Acta Oncologica, 2011; 50(Suppl 1): 12–17

informa
healthcare

REVIEW ARTICLE

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial: The prostate cancer screening results in context

CHRISTINE D. BERG

Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, USA

Abstract

Background. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) was conducted in sites around USA during a period of marked secular changes in the use of prostate specific antigen (PSA) screening for prostate cancer. *Material and methods*. Trends in prostate cancer incidence, stage at presentation and mortality are useful when interpreting the results from a screening trial that commenced in 1993 and enrolled participants through 2001. The last participants completed active screening in 2006. Incidence and mortality data published to date on PLCO need to be placed into the context of the secular trends. Additional data analyses have been conducted on subsets of the participants and these results can also enhance the interpretation of the trial. Additionally, the accompanying biospecimen repository has served as a rich research resource yielding informative findings. *Results*. The PLCO is best viewed as a trial comparing a regimented active annual screening program of PSA screening for six rounds, four of which had accompanying digital rectal examination (DRE) to patterns of screening that were occurring in the population in many academic and community settings across the USA. The epidemiology and molecular genetics of prostate cancer is becoming better understood and analyses of the PLCO resource have contributed. One approach to risk assessment utilizing genetic markers from selected members of the PLCO prostate cancer cohort has been developed. A modeling effort with CISNET-ERSPC-PLCO is underway to compare and contrast findings such as effects of different PSA thresholds and screening intervals. *Conclusions*. The information emerging from PLCO is useful to inform the debate around prostate cancer screening. An understanding of the biologic differences underpinning indolent and aggressive prostate cancer will better guide the future development of screening and treatment strategies.

Background

Prostate cancer has been the leading cause of cancer in males in USA for decades [1]. In the late 1970s near the inception of the Surveillance Epidemiology and End Results (SEER) Registry (http://seer.cancer.gov/), prostate cancer incidence was similar to lung cancer. The decline in smoking in males has led to a gradual decline in incidence in lung cancer. Prostate cancer screening appears to have contributed to the marked rise in incidence witnessed in the late 1980s and early 1990s. Although, prostate cancer incidence has fallen from its peak, it remains elevated compared to the pre-prostate specific antigen (PSA) era. Mortality from prostate cancer fell relatively rapidly after the introduction of PSA testing. Debate has raged as to the extent to which treatment advances and/or widespread PSA testing have contributed to this decline.

The Food and Drug Administration approved the PSA test in 1986 as a way to monitor men after treatment. It was then studied as a means of detection of prostate cancer [2]. The medical community recognized at the time that interest and uptake would be generated particularly as it was a non-invasive, relatively inexpensive, blood test. Many prominent members of the urologic community and the National Cancer Institute (NCI) met to discuss how best to assess the effect of the emergence of PSA testing. A prospective, randomized trial with a prostate cancer specific mortality endpoint was judged as the most definitive approach. Other outstanding screening questions for lung, colorectal and ovarian cancer screening were identified. A multi-modal screening trial was thought to have cost-efficiencies. Also, mature adults when receiving their medical care are

Correspondence: Christine D. Berg, Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD 20852, USA. E-mail: bergc@mail.nih.gov

(Received 27 September 2010; accepted 28 September 2010)

ISSN 0284-186X print/ISSN 1651-226X online © 2011 Informa Healthcare
DOI: 10.3109/0284186X.2010.531283

evaluated for their risk of cancer as it continues to be the second leading cause of death in the United States. Their clinicians would benefit from information to guide screening choices and a multi-modal approach to assessment would better reflect the clinical reality [3].

Material and methods

The design of the PLCO focused on developing a randomized trial in males and females that would be adequately powered to assess the impact on cancer specific mortality of screening for lung and colorectal cancer in males and females, ovarian cancer screening in females and prostate cancer screening in males [4]. The trial initially set out to enroll individuals 60 to 75, reasoning that these were ages of high incidence of cancer. More elderly individuals had and still have higher rates of competing mortality and therefore it is more difficult to assess the effect of screening in this group and they were excluded from the study. As the trial progressed it became clear that the enrollment that was occurring, although more rapid in the younger age groups, was slow and to expand the numbers the age for entry was lowered to 55.

