

# Elevated Prostate-Specific Antigen Levels Up to 25 Years Prior to Death from Prostate Cancer

Lewis H. Kuller,<sup>1</sup> Avis Thomas,<sup>2</sup> Gregory Grandits,<sup>2</sup> and James D. Neaton,<sup>2</sup> for the Multiple Risk Factor Intervention Trial Research Group

<sup>1</sup>Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA and <sup>2</sup>Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN

## Abstract

**Objective:** We tested the hypothesis that prostate-specific antigen (PSA) levels would be higher among prostate cancer deaths as compared with controls over time in the 25-year follow-up of the Multiple Risk Factor Intervention Trial of participants ages 35–57 at entry. **Methods:** The initial stored serum samples were collected in 1973–1975 and the mean length of follow-up to prostate cancer death was 17 years. **Results:** There were 63 prostate cancer deaths and 63 controls matched by age, clinical site, and length of follow-up. The mean PSA level for prostate cancer decedents was 2.84 ng/ml as compared with 1.10 ng/ml for controls ( $P = 0.002$  for difference). There were nine men who died from

prostate cancer and no controls with PSA levels > 4 ng/ml. Risk of prostate cancer death increased with increasing PSA levels, with increased risk observed even at moderate levels of PSA. Many of those with high PSA levels in 1973–1975 died from prostate cancer many years after the elevated PSA. **Conclusion:** PSA levels measured from blood obtained before the introduction of widespread PSA testing were a strong predictor of prostate cancer death over 25 years of follow-up. Studies of prostate cancer etiology and chemoprevention need to focus on middle-aged or younger men with longer follow-up. (Cancer Epidemiol Biomarkers Prev 2004;13(3):373–377)

## Introduction

Prostate cancer is a growing health care problem in North America and Europe (1). Greater life expectancy among men has led to an increasing number of older men at risk for prostate cancer. Prostate cancer incidence and mortality increases dramatically with age (2, 3). Screening for prostate cancer using prostate-specific antigen (PSA) remains controversial. The U.S. Preventive Services Task Force concluded that the evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA or digital rectal examination (4). The U.S. Preventive Services Task Force found good evidence that PSA screening can detect early-stage prostate cancer but found mixed or inclusive evidence that early detection improves health outcomes.

Helzlsouer *et al.* (5) used the Washington County, Maryland Study to evaluate the association between a single PSA measurement and development of prostate cancer (5). They reported that among 35 men who subsequently developed prostate cancer over a 6-year period and 35 matched controls, the levels of PSA were significantly higher for men who went on to develop

prostate cancer. The levels of PSA decreased with increasing time to diagnosis.

Gann *et al.* (6), in a nested case-control study of participants in the Physicians' Health Study, evaluated PSA levels at entry in 366 men who subsequently developed prostate cancer and 1098 age-matched controls. At a cutoff of 4 ng/ml, sensitivity for the entire 10-year follow-up was 46% and specificity was 91%. The relative risk (RR) of prostate cancer over the 10 years of follow-up was 2.2 for men with PSA levels between 1.0 and 1.5 ng/ml compared with men with PSA levels  $\leq 1.0$ . Among men with PSA levels of 2.0–3.0 ng/ml, risk was increased 5-fold and for more aggressive cancers nearly 7-fold. Men with PSA levels > 2.0 ng/ml were >12 times as likely to be diagnosed with prostate cancer over the 10 years compared with men with PSA levels  $\leq 1$  ng/ml. RR estimates were similar in younger and older men.

Fang *et al.* (7) evaluated PSA as a predictor of long-term risk of prostate cancer from the Baltimore Longitudinal Study of Aging. The RR for prostate cancer associated with a median cutoff point of 0.59 ng/ml for those ages 40–50 at entry was 3.6 [95% confidence interval (CI) 1.6–8.6], and the RR for those ages 50–60 at entry with a median cutoff point of 0.70 ng/ml was 3.5 (95% CI 2.0–6.2). One of the limitations of this study is that 45 of the 60 cases occurred after 1990, when widespread prostate cancer screening began, and it is unclear whether the prostate cancer screening of these men resulted in further evaluation and biopsy and the diagnosis of cancer. The cancer detection rate increased substantially in this cohort after the introduction of PSA cancer screening (8), and this increase would presumably be greater in those with elevated PSA levels.

