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ORIGINAL REPORT

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Wen-Qing Li, Abrar A. Qureshi, Jing Ma, Alisa M. Goldstein, Edward L. Giovannucci, Meir J. Stampfer, and Jiali Han

Wen-Qing Li and Alisa M. Goldstein, National Cancer Institute, National Institutes of Health, Rockville, MD; Wen-Qing Li, Abrar A. Qureshi, Jing Ma, Edward L. Giovannucci, Meir J. Stampfer, and Jiali Han, Brigham and Women's Hospital, Harvard Medical School; Edward L. Giovannucci and Meir J. Stampfer, Harvard School of Public Health, Boston, MA; Jiali Han, Richard M. Fairbanks School of Public Health, Simon Cancer Center, Indiana University, Indianapolis, IN; and Jiali Han, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China.

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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Corresponding author: Jiali Han, PhD, 181 Longwood Ave, Boston, MA 02115; e-mail: jiali.han@channing.harvard.edu.

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ABSTRACT

Purpose
Steroid hormones, particularly androgens, play a major role in prostatic carcinogenesis. Personal history of severe acne, a surrogate for higher androgen activity, has been associated with an increased risk of prostate cancer (PCa), and one recent study indicated that severe teenage acne was a novel risk factor for melanoma. These findings suggest a possible relationship between PCa and risk of melanoma. We prospectively evaluated this association among US men.

Methods
A total of 42,372 participants in the Health Professionals' Follow-Up Study (HPFS; 1986 to 2010) were included. Biennially self-reported PCa diagnosis was confirmed using pathology reports. Diagnosis of melanoma and nonmelanoma skin cancer (NMSC) was self-reported biennially, and diagnosis of melanoma was pathologically confirmed. We sought to confirm the association in 18,603 participants from the Physicians' Health Study (PHS; 1982 to 1998).

Results
We identified 539 melanomas in the HPFS. Personal history of PCa was associated with an increased risk of melanoma (multivariate-adjusted hazard ratio [HR], 1.83; 95% CI, 1.32 to 2.54). Although we also detected a marginally increased risk of NMSC associated with PCa (HR, 1.08; 95% CI, 0.995 to 1.16), the difference in the magnitude of the association between melanoma and NMSC was significant (P for heterogeneity = .002). We did not find an altered risk of melanoma associated with personal history of other cancers. The association between PCa and risk of incident melanoma was confirmed in the PHS (HR, 2.17; 95% CI, 1.12 to 4.21).

Conclusion
Personal history of PCa is associated with an increased risk of melanoma, which may not be entirely a result of greater medical scrutiny.

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INTRODUCTION

With advances in cancer survival, second and higher order malignancies compose approximately 18% of incident cancers in the United States, bringing new challenges for cancer control.[1] Prostate cancer (PCa) is the most common noncutaneous cancer in the United States.[2] Steroid hormones, particularly androgens, are implicated in prostatic carcinogenesis, and androgen deprivation therapy has been a mainstay of PCa treatment.[3-6] Acne is a chronic inflammatory disease with androgen-induced sebum production as a major contributing factor.[7] Personal history of severe acne, measured by self-reported tetracycline use for ≥ 4 years, has been associated with an increased risk of PCa, and elevated androgens associated with acne might contribute to this association.[8] Melanoma is another health concern that has long been hypothesized to be androgen dependent.[2,9,10] In our recent analysis, those with severe teenage acne were more likely to have moles and a higher circulating level of free testosterone, and severe teenage acne was associated with an increased melanoma risk (Zhang et al, submitted for publication). These observations suggest a commonality of androgens in both PCa and melanoma etiology.

We hypothesize that men with PCa may have an increased risk of subsequent melanoma, and we prospectively examined this association in 42,372 participants in the Health Professionals' Follow-Up Study (HPFS; 1986 to 2010). To address the potential effects of increased medical surveillance among participants with a history of cancer, we evaluated the risk of nonmelanoma skin cancer (NMSC) and other nonskin cancers by personal history of PCa, as well as risk of melanoma by personal history of nonskin cancers other than PCa. We confirmed

the association between personal history of PCa and melanoma in 18,603 participants from an independent cohort, the Physicians' Health Study (PHS; 1982 to 1998) cohort. Previous reports on the link between different cancers were not hypothesis driven and were largely based on retrospective cancer registry data without adjustment for potential confounders.[11,12]

METHODS

Study Population

The HPFS was initiated in 1986, when 51,529 US male health professionals age 40 to 75 years completed a questionnaire on medical history and lifestyle practices.[13] Participants received a questionnaire biennially, and a follow-up rate exceeding 90% has been achieved. The PHS is a randomized, double-blind, placebo-controlled trial for the prevention of cancer and cardiovascular disease.[14] It was initiated in 1982 among 22,071 male physicians age 40 to 84 years, and participants were observed annually.[14]

The cohorts were approved by the Human Research Committee at Brigham and Women's Hospital and Harvard School of Public Health. Participants' completion and return of the questionnaire was considered informed consent.

Assessment of Main Exposure

In the HPFS, participants have reported diagnoses of PCa biennially since 1986. Approximately 90% of self-reported cases of PCa were confirmed by review of medical records and pathology reports. The remaining 10%, based on self-reports or death certificates, were included because the reporting was highly accurate ($> 98\%$). Deaths are recorded through reports from family members and the National Death Index. The causes of death were determined based on medical history, records, registry, and death certificates. Information on progression, metastases, Gleason grade, and primary treatment was ascertained.[15] PCa was classified as advanced (including lethal cases) or nonadvanced (Appendix, online only).[15] We also categorized PCas by Gleason score as high (score, 8 to 10), medium (score, 7), or low grade (score, 2 to 6), based on pathology reports from prostatectomy specimens or biopsies.

In the PHS, PCa diagnoses were identified by annual follow-up. When a diagnosis of PCa was reported, medical records and pathology reports were requested. Study physicians from the end point committee confirmed the self-reported PCa.