To reflect the geographic, racial and ethnic diversity of the US population a Request for Proposals was broadly solicited. The proposals were reviewed for capabilities of the sites to perform the recruitment, screening, retention and follow-up needed. The resulting sites were distributed throughout the continental US and Hawaii (http://prevention.cancer.gov/plco/centers). One poorly performing site was replaced early in the trial by the University of Alabama which has a strong emphasis on recruiting African-Americans from surrounding communities into trials. Efforts at another site, the University of Colorado Health Systems focused on Hispanic recruitment. A location at the Pacific Health Research Institute (now Pacific Health Research and Education Institute) was aimed at recruiting Asian and Pacific-Islanders. All sites including the NCI had the study approved by their local Institutional Review Boards. The PLCO participants signed an informed consent detailing the nature and risks from the screening interventions. The control participants were encouraged to continue to receive care from their usual health care providers. Screening was neither encouraged nor discouraged for them.

The resulting demographics of the enrolled male population can be seen in Table I. An analysis of the characteristics of the participants confirmed that the PLCO enrollees like many in clinical trials are "healthy volunteers" [5]. They are of higher socio-economic and educational attainment than the population at large and tend to have a better health profile. This needs to be recognized as one analyzes the results of the trial. Enrollment occurred from 1993 to 2001. Prostate cancer screening was with annual PSA testing for six years (T0–T5) and digital rectal examination (DRE) annually for four years (T0–T3). The threshold for an abnormal serum PSA was set at > 4 nanograms per milliliter (ng/ml). A reference laboratory was established at UCLA where all specimens were shipped on dry ice after centrifugation and serum separation. PSA tests were analyzed with the Tandem-R PSA assay until January 1, 2004 and with the Access Hybritech PSA after that (both assays were manufactured by Beckman Coulter). Additional blood specimens were drawn from screening arm participants and buccal cells were collected from control arm participants to establish a biospecimen repository [6]. Tissue samples were also collected from participants in both arms. Tissue microarrays were constructed and cores obtained from formalin-fixed paraffin embedded specimens.

Table I. Demographics of male enrollees in the PLCO.

	percent	
	Screening Group n = 38 343	Control Group n = 38 350
Age		
55–59 yr	32.3	32.3
60–64 yr	31.3	31.3
65–69 yr	23.2	23.2
70–74 yr	13.2	13.2
Race or ethnic group; self-reported		
Non-Hispanic white	86.2	83.8
Non-Hispanic black	4.5	4.3
Hispanic	2.1	2.1
Asian	4.0	3.9
Other	0.8	0.9
Missing data	2.4	5.0
Family history of prostate cancer	7.1	6.7
PSA test within past 3 years		
Once	32.8	31.9
Two or more times	9.4	9.8

Table II. Tumor stage and Gleason score for all prostate cancers at 10 years.

	Screening Group n = 3 452	Control Group n = 2 974
Stage		
I	2 (0.1 %)	15 (0.5 %)
II	1458 (97.2 %)	2790 (93.8 %)
III	22 (1.5%)	56 (1.9 %)
IV	15 (1.0 %)	79 (2.7 %)
Unknown	3 (0.2 %)	34 (1.1 %)
Gleason score on biopsy		
2–4	94 (6.3 %)	137 (4.6 %)
5–6	963 (64.2 %)	1656 (55.7%)
7	318 (21.2 %)	779 (26.2 %)
8–10	98 (6.5 %)	341 (11.5 %)
Unknown	27 (1.8%)	61 (2.1 %)

