Men's health supplement use and outcomes in men receiving definitive intensity-modulated radiation therapy for localized prostate cancer[1–3]

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ABSTRACT

Background: Approximately 50% of newly diagnosed cancer patients start taking dietary supplements. Men's health supplements (MHSs), which we define as supplements that are specifically marketed with the terms men's health and prostate health (or similar permutations), are often mislabeled as having potential anticancer benefits.

Objective: We evaluated the effects of MHSs on patient outcomes and toxicities in patients who were undergoing definitive intensity-modulated radiation therapy (IMRT) for localized prostate cancer.

Design: This retrospective analysis included patients who were being treated at a National Cancer Institute–designated comprehensive cancer center and consented to have information stored in a prospective database. MHSs were queried online. Outcome measures were freedom from biochemical failure (FFBF) (biochemical failure was defined with the use of the prostate-specific antigen nadir + 2-ng/mL definition), freedom from distant metastasis (FFDM), cancer-specific survival (CSS), and overall survival (OS) as well as toxicities. Kaplan-Meier analysis, log-rank tests, Fine and Gray competing-risk regression (to adjust for patient and lifestyle factors), and Cox models were used.

Results: From 2001 to 2012, 2207 patients were treated with IMRT with a median dose of 78 Gy, and a median follow-up of 46 mo. Of these patients, 43% were low risk, 37% were intermediate risk, and 20% were high risk; 10% used MHSs. MHSs contained a median of 3 identifiable ingredients (range: 0–78 ingredients). Patients who were taking an MHS compared with those who were not had improved 5-y OS (97% compared with 92%, respectively; $P = 0.01$), but there were no differences in the FFBF (94% compared with 89%, respectively; $P = 0.12$), FFDM (96% compared with 97%, respectively; $P = 0.32$), or CSS (100% compared with 99%, respectively; $P = 0.22$). The unadjusted association between MHS use and improved OS was attenuated after adjustment for patient lifestyle factors and comorbidities. There was no difference in toxicities between the 2 groups (late-grade 3–4 genitourinary $<3\%$; gastrointestinal $<4\%$).

Conclusion: The use of MHSs is not associated with outcomes or toxicities. *Am J Clin Nutr* 2016;104:1583–93.

Keywords: complementary and alternative medicine, dietary supplements, men's health, prostate cancer, radiation therapy vitamins, multivitamins, saw palmetto, supplements, multi-ingredient nutritional supplements (MINS)

INTRODUCTION

Prostate cancer is the most common noncutaneous malignancy and second leading cause of cancer death in patients in the United States (1). Supplement use (which includes vitamins, minerals, and herbs) is thought to be common in the 10 million adults in the United States who have been diagnosed with cancer (2). Approximately 50% of newly diagnosed cancer patients start taking dietary supplements (2). In addition, >60% of cancer survivors initiate supplement use (3).

Men's health supplements (MHSs),[7] which we define as supplements that are specifically marketed with the terms men's health and prostate health (or similar permutations) (**Supplemental Table 1**), are often mislabeled as having potential anticancer benefits. A previous study reported that the diagnosis of prostate cancer prompted 32% of patients to start taking some form of supplements, and ~50% of patients had used supplements before receiving the diagnosis (4). Men in the United States are likely to use MHSs because of the high incidence of prostate cancer, the stress associated with the diagnosis, the desire to gain a benefit from all potential treatments, and the limited regulation on the marketing and sale of supplements (3).

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[3] Supplemental Figure 1 and Supplemental Tables 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[7] Abbreviations used: ADT, androgen deprivation therapy; BF, biochemical failure; CSS, cancer-specific survival; DM, distant metastasis; FFBF, freedom from biochemical failure; FFDM, freedom from distant metastasis; IMRT, intensity-modulated radiation therapy; MHS, men's health supplement; NCCN, National Comprehensive Cancer Network; NCI, National Cancer Institute; OS, overall survival; PSA, prostate-specific antigen; RT, radiation therapy; SELECT, Selenium and Vitamin E Cancer Prevention Trial; sHR, subdistribution HR.

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It is necessary to understand the effects of MHSs on these patients because, in certain disease sites, dietary supplements have been associated with increased risks of adverse events and death (5). We evaluated the effects of MHSs on patient outcomes and toxicities in patients who were undergoing definitive intensity-modulated radiation therapy (IMRT) for localized prostate cancer. To our knowledge, this is the first report on this topic.

METHODS

We reviewed our prospectively collected institutional database of patients who were undergoing IMRT for localized prostate adenocarcinoma from 2001 to 2012 with clinical stage T1–4, N0/X, M0 (**Supplemental Figure 1**). All patients had a history and physical examination, including a digital rectal examination, initial serum prostate-specific antigen (PSA) test, and histologic confirmation of adenocarcinoma with a Gleason score, that was reviewed at our National Cancer Institute (NCI)–designated cancer center, which is a member institution of the National Comprehensive Cancer Network (NCCN). The T category was established by palpation findings for only 91% of the cohort; for the remainder of the cohort, used additional radiographic imaging was used because of physician preference.

We defined an MHS as any medication that was marketed with any of the following terms: men's health, men's formula, prostate vitamin, or prostate health (or similar permutations). This definition excluded general multivitamins unless the multivitamins were specifically marketed as men's health multivitamins (or other analogous variations). We included multivitamins that were labeled for men's health because they sometimes had ingredients that were different from those in general multivitamins. In addition, the definition of MHSs excluded minerals, fish oil, or prescription medications. We created these inclusion and exclusion criteria (Supplemental Table 1) to most closely approximate the supplements that are marketed to men in a general store or pharmacy.

As part of their evaluation, patients were specifically asked about their use of supplements (we asked specifically about MHSs and, afterward, about any other supplements) on preappointment screening questionnaires (open ended), again by the nurse, and again by the treating physicians. Questionnaires and consultation questions about MHSs focused on the name of the MHS (open-ended questions), if the MHS contained saw palmetto (close-ended question), and whether the patient was taking the MHS before starting IMRT (i.e., before the first fraction), during IMRT (i.e., between the first and last fractions), or after IMRT (i.e., after the last fraction). For example, if, during a course of IMRT, a patient stated that he currently used an MHS (i.e., within the past week) and that he had used it before IMRT and discontinued it during the course of IMRT, he was counted as having used that MHS before and during IMRT but not after IMRT. Unfortunately, we did do not have the start and end dates of patients taking MHSs, and thus, we could not provide specific time intervals of MHS use.