Assessment of Outcome

In the HPFS, participants have reported diagnoses of melanoma or NMSC biennially, including squamous cell carcinoma and basal cell carcinoma. When a diagnosis of melanoma was reported, medical records were obtained and reviewed. Patients who denied the diagnosis or withheld permission to review their records were excluded. Only pathologically confirmed invasive melanomas were included. For self-reported NMSC that developed among patients with other cancers, we did not request all medical records, but previous studies have indicated that self-reports are highly reliable.[16-18]

In the PHS, participants have reported diagnoses of melanoma routinely during follow-up. Self-reported melanomas were confirmed based on medical records and pathology reports.

Statistical Analysis

In the HPFS, 51,430 men provided information on date of birth. We excluded participants reporting a diagnosis of cancer other than PCa at baseline (including NMSC; $n = 6{,}013$), cancers with unknown diagnosis date ($n = 81$), PCas that were not confirmed ($n = 252$), and T1a PCas that were discovered incidentally during treatment for benign prostatic hypertrophy ($n = 254$). After excluding nonwhite participants ($n = 2{,}458$), 42,372 participants remained at baseline.

Person-years of follow-up were calculated from the date of the return of the 1986 questionnaire to the date of melanoma diagnosis, death, last questionnaire response, or end of follow-up (January 2010), whichever came first. Cancer diagnoses other than PCa occurring during the follow-up were excluded for the analyses of the next follow-up periods so that they only contributed to the person-years before cancer diagnoses. We calculated the hazard ratios (HRs) and 95% CIs using Cox proportional hazards regression analysis stratified by age and 2-year interval, adjusting for the following factors: body mass index (BMI); smoking; alcohol intake; physical activity; childhood reaction to sun; ever use of sildenafil citrate; number of sunburns; mole count; hair color; family history of melanoma; sun exposures at high school and at age 25 to 35, 36 to 59, and ≥ 60 years; and UV index at birth, age 15, and age 30 years. An indicator was created for the missing data of each covariate. Secondarily, we adjusted for midrange UV radiation (UVB flux) as a quantitative measure of sun exposure instead of UV index.[19] Assessment and inclusion criteria of covariates are provided in the Appendix. Information on cancers and the covariates was updated in 2-year questionnaire cycles. In the primary analysis, we did not adjust for history of severe acne, which was assessed in 1992 by self-reported tetracycline use for ≥ 4 years.[8] We considered this variable as a covariate in a sensitivity analysis.

In secondary analyses, we performed a lag analysis in which PCa diagnosis occurring at least 2 years before melanoma served as the exposure. We examined melanoma risk associated with a diagnosis of PCa stratified by the presence of moles. We performed analyses by PCa subtypes, median diagnosis age ($\leq$ or $>$ 68 years), and primary treatment (radical prostatectomy, external-beam radiation or brachytherapy, hormones, or watchful waiting and others). Tests of heterogeneity were conducted to evaluate the differences in the association across subtypes.

We conducted several analyses to address the concern that elevated risk of second cancer was a result of increased medical scrutiny among patients with first primary cancers. First, we evaluated the association between personal history of PCa and risk of incident NMSC. Heterogeneity tests were used to examine the difference in magnitude of the associations for melanoma and NMSC. Second, we examined the risk of other major nonskin cancers associated with personal history of PCa, adjusting for age, BMI, smoking, alcohol intake, physical activity, and UV index. Third, we evaluated the association between personal history of total nonskin cancers other than PCa as well as major individual cancers and melanoma risk, adjusting for the same covariates in the primary analyses. Exclusion criteria of participants were modified for these analyses. For example, when evaluating the association between history of colorectal cancer and risk of melanoma, we excluded participants with self-reported diagnosis of cancer other than colorectal cancer at baseline. To test a possible bidirectional relationship between PCa and melanoma, we evaluated the association between personal history of melanoma and risk of PCa.

We sought to confirm the association between personal history of PCa and melanoma risk in the PHS; 18,603 participants were included using the same exclusion criteria as in HPFS. The participants were followed to December 1998 (the end of the PHS I). We used Cox regression analysis adjusting for age, BMI, smoking, alcohol intake, and physical activity. We combined the results in two cohorts to estimate the overall association. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

We show characteristics of the HPFS participants by personal history of PCa during the follow-up (Table 1) and at the midpoint (1998; Appendix Table A1, online only). Participants with PCa were older and tended to report ever-use of sildenafil citrate for erectile dysfunction. During 747,176 person-years, we documented 5,091 PCas and 539 melanomas. Personal history of PCa was significantly associated with an increased risk of melanoma; the HR was 1.83 (95% CI, 1.32 to 2.54; Table 2). The HRs for the covariates are listed in Appendix Table A2 (online only). Adjusting for UVB flux did not materially change the results (Appendix Table A3, online only).

In the secondary analyses (HPFS), the lag analysis did not materially alter the findings (HR, 1.54; 95% CI, 1.03 to 2.29). Additionally,

Table 1. Characteristics of the Study Population According to Personal History of Prostate Cancer During Follow-Up: Health Professionals' Follow-Up Study

Characteristic	History of Prostate Cancer	
	No	Yes
Age, years		
Mean	60.8	72.6
SD	10.5	7.9
Body mass index, kg/m^2		
Mean	26.1	26.0
SD	3.8	3.4
Physical activity, metabolic equivalent hours per week		
Mean	34.7	37.1
SD	40.2	39.5
Current smoking, %	7.6	4.5
Alcohol intake, g/d		
Mean	11.3	11.6
SD	15.0	14.8
Ever-use of sildenafil citrate for erectile dysfunction, %	5.5	24.0
Family history of melanoma, %	3.7	4.7
Burn or blistering skin reaction to the sun, %	67.9	65.3
UV index ≥ 7 of residence, %		
At birth	27.1	31.8
At age 15 years	28.7	33.9
At age 30 years	33.8	31.4
Natural red or blonde hair, %	12.8	15.3
≥ 6 moles on an extremity, ≥ 3 mm in diameter, %	4.8	4.4
History of ≥ 6 severe or blistering sunburns, %	34.2	35.9
Average sun exposure ≥ 11 h/wk, %		
In college/high school	49.6	56.5
At age 25-35 years	31.8	39.4
At age 36-59 years	27.3	31.3
At age ≥ 60 years	26.9	32.3

NOTE. All values other than age were age adjusted.
Abbreviation: SD, standard deviation.

adjusting for severe acne did not alter the association. Mole counts were not significantly associated with risk of PCa (data not shown). We evaluated the association between PCa and melanoma risk by presence of moles and found a borderline significant interaction (*P* for interaction = .08). We examined melanoma risk by PCa subtypes, diagnosis age, and primary treatment and did not observe significant heterogeneity among these categories (Appendix Table A4, online only).