At enrollment, all participants completed a baseline questionnaire that inquired about screening practices in the three year period prior to enrollment, demographic characteristics and potential risk factors for malignancy. Separate dietary questionnaires were also administered. The participants were asked if they had had prior PSA or DRE testing and the number of tests. After 1995, those participants who had more than one PSA blood test in the previous three years were excluded. During the conduct of the screening portion of the trial, participants in the control arm were also assessed for screening test uptake. A randomly selected group was queried every one to two years. For prostate cancer screening, the participants were asked if they had ever had a PSA blood test for prostate cancer or a digital rectal examination of the prostate. Those who answered yes were then asked when the most recent test was. The categories for response were "within the past year", "1–2 years ago", "2–3 years ago" and "more than three years ago." The reasons for the test were also queried to determine if it was routine or for evaluation of a specific health problem. Those participants who had repeated PSA testing prior to entry were assumed to continue screening annually. This comprised 9.8% of the control group. A weighted average, of the percent responding both "within the past year" and routine, and the 100% estimate in the group screened frequently prior to enrollment, was used to provide an estimate of overall contamination. Assessment of compliance in the screening arm was determined by attendance at the annually scheduled screening appointments and an estimate of compliance was calculated by dividing that by the number expected.

Results

The trial was monitored from inception by an independent Data and Safety Monitoring Board. Reviews of the accumulating data were done every six months with regular planned interim analyses. Publication of prostate cancer specific mortality results for up to ten years from recruitment occurred in March 2009 [7]. Median follow-up was 11.5 years and vital status was known for 98% of participants at seven years and 67% at ten years. The decision to report was made as no evidence of difference between arms was emerging at that point but evidence of harms from diagnostic evaluations following screening and after treatment was noticed. Earlier publications had presented results from the baseline [8] and all screening rounds [9].

Six annual rounds of screening were conducted and at seven years, 2 820 prostate cancers and 50 prostate cancer specific deaths were noted in the screened group. In the control group, 2 322 cancers and 44 deaths were noted. The data at ten years (67% complete) showed 3 452 screened versus 2 974 control group cancers and 92 compared to 82 deaths. Of note, the excess number of prostate cancer cases persisted after completion of screening. Also, although 25% more prostate cancers were diagnosed in the active screening arm at seven years, mortality rates through seven to ten years were the same in each arm. Whether or not the small differences in stage and Gleason's score between arms will result in differential survival in the future remains to be seen.

The percentage of patients having late stage disease {AJCC Stages III and IV, [10]} Table II, at diagnosis was low in both arms. At ten years, 3.5% of all screening arm subjects were clinical stage III and IV compared to 4.6% in the control arm. This compares with a 25% incidence of presentation of late stage disease prior to the advent of PSA testing and a rate of 4% in the population as a whole in 2002. A comparison of Gleason's score on biopsy, revealed aggressive Gleason's 8 to 10 in 8.4% of screened arm participants and 11.5% in the control arm participants. Additional follow-up on the entire cohort is continuing. Whether these differences in stage at diagnosis and in Gleason's grade will translate into differences in prostate cancer specific mortality will be seen.

A separate analysis of the effect of the contamination on rates of prostate cancer has been conducted [11]. The rates of reported test usage increase if one includes any testing within the year compared with routine testing. Rates increased from 33 to 40% at study year 0 and from 46% at study year 5 to 54–55%. At year 0, 38% of men reported no history of PSA testing while at year 5, 15% did. Also, at year five, 18% reported testing one to two years earlier. Compliance with the screening protocol overall was 85% for PSA testing and 86% for DRE, lower than the study design estimate of 90%. Clearly, the men in the control arm were being screened but at a lower frequency and intensity than men in the screened arm.

To estimate what would have occurred in the absence of screening, SEER rates from 1985–1987 prior to the onset of the PSA era were utilized. Five year age groups and race (white, black, other) were constructed and the SEER rates were applied to the person-years at risk for control and screened arm men during the screening period of the trial (the first six years). A separate calculation was done utilizing SEER rates contemporaneous to the screening period of the trial. During the six screening years of the trial, 2 538 prostate cancers were identified in the screened arm and 1 958 in the control arm. In the screened arm there were an excess of 1 589 and in the control arm, 1 024 compared to the pre-PSA screening era. When one compares with the contemporaneous

SEER rates, 927 and 354 (screening: control) excess cancers were diagnosed. For the control arm, this reflects a 22% excess over the expected number if screening had been conducted in the control arm as in the populations covered by SEER.