Received 10/14/03; revised 12/15/03; accepted 12/22/03.

**Grant support:** Grant R01-HL-68140 from the National Heart, Lung, and Blood Institute (Bethesda, MD).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

**Note:** The principal investigators and senior staff of the MRFIT clinical, coordinating, and support centers and the National Heart, Lung, and Blood Institute Project Office were published previously (*JAMA* 1982;248:1476–7).

**Requests for reprints:** Greg Grandits, Division of Biostatistics, University of Minnesota 2221, University Ave SE, Suite 200, Minneapolis, MN 55414. Phone: (612) 626-9033; Fax: (612) 626-9054. E-mail: grandool@umn.edu

In the present study, we evaluated the relationship between PSA levels measured from frozen sera obtained from men ages 35–57 at entry to the Multiple Risk Factor Intervention Trial (MRFIT) during 1973–1975 and subsequent death from prostate cancer through 1999. We tested the hypothesis that PSA levels would predict mortality from prostate cancer among relatively young men at entry during the period when screening for prostate cancer was not prevalent in the United States.

## Materials and Methods

**Study Design of the Main Trial.** The design, methods, and results of MRFIT have been reported (9–12). Briefly, MRFIT was a randomized controlled trial on the primary prevention of coronary heart disease (CHD) mortality among 12,866 men ages 35–57 at baseline (mean 46 years) who were at increased risk of CHD but who did not have definitive clinical evidence of CHD at the time of enrollment. Men were randomized between December 1973 and February 1976 and those assigned to the special intervention group received an intensive integrated effort toward hypertension control, quitting smoking, and a nutritional intervention to reduce saturated fat and cholesterol intake and to promote weight loss and physical activity. Men in the usual care group were referred to their usual health care provider. Through February 28, 1982, participants in both groups returned annually for a physician examination, blood collection, and completion of a behavioral and medical history questionnaire. Since the end of the trial, participants have been followed for mortality status through use of the Social Security Administration and National Death Index (NDI).

**Mortality Ascertainment.** Mortality during the trial (through February 28, 1982) was ascertained by clinical staff (11). Post-trial mortality (from March 1, 1982 to December 31, 1999) was determined by matching identifying information originally provided by each participant with NDI records and Social Security Administration (13, 14). For deaths identified through 1990, death certificates were obtained and cause of death was coded independently by two nosologists using *International Classification of Diseases (ICD)-9* (15); a third nosologist adjudicated disagreements. For deaths identified after 1990, causes of death were obtained using the NDI Plus service (16), which provided the *ICD-9* (1991–1998) or *ICD-10* (1999; 17) coding. Deaths due to prostate cancer were defined by an *ICD-9* code of 185 (*ICD-10* code of C61).

**Design of Case-Control Study.** At the second of three screening visits, a serum sample was obtained for future use and stored in freezers at  $-50^{\circ}\text{C}$  to  $-70^{\circ}\text{C}$ . Through December 1999, 121 deaths attributable to prostate cancer were identified. Sixty-three had sera available. The remaining 58 samples were unavailable, having been used as control samples in other case-control studies, none related to prostate cancer. The 63 cases were matched with one control for age at randomization ( $\pm 1$  year), clinical center, and for survival time (*i.e.*, the control needed to be alive at the same follow-up time from randomization as the case's death). The mean

follow-up between randomization (approximate time of blood draw) and death for the 63 cases was  $18 \pm 4$  years (range 6–25 years). For the 56 prostate cancer deaths without sera available, the mean was  $17 \pm 5$  years (range 6–24 years). Morbidity data (*i.e.*, incident prostate cancer cases that did not die) are not available in the MRFIT database, nor are other characteristics, including treatment, of the prostate cancer cases following February 1982.

**Laboratory Methods.** Serum samples were shipped on dry ice from the MRFIT Coordinating Center at the University of Minnesota to the University of Pittsburgh. Aliquots were made and analyzed for PSA at the University of Pittsburgh Central Laboratory using an automated microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL).

