial years of follow-up.

Multivariable adjustment for use of individual supplements did not materially alter the association between multivitamin use and prostate cancer. However, we could not rule out the possibility that residual confounding due to inadequate control for individual

supplements distorted the relation of multivitamin use to prostate cancer. Thus, to control more rigorously for supplement use, we conducted analyses stratified by individual supplements. The associations between multivitamin use and prostate cancer were strengthened substantially when we restricted our analyses to men additionally using certain individual supplements, and no associations were apparent among nonusers of individual supplements. Thus, excessive intake of certain individual micronutrients that are used in combination with multivitamins may be the underlying factor that is related to risk and not the multivitamins themselves. The possibility of excessive use of certain vitamins among men in our study is consistent with recent survey data (27) reporting that US supplement users had several fold greater intakes of vitamins A, C, and E and folate than the estimated average requirements for these micronutrients.

The increased risk of advanced prostate cancer and prostate cancer mortality with heavy use of multivitamins among men with a positive family history of prostate cancer could be due to men with a positive family history taking additional, unspecified supplements as part of a "prostate health" package to prevent the future development of prostate cancer. A recent survey (28) found that 50% of men at high risk for prostate cancer (defined by African American ethnicity, positive family history, or positive BRCA1 gene mutation) took one or more supplements to prevent prostate cancer, and more than 25% took three or more agents concomitantly. Of a total of 40 supplements reported, multivitamins were the most common, followed by supplemental vitamins E and C, zinc, calcium, selenium, saw palmetto, soy isoflavones, and flax seeds. Thus, confounding associations between individual agents that we were unable to assess and the risk of prostate cancer among men with a positive family history in our study were possible.

Our observation of an increase in advanced prostate cancer with heavy multivitamin use in combination with a β-carotene supplement use is troubling, given results from the ATBC study showing that β-carotene supplementation caused a 23% increase in total prostate cancer and a statistically significant 35% increase in the incidence of clinically relevant disease (stages II–IV) (20,29). The Beta-Carotene and Retinol Efficacy Trial (30) did not corroborate the results seen in the ATBC trial (20,29,30), and supplemental levels of β-carotene were also not associated with prostate cancer in the PLCO study (19), but three separate studies (31–33) have found a statistically non-significant increased risk of prostate cancer with high serum levels of β-carotene. The possibility of an adverse effect of β-carotene on prostate cancer risk deserves further study.

We also found an increased risk of prostate cancer mortality among men with heavy multivitamin use who took a zinc supplement. Previous data linking supplemental zinc to increased risk of prostate cancer are sparse, but one study found that dosage of zinc at greater than 100 mg/day was related to an increased risk of advanced prostate cancer (34). The apparent adverse effect of multivitamin supplements in combination with supplemental zinc on prostate cancer risk could be due to nonessential, potentially harmful trace elements contained in zinc supplements, such as cadmium (35,36), a known carcinogen (37).

Strengths of our study include its prospective design and thorough investigation of distinct prostate cancer endpoints related to increasing disease aggressiveness. Previous data from one case–control study (7), two reports from a prospective cohort (8,10) and one clinical trial (9), suggest that multivitamin use may protect against the initiation of prostate cancer but adversely affect the progression of the disease. The only directed epidemiologic research on the effect of multivitamins on prostate cancer risk that will be available in the near future will come from the Physicians' Health Study II, a randomized controlled trial of several supplements, including multivitamins, that is scheduled to conclude in December 2007 (38).

Measurement error in our assessment of multivitamin use should not be a major concern, as the agreement (kappa) between multivitamin use as assessed by the National Cancer Institute/Block Health Habits Questionnaire (39) and that from a detailed in-person interview and transcription of the labels of supplement bottles was 0.68 for one-a-day multivitamins and 0.66 for stress-tab/B complex type multivitamins (40). These results support the validity of our instrument because the National Cancer Institute/Block Health Habits Questionnaire is similar to ours.

Limitations of this study include its lack of information regarding duration of multivitamin use, information which may have helped to determine whether associations were limited to long-time users. Residual confounding due to history of PSA and digital rectal examination screening may exist as this information was not available for all participants at baseline. Small case numbers limited our ability to investigate three-way interactions among multivitamin use, single supplement use, and family history of prostate cancer. Multiple comparisons could have produced chance findings in some subgroup analyses.

In summary, we found evidence to suggest that multivitamin use was not associated with a decreased risk of prostate cancer. In fact, excessive use of multivitamin supplements or a closely related behavior was associated with an increased risk of advanced and fatal prostate cancer. Because multivitamin supplements consist of a combination of several vitamins and men using high levels of multivitamins were also more likely to take a variety of individual supplements, we were unable to identify or quantify individual components responsible for the associations that we observed. Our findings of a markedly increased prostate cancer risk among men using multivitamin supplements is of concern and warrants further research.

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Notes

This research was supported by the Intramural Research Program of the NIH, National Cancer Institute. We are indebted to those who participated in the NIH–AARP Diet and Health Study for their outstanding cooperation. We gratefully acknowledge the contributions of Leslie Carroll and David Campbell at Information Management Services and Tawanda Roy at the Nutritional Epidemiology Branch for research assistance. The funding agencies had no role in the design, conduct, decision to report, or writing of the study.

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health (DOH). The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or the DOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

Manuscript received September 28, 2006; revised March 9, 2007; accepted April 6, 2007.