Ancillary data analyses

The information available from the PLCO prostate cancer screening trial can be analyzed to improve the understanding of the role of other factors that influence the conduct of screening and evaluation for prostate cancer. A large fraction of screened men, initially have low PSA levels ($\leq$ 2 ng/ml). In the PLCO, in men with baseline PSAs less than 1 ng/ml, 1.5% were found to have a PSA of more than 4 ng/ml by year 5, while in those with PSAs between 1.0 and 1.99 ng/ml the rate of progression was somewhat higher with 7.4% progressing by year five [12]. A total of 33.5% and 79% of men with initial PSA of 2.0 to 2.99 and 3.0 to 4.0 converted by year 5. This information could help to inform thresholds for positivity and screening frequency. Information on PSA velocity (PSAV) may also help to inform decisions as to when to biopsy. In 1 441 men enrolled in the PLCO who received $\geq$ 2 PSA screens, and were diagnosed with prostate cancer within one year of the last screen, PSAV was calculated using all available PSA levels [13]. Both PSA and PSAV were related to biopsy Gleason score. The median PSAV was 0.60 ng/ml per year for men with Gleason scores from 2 to 6 versus 0.84 ng/ml for men with Gleason scores from 7 to 10 ($p < 0.0001$). Information such as this can inform watchful waiting and active surveillance approaches as well. Another issue is what happens after an initial negative prostate biopsy. The probability of having a repeat biopsy within three years of initial biopsy was 43% for 1 736 men with suspicious PSA levels after an additional round of screening [14]. An analysis of men who had an initial false positive result was done to assess the impact of this result on subsequent screening behavior. Given the subsequent high risk of repeat biopsy it was worrisome to note that in a multi-variable model being African American ($p = 0.016$ and having a high school education or less $p = 0.007$) were predictive of not returning for prostate cancer screening within the following year [15]. Additional effort may be warranted to facilitate compliance with screening in this group.

The impact of associated diseases and conditions can also be assessed in the PLCO cohort. Analysis within the PLCO has confirmed an inverse relationship between PSA concentration and body mass index [16]. Dietary factors and supplement use have been analyzed within the cohort. There was no overall association between dietary or supplemental intake of vitamin E, beta-carotene or vitamin C and prostate cancer risk [17, 18]. Also, no evidence was found substantiating the hypothesis that lycopene and tomato product intake affected risk of prostate cancer [19].

The PLCO biospecimen repository with high quality DNA specimens has contributed to our understanding of the molecular genetic factors that are associated with increased risk of prostate cancer. A locus within the 8q24 chromosome, rs6983267, was identified separate from the initially reported locus at rs1447295 [20]. Additional SNP analyses done in second stage replication scans confirmed three previously reported loci, two in 8q24 and one in HNF1B [21] and loci on chromosomes 7, 10 (2 loci) and 11 were highly significant. The loci on chromosome 10 include MSMB which encodes β-microseminoprotein, a primary constituent of semen and CTBP2, a gene with antiapoptotic activity. Additional fine mapping and functional analysis confirmed the strong association with prostate cancer risk of the rs10993994 locus in MSMB and gene expression was higher in cell lines with a CC or a CT genotype than with a TT genotype. [22].

Utilizing knowledge of SNPs to assess risk of malignancy is a developing endeavor. A project utilizing a population-based case-control study in Sweden and a nested case-control study from the PLCO developed a risk-prediction model utilizing SNPs and family history [23]. Men with 11 risk alleles (mode) and negative family history were considered at baseline risk and those who had $\geq$ 14 risk alleles and a positive family history had an odds ratio of 4.92 (95% CI: 3.64–6.64) for prostate cancer in the Swedish study and this was confirmed in the PLCO. This could be utilized to calculate a man's absolute risk of prostate cancer. For example, a 65-year-old man in the US with a family history and $\geq$ 14 risk alleles, has a 41% risk of being diagnosed with prostate cancer compared with a population average of 13%. The utility of these types of assessments for screening and consideration of chemoprevention still need to be determined.