**Statistical Methods.** Student's *t* test and conditional logistic regression (18) for matched pairs were used to summarize the association of PSA levels with prostate cancer mortality. Quartiles of the distribution of PSA were formed and odds ratios with 95% CI values for quartiles 2–4 compared with quartile 1 were estimated. A test for linear trend was also performed using PSA as a continuous variable. Adjusted and unadjusted analyses were done. Covariates in the adjusted model were cigarettes/day, race (black *versus* all other), low density lipoprotein (LDL) cholesterol, alcoholic drinks/week, and body mass index (BMI).

With 63 cases and 63 controls, we had 80% power to detect a 0.38 SD unit difference in mean PSA between cases and controls.

## Results

There were 63 prostate cancer decedents: 1 (1.6%) before 1982, 2 (3.2%) between 1982 and 1985, 21 (33.3%) between 1986 and 1990, 15 (23.8%) between 1991 and 1995, and 24 (38.1%) between 1996 and 1999. The mean time between collection of the serum sample and subsequent death from prostate cancer was  $18 \pm 4$  years (range 6–25 years). A comparison of characteristics at entry between the 63 prostate cancer decedents and the 63 controls are shown in Table 1. Mean age was 50.5 years,  $\sim 4$  years higher than the entire MRFIT cohort, and was equal for cases and controls by design. Ten percent of the prostate cancer decedents were black as compared with 8% of the controls. More cases smoked than controls and cases had slightly higher levels of total and LDL cholesterol and 1-h glucose than matched controls. Blood pressure, triglycerides, fasting glucose, alcohol consumption, leisure time physical activity, and percent of dietary fat were similar between cases and controls. None of the differences between cases and controls were statistically different ( $P > 0.05$ ). In addition, there were no significant differences in these characteristics between prostate cancer deaths with stored blood available for PSA testing and prostate cancer deaths without blood available (mean age 50.5 *versus* 50.7, respectively, for those with and without blood available).

The mean PSA for the prostate cancer decedents was 2.84 ng/ml compared with 1.10 ng/ml for the controls ( $P = 0.002$ ; Table 2). Among the 10 cases and controls 35–44 years at entry, the difference was 1.4 ng/ml ( $P = 0.09$ );

**Table 1. Baseline characteristics of MRFIT cases and controls**

Characteristic	Cases	Controls	P
Sample size	63	63	–
Age (yr) at entry	50.5	50.5	–
Black race (%)	9.5	7.9	0.75
Smokers (%)	60.3	54.0	0.47
Cigarettes/day for smokers	32.4	30.5	0.52
BMI (kg/m <sup>2</sup> )	27.4	26.9	0.41
Systolic blood pressure (mm Hg)	137.5	136.6	0.75
Plasma cholesterol (mg/dl)	245.2	240.6	0.48
LDL cholesterol (mg/dl)	163.6	158.1	0.42
High-density lipoprotein cholesterol (mg/dl)	44.1	44.7	0.80
Triglycerides (mg/dl)	185.4	194.3	0.75
Fasting glucose (mg/dl)	101.5	98.1	0.14
1-h glucose (mg/dl)	183.9	169.7	0.07
Alcoholic drinks/week	10.1	11.7	0.38
Leisure time physical activity (% <30 min/day)	34.5	27.6	0.42
Dietary fat (% kcal)	37.4	36.9	0.77
Average years from randomization to death	18.1	–	–

for those 45–57 years, the difference was 2.4 ng/ml ( $P = 0.01$ ). Nine prostate cancer decedents had PSA levels > 4 ng/dl, usually considered to be an abnormal level; no controls had levels > 4 ng/dl. The mean PSA levels when the nine cases with PSA  $\geq 4$  are excluded was  $1.39 \pm 0.83$  for cases and  $1.08 \pm 0.34$  for controls.

The odds ratios by PSA quartiles are shown in Table 3. Risk increased linearly across the quartiles, with increased risk observed even at relatively low levels of PSA. Compared with men who had PSA levels < 0.7 ng/ml, risk was 1.51 greater for PSA levels 0.7–1.0, 3.16 greater for levels 1.1–1.8, and 7.26 greater for levels above 1.8. For PSA levels between 1.9 and 3.9, the RR was 5.0 (95% CI 1.33–18.8). CI values were wide, with the number of men in each category relatively small. Adjustment for race, smoking, LDL cholesterol, alcohol, and BMI yielded similar results to the unadjusted analyses, with slightly higher RR values for each quartile.

