Published in final edited form as:
BJU Int. 2010 March ; 105(6): 824–829. doi:10.1111/j.1464-410X.2009.08853.x.

Serum testosterone is associated with aggressive prostate cancer in older men: results from the Baltimore Longitudinal Study of Aging

Phillip M. Pierorazio, **Luigi Ferrucci***, **Anna Kettermann**, **Dan L. Longo***, **E. Jeffrey Metter***, and **H. Ballentine Carter**
Department of Urology, The Johns Hopkins University School of Medicine, The James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, MD, USA

*National Institute on Ageing, Intramural Research Program, Baltimore, MD, USA

Abstract

OBJECTIVE—To evaluate the relationship between testosterone levels and the development of high-risk prostate cancer, by prospectively examining serum androgen concentrations in a well-studied cohort, as the role of testosterone in prostate cancer progression is debated.

PATIENTS AND METHODS—The study comprised 781 men in the Baltimore Longitudinal Study of Aging who had sex steroid measurements before a diagnosis of prostate cancer, or at their last visit for those without cancer (no cancer, 636; cancer, not high risk, 109; cancer, high risk, 36). High-risk cancer was defined as death from prostate cancer, a prostate specific antigen (PSA) level of ≥20 ng/mL at diagnosis, or a Gleason score of ≥8. The hazard ratio (HR) of high-risk disease was determined using a Cox proportional hazards regression model with simple updating, and risk rates were stratified by age and tercile for androgens of interest based on the proportional hazards analyses.

RESULTS—The likelihood of high-risk prostate cancer doubled per unit (0.1) increase in the free testosterone index (FTI) for patients aged >65 years (HR 2.07, 95% confidence interval, CI, 1.01–4.23; $P = 0.047$); the likelihood for men aged ≤65 years was inversely related to the FTI (HR 0.96, 95% CI 0.35–2.6; $P = 0.9$). The risk rate per person-years increased from lowest to highest tercile of FTI for the oldest men (age >70 years) but this trend was not apparent among younger men.

CONCLUSION—Higher levels of serum free testosterone are associated with an increased risk of aggressive prostate cancer among older men. These data highlight the importance of prospective trials to insure the safety of testosterone-replacement therapy.

Keywords

prostate cancer; testosterone; high-risk

Study Type – Prognosis (inception cohort) Level of Evidence 1b

Correspondence: Phillip M. Pierorazio, Department of Urology, Marburg 100, Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21287-2101, USA. philpierorazio@jhmi.edu.

CONFLICT OF INTEREST
None declared.

INTRODUCTION

Historically, prostate cancer and serum androgens, specifically testosterone, were thought to be directly related. This notion stems from the seminal work of Huggins and Hodges [1] who, in 1941, reported the regression of metastatic prostate cancer in three men after a reduction in serum testosterone levels, and the progression of metastatic disease and symptoms in one man to whom exogenous testosterone was given. Since then, dozens of reports have documented the importance of serum androgens in the progression and control of prostate cancer, a body of work on which many of the present clinical algorithms for advanced disease, specifically androgen-deprivation therapy, are based.

More contemporary work, since the mid-1990s, has challenged the traditional role that androgens were believed to play in prostate cancer, and sparked a controversy about their role in the pathophysiology and clinical treatment of men at risk of prostate cancer. This more recent work claims that low testosterone levels might be related to worse clinical and pathological determinants of prostate cancer including: (i) an increased risk of prostate cancer [2,3]; (ii) a worse 5-year biochemical relapse-free survival [3]; (iii) higher Gleason sums on biopsy [4,5]; (iv) an increased percentage positive-core rate at biopsy [4]; (v) worse pathological stage [6–8]; and (vi) an increased risk of positive surgical margins [9]. From this work, at least two theories have been proposed to explain the relationship between prostate cancer and serum testosterone levels, i.e. the ‘suppression theory’, that malignant prostate cells secrete an androgen inhibitor [10,11], and a ‘saturation theory’, that levels of serum androgens above a sufficiently low baseline level are sufficient to stimulate prostate growth (benign and malignant) [12]. The debates about finasteride in the prevention of prostate cancer (from the Prostate Cancer Prevention Trial) [13] and testosterone replacement in hypogonadal men [14] reflect the uncertainty of the association between androgens and prostate cancer.

