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ACNE AND RISK OF PROSTATE CANCER

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Abstract

In a recent study, prostatectomy specimens from which *Propionibacterium acnes* was cultured were more likely to have inflammation than culture-negative specimens or specimens positive for other bacteria, leading the authors to hypothesize that *P. acnes*-mediated inflammation may contribute to prostate carcinogenesis. To indirectly explore associations between *P. acnes* and prostate cancer, we investigated severe acne, as measured by tetracycline use for four or more years, in relation to incident prostate cancer in the Health Professionals Follow-up Study. On the 1992 follow-up questionnaire, participants were asked whether they had ever used "tetracycline for at least two months at a time (e.g., for acne or other reason)" and their duration of use. Prostate cancer diagnoses were ascertained on each subsequent biennial questionnaire and confirmed by medical record review. Between 1992 and 2002, 2,147 cases of prostate cancer were reported among 34,629 eligible participants. Men who used tetracycline for four or more years had a significantly higher risk of prostate cancer (16 cases, 1,569 person-years) than men who did not use tetracycline (2,071 cases, 304,822 person-years, multivariable-adjusted RR=1.70, 95% CI: 1.03–2.80). Although intriguing, this finding should be viewed cautiously because of the small number of exposed cases, indirect assessment of severe acne, and complex etiology of acne, which is not limited to *P. acnes* infection. Therefore, additional biologic and epidemiologic studies are necessary to determine and elucidate the possible role of *P. acnes* infection in prostate carcinogenesis.

Keywords

Acne vulgaris; tetracycline; prostate cancer; epidemiology; cohort study

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Novelty and impact of the manuscript:
In a recent study, prostatectomy specimens from which *Propionibacterium acnes* was cultured were more likely to have inflammation than culture-negative specimens, leading the authors to hypothesize that *P. acnes*-mediated inflammation may contribute to prostate carcinogenesis. To indirectly explore associations between *P. acnes* and prostate cancer, we conducted a study of severe acne, as measured by tetracycline use for four or more years, in relation to incident prostate cancer in the Health Professionals Follow-up Study, in which we observed that long-term tetracycline users were significantly more likely to develop prostate cancer than non-users. To our knowledge, this is the first such finding in the literature.

INTRODUCTION

An emerging body of literature suggests that inflammation may contribute to prostate carcinogenesis. [1] However, responsible causes of intraprostatic inflammation are, as yet, unknown. Although we and other investigators have observed positive associations between certain sexually transmitted infections and prostate cancer,[2] we do not expect these infections to account for a large proportion of prostate cancer risk because of the low frequency of these infections in the general male population. Therefore, we believe that investigations of more common intraprostatic infections are warranted at this time. In this regard, Cohen and colleagues[3] recently cultured *Propionibacterium acnes*, a slow-growing, gram-positive bacterium associated with acne vulgaris,[4] from one third of a series of radical prostatectomy specimens. They further observed that culture-positive specimens were significantly more likely to have foci of acute and chronic inflammation than culture-negative specimens or specimens positive for other bacteria, leading them to hypothesize that *P. acnes*-mediated inflammation may contribute to prostate carcinogenesis. In support of this hypothesis, Alexeyev and colleagues[5] recently observed a non-significant positive association between detection of *P. acnes* DNA and prostate cancer among men who underwent transurethral resection of the prostate (TURP) for benign prostatic hyperplasia (BPH). Suggestive positive results were also observed in a recent prospective study of acne history and prostate cancer mortality,[6] but not in two earlier case-control studies.[7, 8] Therefore, to further explore associations between *P. acnes* infection and prostate cancer, we conducted a prospective cohort analysis of severe acne, as measured by tetracycline use for four years or more, in relation to incident prostate cancer in the Health Professionals Follow-up Study (HPFS).