Consistency in the recording of MHS use was maintained between the preappointment questionnaires, the nurse, and the treating physicians; if there was an inconsistency in a patient's response regarding the use of a medication, he was asked again by the nurse and the physicians in the room at the same time. The patient's answer regarding MHS use was appropriately marked on the questionnaire and recorded in the electronic medical record, and the questionnaire was sent to our database manager to fill in the database entry regarding the patient's treatment. Thus, there was agreement between the patient, doctors, nurses, questionnaire, medical record, and database regarding whether the patient used an MHS, the name of the MHS (if the patient could remember it), and the timing of its use (before, during, and/or after IMRT). Moreover, this record was reviewed with the patient during on-treatment visits and during follow-up visits in which he again completed questionnaires, spoke to the nurse, and spoke to the physician. The nurse and physician reviewed all medications (including MHSs) that the patient was taking; if there were changes in the medications, the entries were revised in the database. For example, if a patient stopped taking a medication, the entry of the medication was kept in the database, and the timing was changed (as necessary) to before, and/or during, and/or after IMRT. No medications were deleted from a patient's record. If a patient started taking a new type of MHS, the MHS would be added as a new medication. As regards product changes of an individual MHS (i.e., if a manufacturer changed the chemical composition) that a patient was taking, we did not know how or if the ingredients changed over time.

This study was approved by the appropriate ethics committee (protocol IRB 03-835) and, therefore, was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent before their inclusion in the study. This report is a retrospective analysis and does not contain experimentation on human subjects that was performed by any of the authors. All men who were taking MHSs did so without the recommendation of a physician.

The overwhelming majority of patients had the exact name of the MHS they were taking (either from recall or on a medication list), although most subjects did not have the container of the MHS. Our evaluation depended on the recall of most patients, which was a limitation of the study. All MHS names that were provided were queried in an electronic medical-record database (Epic; http://www.epic.com/) that was linked to outside pharmacies and, therefore, provided generic and brand names of all drugs. In addition, MHSs were queried online at the time of the initial consultation to match them to the specific MHSs available in stores. We did not use a dietary supplement–label database, and our current database may not have had updated information on newly released supplements; nonetheless, we were able to confirm all MHS names with patients and found the MHSs online.

We specifically asked about saw palmetto use because this may falsely lower PSA values. We routinely discouraged MHS use; we explained that MHSs that contain saw palmetto may alter PSA values, and we do not know how other ingredients may affect PSA values. If a patient was taking saw palmetto, a repeat PSA was drawn. In our database, we only recorded the PSA (with the patient not using an MHS). MHSs were taken by patients as directed on individual MHS containers (e.g., daily) per patient report. To the authors' knowledge, only a few dietary supplements are prescribed because these are over-the-counter products, MHSs are not an endorsed therapy for any condition, and the patients in this study used the MHSs without the recommendation of a physician.

Each MHS name was queried online to find the individual ingredients, if the ingredients could be identified. We used 6

databases to query about the ingredients and clinical studies that have examined each MHS including Medscape (www.Medscape.com), Micromedex (www.micromedexsolutions.com, UpToDate (www.Uptodate.com), PubMed (www.Pubmed.gov), clinicaltrials.gov (www.clinicaltrials.gov), and Google (www.Google.com). We did not perform chemical analyses of MHSs to determine their contents.

Comorbidities were obtained via patient self-report as well as from the consultation notes of patient primary care physicians, the referring physician (e.g., the urologist), and involved cardiologists and gastroenterologists. Unfortunately, diagnosis codes were not always available, which was a limitation of the study. All patients needed a biopsy (and sometimes MRI and the placement of fiducial markers) before IMRT; thus, the appropriate cardiac history from a cardiologist was mandatory. Similarly, because radiation proctitis is a possible sequela of IMRT, gastroenterology records were mandatory. All comorbidities from records were integrated into our database and were used in the analysis. We updated information regarding risk data over time during follow-up visits.

Per NCCN guidelines (6), treatment options for nonmetastatic prostate cancer typically include active surveillance, radical prostatectomy, and various types of radiation therapy (RT), that are delivered as either external-beam RT or brachytherapy with or without androgen deprivation therapy (ADT), which is typically used for high-risk patients (7). External-beam RT is most commonly delivered with the use of conventional fractionation (i.e., 2 Gy/d, 5 d/wk, for 8 wk up to total dose of 78–80 Gy) (8).

IMRT is an advanced technique to deliver external-beam RT. IMRT was introduced around the year 2000 as a further refinement in the delivery of highly conformal radiation. IMRT increases the dose delivered to the tumor volume and minimizes the dose delivered to surrounding organs with the use of *1*) a multileaf collimator, which is a device that is made up of individual leaves of a high–atomic-numbered material that can move independently in and out of the path of a particle beam to contour its shape to a tumor, and *2*) advanced treatment planning calculation algorithms, which allow for the inverse optimization of multileaf-collimator positioning for complex dose delivery (8–10).

The dose distribution that is created by IMRT is characterized by a concavity or invagination of the edge of the higher radiation doses away from the rectum rather than by a straight edge through the rectum as was used in older techniques to deliver RT (e.g., with 3-dimensional conformal RT) (8). Thus, IMRT is the current standard of care in external radiation-beam RT because it minimizes the chance for severe long-term toxicity (typically for $<5\%$ of patients in trials that have used IMRT) (8, 10).

Although there are many standard treatment options for prostate cancer, randomized clinical trials that were conducted to define the optimal therapy for patients with localized or locally advanced disease have been limited. At our NCI-designated comprehensive cancer center, patients typically meet with a surgical oncologist to discuss surgery and with a radiation oncologist to discuss RT options; we help patients select the option that is best for them depending on their general preferences, overall health, and anticipated toxicities (8). In this study, we included only patients who received dose-escalated conventionally fractionated IMRT (i.e., 76–80 Gy in 2.0-Gy fractions) (11).

For IMRT, all patients were immobilized supine in a thermoplastic cast, and daily prostate localization was performed in all patients with the use of either fiducial markers with an electronic portal, computed tomography imaging, or radiofrequency beacons. The planning target volume included the prostate and 8 mm, except posteriorly, where the margin was less to enable better rectal sparing. The IMRT dose was prescribed such that 95% of the planning target volume received 100% of the prescribed dose. ADT, typically with leuprolide acetate, was prescribed at the discretion of the treating physicians. Of all men, 26% of subjects received ADT. None of the low-risk patients received ADT.