During 692,290 person-years, 11,960 NMSCs were identified. Although patients with PCa had a slightly increased NMSC risk (HR, 1.08; 95% CI, 0.995 to 1.16; Table 2), the magnitude of the association for melanoma and NMSC was significantly different (*P* for heterogeneity = .002).

We performed additional analyses to minimize the concern of detection bias. Personal history of PCa was not significantly associated with risk of other nonskin cancers. For example, the HR associated with personal history of PCa was 1.23 (95% CI, 0.96 to 1.57) for lung cancer and 1.16 (95% CI, 0.82 to 1.63) for colorectal cancer. We did not find significantly altered melanoma risk associated with history of nonskin cancers other than PCa, and few patients with other major individual cancers developed melanoma during follow-up. For example, only three patients with colorectal cancer and no patients with lung cancer were subsequently diagnosed with melanoma. We tested the bidirectional relationship, and personal history of melanoma was not associated with an increased risk of PCa (HR, 0.88; 95% CI, 0.57 to 1.35).

We confirmed the association between a diagnosis of PCa and melanoma risk in the PHS, in which 166 melanomas were identified during 251,850 person-years (HR, 2.17; 95% CI, 1.12 to 4.21; Table 3). Combining the results in two cohorts, the HR for melanoma associated with personal history of PCa was 1.89 (95% CI, 1.41 to 2.54).

DISCUSSION

We prospectively showed that patients with PCa had a significantly increased risk of melanoma, which was confirmed in an independent cohort. The association magnitude was markedly higher than the association between PCa and NMSC. In contrast, we did not observe significant findings for the risk of other noncutaneous cancers associated with PCa, nor did we find an altered risk of melanoma associated with personal history of noncutaneous cancers other than PCa, suggesting that the association between PCa and melanoma risk may not be explained by increased medical surveillance.

PCa develops in an androgen-dependent epithelium and is a well-recognized androgen-related cancer,[3-6] although the relationships between circulating androgens and PCa risk have not been elucidated from epidemiologic studies.[20] Severe acne, a surrogate for androgen activity, has been positively associated with PCa risk.[7,8] Skin is a major target of androgens, and melanoma has been proposed to be associated with androgen levels.[9,10] Melanocytes have the capability to synthesize a potent androgen, 5-dihydrotestosterone, from androgens.[10] Testosterone was shown to increase melanoma cell proliferation.[21] Our group recently showed a significant positive association between severe teenage acne and melanoma risk and an increased circulating level of free testosterone among those with severe teenage acne, indicating a possible role of androgens in melanoma development (Zhang et al, submitted for publication). These results suggest that high androgen levels might contribute to the association between PCa and risk of melanoma.

Androgens may influence melanoma risk by suppressing the host immune response. Blockade of androgen signaling was shown to enhance immune response to melanoma vaccine and improve survival.[22] Androgens could also alter melanoma risk by affecting telomere length. Androgens may play an important role in maintaining telomere stability and replication of telomere DNA.[23,24] Exposure in vitro to androgens was shown to stimulate *TERT* expression and telomerase activity,[25] leading to telomere elongation and melanocyte life span extension. In an epidemiologic study, long telomeres were associated with an increased risk of melanoma.[26]

If imbalanced androgens contribute to the association between personal history of PCa and melanoma risk, they could have played a role in early life. The PCa diagnosis often occurred many years later after the prostatic carcinogenesis process, particularly when prostate-specific antigen screening was not widely adopted. Moreover, severe acne could be a marker of imbalanced androgen level in early life.[7,8]

Table 2. HR of Incident Melanoma and Nonmelanoma Skin Cancer Associated With Personal History of Prostate Cancer: Health Professionals' Follow-Up Study, 1986 to 2010

History of Prostate Cancer	No. of Person-Years	No. of Cancers	Age-Adjusted HR		Multivariate-Adjusted HR*	
			HR	95% CI	HR	95% CI
Melanoma						
No	720,482	495	1.00		1.00	
Yes	26,695	44	1.90	1.37 to 2.63	1.83	1.32 to 2.54
Nonmelanoma skin cancer (SCC and BCC)						
No	667,599	11,247	1.00		1.00	
Yes	24,691	713	1.09	1.00 to 1.17	1.08	0.995 to 1.16

Abbreviations: BCC, basal cell carcinoma; HR, hazard ratio; SCC, squamous cell carcinoma.
*Multivariate-adjusted analyses were performed adjusting for age (continuous variable); body mass index (< 18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, or ≥ 35 kg/m^2); smoking (never-, past, or current smokers); alcohol intake (no, 0.1 to 4.9, 5 to 9.9, 10 to 19.9, or ≥ 20 g/d); physical activity (in quintiles, metabolic equivalent hours per week); ever-use of sildenafil citrate for erectile dysfunction (yes or no); childhood reaction to sun (tan without burn, burn, or painful burn/blisters); number of sunburns (none, one to two, three to five, or ≥ six sunburns); mole count (none, one to two, three to five, or ≥ six moles); hair color (red, blonde, light brown, or dark brown/black); family history of melanoma (yes or no); sun exposures at high school, age 25 to 35, age 36 to 59, and age ≥ 60 years (< 1, 2 to 5, 6 to 10, or ≥ 11 h/wk for each); and UV index at birth, age 15, and age 30 years (≤ 5, 6, or ≥ 7). An indicator variable was created for the missing value of each covariate. *P* for heterogeneity = .002 for the magnitude of associations with melanoma and nonmelanoma skin cancer.

