Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2012 May 1; 83(1): 28–32. doi:10.1016/j.ijrobp.2011.05.032.

Beta-Carotene Antioxidant Use During Radiation Therapy and Prostate Cancer Outcome in the Physicians' Health Study

Danielle N. Margalit, MD MPH, **Julie L. Kasperzyk, ScD**, **Neil E. Martin, MD MPH**, **Howard D. Sesso, ScD MPH**, **J. Michael Gaziano, MD MPH**, **Jing Ma, MD PhD**, **Meir J. Stampfer, MD DrPH**, and **Lorelei A. Mucci, ScD MPH**

Harvard Radiation Oncology Program, Boston, MA (DNM); Channing Laboratory, Department of Medicine (JM, MJS, LAM, JLK), Division of Aging (JMG), Division of Preventive Medicine (HDS, JMG), and Department of Radiation Oncology (NEM, DNM), Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA; VA Boston Healthcare System, Boston, MA (JMG); Department of Epidemiology, Harvard School of Public Health, Boston, MA (JLK, DNM, LAM, MJS)

Abstract

Purpose—The safety of antioxidant supplements during radiation therapy (RT) for cancer is controversial. Antioxidants could potentially counteract the pro-oxidant effects of RT and compromise therapeutic efficacy. We performed a prospective study nested within the Physicians' Health Study (PHS) randomized trial to determine if supplemental antioxidant use during RT for prostate cancer is associated with an increased risk of prostate cancer death or metastases.

Methods and Materials—383 PHS participants received RT for prostate cancer while randomized to beta-carotene (50 mg on alternate days), or placebo. The primary endpoint was time from RT to lethal prostate cancer, defined as prostate cancer death or bone metastases. The Kaplan-Meier method was used to estimate survival probabilities, and the log-rank test to compare groups. Cox proportional hazards regression was used to estimate the effect of beta-carotene compared with placebo during RT.

Results—With a median follow-up of 10.5 years, there was no significant difference in risk of lethal prostate cancer with use of beta-carotene during RT compared with placebo (HR=0.72; 95% CI, 0.42 to 1.24; P=0.24). After adjusting for age at RT, PSA, Gleason score, and clinical stage, the difference remained non-significant. The 10-year freedom from lethal prostate cancer was 92% (95% CI, 87-95%) in the beta-carotene group and 89% (95% CI, 84-93%) in the placebo group.

CORRESPONDING AUTHOR: Danielle N. Margalit MD MPH, Harvard Radiation Oncology Program, Department of Radiation Oncology, Brigham & Women's Hospital/Dana Farber Cancer Institute, 75 Francis Street, LL-2, Boston, MA 02115, Tel. (617) 732-6310, fax (617) 264-5242, dmargalit@partners.org.

CONFLICTS OF INTEREST NOTIFICATION: All authors state that there are no conflicts of interest or disclosures relevant to this original report. HDS would like to report that in the past five years, he received investigator-initiated research funding as Principal Investigator from multiple not-for-profit entities including the National Institutes of Health, the American Heart Association, the American Cancer Society, the California Strawberry Commission, and the Tomato Products Wellness Council. HDS received in the past five years investigator-initiated research funding as PI from for-profit entities including Roche Vitamins, Inc (now DSM Pharmaceuticals) and Cambridge Theranostics, Ltd. HDS served as a Consultant to Iovate Health Sciences USA, Inc.

Conclusion—Use of the supplemental antioxidant, beta-carotene, during RT was not associated with an increased risk of prostate cancer death or metastases. This study suggests a lack of harm from supplemental beta-carotene during radiation therapy for prostate cancer.

Keywords

Antioxidants; prostate cancer; vitamins; beta-carotene; outcomes

Introduction

Many cancer patients use supplemental vitamins and antioxidants (1, 2), but the safety of such supplements during cancer therapy is controversial (3-7). Both radiation therapy and many chemotherapeutic drugs rely on pro-oxidant effects on DNA as a key mechanism to induce tumor cell death. Supplemental antioxidants such as beta-carotene, vitamin E, vitamin C, and selenium may potentially attenuate the oxidizing effect of radiation therapy and decrease treatment efficacy, thereby leading to cancer recurrence.