We assessed the efficacy and toxicity of IMRT with or without MHSs. For efficacy, the outcome measures were freedom from biochemical failure (FFBF), freedom from distant metastasis (FFDM), cancer-specific survival (CSS), and overall survival (OS). For toxicity, we evaluated genitourinary and gastrointestinal toxicities. Biochemical failure (BF) was defined with the use of the PSA nadir + 2-ng/mL definition, and a longer FFBF was favorable because it implied lower risk of metastasis and subsequent death from prostate cancer (12).

Patients were followed with a clinical examination (including a rectal examination) every 6 mo for the first year and, thereafter, yearly with PSAs that were drawn every 6 mo. All patients had $\geq$2 follow-up PSAs. If interim PSAs were missing, subsequent values were used. Of 2186 patients with BF (which was calculated as a 2-ng/mL rise in PSA from the nadir), 1592 subjects (73%) had a PSA measurement within the first 12 mo of RT; 27% of subjects missed the initial PSA measurement. Of 2186 patients with BF, 193 of subjects (9%) had 1 or more intervals between PSA measurements $\geq$18 mo, which suggested that they had missed a PSA reading.

Patients who were lost to follow-up were censored. For BF, the time to the event was determined from the date of initial IMRT to the date of a biochemical event [either the date of nadir + 2 PSAs in ng/mL (13) or the date that salvage hormones were started] or to the date of the last PSA measurement that was recorded in the database for censored patients. For FFDM, CSS, and OS, censoring was determined as the time from the date of the start of IMRT to either the date of an event or the status date (i.e., the most recent date known to be alive, the date of metastasis on the basis of imaging, or the date of death). The time component was from the start of IMRT. We did not test any interactions, and the assumptions of proportional hazards were tested for competing risk and Cox models.

Patients who were lost to follow-up were followed until their last known date of contact. In addition to the information we had on patients from follow-up with our multidisciplinary team members (e.g., urologic oncologists, medical oncologists, and radiation oncologists), our hospital received information on patient death from patients' primary care physicians (for patients who died outside of the hospital). We reviewed all information on patients to determine the cause of death (i.e., cancer compared with other causes). All information was stored in our database.

We used Kaplan-Meier methods to generate survival curves for FFBF, FFDM, CSS, and OS and compared MHS users and nonusers with the use of log-rank tests. For FFBF and FFDM, subdistribution HRs (sHRs) were estimated with the use of Fine and Gray competing risk regression (14) to account for the competing risk of death with adjustment for PSA (log transformed), Gleason score, T stage, and ADT.

To adjust for patient lifestyle factors and comorbidities, we used competing risk regression models (**Supplemental Table 2**). Cox proportional hazards methods were used to estimate HRs for overall mortality that were adjusted for age at the start of IMRT and comorbidities (heart disease, diabetes, and pulmonary disease) in addition to the covariates included in the FFBF models. The presence or absence of these comorbidities or smoking served as surrogate markers for patient lifestyle factors (e.g., healthy diet and exercise); we did not measure patient diet or exercise regimens directly. There were too few prostate cancer deaths for a multivariable analysis for this outcome.

We evaluated genitourinary and gastrointestinal toxicities (which may occur with IMRT) with the use of the modified Radiation Therapy Oncology Group definitions (**Supplemental Table 3**). We analyzed moderate and severe (i.e., combined grade 2–4 toxicities) as well as only severe toxicities (i.e., only grades 3–4). We used competing risk regression to estimate sHRs for late toxicities (occurring >3 mo after IMRT) with adjustment for ADT use, IMRT dose, diabetes, and hypertension and accounting for competing risk of death from any cause (14). We used logistic regression to estimate ORs for MHS use and acute toxicities (occurring during and ≤3 mo of IMRT) that were both unadjusted and adjusted for hormone use, dose, diabetes, and hypertension.

We controlled for multivitamin use and fish-oil use to evaluate any change in the association between MHS use and outcomes by using a proportional hazards model for the subdistribution of competing risk (14). For each outcome, the indicators for multivitamin use (any) and fish-oil use (any) were added to the multivariate model along with MHS interaction terms (model 1). If the interaction terms were NS, an additional model (model 2) was run without the indicators to determine the HR estimate that was adjusted for these additional indicators. If the interaction was significant, the analyses were stratified by the multivitamin or fish-oil indicator. Competing risk regression analyses and survival plots were done with the use of Stata version 12 software (StataCorp LP); additional analyses were performed with SAS 9.2 software (SAS Institute Inc.). $P < 0.05$ was considered significant; a Bonferroni correction was performed for multiplicity-adjusted P values (15).

RESULTS

Patient characteristics are listed in **Table 1**. From 2001 to 2012, 2207 men were treated with IMRT with a median dose of 78 Gy (range: 76–80 Gy). In perspective, from 2002 to 2012, of all patients treated at our NCI-designated comprehensive cancer center, 146 patients elected to have active surveillance, 1853 men underwent a radical prostatectomy, 29 men underwent high–dose rate brachytherapy, 377 men underwent low–dose rate brachytherapy, and 159 underwent nonconventionally fractionated IMRT (e.g., hypofractionated and stereotactic). Our institution was one of the pioneers in developing IMRT; thus, since 2001, all men have been treated with IMRT and not with 3D conformal RT.

Of the men treated with IMRT, 43% of patients were low risk, 37% of patient were intermediate risk, and 20% of patient were high risk on the basis of NCCN criteria. Of 2186 patients with BF, 1592 subjects (73%) had a PSA measurement within the first 12 mo of RT; 27% of subjects missed the initial PSA measurement.