The average PSA levels for the prostate cancer decedents before 1982 ( $n = 1$ ) was 8.4 ng/ml; for those dying between 1982 and 1985, it was 2.8 ng/ml; for those between 1986 and 1990, 3.8 ng/ml; for 1991–1995, 1.9 ng/ml; and for 1996–1999, 2.3 ng/ml (Fig. 1). PSA levels were higher in the cases as compared with the controls at each time point, although the differences between cases tended to be smaller for deaths occurring later in follow-up. Control values were similar across the time intervals. Of the participants with baseline PSA levels > 4 ng/ml, there was one decedent in 1980 with a PSA level of 8.4 ng/ml, one in 1988 with a PSA level of 4.1 ng/ml, one in 1988 with a PSA level of 20.7 ng/ml, one in 1989 with a PSA level of 17.4 ng/ml, one in 1990 with a PSA level at baseline of 11.7 ng/ml, one in 1993 with a baseline PSA of 9.3 ng/ml, one in 1997 with a PSA at baseline of 17.6 ng/ml, and one in 1998 with a PSA level of 9.7 ng/ml. Thus, some of the decedents had extremely high PSA values in 1973–1975 and died many years later.

**Table 2. Distribution of PSA levels for 63 prostate cancer deaths and matched controls**

PSA (ng/ml)	PSA distribution					
	Cases		Controls		Cases + Controls	
	n	%	n	%	n	%
$\leq 0.5$	7	11.1	18	28.6	25	19.8
0.6–1.0	15	23.8	23	65.1	63	30.2
1.1–2.0	20	31.8	14	22.2	34	27.0
2.1–3.0	10	15.9	4	6.4	14	11.1
3.1–4.0	2	3.2	4	6.4	6	4.7
4.1–5.0	2	3.2	0	0	2	1.6
5.1–10.0	3	4.8	0	0	3	2.4
>10.0	4	6.4	0	0	4	3.2
Total	63	100	63	100	126	100
Mean	2.84		1.10		1.97	
SD	4.22		0.81		3.15	
Case control						
Difference $\pm$ SE	1.74 $\pm$ 0.54					
Z-statistic (P)	3.23 (0.002)					

## Discussion

The results of MRFIT are consistent with the three previous studies reported showing that PSA levels, even in relatively young men, over long-term follow-up are predictors of the risk of prostate cancer. Moreover, results from MRFIT were consistent in showing significant elevated risk even among men with modest elevations of PSA. The majority of prostate cancers in this study occurred among men with relatively low PSA levels at entry to MRFIT.

We lack data on incident prostate cancer cases that survived. The risk of prostate cancer death is strongly related to stage at diagnosis. It is very likely that some of the incident prostate cancer cases could have died of other causes than prostate cancer, especially CHD, and be included in the pool of possible “controls” (*i.e.*, nonprostate cancer death). For example, men with localized prostate cancer have only a 4–7% risk of dying from prostate cancer over 15 years as compared with 60–80% risk of prostate cancer death with advanced disease (19).

It is very unlikely that the exclusion of prostate cancer deaths without available serum could have biased the results. There has been no previous study of prostate cancer in MRFIT. The missing bloods were due to their prior use as “random controls” for other studies. Furthermore, important factors such as age, smoking status at entry, and length of time from blood draw to death were similar between prostate cancer deaths with and without stored serum available.

**Table 3. Matched logistic regression summary of the relationship between prostate cancer death and level of PSA: MRFIT men by quartile of PSA**

PSA quartile (ng/ml)	RR	95% CI
0.2–0.6	1.00	–
0.7–1.0	1.51	0.44–5.22
1.1–1.8	3.16	0.99–10.1
1.9–20.7	7.26	1.95–27.0