Although the HRs across the diagnosis age categories were not significantly different, we observed a higher HR of melanoma among patients with PCa diagnosed at ≤ age 68 years (median diagnosis age). Although we empirically used the diagnosis of PCa to define the exposure, it is possible that the androgen imbalance in the prostatic carcinogenic process might have acted in initiating and promoting the melanoma development.

There are other overlaps related both to PCa and melanoma. The deficiency in immune response has been implicated in prostatic tumorigenesis, and immunotherapy is a recommended treatment modality for PCa.[27,28] The blockade of cytotoxic T lymphocyte–associated antigen 4 is an established therapy for melanoma and has shown clinical efficacy for PCa.[28,29] Therefore, PCa and a suppressed immune system might contribute to melanoma development. Common genetic variations have also been identified for PCa and melanoma.[30,31]

The shared etiology might suggest a possible bidirectional relationship between PCa and melanoma. However, we did not observe an increased PCa risk associated with melanoma, which raises a possible concern about the impact of PCa treatment in elevating melanoma risk. We observed that the effect estimates were similar across patients with PCa with varied primary treatments, indicating that the association was less likely a treatment effect. However, we did not record updated PCa treatment in detail, which prevented us from extensively examining the effect of each treatment.

The association between PCa and melanoma was unlikely mediated by known host characteristics. We adjusted melanoma risk estimates for mole counts, sun exposure, and other characteristics, which minimally attenuated the effect magnitude. Melanocytic nevi (moles) were recognized as a risk factor for melanoma,[32] and participants with severe teenage acne were more likely to have moles. The association between PCa and melanoma was not found to be mediated by moles. We observed a borderline effect modification by moles, which might further stress the possible role of androgens in melanoma, given our recent finding on the association between severe teenage acne, moles, and circulating levels of free testosterone (Zhang et al, submitted for publication). Additionally, adjusting for tetracycline use for ≥ 4 years as a surrogate for severe acne did not alter the findings.

An increased risk of melanoma among patients with PCa has been reported using cancer registry data.[11,12] One study revealed a slightly increased melanoma risk in patients with PCa age ≥ 45 years using the Surveillance, Epidemiology, and End Results data.[11] A second study in Germany found a 38% increased risk of melanoma among patients with PCa.[12] However, these studies did not have a cancer-free group as a reference and did not have data on keratinocytic neoplasms and other prevalent disorders among the patients with PCa before cancer diagnosis. They were unable to adjust for covariates except for age and calendar time at most. Cancer registry data also tended to under-report melanomas because thin melanoma may be diagnosed in the outpatient setting.[33]

Table 3. HR of Incident Melanoma Associated With Personal History of Prostate Cancer: Physicians' Health Study, 1982 to 1998

History of Prostate Cancer	No. of Person-Years	No. of Melanomas	Age-Adjusted HR		Multivariate-Adjusted HR*	
			HR	95% CI	HR	95% CI
No	246,632	153	1.00		1.00	
Yes	5,219	13	2.18	1.14 to 4.18	2.17	1.12 to 4.21

Abbreviation: HR, hazard ratio.
*Adjusted for age (1-year categories), body mass index (< 18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, or ≥ 35 kg/m^2), smoking (never-, past, or current smokers), alcohol intake (nondrinkers, one to three times a month, one time a week, two to four times a week, five to six times a week, one time a day, or ≥ two times a day), and physical activity (never, one to three times a month, one time a week, two to four times a week, five to six times a week, or daily). An indicator variable was created for the missing value of each covariate.

Our study was strengthened by its prospective design, updated assessment of PCa diagnosis, detailed information on potential confounders, and confirmation of the association in an independent prospective cohort. The follow-up and response rate has been very high (> 90%), which releases the concern of selection bias as a result of participant dropout. We are aware of some limitations. First, detection bias could be a major concern, although melanoma scrutiny is less likely to be greatly affected by a diagnosis of PCa. We carefully addressed the possible increased surveillance among participants with a diagnosis of cancer by using several sets of analyses. It is worth noting that higher free testosterone was associated with both prostate and lung cancer in one report,[5] but our analysis did not lend support to this finding. PCa with advanced or high Gleason grade might be liable to detection bias. However, we did not find heterogeneity of the melanoma risk according to PCa subtypes. Therefore, detection bias was unlikely to explain our findings. Second, a diagnosis of PCa may be associated with some aspects of lifestyle risk factors. Personal characteristics of participants and their doctors might be correlated with the likelihood of detecting subsequent melanomas among patients with PCa. An observational study cannot rule out the possibility of residual confounding by unmeasured or imperfectly measured confounders. Participants with PCa were older and may have had longer lifetime sun exposure, so residual confounding by sun exposure could be possible. However, this would not be a major concern because lifetime cumulative sun exposure was strongly associated with NMSC, which was weakly associated with personal history of PCa. The results remained essentially the same when adjusting for cumulative UVB flux. The PHS did not collect information on the major skin cancer–related risk factors, and hence, we could not adjust for them. Third, study participants were white health professionals. The homogeneity has enhanced the quality of questionnaire response and minimized confounding from socioeconomic factors, but any extrapolation to other ethnic groups or the general population should be approached with caution.