Discussion

The PLCO trial was conceived at the beginning of utilization of the PSA test for screening for prostate cancer. Rapid dissemination and widespread initial use of PSA testing for prostate cancer screening occurred in the years leading up to the launch of the trial. Subsequent to launch, regular PSA screening remained common in the community. The peak in prostate cancer incidence in males in the US coincided with the launch of the trial in the early 1990s [1]. Also, with the increasing incidence in the disease, a decrease in advanced stage disease was noted. Subsequent modeling was consistent with much of this decline in late stage

disease being a consequence of screening [24]. Several years after the trial launch, prostate cancer mortality in the US fell, going below pre-PSA rates by 2003. The results of the trial must be placed into this context.

When one looks at the incidence rates in the PLCO the control group actually has higher rates than compared with contemporaneous results from the SEER registry. This can be explained by the characteristics of the enrollees. As mentioned earlier, they represent a "healthy volunteer" who is of higher socio-economic status and better educated than average. This demographic undergoes screening more frequently. The prostate cancer specific mortality in both arms of the study is low.

A limitation of the PLCO could be the cut-off of $>$ 4 ng/ml chosen as the threshold for referral for further evaluation. This was the commonly accepted threshold at the time of trial initiation. Subsequently, a trial of finasteride in prostate cancer prevention had as part of the design an exit biopsy in all men in the placebo arm regardless of PSA level. This demonstrated that overall, men with PSAs of less than 4 ng/ml had a 15% incidence of prostate cancer of which 14.9% was Gleason's 7 + [25]. The prevalence of prostate cancer in men with PSAs of $\leq$ 0.5 ng/ml was 6% of which 12.5% were high grade. If PSA screening were to be implemented as an organized program, the ideal threshold value is unclear. Also, the PLCO investigators did not prescribe evaluations or therapy. Participants and their physicians decided on a course of evaluation of an elevated PSA and if prostate cancer were diagnosed the treatments were also determined in the same manner. It should be noted that these same diagnostic and treatment approaches were the ones employed during the period of rapid increase in prostate cancer incidence in SEER and also in the decrease in mortality seen in the US.

An analysis under the auspices of the Cancer Intervention and Surveillance Modeling Network {(CISNET) http://cisnet.cancer.gov/} will compare results across ERSPC and PLCO. Differences in the screening approaches such as PSA threshold and screening interval, and populations will have to be noted when these comparisons are presented.

Conclusion and next steps

Continued collection of endpoint data in the PLCO is critical. An impact of the differential in Gleason's grade between arms and the very small difference in stage may emerge. The analyses of CISNET-ERSPC-PLCO will be revealing. The molecular genetics of prostate cancer risk are better understood through contributions of the PLCO. Much more remains to be accomplished and the prostate tumor cores and TMAs from the PLCO and the matched pre-diagnostic biospecimens are available to the research community. Interesting understandings of the behaviors of indolent and aggressive disease may emerge.

The goal of all is to minimize the adverse impact of prostate cancer in our ageing society. Clearly, the mortality reductions achieved to date are to be applauded. However, they do come with a high rate of overdiagnosis. Treatment side effects are also substantial. Knowledge gained from watchful waiting and active surveillance approaches will be important. As discussed elsewhere in this monograph advances in the chemoprevention of prostate cancer have also been made.

The PLCO trial has contributed to this emerging database. However, it is important when analyzing this trial to place the results in the context of the times. When designing screening trials for the future these issues need to be considered.

Acknowledgements

The PLCO trial was funded by contracts from the National Cancer Institute. The ClinicalTrials.gov identifier for PLCO is NCT00002540. The author acknowledges the contributions to this work made by the co-authors on the other prostate cancer manuscripts emanating from the PLCO. She thanks the study subjects for their contributions in making this study possible. There are no conflicts of interest to report for this article.

Declaration of interest: The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

References

[1] Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer Clin J 2010;60:277–300. Epub 2010 Jul 7.

[2] Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJJ, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med 1991;324:1156–61.

[3] Gohagan JK, Prorok PC, Hayes RB, Kramer BS. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: History, organization, and status. Control Clin Trials 2000;21(Suppl):251S–272S.

[4] Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000;21(Suppl):273S–309S.