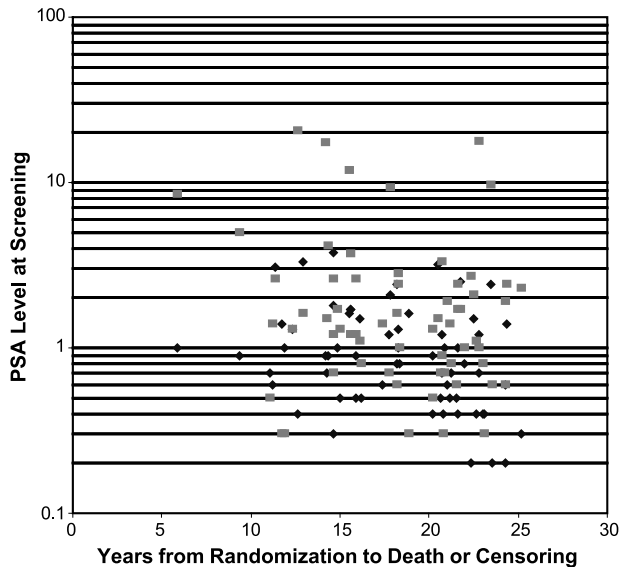


Fig. 1. PSA levels at screening by years to death or censoring. ◆, controls; ■, cases.

The results of MRFIT have important implications both for epidemiological studies of prostate cancer and for screening and early detection of prostate cancer and primary prevention. First, as has been noted in the other studies, the development of prostate cancer likely begins at younger ages (*i.e.*, in the 40s and 50s). The incubation period for the development of clinical prostate cancer and especially death from prostate cancer is very long (7). Epidemiological studies that evaluate biochemical measures, nutrients, or even proteomics 5–10 years prior to the diagnosis of prostate cancer are likely measuring variables related to the progression of subclinical prostate cancer to clinical disease rather than to the etiology of the tumor. Measures of inflammation and growth factors may reflect the evolving pathology of prostate cancer and not be part of the etiological pathway (*i.e.*, reverse causality).

Second, the study of risk factors of prostate cancer probably needs to begin in middle-aged men (<55 years). Studies in older-aged men may not be very enlightening unless variables of interest are stable over a long period of time. Obviously, because genetic factors do not change over time, they would only be influenced by differential survival. However, the study of gene-environmental interaction may be complicated by the long incubation of the evolving prostate cancer (20).

Third, a major criticism of screening for prostate cancer is the long time period between diagnosis and morbidity or death and the likelihood that many older men screened positive for prostate cancer may die of causes other than prostate cancer and would not benefit and potentially be harmed from therapy for their prostate cancer (21). However, our study suggests that men with PSA levels > 4 ng/ml have a particularly high risk of death from prostate cancer. All nine individuals in this study with PSA levels > 4 ng/ml died of prostate cancer. Long-term chemoprevention might be effective for these high-risk men (22–24).

In the European Randomized Study (ERS) of Prostate Cancer Screening, the prevalence of PSA > 4 ng/ml from the population sample in Finland at ages 55, 59, 63, and 67 was 4%, 7%, 11%, and 16%, respectively (25). It is difficult to assess the absolute risk of dying from prostate cancer in these men. The short-term risk, even up to 10–15 years, may be low, although our data suggest that the long-term risk (20–25 years) may be quite high. Using prevalence data from ERS and results from MRFIT, we can obtain a crude estimate of the long-term risk of prostate cancer death for men with PSA > 4.0 ng/ml. In MRFIT, the approximate 25-year death rate from prostate cancer among the 7918 randomized men ages 45–57 was 1.34% (106 men). If we assume 3% (237) of the 7918 men had PSA > 4.0 ng/ml (based on ERS prevalence rate in this age group) and that ~15% of the 106 ( $n = 16$ ) prostate cancer deaths in MRFIT had PSA > 4 ng/ml (based on the current study distribution of PSA among cases), then the absolute risk of prostate cancer death over ~25 years would be about 7% ( $16/237 \times 100$ ) as compared with about 1% risk for men with PSA < 4 ng/ml.

A recent report suggested a lowering of the PSA threshold for biopsy based on the low sensitivity using the current threshold of PSA > 4 ng/ml (26). For men in this study <60 years, changing the PSA threshold from >4 to >1.4 ng/ml increased sensitivity from 18% to 74% with only modest lost in specificity (26). The MRFIT results support this suggestion, with men in MRFIT at elevated risk for prostate cancer at levels as low as 1.0 ng/ml.