Several in vitro studies demonstrate the ability of antioxidants to promote resistance to radiotherapy (8-10). Moreover, clinical studies demonstrate that supplemental antioxidants can lessen radiation side effects such as mucositis and skin fibrosis (11-13), consistent with the theory that antioxidants provide radioprotection to normal tissues. Fewer clinical studies have attempted to assess a decrement in tumor control with use of supplemental antioxidants during radiation therapy. The largest study assessed the association between antioxidant use and risk of a second primary cancer in 540 head and neck cancer patients randomized to placebo or vitamin E and beta-carotene during radiation. The antioxidant arm had decreased toxicities from therapy compared to placebo, but experienced a non-significant increase in local recurrences (11).

We therefore performed a prospective study of randomized Physicians' Health Study participants who received radiation therapy for prostate cancer while randomly allocated to either placebo or beta-carotene. We tested the hypothesis that use of the dietary antioxidant, beta-carotene, during radiation therapy is associated with the risk of prostate cancer death or metastases.

Methods and Materials

Study Population

The study population comprised a cohort of men treated with radiation therapy for prostate cancer while enrolled in the Physicians' Health Study (14-16) and randomized to either beta-carotene or placebo, from 1982 – 2003. The Physicians' Health Study (PHS) I was a randomized double-blind, factorial trial testing aspirin and beta-carotene (50 mg on alternate days) in the primary prevention of cardiovascular disease and cancer among 22,071 men ages 40-84 at baseline in 1982, and free from diagnosed cancer at enrollment. The original trial showed that after a mean of 12 years of treatment and follow-up, beta-carotene was not associated with total cancer or prostate cancer incidence (14). At the completion of PHS I, 7,641 participants entered the PHS II and maintained their original beta-carotene randomization assignment. An additional 7,000 new participants were enrolled into PHS II, a randomized double-blind, placebo-controlled factorial trial testing the effect of beta-carotene, vitamin E, vitamin C, and multivitamin-use on the incidence of cardiovascular disease and cancer. The beta-carotene arm of PHS II was continued until 2003. Participants were asked not to take additional supplements containing more than 100% of the recommended daily allowance of beta-carotene, or vitamin A, for the duration of PHS I and II.

Participants were followed with yearly questionnaires and postcards at 6 month intervals to ascertain endpoints, including prostate cancer. When a participant reported a diagnosis of cancer, we requested hospital records and pathology reports. Study physicians verified all reports of prostate cancer by the participants and reviewed medical records and pathology reports to determine the Gleason score, grade, stage, and prostate specific antigen (PSA) at diagnosis. Clinical stage was reported according to the TNM staging system. Participants continue to be followed for prostate cancer outcomes; this analysis includes follow-up through March 2009. For this study, we excluded participants with prostatectomy prior to radiation therapy or who had metastatic disease at the time of radiation therapy. This study was approved by the Institutional Review Board of Brigham and Women's Hospital and Harvard School of Public Health, Boston, MA.

The primary exposure was use of beta-carotene versus placebo at the time of radiation therapy, as determined by randomization in the PHS trial. The date of radiation therapy initiation, and type of radiation (external beam, brachytherapy, or both) was ascertained by self-report and medical records, where possible. Among these physician participants, such self-reports were highly accurate.

Long-term compliance with beta-carotene and placebo was high during PHS I. At the end of the PHS I trial, 80% of participants in both the beta-carotene group and the placebo group were still taking the study pills. In addition, 6% of participants in the placebo group reported taking supplemental beta-carotene or Vitamin A. In a subset of PHS participants in the Boston area, we conducted unannounced visits to study participants' offices to draw blood for beta-carotene assays, and found a significant correlation with participant reported compliance ($r=0.69$, $P<0.001$) (14).

Endpoints

The primary endpoint was time from radiation therapy initiation to lethal prostate cancer, defined as the date of death from prostate cancer or participant-reported bone metastases among living participants. The endpoint was chosen because of its clinical relevance and because it was unlikely to be subject to misclassification. Cases were censored at the date of last follow-up or death from another cause. Deaths were verified by death certificates and cause of death assigned after review of death certificates, medical records, and information from the family. Metastases were verified with medical records. Follow-up for mortality was 99% complete for the PHS cohort.