Tetracycline was first introduced in 1948 and became widely used for severe acne in the early 1950s.[9] It continued to be used for severe acne through the next several decades, spanning the range of years when a large proportion of the HPFS cohort passed through adolescence and early adulthood. Other therapies for severe acne at the time included other systemic antibiotics, topical preparations containing sulfur, resorcin or antibiotics, major dietary restrictions, X-ray or ultraviolet light therapy, cryotherapy and administration of diethylstilbestrol, thyroid extractor vitamin A, while those for less severe acne included topical preparations, less radical dietary restrictions, exposure to natural sunlight, and administration of vitamin A.[10–12]

MATERIALS AND METHODS

Study population and design

The HPFS is an ongoing, prospective cohort study of cancer and heart disease in men. It includes 51,529 American male health professionals aged 40–75 at enrolment in 1986. Participants enrolled in the study by completing a baseline epidemiologic questionnaire, including information on demographics, lifestyle and medical history, and a semi-quantitative food frequency questionnaire. Since 1986, participants have completed follow-up epidemiologic questionnaires every two years to update exposure and disease information, and food frequency questionnaires every four years to update dietary information. Information on vital status is obtained from the National Death Index, and the U.S. Postal Service or next of kin in response to follow-up questionnaires.

For the present analysis, we excluded men who died before the 1992 follow-up questionnaires were mailed (3.9%), those diagnosed with cancer (except non-melanoma skin cancer) before the date of return of the 1992 questionnaire (7.7%), those who did not provide complete baseline food frequency information (2.7%), and those who did not return the 1992 questionnaire or reply to the tetracycline questions (18.5%). After these exclusions,

34,629 participants remained in the analysis. This study was approved by the Human Subjects Committee at the Harvard School of Public Health and the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health.

Assessment of tetracycline use

On the 1992 follow-up questionnaire, participants were asked whether they had ever used "tetracycline for at least two months at a time (e.g., for acne or other reason)": no or yes, and for how long had they used tetracycline: 2–11 months, 1–2 years, 2–3 years, or four or more years. Based on the observed sample size sand the results of preliminary analyses, we categorized tetracycline use into the following four categories: no use; less then four years of use; four or more years of use; and use of unknown duration for men who replied affirmatively to the first question on ever use but who did not respond to the second question on duration of use. In 2006, we mailed an additional questionnaire to 50 randomly-selected men who reported less than four years of tetracycline use on the 1992 questionnaire and 50 randomly-selected men who reported four or more years of use to inquire about reasons for use and, if for acne, about other acne treatments.

Identification of prostate cancer cases

Information on prostate cancer was ascertained on each biennial follow-up questionnaire. Over 90% of prostate cancer diagnoses were subsequently confirmed by medical record and pathology report review with permission from the participant or next of kin. Many of the remaining 10% provided supporting information (e.g., evidence of treatment) for their diagnosis. Information on disease stage (TNM classification) and Gleason sum was abstracted from participants' medical records and pathology reports by study investigators blinded to participants' exposure status. T1a prostate cancers (n=71) were not included as cases because these tumors are detected, by definition, at TURP for BPH, and may be especially prone to detection bias.

Statistical analysis

Men who did and did not use tetracycline were compared by calculating age-standardized means and proportions of covariates of interest by tetracycline use. Covariates of interest included 1) factors previously observed to be associated with prostate cancer incidence or progression in the HPFS cohort (race/ethnicity, family history of prostate cancer, height, cigarette smoking in the past ten years, intakes of total energy, alcohol, tomato sauce, red meat, fish, calcium, fructose, alpha-linolenic acid and vitamin E, zinc supplementation, vigorous physical activity, having had a vasectomy and a history of diabetes)[13–21]; 2) factors or other medical conditions potentially associated with long-term tetracycline use (regular non-steroidal anti-inflammatory drug (NSAID) use, and histories of periodontal disease and prostatitis), 3) purported surrogate markers of androgenicity (vertex baldness, and body habitus, vigorous physical activity and ejaculation frequency in adolescence and early adulthood), 4) other factors hypothesized to be associated with acne development, aggravation or treatment (intakes of milk, hard cheese, butter, milk shakes, ice cream, cookies and fried potatoes in high school, residence in a Southern state or territory in adolescence or early adulthood, amount of time spent outdoors in a swimsuit in the summer as a teenager, and lifetime number of blistering facial sunburns), and 5) other early life factors (body mass index, cigarette smoking and alcohol consumption in adolescence and early adulthood, and histories of gonorrhea or syphilis). Food and sun exposure as a teenager was explored because certain foods (carbohydrates, such as bread, potatoes, pastries, candy and sugar, fatty or greasy foods, dairy and pork products, shellfish, nuts, spicy foods and chocolate) were commonly believed to cause or exacerbate acne, and natural sunlight was believed to improve acne.[11, 12, 22] Age-adjusted (five-year age intervals) associations between tetracycline use and prostate cancer were explored using Mantel-Haenszel rate