In conclusion, based on two large, well-established, long-term cohorts, we suggest an association between a diagnosis of PCa and risk of subsequent melanoma in white men, which may not be entirely a result of greater medical scrutiny. We postulated a potential role for androgens in the etiology of melanoma, which might contribute to the observed association. Pending biologic investigation, further understanding of the mechanisms that mediate the associations could eventually lead to elucidation of new targets for interventions that may modulate their incidence or activity. For example, it will be interesting to investigate the effects of continuous androgen deprivation for PCa on the risk of melanoma. Our finding of PCa diagnosis as a risk predictor for melanoma holds general public health significance, which may inform clinical practice to address the queries and aid the care of patients with PCa.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Wen-Qing Li, Jiali Han
Collection and assembly of data: Wen-Qing Li, Jiali Han
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Travis LB, Demark Wahnefried W, Allan JM, et al: Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors. Nat Rev Clin Oncol 10:289-301, 2013
2. Siegel R, Naishadham D, Jemal A: Cancer statistics, 2013. CA Cancer J Clin 63:11-30, 2013
3. Bosland MC: The role of steroid hormones in prostate carcinogenesis. J Natl Cancer Inst Monogr 27:39-66, 2000
4. Nguyen PL, Je Y, Schutz FA, et al: Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: A meta-analysis of randomized trials. JAMA 306:2359-2366, 2011
5. Hyde Z, Flicker L, McCaul KA, et al: Associations between testosterone levels and incident prostate, lung, and colorectal cancer: A population-based study. Cancer Epidemiol Biomarkers Prev 21:1319-1329, 2012
6. Gann PH, Hennekens CH, Ma J, et al: Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 88:1118-1126, 1996
7. Williams HC, Dellavalle RP, Garner S: Acne vulgaris. Lancet 379:361-372, 2012
8. Sutcliffe S, Giovannucci E, Isaacs WB, et al: Acne and risk of prostate cancer. Int J Cancer 121:2688-2692, 2007
9. Rampen FH, Mulder JH: Malignant melanoma: An androgen-dependent tumour? Lancet 1:562-564, 1980
10. Slominski A, Tobin DJ, Shibahara S, et al: Melanin pigmentation in mammalian skin and its hormonal regulation. Physiol Rev 84:1155-1228, 2004
11. Yang GB, Barnholtz-Sloan JS, Chen Y, et al: Risk and survival of cutaneous melanoma diagnosed subsequent to a previous cancer. Arch Dermatol 147:1395-1402, 2011
12. Braisch U, Meyer M, Radespiel-Tröger M: Risk of subsequent primary cancer among prostate cancer patients in Bavaria, Germany. Eur J Cancer Prev 21:552-559, 2012
13. Giovannucci E, Rimm EB, Colditz GA, et al: A prospective study of dietary fat and risk of prostate cancer. J Natl Cancer Inst 85:1571-1579, 1993
14. Steering Committee of the Physicians' Health Study Research Group: Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 321:129-135, 1989
15. Wilson KM, Kasperzyk JL, Rider JR, et al: Coffee consumption and prostate cancer risk and progression in the Health Professionals Follow-up Study. J Natl Cancer Inst 103:876-884, 2011
16. Colditz GA, Martin P, Stampfer MJ, et al: Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. Am J Epidemiol 123:894-900, 1986
17. Hunter DJ, Colditz GA, Stampfer MJ, et al: Diet and risk of basal cell carcinoma of the skin in a prospective cohort of women. Ann Epidemiol 2:231-239, 1992
18. van Dam RM, Huang Z, Giovannucci E, et al: Diet and basal cell carcinoma of the skin in a prospective cohort of men. Am J Clin Nutr 71:135-141, 2000
19. Fears TR, Bird CC, Guerry DT 4th, et al: Average midrange ultraviolet radiation flux and time outdoors predict melanoma risk. Cancer Res 62:3992-3996, 2002
20. Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, et al: Endogenous sex hormones and prostate cancer: A collaborative analysis of 18 prospective studies. J Natl Cancer Inst 100:170-183, 2008
21. Allil PA, Visconti MA, Castrucci AM, et al: Photoperiod and testosterone modulate growth and melanogenesis of s91 murine melanoma. Med Chem 4:100-105, 2008
22. Hsueh EC, Gupta RK, Lefor A, et al: Androgen blockade enhances response to melanoma vaccine. J Surg Res 110:393-398, 2003
23. Zhou J, Richardson M, Reddy V, et al: Structural and functional association of androgen receptor with telomeres in prostate cancer cells. Aging (Albany NY) 5:3-17, 2013
24. Kim SH, Richardson M, Chinnakannu K, et al: Androgen receptor interacts with telomeric proteins in prostate cancer cells. J Biol Chem 285:10472-10476, 2010
25. Calado RT, Yewdell WT, Wilkerson KL, et al: Sex hormones, acting on the TERT gene, increase telomerase activity in human primary hematopoietic cells. Blood 114:2236-2243, 2009
26. Nan H, Du M, De Vivo I, et al: Shorter telomeres associate with a reduced risk of melanoma

development. Cancer Res 71:6758-6763, 2011

27. Cha E, Fong L: Immunotherapy for prostate cancer: Biology and therapeutic approaches. J Clin Oncol 29:3677-3685, 2011

28. Kwek SS, Cha E, Fong L: Unmasking the immune recognition of prostate cancer with CTLA4 blockade. Nat Rev Cancer 12:289-297, 2012

29. Wolchok JD, Neyns B, Linette G, et al: Ipilimumab monotherapy in patients with pretreated advanced melanoma: A randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 11:155-164, 2010

30. Palanisamy N, Ateeq B, Kalyana-Sundaram S, et al: Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. Nat Med 16:793-798, 2010

31. Cooper PR, McGuire BB, Helfand BT, et al: Prostate cancer risk alleles and their associations with other malignancies. Urology 78:970.e15–e20, 2011

32. Goldstein AM, Tucker MA: Dysplastic nevi and melanoma. Cancer Epidemiol Biomarkers Prev 22:528-532, 2013

33. Spanogle JP, Clarke CA, Aroner S, et al: Risk of second primary malignancies following cutaneous melanoma diagnosis: A population-based study. J Am Acad Dermatol 62:757-767, 2010

GLOSSARY TERMS

Confounding: Confounding variables are extraneous variables in a statistical model that are associated/correlated with both the independent and dependent variables but are not on the causal pathway between independent and dependent variables. When confounding variables are present, crude (unadjusted) statistical models describing the association between independent and dependent variables are biased (i.e., wrong) as the risk estimate includes the effect of the confounding variable as well (Type 1 error). As a result, to properly describe the relationship between independent and dependent variables, a multivariable model that includes both the independent variable and all relevant confounding variables as predictors must be executed.

Cox proportional hazards regression: The Cox proportional hazards regression model is a statistical model for regression analysis of censored survival data. It examines the relationship of censored survival distribution to one or more covariates. It produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

Cytotoxic T lymphocyte: A T lymphocyte (a type of white blood cell) that is capable of inducing the death of tumor cells; they also kill cells that are infected with viruses.

