Title

The epidemiology of high-risk prostate cancer

Permalink

Journal

Current Opinion in Urology, 23(4)

ISSN

0963-0643

Authors

Punnen, Sanoj
Cooperberg, Matthew R

Publication Date

2013-07-01

DOI

10.1097/mou.0b013e328361d48e

Peer reviewed

CURRENT OPINION

The epidemiology of high-risk prostate cancer

Sanoj Punnen and Matthew R. Cooperberg

Purpose of review
Concern for over and under-treatment of men with prostate cancer has led to an increased focus on the identification and selective treatment of men with high-risk features. The purpose of this review is to summarize the epidemiology, risk factors, and treatment trends of men with high-risk prostate cancer.

Recent findings
Findings from recent trials on prostate-specific antigen-based screening suggest that screening has substantially reduced the incidence of high-risk prostate cancer. Men with high-risk disease tend to be older at diagnosis than those with low-risk disease. There is marked variation in the treatment of men with high-risk features; contemporary studies favor multimodal therapy, but high-risk disease is often under-treated with androgen deprivation alone, particularly among older men.

Summary
Variations in the incidence, mortality, and treatment of men with high-risk prostate cancer may reflect heterogeneity among studies in the definition of high-risk disease. Future research should attempt to standardize definitions of high-risk prostate cancer to allow better comparison between studies and provide a more homogeneous assessment of natural history.

Keywords
epidemiology, high risk, prostate cancer, prostate neoplasms, risk assessment

INTRODUCTION

Prostate cancer is the most common cancer among men in the USA, expected to account for 238 590 estimated new cases in 2013 [1]. The majority of these patients have low-risk, relatively indolent tumors that are unlikely to progress or require treatment, leading to growing concerns regarding over-diagnosis and subsequent over-treatment of prostate cancer [2]. However, approximately 20–30% of men with localized prostate cancer present with high-risk tumor characteristics [3]. Randomized trials have suggested that for this group of men, there is a considerable benefit in survival from treatment over observation [4,5▪▪]. As a result, increased efforts have been directed towards identifying these men early and providing selective therapy to those who are most likely to benefit from treatment [6▪]. Recently, the United States Preventive Services Task Force (USPSTF) issued a blanket recommendation against screening for prostate cancer, concluding that the risk of screening outweighed the benefits [7▪]. This recommendation reflected concern regarding a significant over-treatment of men with prostate cancer, particularly those with low-risk features. Whereas over-treatment of low-risk disease is unquestionably a major problem, there is also a clear evidence of

under-treatment of men with high-risk features. Men with high-risk disease are those most likely to benefit from treatment [8], and should be the primary targets of screening efforts [9]. Indeed, a more favorable risk/benefit ratio for screening and treatment is likely achievable by focusing on men with high-risk prostate cancer. The objective of this review is to summarize the epidemiology, risk factors, and treatment trends of men with high-risk prostate cancer.

PREVALENCE OF HIGH-RISK PROSTATE CANCER

A fair assessment of the impact of these interventions on men with high-risk features first requires an understanding of the natural history of high-risk

Helen Diller Comprehensive Cancer Center, University of California, San Francisco, California, USA

Correspondence to Matthew R. Cooperberg, Departments of Urology and Epidemiology & Biostatistics, University of California, 1600 Divisadero St, Box 1695, San Francisco, CA 94143-1695, USA. Tel: +1 415 885 3660; fax: +1 415 353 7093; e-mail: mcooperberg@urology.ucsf.edu

prostate cancer. Several definitions of high-risk prostate cancer are available in the literature [10]. Most of these include men with high-grade (Gleason ≥8) and/or high-stage (T3) disease. Previous studies have shown that men with these features are most likely to display poor cancer control, progressing to metastasis and death, regardless of the primary treatment modality chosen [11,12].

An analysis of the Surveillance, Epidemiology, and End Results (SEER) database in the US from 1999 to 2006 suggested that among men diagnosed with prostate cancer, 80% presented with localized disease, 12% had regional disease, and 4% had distant disease [13]. Although large cancer registries provide valuable information on cancer incidence and mortality, they are limited in terms of details on risk stratification, providing only the stage and summary grade of disease, when available, to provide some measure of risk assessment.