ratios. Person-time was calculated from the month of return of the 1992 questionnaire to the month of prostate cancer diagnosis, death or end of the analysis period on January 31, 2002. Multivariable-adjusted associations between tetracycline use and prostate cancer were investigated using Cox proportional hazards regression. All models included a term for missing duration of tetracycline use. To investigate the influence of this missing information, sensitivity analyses were performed by including all participants with missing duration of use in either the group of men who reported less than four years of tetracycline use or the group of men who reported four or more years of tetracycline use. Similar inferences were observed as in analyses that used a separate missing term. Age (one-month intervals) and calendar time (two-year intervals) were controlled for as stratification variables in all regression models. Confounding by the aforementioned covariates was explored by adding each covariate individually and in combination to the regression model, and comparing to univariable results. As the number of exposed cases was low and none of the explored covariates altered the magnitude or significance of the main findings, only known risk factors for prostate cancer (age, race/ethnicity and family history of prostate cancer) were retained in the final multivariable model.

Possible detection bias was explored by restricting the analyses to men who reported prostate cancer screening, either a routine prostate specific antigen test or digital rectal examination. The specificity of long-term tetracycline use for acne was explored in three different ways. First, we explored the age distribution of men who reported four or more years of tetracycline use to determine whether this distribution was consistent with the availability of tetracycline (introduced in 1948 and more widely used for acne in the early 1950s[9]), and the maximum age of acne persistence in men (usually 25 years of age, although 7% of cases may still have acne up to age 45[23]). Second, we performed analyses restricted to men 25 years of age or less in the early 1950s who would have been more likely than older men to receive tetracycline for their acne, and men with no reported histories of periodontal disease or prostatitis, as these might have also been reasons for long-term tetracycline use. Finally, we tabulated reasons for tetracycline use by duration of use in the sample of participants who completed the supplemental questionnaire in 2006 regarding indications for tetracycline use.

Total prostate cancer was used as the outcome in the main analyses. Too few men who reported four or more years of tetracycline use were diagnosed with advanced stage (n=1) or high-grade prostate cancer (n=4) to investigate associations by prostate cancer stage or grade. All statistical analyses were performed using SAS version 9 (SAS Institute, Cary, NC).

RESULTS

Of the 34,629 eligible participants, 2,147 reported a diagnosis of prostate cancer between the date of return of the 1992 questionnaire and January 31, 2002. Two hundred nineteen cases were advanced (T3b or worse) and 761 were high grade (Gleason sum of 7 or more). Approximately 97% of participants reported never using tetracycline for at least two months, 2.8% reported using tetracycline for less than four years (the majority of whom used tetracycline for less than one year), and 0.50% reported using tetracycline for four or more years. Compared to men who never used tetracycline, those who used tetracycline for four or more years were more likely to report greater alcohol and lesser milk and calcium consumption, more regular NSAID use, less vertex baldness, histories of young-onset and other prostatitis, greater consumption of alcohol in adolescence and early adulthood, more time spent outdoors in a swimsuit in the summer as a teenager, and a greater lifetime number of blistering facial sunburns (Table 1).