The results of individual studies of androgens and prostate cancer vary, and fail to promote consensus on any one theory. Many of these studies are cross-sectional in design, examining serum hormone levels at one time point and neglecting the importance of longitudinal exposure to serum androgens [2–9]. Finally, many of these studies are in men with baseline hormonal dysfunction (i.e. hypogonadal men) [2,5] that might not be representative of the general population, and prevent the formation of universal guidelines or understanding of the disease process.

Therefore, we sought to examine the effect of longitudinal serum hormone exposure on the risk of developing high-risk prostate cancer in an ageing study, the Baltimore Longitudinal Study of Aging (BLSA, National Institute on Aging, NIA).

PATIENTS AND METHODS

The study population was extracted from the BLSA, a prospective cohort study begun in 1958 by the NIA (Bethesda and Baltimore, MD) [15]. Participants receive a comprehensive medical, physical and neuropsychological examination at regular intervals, including serial hormone measurements over a period of several decades. The Medical Star Institutional Review Boards and the Institutional Review Boards of the Johns Hopkins Medical Institutions (Baltimore, MD) approved this study, and all subjects gave written informed consent for their participation.

In 1991, a systematic review of BLSA records and questionnaires confirmed previous diagnoses of prostate cancer since 1958. Starting in 1991, men enrolled in the study had routine prostate cancer screening by a DRE and serum PSA measurements. A diagnosis of prostate cancer was confirmed by TRUS-guided biopsy in all men with a PSA level of >4.0 ng/mL or an abnormal DRE. Previous studies described the BLSA and the specific management of prostate cancer in greater detail [16,17].

In all, 1806 men have been enrolled in the BLSA, 794 with at least one serum androgen measurement. Thirteen men were excluded due to lack of a serum testosterone measurement before the diagnosis of prostate cancer, or the use of finasteride (a 5α-reductase inhibitor known to alter both serum androgen and PSA levels) leaving a total of 781 men and 2888 serum hormone measurements. The characteristics of these men are detailed in Table 1.

Serum assays were obtained from BLSA subjects between 07.00 and 09.30 h after a night of fasting. Sera were banked at the NIA and sent to Covance Laboratories, Inc. (Vienna, VA, USA) for the measurement of sex steroids, including serum testosterone, sex hormone-binding globulin (SHBG) and dehydroepiandrosterone sulphate (DHEAS). Specifics of the laboratory examination, processing and testing statistics were described previously [17,18]. The free testosterone concentration was calculated by the mass action equation [19]; the free testosterone index (FTI) was calculated as the molar ratio of testosterone to SHBG.

High-risk disease cancer was defined as prostate cancer with adverse clinical and pathological features including death from disease, a PSA level of >20 ng/mL or a Gleason sum of ≥8 (according to the modified criteria of D'Amico *et al.* [20]). The D'Amico criteria have been investigated and validated as surrogate markers for outcome after radiotherapy and radical prostatectomy for prostate cancer [21].

Of the 781 men studied, 636 were not diagnosed with prostate cancer; of the 145 men diagnosed with prostate cancer, 36 were identified as having high-risk disease. The remaining 109 were identified as having prostate cancer, but not high-risk disease. For the purposes of statistical analysis, the patients without high-risk prostate cancer and those without prostate cancer were combined into one larger group of 745 patients.

Anthropometric characteristics (e.g. height and weight), age, number of visits, time between the visits and levels of sex steroids were compared between the high-risk group and the remaining men using pooled *t*-tests in the case of equal variances and Cochran *t*-tests in the case of unequal variances. All statistical tests were two-sided and $P < 0.05$ was considered to indicate statistical significance.