TABLE 1
Characteristics of patients, tumors, and medications between patients who were taking MHSs and patients who were not taking MHSs[1]

	No MHS use	MHS use	*P*
n (%)	1990 (90)	217 (10)	
Age, y			0.032
36–59	347 (17)	35 (16)	
60–69	808 (41)	102 (47)	
70–79	740 (37)	78 (36)	
≥80	95 (5)	2 (1)	
Race			0.051
Black	293 (15)	36 (17)	
White	1616 (81)	165 (76)	
Other	81 (4)	16 (7)	
NCCN risk group			0.23
Low	860 (43)	106 (49)	
Intermediate	727 (37)	75 (35)	
High	403 (20)	36 (17)	
Gleason score			0.12
6	1011 (51)	127 (59)	
7 (3 + 4)	406 (20)	42 (19)	
7 (4 + 3)	264 (13)	20 (9)	
8–10	309 (16)	28 (13)	
T stage			0.13
T1–2a	1655 (83)	192 (88)	
T2b–T2c	214 (11)	16 (7)	
T3–4	121 (6)	9 (4)	
PSA, ng/mL			0.46
<10	1652 (83)	173 (80)	
10 to <20	247 (12)	33 (15)	
≥20	91 (5)	11 (5)	
PSA[2]	5.4 (3.9, 8.2)	5.8 (4.4, 8.8)	0.015
BMI pre-RT, kg/m^2			0.55
<25	368 (18)	45 (21)	
25 to <30	873 (44)	101 (47)	
≥30	599 (30)	57 (26)	
Unknown	150 (8)	14 (6)	
Time of MHS use			NA
Before IMRT only	—	123 (57)	
Post-IMRT only	—	24 (11)	
Pre- and post-IMRT	—	70 (32)	
Smoking status			0.13
Current	202 (10)	16 (7)	
Former	943 (47)	92 (42)	
Never	794 (40)	101 (47)	
Unknown	51 (3)	8 (4)	
Androgen deprivation therapy	536 (27)	42 (19)	0.016
Diabetes	384 (19)	28 (13)	0.022
Hypertension	1179 (59)	108 (50)	0.0072
Heart disease	355 (18)	34 (16)	0.43
Pulmonary disease	251 (13)	25 (12)	0.64
Multivitamin use	781 (39)	134 (62)	<0.0001
Fish-oil use	226 (11)	42 (19)	0.0006

[1] Values are *n* (%) unless otherwise specified. All staging information (e.g., risk group, PSA, T stage, Gleason score) was pre-RT. Comorbidities (e.g., diabetes and hypertension) were typically present pre-RT; some patients were diagnosed with these conditions during RT or post-RT, but detailed information on the exact date of diagnosis was unavailable. The use of multivitamins and use of fish oil reflect pre- and/or post-IMRT use. Wilcoxon's rank-sum test was used to compare PSA (continuous) between MHS users and nonusers; chi-square tests were used for categorical characteristics. For multiplicity-adjusted *P* values with the use of the Bonferroni correction (for 16 tests), $P < 0.0031$ was significant (15). IMRT, intensity-modulated radiation therapy; MHS, men's health supplement; NA, not applicable; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; RT, radiation therapy.

[2] Values are medians; 25th, 75th percentiles in parentheses.

Of these 2186 patients with BF, 193 subjects (9%) had 1 or more intervals between PSA measurements ≥18 mo, which suggested that they had missed a PSA reading. The median interval in between PSA measurements within 72 mo from the end of IMRT was 6.15 mo (25th and 75th percentiles: 5.19, 7.21 mo). There were no differences of missed initial PSAs, PSA intervals >18 mo, or mean intervals within PSA measurements between MHS and non-MHS groups.

MHS use was reported in 217 men (10% of all patients). MHS use was similar across races, NCCN risk groups, Gleason scores, T-stage PSA categories, and BMI ranges. Most MHS users (123 of 217 men) discontinued MHS use before RT (as recommended); however, 24 men (11%) started MHS use only after IMRT, and 70 men (32%) used MHSs before and after IMRT (against physician recommendations). MHS users were less likely to have hypertension or diabetes ($P < 0.05$). MHS users compared with nonusers of MHSs were more likely to use multivitamins (62% compared with 39%, respectively; $P < 0.001$) and fish oil (19% compared with. 11%, respectively; $P < 0.001$).

In our Internet query of the MHSs that were used by our patients, we identified a total of 26 unique brand names in all men who were taking MHSs. MHSs contained a median of 3 identifiable ingredients (range: 0–78 ingredients); the most common was saw palmetto (91%) followed by ingredients that were no different from standard multivitamins (5%) or no identifiable ingredients (4%). The ingredients were unidentifiable because they contained terms that could not be queried (e.g., other, trade-secret enzyme, and prostate complex). After asking about all MHSs used by the patients, none of the MHSs was shown to have been used in a study that was published on clinicaltrials.gov or pubmed.gov.

Patient outcomes are shown in **Figure 1** and **Table 2**. The number of men who were taking MHSs was relatively small, there were few events, many men were lost to follow-up, there was little room for improvement in outcomes or toxicities, and these limitations decreased the power. At the initial time point, there were 1990 men who were not taking an MHS and 217 men who were taking an MHS. With respect to BF, there were 185 events in MHS nonusers and 8 events in MHS users; by 84 mo,