In age-adjusted analyses, no association was observed between use of tetracycline for less than four years and prostate cancer (Table 2). Similar null results were observed for each category of tetracycline use under four years (2–11 months: 46 cases, 6,548 person-years, RR=1.16, 95% CI: 0.87–1.56; and 1–3 years: 9 cases, 2,371 person-years, RR=0.74, 95% CI: 0.38–1.42). In contrast, use of tetracycline for four or more years was positively associated with risk of prostate cancer in both age-and multivariable-adjusted analyses (Table 2). The magnitude and significance of the results were essentially unchanged after adjustment for other previously identified risk factors for prostate cancer in this cohort, factors associated with long-term tetracycline use, surrogate markers of androgenicity, other factors hypothesized to be associated with acne development, aggravation or treatment, and other early life factors (data not shown). Similar results were also observed when the analyses were restricted to men who reported routine prostate cancer screening (multivariable-adjusted RR=1.79, 95% CI: 1.02–3.12).

The oldest man to report four or more years of tetracycline use was 32.5 years of age in 1948 when tetracycline was first introduced, and approximately 37 years of age in the early 1950s when antibiotics became widely used for acne. Although this man is older than the typical acne patient, it is still plausible that he may have taken tetracycline for persistent adult acne. When the analyses were restricted to men 25 years of age or less in the early 1950s who would have been more likely to receive tetracycline for their acne than older men, a similar increased risk of prostate cancer was observed for men who used tetracycline for four or more years as in the full cohort (multivariable-adjusted RR=1.69, 95% CI: 0.90–3.17). Slightly stronger results were observed when the analyses were restricted to men without histories of periodontal disease (RR=1.84, 95% CI: 1.08–3.14) or prostatitis(RR=1.85, 95% CI: 1.06–3.22), two conditions for which tetracycline may have been prescribed.

In 2006, 83 out of 100 selected participants completed a supplemental questionnaire on indications for tetracycline use. Of the 41 participants who reported *less than four* years of use, 41.5% reported use for acne, 14.6% for rosacea, 21.9% for various other conditions, and 22.0% denied or could not remember using tetracycline for at least 2 months. Most of these latter men originally reported using tetracycline for only 2–11 months. Of the 42 participants who reported *four or more* years of use, 61.9% reported use for acne, 23.8% for rosacea, 4.8% for folliculitis, 7.1% for various other conditions or reasons that they had since forgotten, and 2.4% (1 man) denied using tetracycline for at least two month s. Regarding other acne treatments, 41.2% of those who reported *less than four* years of tetracycline use for acne and 57.7% who reported *four or more* years of use for acne also reported other acne treatments. The most commonly reported other acne treatments were topical preparations (25.6%), followed by ultraviolet light (14.0%) and X-ray (9.3%) therapy. A few participants also reported other systemic antibiotics, salicylic acid, sulfur soap, dry ice applications and/or diet modification.

DISCUSSION

In this large, prospective cohort of American male health professionals, a history of severe acne, as measured by self-reported tetracycline use for four or more years, was associated with a significantly increased risk of prostate cancer. This association persisted after adjustment for correlates and risk factors of acne and prostate cancer, and factors associated with long-term tetracycline use.

Our positive study findings are similar to those from two previous prospective studies, [5, 6] one of which observed a non-significant positive association between self-reported history of acne and prostate cancer mortality,[6] and the other observed a non-significant positive

association between detection of *P. acnes* DNA in TURP specimens and incident prostate cancer.[5] Our findings differ, however, from those from two case-control studies.[7, 8] The first of these studies observed a non-significant inverse association between a history of acne and prostate cancer, and more pronounced inverse associations for interviewer-observed facial acne scarring, self-reported onset of acne after 15 years of age, and greater than 24 months treatment for acne,[7] while the second observed no association between self-reported history of acne during participants' mid-teens and prostate cancer.[8]