Gleason score: A pathologic description of prostate cancer grade based on the degree of abnormality in the glandular architecture. Gleason patterns 3, 4, and 5 denote low, intermediate, and high levels of histologic abnormality and tumor aggressiveness, respectively. The score assigns primary and secondary numbers based on the most common and second most common patterns identified.

Telomerase: Also called telomere terminal transferase, it is an enzyme made of protein and RNA subunits. Its role is to elongate chromosomes by adding telomeric sequences to the end of existing chromosomes.

Telomeres: A tandem array of short DNA sequences that occur at the physical ends of chromosomes, telomeres have addressed the issue of the inability of DNA polymerases to replicate the ends of DNA strands. As a result, during the course of replication, telomeres in somatic cells shorten with each cell division.

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Appendix

Assessment and Selection of Covariates

In the Health Professionals' Follow-Up Study, information on smoking, body mass index, and physical activity was available in the biennial questionnaire from 1986. Questions about alcohol intake were asked in 1986, 1990, 1994, 1998, and 2002. Ever-use of sildenafil citrate for erectile dysfunction was asked in 2000. Information on the number of moles with $\geq$ 3-mm diameter on arms was collected in 1987. Natural hair color at age 18 years was asked in 1988. Questions about state of residence at birth, age 15 years, and age 30 years; number of blistered sunburns throughout life; and adolescent tendency to sunburn were asked in 1992. According to the state of residence reported, the UV index at birth, age 15, and age 30 years was divided into the following three categories: $\leq$ 5 (low), 6 (medium), or $\geq$ 7 (high). Family history of melanoma in first-degree relatives was asked in 1990 and 1992. Information on outdoor sun exposure between 10:00 AM and 3:00 PM in summer during high school/college and at age 25 to 35, 36 to 59, and $\geq$ 60 years was collected in 2008. These covariates were included in the multivariate-adjusted models because they are previously established skin cancer risk factors or have recently been associated with skin cancer in our cohorts, which may confound the association between the main exposure and the outcome. It is accepted that the multivariate-adjusted model should have the well-known confounders of the association and the other risk factors previously recognized to minimize the residual confounding. A popular approach that selects factors for inclusion only if the factors are statistically significant in bivariate screening is not optimal, because a factor can be a confounder even if it is not statistically significant with the exposure or outcome by itself because it changes the effect of the exposure of interest when it is included in the model or because it is a confounder only when included with other covariates (Sun GW, et al: J Clin Epidemiol 49:907-916, 1996). Our approach also tended to get conservative risk estimates of the main exposure.

Severe acne was indirectly assessed in 1992 by self-reported tetracycline use for $\geq$ 4 years. In 1992, participants were asked whether they had ever used "tetracycline for at least 2 months at a time (e.g., for acne or other reason)." Approximately 0.50% of participants reported using tetracycline for $\geq$ 4 years. Because severe acne was indirectly assessed in 1992 by self-reported tetracycline use for $\geq$ 4 years, we did not adjust for it in the primary analysis. Using a supplemental questionnaire, 61.9% of those who used tetracycline for $\geq$ 4 years reported use for acne, which was significantly higher than the rate among those who used it for $<$ 4 years. A previous study in the Health Professionals' Follow-Up Study applied the indirect measure of severe acne, setting 1992 as the baseline, and found that personal history of severe acne was significantly associated with incident prostate cancer.[8] Using the same approach, we considered severe acne (self-reported tetracycline use for $\geq$ 4 years) as a covariate in a sensitivity analysis. The association magnitude for personal history of prostate cancer associated with melanoma risk (hazard ratio [HR], 1.94; 95% CI, 1.38 to 2.72) was even slightly stronger than that in the primary analysis (HR, 1.83; 95% CI, 1.32 to 2.54).

We further considered other sun exposure variables in our models. The sun exposure and UV index variables at different life stages cannot provide information on the UV dose received over a period of time, limiting clear quantification of the relationship between chronic sun exposure and skin cancer risk. After obtaining histories of state of residence, we created the midrange UV radiation (UVB) flux for each 2-year period and cumulative UVB flux, derived based on latitude, altitude, and cloud cover of residence.[19] UVB flux variables are measured in Robertson-Berger meter units and are quantitative measures of sun exposure.[19] UVB flux has been associated with increased risk of melanoma previously[19] and nonmelanoma skin cancer in our recent study (Han et al, manuscript under review). Cumulative UVB flux is the total UVB flux in the previous follow-up period. For example, the cumulative UVB flux in 1996 is the total UVB flux in 1986, 1988, 1990, 1992, 1994, and 1996. As a secondary analysis, we adjusted for UVB flux or cumulative UVB flux in each 2-year questionnaire cycle, instead of UV index, and the results are listed in Appendix Table A3.

We recently evaluated the association between sildenafil citrate use for erectile dysfunction and risk of incident melanoma, for which our hypothesis was based on current literature (Mitra D, et al: Pigment Cell Melanoma Res 24:16-18, 2011). Sildenafil citrate use was significantly associated with risk of melanoma, after adjusting for age and other covariates (Li et al, manuscript under review). Therefore, sildenafil citrate use is a possible confounder for our present analysis. A sensitivity analysis without adjusting for sildenafil citrate use did not materially change the effect magnitude (HR, 1.82; 95% CI, 1.30 to 2.50).

In the PHS, data on smoking, alcohol intake, body mass index, and physical activity were collected at enrollment. The PHS did not collect data on other major skin cancer–related risk factors.

Definition of Prostate Cancer Subtypes

Patients with advanced prostate cancer were those who had cancer that had spread beyond the prostate to the seminal vesicle, lymph nodes, or bone, including stage T3b, T4, N1, or M1 at diagnosis; patients who developed lymph node or distant metastases; and patients who died of prostate cancer during the follow-up. Lethal cancers, a subset of advanced cancers, were those that caused death or metastasis

to bone during the follow-up. Nonadvanced cancers were stage T1 or T2 and N0 and M0 at diagnosis and did not progress to lymph node or distant metastases or death during the follow-up period. Some cancers that were diagnosed near the end of the follow-up period will be misclassified as nonadvanced because they had less time to progress before the end of follow-up.[15] Cancers were also categorized as high grade (Gleason score at diagnosis, 8 to 10), intermediate grade (Gleason score, 7), or low grade (Gleason score, 2 to 6) at diagnosis based on prostatectomy or biopsy pathology reports; Gleason grade was not available for all men with prostate cancer, particularly for those who were diagnosed earlier in the follow-up period.