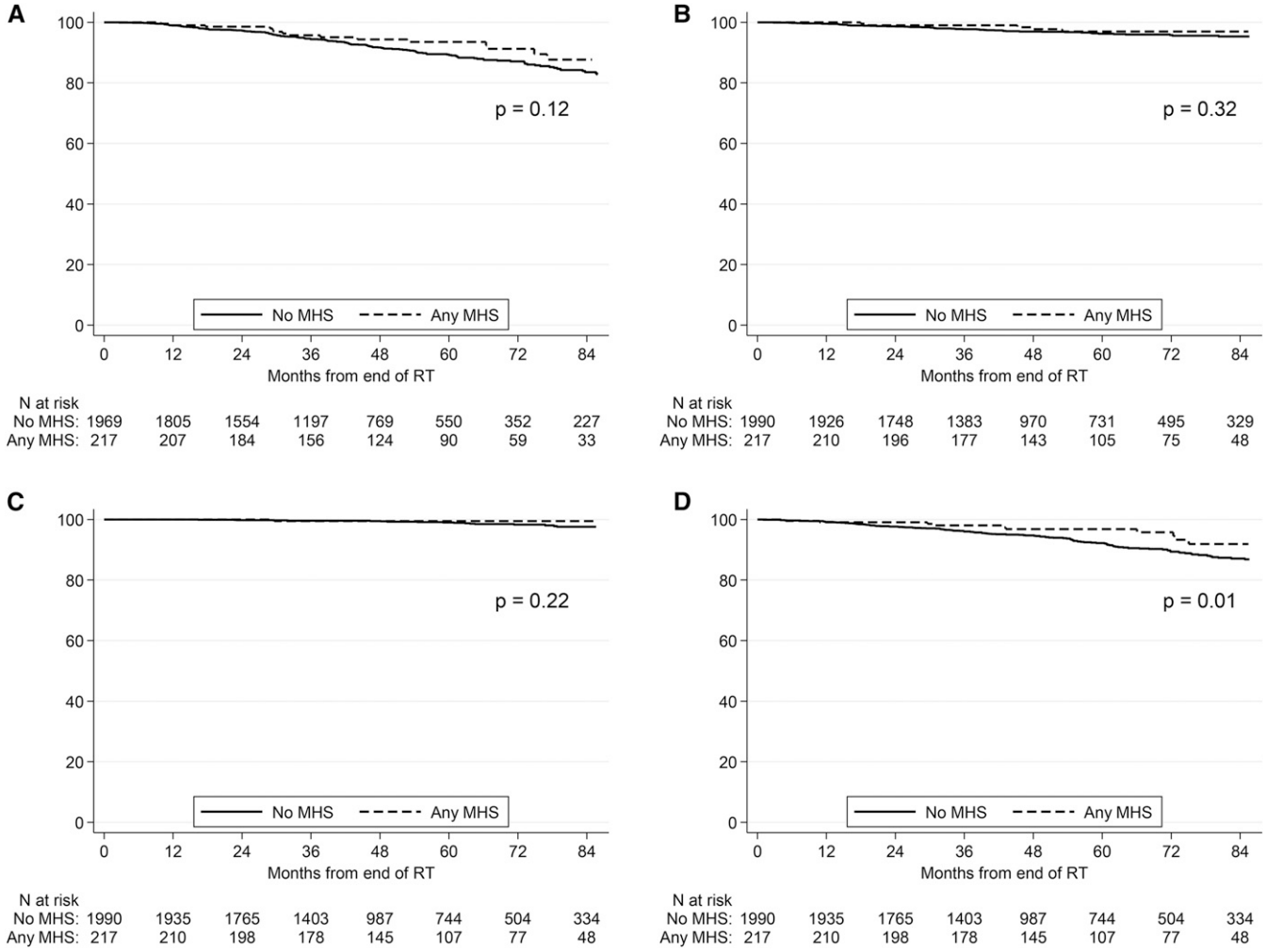

FIGURE 1 Kaplan-Meier curves of FFBF for all patients (A), FFDM (B), CSS (C), and OS (D). The *x*-axis of each plot is the follow-up time (in months), and the *y*-axis of each plot is the percentage. The number of at-risk patients who were taking MHSs (solid lines) and those who were not taking MHSs (dashed lines) are listed for reference in each plot. MHS use was associated with improved OS in this analysis but not with a change in FFBF, FFDM, or CSS. CSS, cancer-specific survival; FFBF, freedom from biochemical failure; FFDM, freedom from distant metastasis; MHS, men's health supplement; OS, overall survival; RT, radiation therapy.

TABLE 2
Kaplan-Meier analysis of outcomes for patients who were or were not taking MHSs and were being treated for prostate cancer with the use of definitive IMRT[1]

	MHS nonusers with events (total n = 1990), n (%)	% (95% CI)	MHS users with events (total n = 217), n (%)	% (95% CI)	Log-rank P	sHR (95% CI)	P
5-y FFBF all	185 (9)	89 (87, 91)	17 (8)	94 (89, 96)	0.12	0.75 (0.45, 1.23	0.25
Low risk	—	96 (93, 97)	—	99 (91, 100)	0.37	—	—
Intermediate risk	—	87 (83, 90)	—	88 (76, 94)	0.68	—	—
High risk	—	78 (72, 84)	—	88 (66, 96)	0.27	—	—
5-y FFDM	64 (3)	96 (95, 97)	5 (2)	97 (93, 99)	0.32	0.75 (0.30, 1.88	0.54
5-y CSS	25 (1)	99 (98, 100)	1 (1)	100 (96, 100)	0.22	0.41 (0.05, 3.16	0.39
5-y OS	171 (9)	92 (91, 94)	10 (5)	97 (93, 99)	0.01[2]	0.61 (0.32, 1.16	0.133

[1] Columns on the left side (number of events, their 95% CIs, and the log-rank P values) of the table (Kaplan Meier analysis) were unadjusted. Adjusted ratios are provided on the right side (sHRs and P values) of the table. CSS, cancer-specific survival; FFBF, freedom from biochemical failure; FFDM, freedom from distant metastasis; IMRT, intensity-modulated radiation therapy; MHS, men's health supplement; OS, overall survival; sHR, subdistribution HR.
[2] $P < 0.05$.

there were 227 MHS nonusers and 33 MHS users who were available for analysis. Thus, 1578 MHS nonusers (79% of the initial 1990 nonusers) were lost to follow-up, and 176 users (81% of the initial 217 users) were lost to follow-up by 84 mo. With respect to distant metastasis (DM), there were 64 events in MHS nonusers and 5 events in MHS users; by 84 mo, there were 393 MHS nonusers and 53 MHS users who were available for analysis. With respect to death that was due to prostate cancer, there were 25 events in MHS nonusers and 1 event in MHS users; by 84 mo, there were 359 MHS nonusers and 49 MHS users who were available for analysis. With respect to OS, there were 171 events in MHS nonusers and 10 events in MHS users; by 84 mo, there were 505 MHS nonusers and 58 MHS users who were available for analysis.

Unfortunately, we could not explain why patients were lost to follow-up. We typically recommend that patients follow up with us yearly after the first year (with biannual PSAs). However, because some patients travel from long distances, they prefer to follow up with their local urologist. We were unable to assess if patients who were lost to follow-up were different from those who were not lost to follow-up; there were likely unmeasured factors of patients who were lost to follow-up (e.g., diagnoses of new medical problems, changes in addresses and living situations, and changes in the health of their spouses). The loss to follow-up was significant and may have biased estimates.

At a median follow-up time of 46 mo (mean: 58 mo; range: 1–190 mo), MHS use was associated with improved OS [97% (95% CI: 93%, 99%) compared with 92% (95% CI: 90%, 93%); P = 0.02]. MHS use was not associated with a difference in FFBF (P = 0.12), FFDM (P = 0.32), or CSS (P = 0.22). In the competing risk regression analysis (Table 2, right side; Supplemental Table 2), MHS use was not associated with improved FFBF (sHR: 0.75; 95% CI: 0.45, 1.22; P = 0.25). A higher T stage, higher Gleason score, and higher initial PSA were all associated with worse FFBF. Similarly, MHS use was not associated with improved FFDM (sHR: 0.75; 95% CI: 0.30, 1.88; P = 0.54). A higher T stage, higher Gleason score, higher initial PSA, and nonuse of ADT were all associated with worse FFDM. In addition, MHS use was not associated with improved CSS (sHR: 0.41; 95% CI: 0.05, 3.16; P = 0.39). A higher NCCN risk group was associated with worse CSS. Finally, MHS use was not associated with improved OS (sHR: 0.61; 95% CI: 0.32, 1.16; P = 0.13). Age, initial PSA, hypertension, and heart disease were all prognostic of OS (data not shown). The presented HRs included only men with events and those at risk (i.e., not lost to follow-up). Because 79% of patients were lost to follow-up by 84 mo, and there were few events for all outcomes, the CIs were relatively wide, which was a limitation of the study.