One possible explanation for our positive findings is general immune sensitivity to *P. acnes* in men with a history of severe acne.[24] Although most boys are colonized by *P. acnes*, only a small proportion go on to develop severe acne vulgaris,[4] possibly due to stronger humoral or cell-mediated immune responses to *P. acnes.*[25, 26] By extension, these same individuals may also be more likely to develop stronger inflammatory immune responses to intraprostatic *P. acnes*. Persistent low-grade *P. acnes*-mediated inflammation may then lead to the development of proliferative inflammatory atrophy lesions,[24] regenerative lesions that have been proposed to serve as either precursor lesions for prostate cancer or as markers of an intraprostatic environment conducive to the development of prostate cancer.[27] Although all of the exposed men in our study used tetracycline, an anti-*P. acnes* and anti-inflammatory drug,[28, 29] it is unclear what effect use of this drug would have had on low-grade intraprostatic *P. acnes* infection because tetracycline has not proven useful in treating other non-acute intraprostatic infections caused by tetracycline-sensitive bacteria, such as chronic bacterial prostatitis, [30] despite its use in treating recurrent urinary tract infections (UTIs) due to bacterial prostatitis.[31] For this same reason, we believe that tetracycline is unlikely to have an independent effect on prostate cancer risk because of its questionable diffusion into the non-acutely inflamed prostate. Other possible biologic explanations for our positive findings include *P. acnes*-mediated enhanced immune sensitivity to other stimuli,[24] greater general immune sensitivity to infection regardless of the specific pathogen or site of infection, or greater general susceptibility to infection.

Although intriguing, our findings should be viewed as preliminary for several reasons. First, they rely on a small number of exposed cases and thus may be imprecise. Second, they are based on a surrogate measure of severe acne. Although participants were reminded of acne as an indication for tetracycline use on the follow-up questionnaire, the sensitivity of long-term tetracycline use for severe acne may be limited by its availability, cost, distribution under different names, or acceptability as an acne therapy over time. Its specificity may also be limited by its prescription for other medical indications, such as rosacea,[9] periodontal disease [9] and recurrent UTIs due to chronic bacterial prostatitis.[31] Although some men reported these and other indications in our supplemental study, they were less likely to report alternate indications if they used tetracycline for four or more years than if they used tetracycline for less then four years, thus increasing the specificity of tetracycline as a surrogate for severe acne among the long-term users. Additionally, although indirect, our measure of severe acne may have been as or more specific than more direct measures, such as self-reported history of severe acne, because these measures may be more influenced by individual perception of acne severity. Irrespective of the sensitivity and specificity of long-term tetracycline use for severe acne, if *P. acnes* infection is truly associated with prostate cancer, then misclassification of some men with a history of acne who did not use tetracycline or some men without a history of acne who used tetracycline for other indications should only have resulted in an attenuation of even stronger findings because misclassification is unlikely to have been differential by later prostate cancer status. Indeed, when we restricted the analyses to men without histories of periodontal disease or clinical prostatitis, indications for which information was available in this cohort, slightly stronger associations were observed. Although long-term tetracycline use may also serve as a surrogate for exposure to possibly harmful acne therapies used prior to or in conjunction

with tetracycline therapy, we believe this is unlikely to explain our findings because most of the men in our supplemental study who reported other acne treatments used facially-oriented therapies, such as topical preparations, and ultraviolet light and X-ray therapy.

Just as long-term tetracycline use may serve as a surrogate for severe acne, severe acne may also serve as a surrogate for other measures. In previous epidemiologic studies,[6, 7] acne has been used as a marker of hormonal activity, particularly androgen activity, but also possibly growth hormone and insulin-like growth factor activity. We explored this hypothesis by investigating possible associations between long-term tetracycline use and factors believed to be associated with androgen activity, such as vertex baldness later in life, and body habitus, vigorous physical activity and ejaculation frequency earlier in life. However, none of these factors were associated with long-term tetracycline use, except for vertex baldness, which was inversely associated.

In summary, men with a history of severe acne, as measured by tetracycline use for four or more years, were significantly more likely to develop prostate cancer than men without a history of severe acne in this large prospective study of American health professionals. Although intriguing, these findings should be interpreted cautiously because of the small number of exposed cases, the indirect assessment of severe acne and the complex and incompletely defined etiology of acne, which is not limited to *P. acnes* infection. Therefore, additional biologic and epidemiologic studies are necessary to determine and elucidate the possible role of *P. acnes* infection in prostate carcinogenesis.