Statistical Analysis

We evaluated clinical characteristics to characterize the population, describing continuous variables as medians, and comparing them using the Wilcoxon rank-sum test. Differences in frequencies of categorical variables were compared using the Fisher's Exact test. We used the Kaplan Meier method to estimate survival probabilities and the Mantel-Haenszel log-rank test to compare groups. Cox proportional hazards regression was used to estimate crude and adjusted hazard ratios and 95% confidence intervals among those who received radiation therapy while randomized to beta-carotene, compared with those who received radiation therapy while randomized to placebo. Prior to analysis, we planned to adjust for age at treatment (continuous), Gleason score (treated as an ordinal categorical variable with categories of Gleason 2-6, Gleason 7, and Gleason 8-10), PSA at diagnosis (continuous), and clinical T-stage (treated as a binary variable of T1/2 or T3/T4N1). A missing data indicator was used for missing PSA, Gleason score, and T-stage values. The proportional hazards assumption was verified graphically using the log -log survival curves and statistically using Schoenfeld residuals. Tests of interaction incorporated both the multiplicative interaction term and main effects in the multivariate model. Significant

heterogeneity was determined using the Wald test. The statistical analysis was conducted using SAS version 9 (SAS Institute, Cary, NC), and P<.05 (two-sided) was considered statistically significant.

Results

Participant Characteristics

Table 1 shows the characteristics of the 383 participants who received radiation therapy for prostate cancer while randomized to either placebo (N=191) or beta-carotene (N=192). The median age at diagnosis and treatment was 73 years of age. Groups had similar characteristics except for the distribution of low grade Gleason score; the beta-carotene group had a higher proportion of participants with Gleason score ≤6 than the placebo group.

We investigated the association of beta-carotene with Gleason score and clinical stage among all participants in PHS who were diagnosed with prostate cancer (N=1,734; supplementary Table e1, www.redjournal.org) while randomized to beta-carotene or placebo, regardless of initial therapy. In this larger cohort of participants, clinical variables were evenly distributed between the beta-carotene and placebo groups. With a median follow-up of 13.9 years for living participants (range 6.9-27.2), beta-carotene use was not associated with prostate cancer death or metastases in this larger cohort (HR 1.01; 95% CI 0.81 -1.27).

Primary Outcome

During a median follow-up of 10.5 years, we confirmed 53 primary events (Table 2), including 45 deaths from prostate cancer and 8 cases of metastatic disease among living participants, and 119 deaths from other causes. Figure 1 shows the Kaplan Meier survival probability plots. We found no significant difference in the primary endpoint of time to lethal prostate cancer between participants who received beta-carotene and those that received placebo during radiation therapy (HR 0.72, 95% CI 0.42-1.24). After adjusting for age at treatment, Gleason score, PSA, and clinical stage, the results were similar, though with wider confidence intervals (HR 0.85, 95% CI 0.49-1.50). Gleason score, PSA at diagnosis, and clinical stage were significant independent predictors of lethal prostate cancer (Table 3). The hazard ratio changed minimally when radiation modality (external beam, brachytherapy, and both) was added to the multivariate model (HR 0.76, 95% CI 0.43-1.35) since radiation modality was evenly distributed between groups.

To examine whether antioxidant use during other treatment modalities was associated with the subsequent risk of lethal prostate cancer, we compared the results for radiation therapy with findings among men treated with prostatectomy (n=690). Men treated with prostatectomy (supplementary Table e2, www.redjournal.org) tended to be younger than those treated with radiation therapy, with a median age of 65.6 years, and clinical characteristics were well balanced by treatment assignment. During a median follow-up of 14.8 years, we ascertained 17 lethal cases in the placebo arm and 35 in the beta-carotene arm, (HR 1.92; 95% CI 1.08-3.43, P=0.03). However, after adjustment for age at diagnosis, Gleason score, clinical stage, and PSA at diagnosis, we no longer observed a significant difference in lethal prostate cancer between the beta-carotene and placebo groups among prostatectomy-treated participants (HR 1.54; 95% CI 0.86-2.78; P=0.15).