Note that the unadjusted association between MHS use and improved OS (Figure 1, Table 2, left side) attenuated after adjustment for patient lifestyle factors and comorbidities with competing risk regression (Table 2, right side; Supplemental Table 2). Cancer-related factors, including the Gleason score, PSA, and T stage, were all associated with patient outcomes (data not shown).

In the analyses of multivitamin use and fish-oil use for FFBF, there was no significant interaction between MHS use and multivitamin use (P = 0.17) or between MHS use and fish-oil use (P = 0.54). The adjusted sHR was 0.706 (95% CI: 0.42, 1.18; P = 0.19). Both multivitamin use and fish-oil use were not associated with FFBF. For FFDM, there was no significant interaction between MHS use and multivitamin use (P = 0.632); there were too few events for fish-oil use and MHS use to run the interaction model. The adjusted sHR was 0.691 (95% CI: 0.27, 1.76; P = 0.44). There were too few events to run interaction models for CSS. For OS, there was no significant interaction between MHS use and multivitamin use (P = 0.77) or between MHS use and fish-oil use (P = 0.98). Both multivitamin use and fish-oil use were significantly inversely associated with overall mortality (each $P < 0.05$). The adjusted sHR was 0.701 (95% CI: 0.36, 1.35; P = 0.29). The presented HRs included only men with events and those at risk (i.e., not lost to follow-up). Because ~79% of patients were lost to follow-up by 84 mo. and there were few events for all outcomes, the CIs were relatively wide, which was a limitation of the study.

In the acute-toxicity analysis (**Table 3**), there was no difference in genitourinary or gastrointestinal toxicities between the 2 groups. The rate of acute grade 3–4 genitourinary toxicity was 5% in patients taking MHSs and 6% in patients who were not taking MHSs (chi-square P = 0.76). The rate of acute grade 3–4 gastrointestinal toxicity was 0% in patients who were taking MHSs and 1% in patients who were not taking MHSs (chi-square P = 0.63).

TABLE 3
χ^2 Analysis and ORs of acute toxicities for men who were or were not taking MHSs and were treated for prostate cancer with the use of definitive IMRT[1]

Toxicity	MHS nonusers with events, *n* (%)	MHS users with events, *n* (%)	Chi-square *P*	OR (95% CI)	*P*
Genitourinary					
Grades 2–4	683 (34)	67 (31)	0.33	0.94 (0.69, 1.29)	0.71
Grades 3–4	116 (6)	11 (5)	0.76	0.96 (0.50, 1.83)	0.90
Gastrointestinal					
Grades 2–4	122 (6)	14 (6)	0.88	1.12 (0.63, 2.00)	0.70
Grades 3–4	13 (1)	0 (0)	0.63	MNR[2]	—

[1] IMRT, intensity-modulated radiation therapy; MHS, men's health supplement; MNR, model not run.
[2] Because there were too few events.

In the late-toxicity analysis (**Table 4**), there was no difference in genitourinary or gastrointestinal toxicities between the 2 groups. The freedom from late grade 3–4 genitourinary toxicity at 60 mo was 99% in patients who were taking MHSs and 98% in patients who were not taking MHSs ($P = 0.87$). The freedom from late grade 3–4 gastrointestinal toxicity was 96% in patients who were taking MHSs and 97% in patients who were not taking MHSs ($P = 0.28$).

DISCUSSION

There has been an increased trend in supplement use in the United States, particularly in cancer patients. To our knowledge, this is the first study to have evaluated the outcomes and toxicities of men who were taking MHSs and received definitive IMRT for prostate cancer. We showed that MHS use was present in 10% of men in our study. MHS users tended to be healthier than nonusers, which may have been attributed to increased health consciousness. MHS use was not associated with differences in outcomes or toxicities. The unadjusted association between MHS use and improved OS attenuated after adjustment for patient lifestyle factors and comorbidities.

In the NHANES III, which was conducted from 1988 to 1994, ~40% of the adult noninstitutionalized US population reported having taken ≥1 dietary supplement; subsequently, reports from 1999 to 2000 (16) and 2006 (17) revealed that this rate had increased to >50% of the adult population. Factors that are associated with an increased likelihood to take supplements include female sex, older age, higher education, non-Hispanic white race, physical activity, healthy BMI, and higher income (3, 16, 18).

Once patients are diagnosed with a cancer, 66% of them report making lifestyle changes, and ~50% start taking dietary supplements (2). Multimodality therapy (e.g., ADT use in prostate cancer patients) increases the chance that patients take supplements. After the completion of cancer treatment, the rate of supplement use further increases to 64–91% (3).

In our patient population, the rate of MHS use was 10%, and this rate did not include the use of general multivitamins, fish oil, and minerals, although these items were typically used more frequently by men who were taking MHSs than by men who were not taking MHSs (Table 1). We showed that older men were less likely to use MHSs, in contrast with other retrospective studies, which have shown no association between supplement use and age (18, 19).