Another study used SEER data to assess temporal trends in the stage and grade of disease at presentation in men with newly diagnosed prostate cancer [14]. The authors found that between 1988–1989 and 2004–2005, the incidence rate of T3 or T4 cancer decreased from 52.7 per 100 000 to 7.9 per 100 000 among white men, and from 90.9 per 100 000 to 13.3 per 100 000 among black men. In addition, the incidence of poorly differentiated disease on biopsy decreased from 47.5 per 100 000 in 1988–1989 to 38.3 per 100 000 in 2004–2005. These two findings suggest that over time there has been a decrease in the incidence of men with high-risk features in the USA, which has been confirmed in other studies [15].

This change in risk distribution over the years can be largely attributed to the uptake of widespread prostate-specific antigen (PSA) screening, which has impacted the incidence of both high-risk and overall prostate cancer. The recent screening trials in both the USA and Europe yield useful insights into the effect of screening on the incidence of men diagnosed with high-risk features. In the European Randomized Study of Screening for Prostate Cancer (ERSPC), the incidence of men with Gleason grade at least 8 was 10.6% in the nonscreened arm vs. 6.1% in the screened arm [16■■]. Similarly, the incidence of stage T3 or higher disease was 15.7% in the nonscreened arm vs. 8.6% in the screened arm. These results suggest that screening with serum PSA can allow early detection of disease, thereby reducing the proportion of men found to have high-risk disease at diagnosis.

In contrast, the Prostate, Lung, Colorectal and Ovary (PLCO) trial found the incidence of Gleason grade higher then 7 was similar between the two groups with 37.7% in the nonscreened arm and 32% in the screened arm [17]. Likewise, there was minimal difference in the incidence of stage T3 or higher disease between the two arms, with 4.5% in the nonscreened arm and 3.5% in the screened arm. Although screening appeared to have no effect on risk distribution in this trial, a major flaw of this study was the extensive contamination of the control group, with fully 79% of men randomized to no screening receiving a PSA test before and/or during the trial period [18]. Therefore, this trial was more a comparison of annual screening with ad-hoc screening [19], which explains its limited ability to reflect the impact of screening on reducing the incidence of high-risk disease.

Detailed data on tumor characteristics are limited in the international setting. However, existing registries do include robust data on cancer incidence mortality at the international level [20]. Since men with high-risk features are most likely to die from this disease [12], mortality may be a reasonable surrogate to provide us with an estimate of the relative prevalence of high-risk disease. A recent study examining geographic variation of mortality rates worldwide found no consistent trend in the direction or magnitude of recent mortality from prostate cancer around the world [21]. The authors reported decreasing mortality rates in 27 of 53 countries including North America, Oceania, western Europe, and parts of northern Europe. Mortality appeared to increase in 16 countries including central and eastern Europe, parts of Asia, and Africa. Finally, in the 10 remaining countries, mortality rates appeared to remain stable. Among men in the USA, mortality appears to be intermediate compared to other countries, and decreasing at a rate of 4.3% over the past decade for which data were available [21]. It is important to stress that

geographic variations in mortality rates may, in part, reflect differences in the prevalence of high-risk disease in different countries, but may also be due to differences in screening, treatment, and availability of resources.

RISK FACTORS FOR HIGH-RISK PROSTATE CANCER

Established risk factors for prostate cancer include family history, genetics, age, race/ethnicity, obesity, and others [6■]. Although most of these risk factors have similar associations with high-risk prostate cancer, some of these relationships may be stronger or weaker compared to that of overall prostate cancer.

Age

In order to elucidate the relationships between age and prostate cancer mortality, Bechis and Carroll [22] conducted a study using the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), a primarily community-based, nationwide prostate cancer registry in the USA. The authors found an association between older age at diagnosis and high-risk prostate cancer. Among patients in the registry, 26% of men at least 75 years old had high-risk features, whereas among various age groups below 75 years, the proportion of men with high-risk features was less then 15%. This finding of increased risk among older men may reflect the fact that men who are older at the time of diagnosis likely were less intensely screened at younger ages.