[5] Pinsky PF, Miller A, Kramer BS, Church T, Reding D, Prorok P, et al. Evidence of a healthy volunteer effect in the Prostate, Lung, Colorectal and Ovarian cancer screening trial. Am J Epidemiol 2007;165:874–81.

[6] Hayes RB, Reding D, Kopp W, Subar A, Bhat N, Rothman R, et al. Etiologic and early marker studies in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000;21(Suppl):349S–355S.

[7] Andriole GL, Crawford ED, Grubb RL, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360: 1310–9.

[8] Andriole GL, Levin DL, Crawford ED, et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: Findings from the initial screening round of a randomized trial. J Natl Cancer Inst 2005;97:433–8.

[9] Grubb RL III, Pinsky PF, Greenlee RT, et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial: Update on findings from the initial four rounds of screening in a randomized trial. BJU Int 2008;102:1524–30.

[10] Fleming JD, Cooper JS, Henson DE, et al., editors. AJCC cancer staging manual. 5th ed. Philadelphia: Lippincott-Raven; 1997.

[11] Pinsky PF, Black A, Kramer BS, Miller A, Prorok PC, Berg C. Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Clin Trials 2010;7: 303–11.

[12] Crawford ED, Pinsky PF, Chia D, Kramer BS, Fagerstrom RM, Andriole G, et al. Prostate specific antigen changes as related to the initial prostate specific antigen: Data from the prostate, lung, colorectal and ovarian cancer screening trial. J Urol 2006;175:1286–90.

[13] Pinsky PF, Andriole G, Crawford ED, Chia D, Kramer BS, Grubb R, et al. Prostate-specific antigen velocity and prostate cancer Gleason grade and stage. Cancer 2007;109: 1689–95.

[14] Pinsky PF, Crawford ED, Kramer BS, Andriole GL, Gelmann EP, Grubb R, et al. Repeat biopsy in the prostate, lung, colorectal and ovarian cancer screening trial. BJU Int 2007; 99:775–9.

[15] Ford ME, Havstad SL, Demers R, Cole-Johnson C. Effects of false-positive prostate cancer screening results on subsequent prostate cancer screening behavior. Cancer Epidemiol Biomarkers Prev 2005;14:190–4.

[16] Grubb RL, Black A, Izmirlian G, Hickey TP, Pinsky PF, Mabie JE, et al. Serum prostate-specific antigen hemodilution among obese men undergoing screening in the Prostate, Lung, Colorectal, and Ovarian cancer screening trial. Cancer Epidemiol Biomarkers Prev 2009;18:748–51.

[17] Koralek DO, Peters U, Andriole G, Reding D, Krish V, Subar A, et al. A prospective study of dietary alpha-linoleic acid and the risk of prostate cancer (United States). Cancer Causes Control 2006;17:783–91.

[18] Kirsh VA, Hayes RB, Mayne ST, Chatterjee N, Subar AF, Dixon LB, et al. Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. J Natl Cancer Inst 2006;98:245–54.

[19] Kirsh VA, Mayne ST, Peters U, Chatterjee N, Leitzmann MF, Dixon LB, et al. A prospective study of lycopene and tomato product intake and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2006;15:92–8.

[20] Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet 2007;39:645–9. Epub 2007 Apr 1.

[21] Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, et al. Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet 2008;40:310–5.

[22] Lou H, Yeager M, Li H, Bosquet JG, Hayes RB, Orr N, et al. Fine mapping and functional analysis of a common variant in MSMB on chromosome 10q11.2 associated with prostate cancer susceptibility. Proc Natl Acad Sci USA 2009;106:7933–8.

[23] Xu J, Sun J, Kader AK, Lindström S, Wiklund F, Hsu FC, et al. Estimation of absolute risk for prostate cancer using genetic markers and family history. Prostate 2009;69:1565–72.

[24] Etzioni R, Gulati R, Falcon S, Penson DF. Impact of PSA screening on the incidence of advanced stage prostate cancer in the United States: A surveillance modeling approach. Med Decis Making 2008;28:323–31.

[25] Thompson I, Pauler D, Goodman P, Tangen C, Lucia M, Parnes H, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level of ≤ 4.0 ng per milliliter. N Engl J Med 2004;350:2239–46.