A Cox proportional-hazard analysis was used to determine the longitudinal contribution of multiple repeat serum hormone levels to the development of high-risk prostate cancer. The time-dependent approach used the Anderson-Gill formulation as a counting process using functions developed by Therneau and Grambsch [22]. Hazard proportionality was tested by plotting the Schoenfeld residuals against a log function of time. No evidence was found for nonproportionality for the variables examined in this study.

The risk rate of high-risk disease per person-years was determined for three separate age groups (<60, 60–70 and >70 years) and stratified into terciles for variables of interest identified in the proportional-hazard analyses. For each age group only one observation per person was analysed. The observations were taken closest to age 55 years in the youngest group, closest to the 65 years in the 60–70 group and 75 years in the oldest group. The risk rate within each group was calculated as a ratio of the number of events to the total follow-up time for all subjects, multiplied by 100 000.

RESULTS

The median age at the first visit was 51.4 years for the entire cohort (Table 1). Notably, the men who developed high-risk prostate cancer were a mean of 7.7 years older at presentation than the remainder ($P < 0.001$). Sex steroid data spanned a median of 22 years, and the median number of measurements was four. The mean and median hormone levels at the first visit are shown for all men in Table 1.

The proportional-hazard analysis was conducted for each hormone, with adjustment for age and date of the sample. Three of the hormones were significantly associated with high-risk prostate cancer and two were not. SHBG was significantly associated with high-risk disease, with a per nmol/L hazard ratio (HR, 95% CI) of 0.98 (0.971–0.996) ($P = 0.008$), as was FTI (per 0.1 unit) of 1.91 (1.101–3.321) ($P = 0.02$) and calculated free testosterone (per ng/dL) of 1.61 (1.18–2.204) ($P = 0.003$). Total serum testosterone (per ng/dL) had a HR of 1.002 (0.998–1.007) ($P = 0.28$) and DHEAS (per ng/ mL) of 1 (0.999–1.0) ($P = 0.66$), and were not significantly associated with high-risk prostate cancer.

To show the association between FTI and the development of high-risk prostate cancer, the proportional-hazards model that included FTI, age and date of sample was solved for three hypothetical 50-year-old men, each of whom were tracked with constant age-adjusted FTI levels, at the 5th, 50th and 95th percentiles, respectively (Fig. 1). Differences in survival began to appear close to the age of 65 years, so that by the age of 80 years the probability of developing high-risk prostate cancer for a man at the fifth percentile and 50th percentile of FTI was estimated as 3.8% and 6.4%, respectively, compared to a rate of 13.6% for a man at the 95th percentile of FTI ($P < 0.001$).

Risk rates per 100 000 person-years in each age group subdivided by tercile of FTI are shown in Table 2. Notably, the rate per 100 000 patient-years increased from 679 to 1166 between the lowest and highest tercile in men aged >70 years. By contrast, in the youngest group the rate was 760 per 100 000 in the lowest tercile and decreased to 590 per 100 000 for the highest tercile. These observations suggest a differential risk of high-risk prostate cancer by FTI for younger and older men.

We repeated the hazard analysis for high-risk disease by FTI for those patients aged <65 years (625 men; high-risk disease, 26) and those aged ≥65 years (381; high-risk disease, 26). In this analysis the longitudinal cohort was divided into two groups based on age, and thus a patient could appear in both groups at different times in the course of enrolment in the study. For men aged >65 years the likelihood of high-risk disease increased (HR 2.07, 95% CI 1.01–4.23, $P = 0.047$), with double the likelihood of high-risk disease per unit increase (0.1) in FTI. For men aged <65 years there was an inverse association between FTI and high-risk prostate cancer (HR 0.96, 95% CI 0.35–2.6, $P = 0.9$) that was not statistically significant. When we removed men with prostate cancer who were not high-risk from the analysis, the trend for FTI did not change when comparing those aged >65 years (HR 2.35, 95% CI 1.17–4.72) and those age ≤65 years (HR 0.98, 95% CI 0.39–2.49).