Indeed, a different study compared men in the CaPSURE database to men in the Japan Study Group of Prostate Cancer (J-CaP) database, a national Japanese registry of men receiving primary androgen deprivation therapy (ADT). The study found a higher proportion of men with high-risk disease in J-CaP compared to CaPSURE, with an opposite association between age and risk than what was seen in CaPSURE. For instance, approximately 10% of men below 55 years of age in CaPSURE were found to have high-risk or advanced disease compared to nearly 90% of men below 55 years in J-CaP. This disparity may reflect differences in screening rates; Japan is a relatively unscreened population, in which cancers detected at younger ages are those aggressive enough to cause early clinical symptoms. Therefore, when looking at the association between age and high-risk prostate cancer in any population, we must also consider the effect of screening.

Race

Multiple studies have found that black men have a higher stage of disease at presentation and are more

likely to die of their prostate cancer then their white counterparts [23]. However, what is unclear is which factors – access to and utilization of early detection and treatment, genetic variation, socioeconomic status, or differences in diet and other environmental exposures – may explain the relationship between race and high-risk prostate cancer [24]. In fact, previous studies looking at underserved populations at the extremes of socioeconomic disadvantage – regardless of race – have suggested that men in these health systems are more likely to have a higher grade and stage of disease at diagnosis compared to men in the broader US population [25,26].

A recent study among 77 038 black and white men with prostate cancer and 49 769 controls without prostate cancer in the SEER database attempted to explain how much of the racial disparity in prostate cancer mortality could be explained by such potential confounders [27]. The authors estimated the mortality difference to be 1320 more cases per 100 000 men among black compared to white men. They considered differences in rates of screening, comorbidity, and socioeconomic status, but estimated that these factors could only account for approximately 25% of the total mortality difference between black and white men. It is possible that other factors related to race (behavioral or genetic) might confer the remainder of the risk, but to what extent still remains unclear. A recent study showing similar rates of high-grade disease among a population of black men from the USA, Jamaica, West Africa, and other sub-Saharan African countries suggests an element of shared genetics or sociodemographic disadvantage may play a role in the development of high-risk disease [28].

Family history and genetics

A positive family history of prostate cancer can result in an increased risk of prostate cancer diagnosis [29], yet few studies have specifically examined the association between family history and high-risk or advanced prostate cancer. One recent study, using the Swedish Family Cancer Database, assessed the impact of family history on the likelihood of prostate cancer mortality in an attempt to elucidate the effect of family history on a more aggressive phenotype of prostate cancer. The authors reported a hazard ratio of 2.03 for men with a family history of fatal prostate cancer, and a hazard ratio of 1.59 for men with a family history of nonfatal prostate cancer compared to men with no family history of prostate cancer. However, they did not identify an association between family history (fatal or not) on stage at diagnosis. Therefore,

although it appears that family history may impact the risk of aggressive and fatal prostate cancer, the exact degree to which it does this, and via what pathways, remains unclear.

Although genetic markers appear to modestly improve our ability to detect prostate cancer [30], their role in the identification of high-risk tumors remains uncertain. One recent review identified more then 40 germ-line genetic variants associated with prostate cancer by genome-wide association studies, but found they had limited ability to discern between aggressive and nonaggressive forms of the disease [31]. Although studies have shown a modest benefit from genetic markers in the detection of overall prostate cancer [32], their true utility will be in there ability to identify more aggressive phenotypes of prostate cancer, allowing the institution of more selective screening and treatment strategies to those who are most likely to suffer significant burden from their disease.

Obesity and diet

A recent review looking at the impact of obesity on prostate cancer found that obesity was associated with a higher incidence of aggressive prostate cancer. In addition, the authors found that obesity was associated with a higher incidence of prostate cancer recurrence after surgery or radiation and an increased risk of prostate cancer-specific mortality [33]. Studies examining nutrition and prostate cancer have yielded heterogeneous results, but the number of studies assessing the impact of nutrition on high-risk prostate cancer are limited [34]. One recent case-control study focused on aggressive prostate cancer found that a higher intake of well done, grilled, or barbequed red meat and its ensuing carcinogens (heterocyclic amines) could increase the risk of aggressive prostate cancer [35]. The link between nutrition and aggressive prostate cancer remains incompletely defined, and is a focus of ongoing studies.