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Abbreviations

BPH	benign prostatic hyperplasia
CI	confidence interval
HPFS	Health Professionals Follow-up Study
NSAID	non-steroidal anti-inflammatory drug
RR	relative risk
TURP	transurethral resection of the prostate
UTI	urinary tract infection

References

1. Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. N Engl J Med. 2003; 349:366–81. [PubMed: 12878745]
2. Sutcliffe S, Platz EA. Inflammation in the etiology of prostate cancer: an epidemiologic perspective. Urol Oncol. 2007; 25:242–9. [PubMed: 17483023]

3. Cohen RJ, Shannon BA, McNeal JE, Shannon T, Garrett KL. *Propionibacterium acnes* associated with inflammation in radical prostatectomy specimens: a possible link to cancer evolution? J Urol. 2005; 173:1969–74. [PubMed: 15879794]
4. Bojar RA, Holland KT. Acne and *Propionibacterium acnes*. Clin Dermatol. 2004; 22:375–9. [PubMed: 15556721]
5. Alexeyev O, Bergh J, Marklund I, Thellenberg-Karlsson C, Wiklund F, Gronberg H, Bergh A, Elgh F. Association between the presence of bacterial 16S RNA in prostate specimens taken during transurethral resection of prostate and subsequent risk of prostate cancer (Sweden). Cancer Causes Control. 2006; 17:1127–33. [PubMed: 17006718]
6. Galobardes B, Davey Smith G, Jeffreys M, Kinra S, McCarron P. Acne in adolescence and cause-specific mortality: lower coronary heart disease but higher prostate cancer mortality: the Glasgow Alumni Cohort Study. Am J Epidemiol. 2005; 161:1094–101. [PubMed: 15937017]
7. Giles GG, Severi G, English DR, McCredie MR, MacInnis R, Boyle P, Hopper JL. Early growth, adult body size and prostate cancer risk. Int J Cancer. 2003; 103:241–5. [PubMed: 12455039]
8. Lightfoot N, Conlon M, Kreiger N, Sass-Kortsak A, Purdham J, Darlington G. Medical history, sexual, and maturational factors and prostate cancer risk. Ann Epidemiol. 2004; 14:655–62. [PubMed: 15380796]
9. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. J Am Acad Dermatol. 2006; 54:258–65. [PubMed: 16443056]
10. Andrews GC, Domonkos AN. Treatment of acne vulgaris. JAMA. 1951; 146:1107–13.
11. Pillsbury, DM.; Shelley, WB.; Kligman, AM. Dermatology. Philadelphia: W. B. Saunders Company; 1956.
12. Bobroff, A. Acne and related disorders of complexion and scalp. Springfield, IL: Charles C. Thomas; 1964.
13. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. Int J Cancer. 2007
14. Leitzmann MF, Stampfer MJ, Wu K, Colditz GA, Willett WC, Giovannucci EL. Zinc supplement use and risk of prostate cancer. J Natl Cancer Inst. 2003; 95:1004–7. [PubMed: 12837837]
15. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Diabetes mellitus and risk of prostate cancer (United States). Cancer Causes Control. 1998; 9:3–9. [PubMed: 9486458]
16. Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, Giovannucci E. A prospective study of intake of fish and marine fatty acids and prostate cancer. Cancer Epidemiol Biomarkers Prev. 2003; 12:64–7. [PubMed: 12540506]
17. Giovannucci E, Rimm EB, Wolk A, Ascherio A, Stampfer MJ, Colditz GA, Willett WC. Calcium and fructose intake in relation to risk of prostate cancer. Cancer Res. 1998; 58:442–7. [PubMed: 9458087]
18. Chan JM, Stampfer MJ, Ma J, Rimm EB, Willett WC, Giovannucci EL. Supplemental vitamin E intake and prostate cancer risk in a large cohort of men in the United States. Cancer Epidemiol Biomarkers Prev. 1999; 8:893–9. [PubMed: 10548318]
19. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. A prospective cohort study of vasectomy and prostate cancer in US men. Jama. 1993; 269:873–7. [PubMed: 8426446]
20. Platz EA, Leitzmann MF, Rimm EB, Willett WC, Giovannucci E. Alcohol intake, drinking patterns, and risk of prostate cancer in a large prospective cohort study. Am J Epidemiol. 2004; 159:444–53. [PubMed: 14977640]
21. Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willet WC, Giovannucci E. A prospective study on intake of animal products and risk of prostate cancer. Cancer Causes Control. 2001; 12:557–67. [PubMed: 11519764]
22. Hodson, G. Rosacea, including seborrhoea oleasa, acne vulgaris and hyperidrosis. In: Mitchell-Heggs GB. Modern practice in dermatology. New York: Paul B. Hoeber Inc; 1950. p. 205-20.
23. Cunliffe, WJ.; Gollnick, HPM. Acne: diagnosis and management. London: Mark Dunitz Ltd; 2001.
24. Shannon BA, Garrett KL, Cohen RJ. Links between *Propionibacterium acnes* and prostate cancer. Future Oncol. 2006; 2:225–32. [PubMed: 16563091]