In summary, we showed that men with even moderately elevated PSA levels were at increased risk of prostate cancer mortality over an approximate 25-year follow-up period.

## Acknowledgments

We thank the many colleagues who contributed to the accomplishment of the MRFIT.

## References

1. Gronberg H. A small organ with a vital function. *Lancet*, 2001; 358(Suppl):s55.
2. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. *CA Cancer J Clin*, 2002;52:23–47.
3. Weir HK, Thun MJ, Hankey BF, et al. Annual Report to the Nation on the Status of Cancer, 1975–2000, featuring the uses of surveillance data for cancer prevention and control. *J Natl Cancer Inst*, 2003;95: 1276–99.
4. U.S. Preventive Services Task Force. Screening for prostate cancer: an update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*, 2002;137:917–29.
5. Helzlsouer KJ, Newby J, Comstock GW. Prostate-specific antigen levels and subsequent prostate cancer: potential for screening. *Cancer Epidemiol Biomarkers & Prev*, 1992;1:537–40.
6. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA*, 1995;273:289–94.
7. Fang J, Metter EJ, Landis P, Chan DW, Morrell CH, Carter HB. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging. *Urology*, 2001;58:411–6.
8. Schroder FH, Wildhagen MF. Low levels of PSA predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging [letter to the editor]. *Urology*, 2001;59:462–3.
9. Multiple Risk Factor Intervention Group. The MRFIT: A national study of primary prevention of coronary heart disease. *JAMA*, 1976;235:825–7.

10. Multiple Risk Factor Intervention Trial Research Group. Statistical design considerations in the NHLBI Multiple Risk Factor Intervention Trial. *J Chronic Dis*, 1977;30:261–75.
11. Benfari RC, Sherwin R, editors. Forum: The Multiple Risk Factor Intervention Trial (MRFIT). The methods and impact of intervention over four years. *Prev Med*, 1981;10:387–553.
12. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA*, 1982;248:1465–77.
13. Wentworth D, Neaton JD, Rasmussen W. An evaluation of the Social Security Administration Master Beneficiary Record Index File and the National Death Index in the ascertainment of vital status. *Am J Public Health*, 1982;73:1270–4.
14. Horm J. Assignment of probabilistic scores to National Death Index Record matches. Hyattsville (MD): National Center for Health Statistics; 1996.
15. International Classification of Diseases, Ninth Revision, North American clinical modification. Volume I. Ann Arbor (MI): Edwards Brothers, Inc.; 1981.
16. Doody MM, Hayes HM, Bilgrad R. Comparability of National Death Index Plus and standard procedures for determining causes of death in epidemiologic studies. *Ann Epidemiol*, 2001;11:46–50.
17. WHO. International Classification of Diseases, Tenth Revision. Geneva: WHO; 1992.
18. Breslow NF, Day NE. Statistical methods in cancer research. The analyses of case-control studies. Volume 1. Lyon (France): IARC (Scientific Publication No. 32); 1980.
19. Frankel S, Smith GD, Donovan J, Neal D. Screening for prostate cancer. *Lancet*, 2003;361:1122–8.
20. Nelson WG, De Marzo AM, Isaacs WB. Mechanisms of disease. Prostate cancer. *N Engl J Med*, 2003;349:366–81.
21. Carter HB, Landis PK, Metter EJ, Fleisher LA, Pearson JD. Prostate-specific antigen testing of older men. *J Natl Cancer Inst*, 1999;91:1733–7.
22. Clark LC, Dalkin B, Krongrad A, et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol*, 1998;81:730–4.
23. Hoque A, Albanes D, Lippman SM, et al. Molecular epidemiologic studies within the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Cancer Causes & Control*, 2001;12:627–33.
24. 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.
25. Maattanen L, Auvinen A, Stenman U-H, et al. European randomized study of prostate cancer screening: first-year results of the Finnish trial. *Br J Cancer*, 1999;79:1210–4.
26. Punglia RS, D'Amico AV, Catalona WJ, Roehl KA, Kuntz KM. Effect of verification bias on screening for prostate cancer by measurement of prostate-specific antigen. *N Engl J Med*, 2003;349:335–42.