We evaluated the use of MHSs before, during, and/or after IMRT (instead of focusing on a particular time) because we were interested in detecting any possible impact of MHSs on patient outcomes and toxicities. Biologically, prostate cancer cell mutations are punctuated or gradual (20), occurring over many years, and these mutations are influenced by environmental factors (e.g., MHSs) at any time; moreover, the natural history of prostate cancer is relatively long (>10 y from BF to patient death) (21). We were interested in studying the impact of any exposure to MHSs in relation to the history of prostate cancer rather than focusing on a particular time with respect to IMRT. To quantify when men were taking MHSs and to gauge how many men

TABLE 4
Log-rank analysis and subdistribution HRs of freedom from late toxicities for patients who were or were not taking MHSs and were treated for prostate cancer with the use of definitive IMRT[1]

Late toxicity	With events, *n* (%)	Free from toxicity, % (95% CI)	With events, *n* (%)	Free from toxicity, % (95% CI)	Log-rank *P*	sHR (95% CI)	*P*
Genitourinary							
Grades 2–4	135 (7)	91 (89, 92)	13 (6)	93 (87, 96)	0.36	0.91 (0.51, 1.63)	0.76
Grades 3–4	24 (1)	98 (97, 99)	1 (1)	99 (96, 100)	0.87	MNR[2]	—
Gastrointestinal							
Grades 2–4	287 (15)	80 (77, 82)	31 (14)	84 (76, 89)	0.43	0.91 (0.62, 1.33)	0.62
Grades 3–4	36 (2)	97 (96, 98)	5 (2)	96 (89, 98)	0.28	1.16 (0.45, 2.97)	0.75

[1] Columns on the left side (number of events, their 95% CIs, and the log-rank *P* values) of the table (log-rank tests) were unadjusted. Adjusted ratios are provided on the right side (sHRs and *P* values) of the table. IMRT, intensity-modulated radiation therapy; MHS, men's health supplement; MNR, model not run; sHR, subdistribution HR.
[2] Because there were too few events in the MHS group.

discontinued MHSs and how many men started MHSs after treatment, we routinely asked them if they were taking MHSs at the time of the initial patient evaluation (if so, we asked them to discontinue the MHSs and rechecked their PSAs); then, we asked men if they were taking MHSs during IMRT and at follow-up visits (after IMRT).

We included the timing of MHS use in our multivariate models. We did not run further models to compare all supplement users with nonusers to specifically assess the timing of use (before IMRT only, post-IMRT only, or pre- and post-IMRT) because there was an overlap of patients in these categories (e.g., there were pre-IMRT–only users, pre-IMRT and during-IMRT users, and pre-IMRT, during-IMRT, and post-IMRT users); thus, we would have needed to separate the various subcategories. The remaining numbers would have been relatively small and would have precluded a meaningful analysis.

We evaluated MHSs (and not multivitamins or fish oil) because MHSs have a particular product marketing and branding that are aimed at men with prostate cancer during a vulnerable time. During the distressful time of being diagnosed with prostate cancer, supplements that mention men or prostate on the container would likely appeal to men as a potential treatment option or as adjunctive therapy to improve outcomes or toxicities from therapy; in juxtaposition, multivitamins or fish-oil tablets do not have these specific claims.

There is unclear verbiage on MHS containers (e.g., approved by urologists, clinically proven for prostate health, and clinically tested) that suggests that MHSs would improve the efficacy or decrease the toxicity of treatment (in our population, IMRT). Subsequently, the unclear terms that are present on MHS bottles are not necessarily mislabeling but misleading, which leave a gray area that is open to interpretation. There is heterogeneity in the ingredients of MHSs, and some MHSs may have certain antioxidants, which may be inversely associated with biomarkers of oxidative stress in prostate cancer (22). However, the exact antioxidants, their sources (e.g., fruit or vegetables compared with being synthetically constructed), settings (e.g., in vitro, in vivo, and clinical trials), doses, purported mechanisms, associated biomarkers, and the cancers targeted are not listed on MHS containers. These are medical nuances that would overwhelm potential customers who would much rather purchase the clinically proven product. We specifically focused on these MHSs in our work.

Note that, although some of the supplements mentioned men's health or prostate health, they frequently had ingredients that were very similar to the generic multivitamins that were produced by the same company (Supplemental Table 1) and contained extra ingredients (e.g., lycopene, selenium, and cholecalciferol) which have either not been tested in randomized trials or have clearly been shown to provide no benefit compared with a placebo (23–25). We ran further models to control for the use of multivitamins and fish oil, and there was still no difference in outcomes or toxicities in MHS users and nonusers. We remain interested in the impact of multivitamins and various vitamin complexes on outcomes and toxicities of prostate cancer patients; we hope to pursue this analysis in a future research endeavor because analysis was beyond the scope of the current work.

In addition, 91% of MHSs contained saw palmetto (*Serenoa repens*), which has some efficacy in treating benign prostatic hyperplasia and improving urinary symptoms (26, 27). Saw palmetto may decrease PSA. Men on saw palmetto may have improvement in urinary symptoms and have false reassurance that the MHSs are also treating their prostate cancer. We did not perform a subset analysis of patients who were taking MHSs with saw palmetto compared with those who were not because we were interested in performing an analysis of all supplements that were marketed as men's health or prostate health. Saw palmetto is not a recommended treatment of prostate cancer (6), and it would not be expected to change outcomes. The ingredients in MHSs besides saw palmetto were heterogeneous and largely unidentifiable (e.g., trade-secret complex), which precluded a meaningful analysis.

The secondary analyses of the 2 randomized controlled trials, the Nutritional Prevention of Cancer study and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, revealed prostate cancer risk reductions of selenium and vitamin E (28–31). Subsequently, One-A-Day Men's Health Formula (One-A-Day) was advertised as containing selenium and vitamin E for the prevention of prostate cancer.

The SELECT (Selenium and Vitamin E Cancer Prevention Trial) set out to determine whether selenium, vitamin E, or both could prevent prostate cancer and other diseases with little or no toxicity in relatively healthy patients. The trial included 35,533 patients from 427 participating sites in the United States, Canada, and Puerto Rico. Patients were randomly assigned to 4 groups (selenium, vitamin E, selenium + vitamin E, and placebo) in a double-blind fashion between 2001 and 2004. The trial revealed that vitamin E significantly increased risk of prostate cancer in healthy patients (25). Strikingly, the manufacturer of One-A-Day Men's Health Formula continued to advertise that it could prevent prostate cancer because it contained selenium and vitamin E, and only a lawsuit threat stopped the company from making this claim (32).

Systematic reviews that have been published since 2010 have stated that there are a limited number of trials that have examined the effects of dietary supplements on the primary prevention of cancer; the majority of trials have shown no effect in healthy populations (23). Specifically, vitamin supplements have not been recommended for prostate cancer prevention, and the use of certain supplements (e.g., vitamin E) has been discouraged because these supplements have been associated with a worse prognosis (24, 25).

In the univariate analysis, MHS use was associated with improved OS (Figure 1; Table 2, left side); however, we showed no differences in outcomes of patients who were taking MHSs after adjustment for patient lifestyle factors and comorbidities (Table 2, right side). This result was not surprising because our Internet search revealed that most MHSs typically contain saw palmetto, which does not affect patient outcomes. Nonetheless, supplements are not innocuous, because the SELECT revealed that vitamin E may increase prostate cancer incidence and aggressiveness (25). In other disease sites (e.g., head and neck), supplementation with high doses of α-tocopherol and β-carotene during RT has been shown to compromise RT efficacy (33).