25. Burkhart CG, Burkhart CN, Lehmann PF. Acne: a review of immunologic and microbiologic factors. Postgrad Med J. 1999; 75:328–31. [PubMed: 10435165]

26. Webster GF. Inflammation in acne vulgaris. J Am Acad Dermatol. 1995; 33:247–53. [PubMed: 7622652]

27. De Marzo AM, Meeker AK, Zha S, Luo J, Nakayama M, Platz EA, Isaacs WB, Nelson WG. Human prostate cancer precursors and pathobiology. Urology. 2003; 62:55–62. [PubMed: 14607218]

28. Chambers, H. Antimicrobial agents (continued): Protein synthesis inhibitors and miscellaneous antibacterial agents. In: Hardman, J.; Limbird, L.; Gilman, A., editors. Goodman & Gilman's The pharmacologic basis of therapeutics. 10. New York: McGraw-Hill Companies, Inc; 2001. p. 1939-71.

29. Wyatt, E.; Sutter, S.; Drake, L. Dermatological pharmacology. In: Hardman, J.; Limbird, L.; Gilman, A., editors. Goodman & Gilman's The pharmacologic basis of therapeutics. 10. New York: McGraw-Hill Companies, Inc; 2001. p. 1795-818.

30. Ristuccia AM, Cunha BA. Current concepts in antimicrobial therapy of prostatitis. Urology. 1982; 20:338–45. [PubMed: 6981874]

31. Leigh DA. Prostatitis--an increasing clinical problem for diagnosis and management. J Antimicrob Chemother. 1993; 32 (Suppl A):1–9. [PubMed: 8407691]

Table 1

Age-standardized characteristics by tetracycline use as a surrogate for severe acne among participants in the Health Professionals Follow-up Study (HPFS), 1992

	Tetracycline use of at least two months duration		
	None (n=33,437)	<4 years duration (n=966)	≥4 years duration (n=173)
Mean age (years)	59.4	56.7	57.4
Race/ethnicity (%):			
Southern European	23.5	20.7	21.6
Scandinavian	10.4	11.9	9.7
Other white	57.6	60.5	59.7
African American	0.8	0.2	0.0
Asian	1.6	0.9	1.8
Other	6.1	5.8	7.2
Family history of prostate cancer (%)*	13.5	14.0	9.7
Mean height in 1986 (inches)	70.2	70.3	70.2
Smoked cigarettes in the past 10 years (%)	20.0	24.8	22.0
Mean intakes of:			
Total energy (kcal/day)†	1926	1998	1987
Alcohol (g/day)†	10.3	10.9	16.1
Tomato sauce (servings/day) ‡	0.22	0.22	0.25
Red meat (servings/day) ‡	1.04	1.14	1.13
Fish (servings/day) ‡	0.34	0.33	0.34
Skim milk (servings/day) ‡	0.78	0.81	0.67
Whole milk (servings/day) ‡	0.12	0.13	0.07
Calcium (mg/day)†	870	908	807
Fructose (g/day)†,§	49.8	48.4	47.3
Alpha-linolenic acid (g/day)†,§	1.04	1.06	0.98
Vitamin E intake (≥15 mg/day mostly from supplements, %)†	39.7	39.1	44.5
Zinc supplementation (≥101 mg/day, %)†	0.4	0.6	0.6
Regular (≥2 times/week) use of non-steroidal anti-inflammatory drugs (%)	40.5	44.8	49.4
Any vigorous leisure-time physical activity (%)	60.6	58.0	63.1
Screening prostate specific antigen test (%)‖	88.2	89.1	89.8
Screening digital rectal examination (%)‖	85.7	85.9	88.2
Vasectomy (%)	25.0	25.2	27.0
Diabetes mellitus type 2 (%)	4.7	3.8	5.9
Vertex baldness (%)	30.6	27.1	19.8
History of periodontal disease with bone loss (%)	18.9	19.8	16.0
History of prostatitis (%):			
No	83.4	74.7	74.0