Effect Modification

We hypothesized that the effect of beta-carotene use during radiation may differ by type of radiation therapy. The antioxidant effect of beta-carotene may attenuate the effect of external beam radiation more than brachytherapy, which delivers a higher effective dose to

the prostate gland. The effect of beta-carotene use during radiation did not differ significantly between external beam radiation therapy or brachytherapy ($P_{interaction}$=0.52), but we had inadequate statistical power to detect a small to moderate interaction.

Discussion

Despite several decades of preclinical and clinical research, there is still no consensus regarding the safety of supplementary antioxidant use during radiation therapy. In a prospective study, we found no significant difference in lethal outcomes among 383 PHS participants who received radiation therapy for prostate cancer while randomized to the antioxidant, beta-carotene, or placebo (HR=0.72; 95% CI, 0.42 to 1.24; P=0.24). Antioxidants have been extensively studied for chemoprevention of prostate cancer with the primary rationale of reducing oxidative DNA damage. Three large, randomized, double-blind, placebo-controlled trials, including the Physicians' Health Study, the Beta-Carotene and Retinol Efficacy Trial (CARET), and the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study (ATBC), showed no significant association of beta-carotene with cancer incidence (14, 17, 18). Both the ATBC and CARET trials, conducted among smokers, demonstrated an increased risk of incident lung cancer in the beta-carotene arms compared to placebo. Frequent explanations for this positive association between beta-carotene and incident lung cancer among smokers include: (1) beta-carotene may act as a pro-oxidant in oxygen-rich environments (19, 20) and (2) antioxidants may promote survival of cells that have already acquired malignant characteristics (9).

Far fewer studies have assessed the impact of antioxidants during radiation therapy to address the potential interaction between antioxidant supplements and pro-oxidant therapy. The most rigorous study (11) was a randomized double-blind placebo-controlled trial of α-tocopherol (400 IU daily) and beta-carotene (30 mg daily) versus placebo in head and neck cancer patients. The primary outcome was incidence of second malignancies after radiation therapy. The study showed a nonsignificant increase in cancer recurrence among patients treated with radiation and supplemental antioxidants (HR, 1.37; 95% CI 0.93 to 2.02) (11). However, this risk was limited to the 164 patients that smoked during radiation therapy (HR 2.41; 95% CI 1.25-4.64). Antioxidant use among the 370 non-smokers was not associated with the risk of recurrence (HR 1.07; 95% CI 0.68-1.68) (21).

What factors may account for the lack of harm seen in our study when participants received radiotherapy while randomized to beta-carotene or placebo? In order to attenuate the effect of free-radicals induced by radiation, a sufficient antioxidant concentration in the prostate tissue would be required to scavenge a large proportion of the free radicals generated by ionizing radiation. The mean concentration of beta-carotene in non-malignant prostate tissue ranges from 0.24-0.48 nanomoles per gram (22, 23) and is estimated to be slightly higher in malignant tissue (22). The supraphysiologic concentration of reactive oxygen species generated by therapeutic radiation may greatly exceed the tissue concentration of beta-carotene, limiting the ability of beta-carotene to attenuate the radiation effect. In vitro studies typically use micromolar or millimolar concentrations of antioxidants to demonstrate a radioprotective effect. Such concentrations are unlikely to be achieved *in vivo*.

The tumor microenvironment may also influence the biologic effect of antioxidants. Beta-carotene acts as a pro-oxidant at elevated partial pressures of oxygen (19). Varying degrees of tumor hypoxia both within a tumor and between different tumor types (eg. head and neck cancer compared to prostate cancer) may alter the antioxidant properties of beta-carotene, and its effectiveness in scavenging free radicals.

The study has several strengths including the randomized exposure status, large sample size, duration of follow-up, and use of lethal outcomes as the endpoint. Furthermore, we demonstrated good compliance with beta-carotene use. We could not exclude the possibility that participants temporarily discontinued the study supplement during the course of radiation therapy. The double-blind design of the PHS also prevents bias that would occur due to differential care or follow-up in the antioxidant arm. This study provides the largest study to date examining the effect of concurrent antioxidant use with radiation on cancer mortality as the primary outcome. The long follow-up and complete endpoint ascertainment are particularly important in the study of prostate cancer with its long natural history.