Adverse events that are secondary to supplement use are difficult to monitor in the United States. In 1998, there were 2332 phone calls to 11 poison-control centers about supplements (5). Although the SELECT did not reveal the toxicity associated with

either vitamin E or selenium, in 2008 (before the publication of the SELECT and likely during the peak of interest in using selenium for prostate cancer treatment), there was a selenium toxicity outbreak in the United States. This outbreak was caused by a supplement that contained 200 times the labeled concentration of selenium; the outbreak resulted in 201 cases of toxicities in the United States (34, 35). We did not identify an increase in acute toxicities in patients who were taking MHSs (Table 3).

With respect to late toxicities (Table 4), we also noted no differences in MHS users than in nonusers. At 2.5 y of follow-up of the SELECT, >50% of patients complained of chronic toxicities including abnormal nails and hair, myalgias, fatigue, anxiety, memory loss, and depression. Notably, the company producing this supplement advertised it for prostate health and did not pull the product until after the peak of the outbreak (34, 35).

This study has limitations besides those listed in the previous sections. First, the study was retrospective in nature, and thus, we could only show association and not causation. Second, we had a broad definition of MHSs because we wanted to incorporate all of the potential choices that patients would have at a general grocery store or pharmacy. It is possible that certain ingredients could improve staging or outcomes of specific subgroups of prostate cancer patients; the benefit of such agents would not have been shown in this type of analysis. For example, although certain supplements (e.g., fish oil) are theorized to have anti-inflammatory and anticancer properties (36), they were excluded from this analysis because they are not typically marketed for men's health or prostate health, and if our patients were taking fish oil, they provided a different indication. Some supplements may have come off the market during the study period [e.g., those containing selenium in 2008 (34, 35)], whereas other supplements may have been introduced to the market in the same time period. We asked open-ended questions about all medications and supplements that the patients took, and we did not focus on specific MHSs or drug names. From a clinical perspective, we were most concerned in knowing that the MHSs did not contain saw palmetto (because it alters PSAs). Therefore, we were diligent in querying MHSs for saw palmetto; we discussed how saw palmetto affects PSA.

Another limitation of this study is the relatively small number of events. For example, there were only 185 BFs in 1990 MHS nonusers and 17 BFs in 217 MHS users (Table 2). In addition, there were only 5 patients with DM, 14 patients who experienced mortality, and 2 patients with death that was due to prostate cancer. Thus, the upper limits of the CIs approached 100%, and the detection of an event may not have been possible because of these data.

In addition, for certain patient subgroups, the number of events was a fraction of these low events. In the multivariate models of competing risk (Supplemental Table 2), note that, in some cases, there were very small cell sizes (e.g., there was an *n* of 1 for MHS use in the >80-y-old group). This aspect limited the reliability of estimates, and (in some cases) it may not be reliable to extrapolate the results to patient subpopulations. A continuous model may be used for this case; however, most physicians may prefer an analysis with discrete ranges because it is more applicable to clinical practice. Notably, all patient subpopulations may have a different likelihood in taking MHSs; e.g., older patients may not be exposed to advertisements that younger patients see. Also, certain patient subpopulations [e.g., elderly (37), overweight or obese (38), patients taking hormones (39), patients with comorbidities (40), and minorities (41)] may be more likely to have events (BF, metastasis, death from any cause, and toxicity), and a separate analysis solely regarding these patients would be necessary for these subpopulations. Ideally, continuous models should be used for certain variables (e.g., age, BMI, time taking hormones, and laboratory values as a surrogate for the severity of a comorbidity); unfortunately, we did not have this data available for all patients and, thus, were unable to run these models.

Nonetheless, our rates of FFBF, FFDM, CSS, and OS were consistent with randomized controlled trials of prostate cancer. For example, the 5-y FFBF rates in most dose-escalation and hypofractionation studies have been >90% (8, 40, 42). With the assumption that from the date of BF to the date of DM is >5 y and from the date of DM to death from cancer is an additional 5 y (21), there may not be difference shown in DM or CSS until 15–20 y of actuarial follow-up time. Moreover, at >5–10 y after external beam RT, the subsequent rise in PSA may be secondary to benign prostate diseases and not to cancer recurrence (43). Thus, there are typically very few events in overall patient outcomes (i.e., DM and CSM). For example, the 10-y CSM rates in some of the dose-escalation trials have frequently been <10% (8). The median age (in years) of diagnosis is in the late 60s (similar to that in the current study), and waiting for an additional 10–20 y may result in patient death from noncancer causes, which would preclude an analysis of the intervention. Thus, because the outcomes of prostate cancer patients are generally favorable, it is unlikely that we could detect a difference between MHS users and nonusers if such a difference existed.

Similarly, in terms of toxicities, the rate of grade 3–4 genitourinary and gastrointestinal toxicity has typically been ~5% in randomized trials (9), which has been attributed to the use of IMRT (9, 10). Thus, it is unlikely that we would be able to detect a difference in rates of toxicities between MHS user and nonusers (Tables 3 and 4). In summary, the data presented in this study underscore the likely inability of MHSs to improve the outcomes or toxicities of prostate cancer patients.

We did not perform chemical tests to assess for MHS contents. Therefore, we do not know the exact doses or amounts of the ingredients; nonetheless, many of the MHSs that were included in this analysis did not provide doses on the containers, or they used terms such as trade secret enzyme, which would have precluded a meaningful chemical analysis. We also did not have data on the duration of use, frequency of use, or the dose of the MHSs taken. In addition, we did not screen for potential systemic toxicities of MHSs. Supplements, including those that are aimed at men's health, are the leading cause of acute liver injury in the United States (44); we may have missed such toxicities if they occurred. We also did not have detailed family histories regarding cancer on all patients.

In conclusion, in this study, 2207 patients were treated with IMRT for prostate cancer at an NCI-designated comprehensive cancer center; 10% of these patients used MHSs. MHSs mostly commonly contained saw palmetto although their ingredients were heterogeneous. The use of MHSs is not associated with outcomes or toxicities of prostate cancer patients receiving

IMRT. Although there is an association between MHS use and improved OS, this association is attenuated after adjustment for patient lifestyle factors and comorbidities.

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