DISCUSSION

In summary, older men in the highest tercile of serum testosterone measurements, in the form of calculated free testosterone and FTI, are at greater risk of developing aggressive prostate cancer that caused the death of the patient, or cancer with adverse pathological features known to portend a worse prognosis [21]. Our study is an extension of two previous studies from the BLSA involving serum androgens and prostate cancer. These studies, respectively, showed no difference in serum androgens among men destined to develop prostate cancer and those with benign prostatic disease, in a small case-control analysis [23]; and an increased risk of developing prostate cancer in men with higher levels of calculated free testosterone with a concomitant 49% decrease in the risk of prostate cancer for men with hypogonadal levels of FTI (<0.153) [17]. In all, our studies in the BLSA show an increased risk of prostate cancer in general and high-risk disease in particular, with increasing levels of free testosterone. This is an important conclusion in the light of several contemporary publications championing the safety and efficacy of testosterone replacement in hypogonadal men at risk of developing prostate cancer or with a history of prostate cancer [2,14,24,25].

While many studies have explored the relationship between prostate cancer and serum androgens, the association remains ill-defined and clinical implications are difficult to decipher. Age is one factor that complicates the interaction between prostate malignancy and serum hormone levels, especially as testosterone levels begin to decrease in the ageing man coincidentally as the incidence of prostate cancer starts to increase. When exploring the data in this study, it was increasingly apparent that age was one of the most important factors driving the observed relationship between elevated free testosterone measures and the likelihood of high-risk prostate cancer. The decade difference in age at presentation among the patients at risk of aggressive disease certainly accounts for some of the increased observed rate of high-risk disease in these men. Adjustment for age and age stratification suggested that it is older men for whom the relationship between FTI and aggressive cancer is strongest; the risk of a diagnosis of aggressive cancer is increased only among men at a greater age as FTI increases (Table 2). Although speculative, this might be explained by a dichotomy in the effect of testosterone on prostate cancer development and progression by age. For example, for younger men androgens might be protective by promoting typical growth and maturation of the prostate, while for older men in whom malignant transformation has occurred, androgens might be harmful by promoting disease progression. The importance of age-related androgen levels is highlighted by the analysis described in Table 2 and the Cox multivariate models, which showed a strong relationship between age, testosterone levels and the likelihood of high-risk disease. This lends strength to the argument that high or even normal values of serum testosterone might be related to the development of high-risk prostate cancer in older men.

Other investigations, including a nested case-control study of the US Physicians' Health Study, observed a direct relationship between total serum testosterone and FTI and the risk of prostate cancer that was accentuated in an older population of men [26]. However, most prospective studies, including a recent meta-analysis of 18 such studies, found no significant association between hormone levels and the risk of prostate cancer [27]. The unique feature and strength of the present study that separates it from others, and might explain the discrepancy between findings, is the examination of longitudinal hormone measures that account for serial exposure as each man ages, instead of point evaluations of hormone status. The current analysis represents a total of 781 men and nearly 3000 total hormone measurements that were gathered in a cohort of the American population at risk of prostate cancer over a median of four visits, spanning two decades. This might provide a more complete and inclusive depiction of hormone levels and exposure to androgens than previous studies that only included single hormone measures [2–9].

When analysing serum androgens in relation to prostate cancer, the focus is often on testosterone and its varying forms, especially in the contemporary debate over testosterone replacement in men at risk of prostate cancer. The quantitative relationship between testosterone and other serum proteins, e.g. SHBG, is closely related; however, the relationship of pathological processes, like prostate cancer, to varying levels of androgens is not well elucidated, nor is their relationship in hypogonadal vs eugonadal men. Interestingly, when compared to men from the Physicians' Health Study [26], which similarly reported an increased risk of prostate cancer with elevated levels of serum testosterone and lower levels of SHBG, men in the present study had similar (eugonadal) levels of circulating androgens. On the other hand, the study from Morgentaler and Rhoden [2], which showed an increased risk of prostate cancer with lower levels of serum testosterone, was a markedly different population, one with distinctly hypogonadal men with low levels of circulating androgens.

Therefore, it is important to recognize the androgen status of each study population, and that high or low serum androgens might have distinct implications in different subpopulations of men (i.e. the hypogonadal vs the eugonadal) at risk of prostate cancer. This might help to explain the heterogeneity of results in many studies investigating the risk of prostate cancer as

a function of androgen level, especially as testosterone replacement can alter levels of other circulating hormones and proteins [28].