Several limitations should be noted. We lack detailed information on the participants' dietary sources of antioxidants, use of concurrent androgen deprivation therapy, and rate of local tumor recurrence. Therefore, we were unable to study the association between antioxidant use and local tumor recurrence after radiation therapy. Many study participants were treated in the pre-PSA era, or did not report PSA-failure despite verified prostate cancer specific death, limiting our ability to reliably assess biochemical failure as an endpoint. The use of salvage hormonal therapy and details regarding radiation dose and technique was not consistently ascertained by the follow-up questionnaires and therefore we were not able to assess these clinical variables. It is conceivable that if there were differences in clinical variables such radiation dose and technique, or use of definitive or salvage hormonal therapy, that this may result in bias. However, since this study was nested within a randomized trial, such clinical variables are likely to be similarly distributed between the placebo and beta-carotene groups.

We recognize that the results of this study may not be generalizable to all tumors types treated with radiation therapy. Different tissues may have variable levels of antioxidants, tumor hypoxia, and other factors which may influence the interaction between antioxidants and radiation therapy. Other commonly used dietary antioxidants, such as vitamin E and vitamin C, deserve further study to determine their safety with concurrent radiation therapy.

In summary, our data show that the use of supplemental beta-carotene during radiation therapy, at doses commonly found in nutritional supplements, is not associated with the risk of prostate cancer death or metastases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the dedicated participation among the men in the Physicians' Health Study. We thank Hannah Mandel for her work as a research assistant.

FUNDING: This work was supported by the National Institutes of Health (T32 CA09001 to DNM and JLK, Principal Investigator MJS; American Institute for Cancer Research to JLK; CA-34944, CA-40360, CA-097193, HL-26490, and HL-34595 for the Physicians' Health Study); study agents and packaging were provided in part by BASF Corporation (Florham Park, NJ), Wyeth Pharmaceuticals (Madison, NJ), and DSM Nutritional Products, Inc. (formerly Roche Vitamins) (Parsippany, NJ); and the Prostate Cancer Foundation (LAM).

References

1. Velicer CM, Ulrich CM. Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. J Clin Oncol. 2008; 26:665–673. [PubMed: 18235127]
2. Ladas EJ, Jacobson JS, Kennedy DD, et al. Antioxidants and cancer therapy: a systematic review. J Clin Oncol. 2004; 22:517–528. [PubMed: 14752075]