	Tetracycline use of at least two months duration		
	None (n=33,437)	<4 years duration (n=966)	≥4 years duration (n=173)
Young-onset prostatitis**	2.0	2.8	4.3
Other prostatitis	13.6	20.9	17.8
Mean body mass index at age 21 (kg/m^2)††	23.0	22.8	22.5
Body habitus, ages 20 to 21‡‡,§§:			
Lean|| ||	70.8	73.0	74.7
Muscular***	17.9	17.5	16.3
Fat†††	2.6	1.7	1.6
Smoked cigarettes before age 30 (%)††	46.9	51.5	49.0
Consumed alcohol, ages 18 to 22 (%)‡‡	65.2	64.1	69.4
Mean intakes in high school of‡‡:			
Skim milk (servings/day)	0.15	0.19	0.18
Whole milk (servings/day)	1.99	2.05	2.03
Hard cheese (servings/day)	0.32	0.33	0.31
Butter (servings/day)	1.28	1.31	1.19
Milk shakes (servings/day)	0.17	0.17	0.16
Ice cream (servings/day)	0.33	0.33	0.34
Cookies (servings/day)	0.94	0.96	0.84
Fried potatoes (servings/day)	0.28	0.30	0.27
Any vigorous physical activity (%) in:			
High school	88.4	87.6	86.1
College	80.0	79.4	76.2
Residence in a Southern state or territory at age (%):			
15	22.2	24.9	26.4
25	25.9	28.9	30.8
Average time spent outdoors as a teenager in a swimsuit during the summer (%):			
Less than once/week	23.2	24.0	17.8
Once or twice/week	31.6	31.0	25.2
More than twice/week	43.5	43.3	49.4
Number of times had a blistering sunburn on the face (%):			
0	40.0	35.4	37.7
1–5	32.1	33.5	22.4
≥6	16.9	19.8	28.6
Mean ejaculation frequency, ages 20 to 29 (times/month)	14.0	14.2	14.5
History of gonorrhea (%)	2.7	2.5	1.5
History of syphilis (%)	0.2	0.4	0.5

*Assessed in 1990 through 1996.

†Assessed in 1990.

‡Cumulative mean intake between 1986 and 1990.

§ Adjusted for total energy intake.

|| Assessed through 2002.

** Defined as prostatitis of less than one years duration and treated before the age of 30.

†† Assessed in 1986.

‡‡ Assessed in 1988.

§§ Percentages do not sum to 100 due to missing responses.

|||| Defined by a body mass index <24.4 (75^{th} percentile) at age 21.

*** Defined by a body mass index ≥24.4 at age 21 and the lowest five of nine possible body pictograms at age 20.

††† Defined by the highest four of nine possible body pictograms at age 20.

Table 2

Relative risks (RRs) and 95% confidence intervals (CIs) of total prostate cancer for tetracycline use as a surrogate for severe acne among participants in the Health Professionals Follow-up Study, 1992–2002

	Tetracycline use of at least two months duration*		
	None	<4 years duration	≥4 years duration
Cases/person-years	2,071/304,822	55/8,919	16/1,569
Age-adjusted RR (95% CI)	1.00	1.06 (0.81–1.39)	1.63 (1.00–2.67)
Multivariable-adjusted RR† (95% CI)	1.00	1.05 (0.80–1.38)	1.70 (1.03–2.80)

*Participants with missing duration of tetracycline use (cases=5, person-years=422) were included in all regression models; results not shown.

†Adjusted for age, race/ethnicity (Caucasian, non-Caucasian) and cumulative family history of prostate cancer through 1996.