Although formal clinical recommendations for the use of hormonal-replacement therapy in ageing men cannot be gleaned from our analyses, this study stresses the importance of defining the role of androgens in prostate cancer development and progression before recommending the widespread use of these agents with the hope of improving quality of life. This consideration is more relevant, as recent studies failed to show an improvement in quality of life in men who had androgen-replacement therapy [25]. The efficacy of androgen replacement in improving the quality of life of men remains unclear. The question remains, to what risks and what benefits are hypogonadal men exposed when the magnitude of neither the risks nor the benefits is well-known?

Important limitations of this study include long shelf-lives for many of the serum samples. Although this was accounted for in multivariable analysis, the time to serum analysis in a sample this large, and spanning so many decades, might introduce both measurement bias and statistical errors. However, it remains consistent with previous studies from the BLSA. In addition, FTI remains an unvalidated surrogate of androgen function when compared to calculated free testosterone. Despite the longitudinal analysis, this study is retrospective and the BLSA was not specifically designed to assess male androgen function and the development of prostate cancer.

Therefore we conclude that higher levels of calculated serum free testosterone are associated with an increased risk of aggressive prostate cancer among older men. Well-designed prospective trials are necessary to define the role of testosterone in the development of prostate cancer and insure the safety of testosterone-replacement therapy.

Acknowledgments

Supported by the Intramural Research Program of the NIH, National Institute on Ageing.

Abbreviations

BLSA	Baltimore Longitudinal Study of Aging
NIA	National Institute on Aging
FTI	free testosterone index
SHBG	sex hormone-binding globulin
DHEAS	dehydroepiandrosterone sulphate
HR	hazard ratio

REFERENCES

1. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate 1941. J Urol 2002;168:9–12. [PubMed: 12050481]
2. Morgentaler A, Rhoden EL. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less. Urology 2006;68:1263–7. [PubMed: 17169647]
3. Yamamoto S, Yonese J, Kawakami S, et al. Preoperative serum testosterone level as an independent predictor of treatment failure following radical prostatectomy. Eur Urol 2007;52:696–701. [PubMed: 17412490]

4. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? J Urol 2000;163:824–7. [PubMed: 10687985]
5. Schatzl G, Madersbacher S, Thurridl T, et al. High-grade prostate cancer is associated with low serum testosterone levels. Prostate 2001;47:52–8. [PubMed: 11304729]
6. Massengill JC, Sun L, Moul JW, et al. Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. J Urol 2003;169:1670–5. [PubMed: 12686805]
7. Imamoto T, Suzuki H, Fukasawa S, et al. Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with radical prostatectomy. Eur Urol 2005;47:308–12. [PubMed: 15716191]
8. Isom-Batz G, Bianco FJ Jr, Kattan MW, Mulhall JP, Lilja H, Eastham JA. Testosterone as a predictor of pathological stage in clinically localized prostate cancer. J Urol 2005;173:1935–7. [PubMed: 15879785]
9. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM. Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. J Urol 2005;174:2178–80. [PubMed: 16280759]
10. Miller LR, Partin AW, Chan DW, et al. Influence of radical prostatectomy on serum hormone levels. J Urol 1998;160:449–53. [PubMed: 9679896]
11. Schaeffer EM, Walsh PC. Risks of testosterone replacement. N Engl J Med 2004;350:2004–6. author reply 2006. [PubMed: 15131839]
12. Fowler JE Jr, Whitmore WF Jr. The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. J Urol 1981;126:372–5. [PubMed: 7277602]
13. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215–24. [PubMed: 12824459]
14. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 2004;350:482–92. [PubMed: 14749457]
15. Shock, NW.; Greulich, RC.; Andres, R., et al. Normal Human Aging: the Baltimore Longitudinal Study of Aging. US GPO; Washington, DC: 1984. (NIH publication no. 84-2450)
16. Carter HB, Ferrucci L, Kettermann A, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. J Natl Cancer Inst 2006;98:1521–7. [PubMed: 17077354]
17. Parsons JK, Carter HB, Platz EA, Wright EJ, Landis P, Metter EJ. Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. Cancer Epidemiol Biomarkers Prev 2005;14:2257–60. [PubMed: 16172240]
18. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724–31. [PubMed: 11158037]
19. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84:3666–72. [PubMed: 10523012]
20. D'Amico AV, Moul JW, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. J Natl Cancer Inst 2003;95:1376–83. [PubMed: 13130113]
21. McAleer SJ, Schultz D, Whittington R, et al. PSA. outcome following radical prostatectomy for patients with localized prostate cancer stratified by prostatectomy findings and the preoperative PSA level. Urol Oncol 2005;23:311–7. [PubMed: 16144663]
22. Therneau, T.; Grambsch, P. Modeling Survival Data: Extending the Cox Model. Springer; New York: 2000.
23. Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. Prostate 1995;27:25–31. [PubMed: 7541528]
24. Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. JAMA 2006;296:2351–61. [PubMed: 17105798]

25. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. JAMA 2008;299:39–52. [PubMed: 18167405]

26. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 1996;88:1118–26. [PubMed: 8757191]

27. Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 2008;100:170–83. [PubMed: 18230794]

28. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. J Clin Endocrinol Metab 2002;87:1467–72. [PubMed: 11932266]

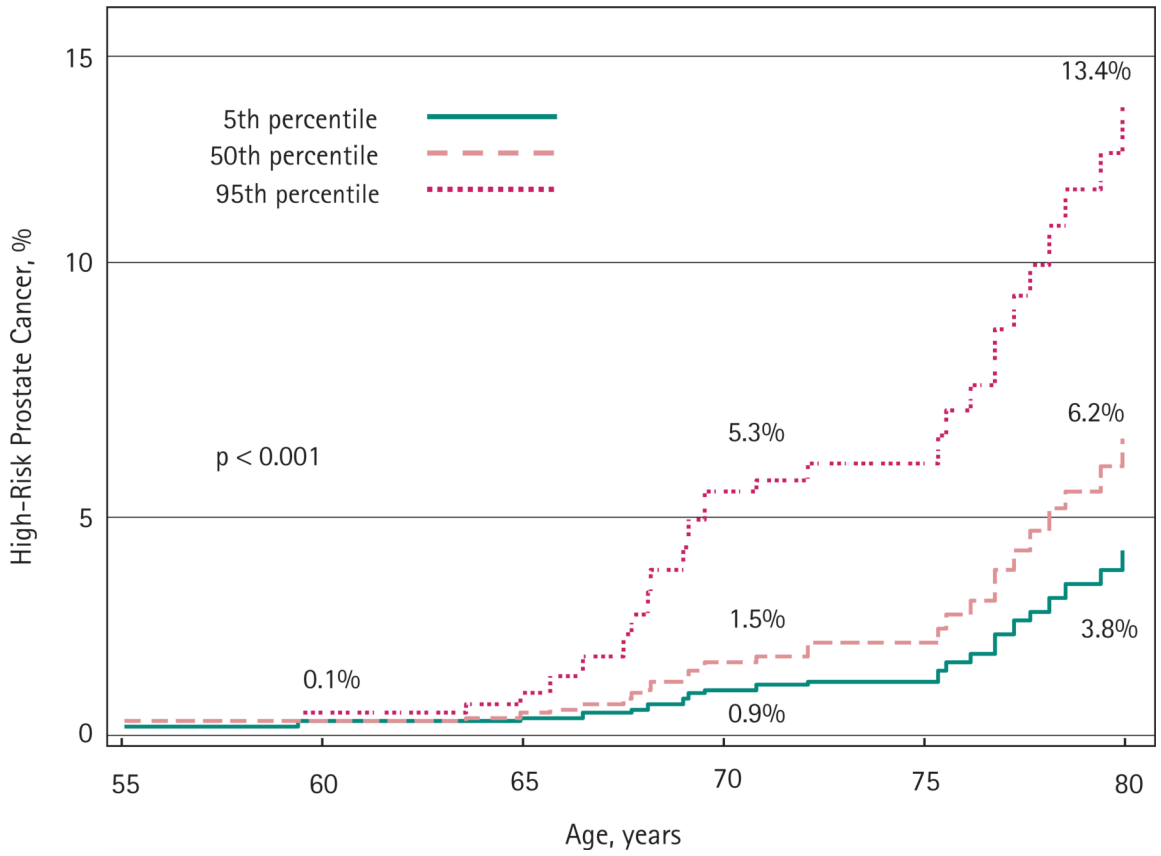

FIG. 1.

The FTI vs the rate of high-risk prostate cancer; results of proportional-hazards model that includes FTI, age and date of sample that was solved for three hypothetical 50-year-old men, each of whom were tracked with constant age-adjusted FTI levels, at the fifth, 50th and 95th percentiles, respectively. Differences in survival appear to be similar to age 65 years, so that by age 80 years the probability of developing high-risk prostate cancer for a man at the fifth percentile and the 50th percentile of FTI was estimated as 3.8% and 6.4%, respectively, compared to a rate of 13.6% for a man at the 95th percentile of FTI (P < *0.001).*

TABLE 1

The characteristics of the men at the initial visit

Median (range), mean (SD) variable	All men	Others*	High-risk	*P*
No. of men	781	745	36	
Age, years	51.4 (22.5, 90)	50.7 (22.5, 90)	58.4 (43.2, 86)	
	51.6 (15.2)	51.2 (15.2)	60.3 (11)	<0.001
Height, cm	176.8 (157.7, 197.6)	176.8 (157.7, 197.6)	176.5 (158.5, 192.4)	