3. Lawenda BD, Kelly KM, Ladas EJ, et al. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? J Natl Cancer Inst. 2008; 100:773–783. [PubMed: 18505970]
4. Simone CB 2nd, Simone NL, Simone V, et al. Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, part 1. Altern Ther Health Med. 2007; 13:22–28. [PubMed: 17283738]
5. Weiger WA, Smith M, Boon H, et al. Advising patients who seek complementary and alternative medical therapies for cancer. Ann Intern Med. 2002; 137:889–903. [PubMed: 12458989]
6. Seifried HE, McDonald SS, Anderson DE, et al. The antioxidant conundrum in cancer. Cancer Res. 2003; 63:4295–4298. [PubMed: 12907593]
7. D'Andrea GM. Use of antioxidants during chemotherapy and radiotherapy should be avoided. CA Cancer J Clin. 2005; 55:319–321. [PubMed: 16166076]
8. Diehn M, Cho RW, Lobo NA, et al. Association of reactive oxygen species levels and radioresistance in cancer stem cells. Nature. 2009; 458:780–783. [PubMed: 19194462]
9. Schafer ZT, Grassian AR, Song L, et al. Antioxidant and oncogene rescue of metabolic defects caused by loss of matrix attachment. Nature. 2009; 461:109–113. [PubMed: 19693011]
10. Samuni AM, DeGraff W, Cook JA, et al. The effects of antioxidants on radiation-induced apoptosis pathways in TK6 cells. Free Radic Biol Med. 2004; 37:1648–1655. [PubMed: 15477016]
11. Bairati I, Meyer F, Gelinas M, et al. Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. J Clin Oncol. 2005; 23:5805–5813. [PubMed: 16027437]
12. Ferreira PR, Fleck JF, Diehl A, et al. Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucositis: a double-blind randomized trial. Head Neck. 2004; 26:313–321. [PubMed: 15054734]
13. Mills EE. The modifying effect of beta-carotene on radiation and chemotherapy induced oral mucositis. Br J Cancer. 1988; 57:416–417. [PubMed: 3390377]
14. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med. 1996; 334:1145–1149. [PubMed: 8602179]
15. Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II--a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. Ann Epidemiol. 2000; 10:125–134. [PubMed: 10691066]
16. Gaziano JM, Glynn RJ, Christen WG, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2009; 301:52–62. [PubMed: 19066368]
17. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med. 1996; 334:1150–1155. [PubMed: 8602180]
18. The effect of vitamin beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med. 1994; 330:1029–1035. [PubMed: 8127329]
19. Burton GW, Ingold KU. beta-Carotene: an unusual type of lipid antioxidant. Science. 1984; 224:569–573. [PubMed: 6710156]
20. Schwartz JL. The dual roles of nutrients as antioxidants and prooxidants: their effects on tumor cell growth. J Nutr. 1996; 126:1221S–1227S. [PubMed: 8642460]
21. Meyer F, Bairati I, Fortin A, et al. Interaction between antioxidant vitamin supplementation and cigarette smoking during radiation therapy in relation to long-term effects on recurrence and mortality: a randomized trial among head and neck cancer patients. Int J Cancer. 2008; 122:1679–1683. [PubMed: 18059031]
22. Clinton SK, Emenhiser C, Schwartz SJ, et al. cis-trans lycopene isomers, carotenoids, and retinol in the human prostate. Cancer Epidemiol Biomarkers Prev. 1996; 5:823–833. [PubMed: 8896894]

23. Freeman VL, Meydani M, Yong S, et al. Prostatic levels of tocopherols, carotenoids, and retinol in relation to plasma levels and self-reported usual dietary intake. Am J Epidemiol. 2000; 151:109–118. [PubMed: 10645812]