Table A1. Characteristics of the Study Population According to Personal History of Prostate Cancer in 1998: Health Professionals' Follow-Up Study

Characteristic	History of Prostate Cancer	
	No (n = 30,235)	Yes (n = 1,492)
Age, years		
Mean	63.0	71.5
SD	8.9	7.5
Body mass index, kg/m^2		
Mean	26.3	26.1
SD	3.8	3.4
Physical activity, metabolic equivalent hours per week		
Mean	21.4	20.8
SD	30.6	29.1
Current smoking, %	6.7	4.6
Alcohol intake, g/d		
Mean	10.8	11.1
SD	14.0	13.8
Ever-use of sildenafil citrate for erectile dysfunction, %	5.6	27.1
Family history of melanoma, %	4.0	6.1
Burn or blistering skin reaction to the sun, %	67.6	67.3
UV index ≥ 7 of residence, %		
At birth	26.9	27.9
At age 15 years	28.5	30.6
At age 30 years	33.6	34.5
Natural red or blonde hair, %	12.8	15.2
≥ 6 moles on an extremity, ≥ 3 mm in diameter, %	4.7	4.9
History of ≥ 6 severe or blistering sunburns, %	34.2	31.4
Average sun exposure ≥ 11 h/wk, %		
In college/high school	49.6	52.9
At age 25-35 years	31.9	35.2
At age 36-59 years	27.4	29.3
At age ≥ 60 years	26.9	29.1

NOTE. All values other than age were age adjusted.
Abbreviation: SD, standard deviation.

Table A2. HR for All Variables in the Primary Analysis Evaluating the Association Between Personal History of Prostate Cancer and Risk of Melanoma: Health Professionals' Follow-Up Study, 1986 to 2010

Variable	HR*	95% CI
History of prostate cancer (main exposure)		
No	1.00	Reference
Yes	1.83	1.32 to 2.54
BMI, kg/m^2		
< 18.5	1.60	0.51 to 5.05
18.5-24.9	1.00	Reference
25-29.9	1.09	0.91 to 1.31
30-34.9	0.99	0.72 to 1.35
≥ 35	0.76	0.39 to 1.49
Smoking		
Never	1.00	Reference
Past < 10 pack-years	0.79	0.57 to 1.10
Past 10-20 pack-years	0.89	0.67 to 1.18
Past 20-40 pack-years	0.92	0.71 to 1.18
Past ≥ 40 pack-years	0.73	0.52 to 1.02
Current	0.75	0.51 to 1.12
Physical activity		
Quintile 1 (the lowest)	1.00	Reference
Quintile 2	0.83	0.60 to 1.15
Quintile 3	1.31	0.98 to 1.75
Quintile 4	1.20	0.89 to 1.62
Quintile 5 (the highest)	1.15	0.85 to 1.57
Alcohol intake		
Non-drinkers, g/d	1.00	Reference
0.1-4.9	1.16	0.90 to 1.49
5-9.9	1.00	0.74 to 1.35
10-19.9	1.15	0.89 to 1.49
≥ 20	1.23	0.94 to 1.62
Childhood reaction to sun		
Tan without burn	1.00	Reference
Burn	1.44	1.11 to 1.85
Painful burn/blisters	1.85	1.39 to 2.46
No. of sunburns		
0	1.00	Reference
1-2	0.95	0.68 to 1.33
3-5	1.13	0.82 to 1.57
≥ 6	1.27	0.93 to 1.73
No. of moles		
0	1.00	Reference
1-2	1.31	1.01 to 1.69
3-5	1.95	1.42 to 2.69
≥ 6	1.92	1.31 to 2.81
Hair color		
Red	1.52	0.94 to 2.48
Blonde	1.15	0.86 to 1.55
Light brown	1.00	Reference
Dark brown/black	0.82	0.66 to 1.02
Sun exposures at high school, h/wk		
≤ 1	1.00	Reference
2-5	1.93	0.86 to 4.31
6-10	1.70	0.73 to 3.94
≥ 11	2.23	0.96 to 5.18
Sun exposures at age 25-35 years, h/wk		
≤ 1	1.00	Reference
2-5	0.88	0.49 to 1.58
6-10	0.83	0.42 to 1.63
≥ 11	0.86	0.41 to 1.82

(continued on following page)

Table A2. HR for All Variables in the Primary Analysis Evaluating the Association Between Personal History of Prostate Cancer and Risk of Melanoma: Health Professionals' Follow-Up Study, 1986 to 2010 (continued)

Variable	HR*	95% CI
Sun exposures at age 36-59 years, h/wk		
≤ 1	1.00	Reference
2-5	0.88	0.50 to 1.56
6-10	0.80	0.41 to 1.54
≥ 11	0.61	0.30 to 1.29
Sun exposures at age ≥ 60 years, h/wk		
≤ 1	1.00	Reference
2-5	0.84	0.50 to 1.39
6-10	0.86	0.49 to 1.51
≥ 11	1.15	0.64 to 2.07
Family history of melanoma		
No	1.00	Reference
Yes	1.55	0.98 to 2.43
UV index at birth		
≤ 5	1.00	Reference
6	1.16	0.77 to 1.77
≥ 7	0.61	0.38 to 0.98
UV index at age 15 years		
≤ 5	1.00	Reference
6	0.59	0.37 to 0.94
≥ 7	0.88	0.53 to 1.44
UV index at age 30 years		
≤ 5	1.00	Reference
6	1.47	1.05 to 2.06
≥ 7	1.60	1.13 to 2.25
Ever-use of sildenafil citrate		
No	1.00	Reference
Yes	0.86	0.60 to 1.25

NOTE. The HRs and 95% CIs for the covariates were listed for readers' information, but the interpretation requires caution. The data for analyses were arranged based on the primary focus (personal history of prostate cancer and risk of melanoma), so that the inclusion/exclusion criteria do not apply to the circumstances when other factors are examined as the main exposure. We created an indicator variable for each covariate with missing information to preserve the power for the primary analyses, whereas when evaluating the association between these covariates and melanoma, we need to exclude the missing data. Because these covariates are either established risk factors for skin cancer or have recently been associated with skin cancer in our cohorts, results shown in this table may not reflect the true associations between these covariates and risk of melanoma in the entire cohort considering our particular research objectives. The HR and 95% CI for the missing category of each covariate are not shown.