	177 (6.7)	177.1 (6.7)	176.2 (6.3)	0.42
Weight, kg	79 (53.3, 152)	79.0 (53.3, 152.1)	76.9 (64.8, 105.5)	
	80.5 (12.5)	80.6 (12.6)	77.6 (9)	0.06
Number of visits	4 (1, 8)	4 (1, 8)	4 (1, 7)	
	3.7 (1.8)	3.7 (1.8)	3.8 (1.7)	0.64
Time between visits, years	2.6 (0.9, 18.3)	2.6 (0.9, 18.3)	3.6 (0.9, 11.5)	
	4 (2.9)	4 (2.9)	4.1 (2.6)	0.82
Total testosterone, ng/dL	450.9 (72.3, 856.9)	451.2 (72.3, 856.9)	435.2 (134.1, 726.3)	
	460.4 (116.1)	461.4 (115.6)	440.3 (127.1)	0.29
FTI	0.24 (–0.05, 0.75)	0.24 (–0.05, 0.75)	-	
	0.25 (0.12)	0.25 (0.12)	0.20 (0.09)	0.083
SHBG, nmol/L	78.3 (18.73, 229.7)	78.5 (18.73, 229.7)	72.7 (33.41, 150.8)	
	81.97 (26.5)	82.08 (26.4)	79.68 (28.0)	0.06
DHEAS, ng/mL	1630 (112, 6666)	1670 (112, 6666)	1330 (367, 4720)	
	1828.3 (1108)	1846.3 (1108.8)	1473.47 1045)	0.063
Free testosterone, ng/dL	5.05 (0.62, 13.52)	5.05 (0.62, 13.52)	4.84 (1.59, 8.745)	
	5.21 (1.74)	5.22 (1.75)	5.02 (1.63)	0.52

* Includes non-cancers and cancers defined as not high-risk.

TABLE 2

Patients with high-risk prostate cancer (events) per person-years by tercile of FTI

	Age group, years		
FTI tercile	**≤60**	**60–70**	**>70**
I			
Events/person-years*	760	730	679
N events	7	7	4
N other	172	116	83
II			
Events/person-years	494	884	864
N events	7	10	7
N other	171	112	81
III			
Events/person-years	590	684	1166
N events	7	9	11
N other	176	117	81

*Rates per 100 000 person-years.