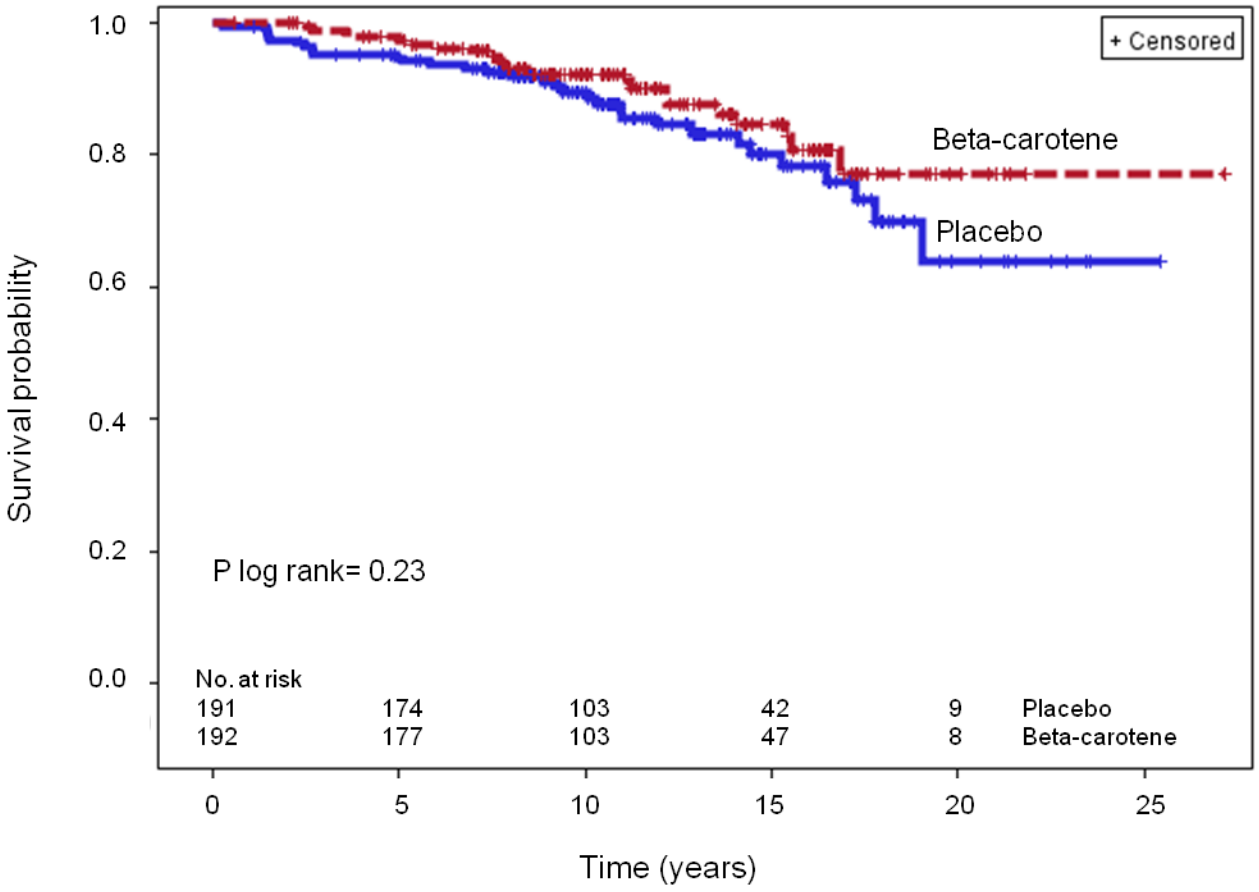

FIGURE 1.
Freedom from lethal prostate cancer, Physicians' Health Study, 1982-2010.

Table 1

Participant characteristics.*

Characteristic	Placebo (N=191)	Beta-carotene (N=192)	P
Age at diagnosis - yrs			
Median [IQR]	73 [69,76]	73 [68, 76]	0.90
Age at treatment - yrs			
Median [IQR]	73 [69, 76]	73 [68, 76]	0.82
Gleason Score – no (%)			0.08
2-6	105 (55)	128 (67)	
7	52 (27)	42 (22)	
8-10	31 (16)	21 (11)	
Missing	3 (2)	1 (1)	
Clinical Stage – no (%)			0.86
T1/2	163 (85)	169 (88)	
T3	15 (8)	13 (7)	
T4 or N1	5 (3)	6 (3)	
Missing	8 (4)	4 (2)	
PSA – ng/ml			
Median [IQR]	8.2 [5.5, 15.8]	7.1 [5.6, 13.0]	0.29
Missing (%)	46 (24)	40 (21)	
Radiation Type – no (%)			0.73
External beam	129 (68)	133 (69)	
Brachytherapy	39 (20)	40 (21)	
Both	21 (11)	16 (8)	
Unknown/missing	2 (1)	3 (2)	

* Percentages may not total 100 because of rounding.

Table 2

Events in the study cohort at a median follow-up of 10.5 years (range 0.3-27.2) for all participants and 10.5 years (range 7.0-27.2) for living participants.

Event	Placebo (N=191)	Beta-carotene (N=192)
	no. of events	
Primary endpoint *	31	22
Bone Metastases	6	2
Prostate cancer death	25	20
Non-prostate cancer death	63	56

* The primary endpoint is defined as prostate cancer death or metastases.

Table 3

Predictors of lethal prostate cancer among 383 participants treated with radiation therapy for prostate cancer during the Physicians' Health Study.

Variable	Referent	HR	95% CI	P
Univariate				
Beta-carotene	*Placebo*	0.72	0.42-1.24	0.24
Multivariate Model				
Beta-carotene	P*lacebo*	0.85	0.49-1.50	0.58
Age at treatment	*Per year increase*	1.06	1.01 -1.11	0.03
Gleason Score (GS)	*GS 8-10 v. GS 7 v. GS 2-6*	2.67	1.89-3.77	<0.001
PSA at Diagnosis	*Per unit PSA increase*	1.02	1.01-1.03	0.003
Clinical Stage	*T3/4 or N1 v. T1/2*	3.09	1.63-5.85	<0.001