Abbreviations: BMI, body mass index; HR, hazard ratio.

*Analyses were stratified by age and 2-year time interval and adjusted for the other covariates in the table. History of prostate cancer is the examined main exposure.

Table A3. HR of Incident Melanoma and Nonmelanoma Skin Cancer Associated With Personal History of Prostate Cancer, Adjusting for UVB Flux: Health Professionals' Follow-Up Study, 1986 to 2010

History of Prostate Cancer	No. of Person-Years	No. of Cancers	HR*† Adjusted for UV Flux		HR*‡ Adjusted for Cumulative UV Flux	
			HR	95% CI	HR	95% CI
Melanoma						
No	720,482	495	1.00		1.00	
Yes	26,695	44	1.85	1.34 to 2.57	1.86	1.34 to 2.57
Nonmelanoma skin cancer (SCC and BCC)						
No	667,599	11,247	1.00		1.00	
Yes	24,691	713	1.07	0.99 to 1.16	1.07	0.99 to 1.16

Abbreviations: BCC, basal cell carcinoma; HR, hazard ratio; SCC, squamous cell carcinoma.

*Analyses were performed adjusting for age (continuous variable); body mass index (< 18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, or ≥ 35 kg/m^2); smoking (never, past, or current smokers); alcohol intake (no, 0.1 to 4.9, 5 to 9.9, 10 to 19.9, or ≥ 20 g/d); physical activity (in quintiles, metabolic equivalent hours per week); ever-use of sildenafil citrate for erectile dysfunction (yes or no); childhood reaction to sun (tan without burn, burn, or painful burn/blisters); number of sunburns (none, one to two, three to five, or ≥ six sunburns); mole count (none, one to two, three to five, or ≥ six moles); hair color (red, blonde, light brown, or dark brown/black); family history of melanoma (yes or no); and sun exposures at high school, age 25 to 35, age 36 to 59, and age ≥ 60 years (< 1, 2 to 5, 6 to 10, or ≥ 11 h/wk for each). An indicator variable was created for the missing value of each covariate. *P* for heterogeneity = .002 for the magnitude of associations with melanoma and nonmelanoma skin cancer.

†Additionally adjusting for UVB flux in each 2-year questionnaire cycle (in quintiles). *P* for heterogeneity = .001 for the magnitude of associations with melanoma and nonmelanoma skin cancer.

‡Additionally adjusting for cumulative UVB flux (in quintiles) in each 2-year questionnaire cycle, which is the cumulative UVB flux of previous cycles (eg, the UVB flux in 2000 is the cumulative of all the previous UVB flux for 1986 to 2000). *P* for heterogeneity = .001 for the magnitude of associations with melanoma and nonmelanoma skin cancer.

Table A4. HR of Incident Melanoma by Personal History of Prostate Cancer Subtypes or Diagnosis Age: Health Professionals' Follow-Up Study, 1986 to 2010

History of Prostate Cancer	No. of Person-Years	No. of Patients	Multivariate-Adjusted HR*†	95% CI
Total, reference	720,482	495	1.00	
Subtypes of prostate cancer				
Lethal prostate cancer	2,951	6	1.99	0.87 to 4.53
Advanced prostate cancer	4,336	8	1.96	0.96 to 3.99
Nonadvanced prostate cancer	18,427	27	1.56	1.04 to 2.34
Gleason score 8-10 prostate cancer	2,734	3	1.13	0.36 to 3.56
Gleason score 7 prostate cancer	8,192	12	1.59	0.89 to 2.86
Gleason score 2-6 prostate cancer	12,032	17	1.51	0.92 to 2.48
Age at diagnosis of prostate cancer, years				
≤ 68	13,665	24	2.09	1.37 to 3.19
> 68	13,020	20	1.57	0.97 to 2.54
Primary treatment of prostate cancer				
Radical prostatectomy	13,471	20	1.73	1.09 to 2.74
External-beam radiation therapy or brachytherapy	7,288	12	1.68	0.93 to 3.03
Hormones	1,254	2	1.62	0.39 to 6.70
Watchful waiting/others	1,955	4	1.99	0.73 to 5.41

Abbreviation: HR, hazard ratio.

*Adjusted for age; body mass index (< 18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, or ≥ 35 kg/m^2); smoking (never; past < 10, past 10 to 20, past 20 to 40, past ≥ 40 pack-years; or current smokers); alcohol intake (no, 0.1 to 4.9, 5 to 9.9, 10 to 19.9, or ≥ 20 g/d); physical activity (in quintiles, metabolic equivalent hours per week); ever-use of sildenafil citrate for erectile dysfunction (yes or no); childhood reaction to sun (tan without burn, burn, or painful burn/blisters); number of sunburns (none, one to two, three to five, or ≥ six sunburns); mole count (none, one to two, three to five, or ≥ six moles); hair color (red, blonde, light brown, or dark brown/black); family history of melanoma (yes or no); sun exposures at high school, age 25 to 35, age 36 to 59, and age ≥ 60 years (< 1, 2 to 5, 6 to 10, or ≥ 11 h/wk for each); and UV index at birth, age 15, and age 30 (≤ 5, 6, or ≥ 7). An indicator variable was created for the missing value of each covariate.

†*P* for heterogeneity = .60 for the comparison of lethal and nonadvanced prostate cancer; *P* for heterogeneity = .59 for advanced and nonadvanced prostate cancer; *P* for heterogeneity = .87 for three subtypes classified by Gleason scores; *P* for heterogeneity = .68 for age of diagnosis of prostate cancer ≤ 68 years (median diagnosis age of prostate cancer in this cohort) or > 68 years; *P* for heterogeneity = .99 for four categories of primary treatment of prostate cancer.