TREATMENT TRENDS FOR HIGH-RISK PROSTATE CANCER

Academic opinion regarding the optimal treatment for high-risk prostate cancer has changed substantially in recent years, with a greater focus on multimodal therapy in more contemporary studies [10]. In an effort to analyze trends in the treatment of localized prostate cancer, Hamilton *et al.* [36] obtained treatment patterns in 2002 from the Patterns of Care study conducted annually by the National Cancer Institute. The authors reported considerable variation in the treatment of men

with intermediate/high-risk (Gleason ≥7, PSA >10 ng/ml) tumors based on age. For instance, men above the age of 75 were primarily managed with primary ADT (45.2%) or external beam radiotherapy (EBRT) (29.6%), whereas men under the age of 60 were primarily managed with surgery (74.6%).

Data from the CaPSURE registry also noted temporal changes in the management of high-risk prostate cancer, defined by D'Amico criteria (PSA >20 ng/ml, Gleason score ≥8, and/or clinical stage T2c–3a), from 1990 to 2007 [3]. The study found that rates of surgery remained stable over time (~40%), whereas rates of EBRT declined somewhat from 21.6% in 1990–1994 to 10.9% in 2004–2007, and rates of primary ADT increased from 18.5% in 1990–1994 to 29.1% in 2004–2007. The authors stratified men with D'Amico high-risk tumors by the Cancer of the Prostate Risk Assessment (CAPRA) score, which is a 0–10 score based on age, serum PSA, biopsy Gleason score, percentage of positive cores on biopsy, and clinical stage. They noticed a decreased use of surgery and increased use of primary ADT with increasing CAPRA risk score, and it appeared that age, rather than risk, was driving treatment decision-making. Despite the observed trend it should be noted that the use of primary ADT as treatment for nonmetastatic prostate cancer is not endorsed by either US or European guidelines, and should be considered under-treatment in many circumstances [10,37]. Finally, the authors commented on a relatively uncommon and decreasing use of adjuvant radiotherapy after surgery (7.3% in 1990–1994 to 2.3% in 2004–2007) and an increased use of neo-adjuvant or adjuvant ADT with brachytherapy and EBRT (11.5–38.5% in 1990–1994 to 34.3–84.5% in 2004–2007).

It should be noted that SEER, a population-based registry, and CaPSURE, a predominantly community-based registry, provide data that are generalizable to overall patterns of practice in the USA. Data from large-volume academic centers suggest a favoring of multimodal therapy in the management of high-risk tumors [10] and in certain institutions a trend towards initial treatment with surgery [11,38].

Although the choice of treatment for men with high-risk prostate cancer depends heavily on cancer control or cure, the importance of quality of life and cost must not be underestimated. A recent comprehensive cost-effectiveness study of men with localized prostate cancer suggested modest differences between treatments in quality-adjusted life years (QALYs) gained [39▪]. The study suggested that for high-risk patients, EBRT and brachytherapy taken together was the most effective radiotherapy option

with 9.1 QALYs, whereas there was no significant difference among surgical methods with 9.2–9.3 QALYs. The study found that surgical options tended to be more effective than radiation options in all situations other than combined EBRT and brachytherapy for high-risk disease. Finally, the study also noted that radiation options were consistently more expensive then surgical options with costs ranging from $35 014 for robot-assisted radical prostatectomy to $50 276 for combined radiotherapy in the setting of high-risk disease. These results suggest that although there are small differences in outcomes (both clinical and quality of life) between various treatments, the relative differences in cost are substantial.

CONCLUSION

One of the issues in establishing the incidence and primary treatment patterns of men with high-risk prostate cancer is heterogeneity in the definition of high-risk disease. Future studies should focus on standardizing definitions so that temporal and geographic variations in incidence and treatment can be compared. Furthermore, incorporation of more clinical details to facilitate risk stratification in large tumor registries will improve their ability to characterize the epidemiology of high-risk prostate cancer.

Among men diagnosed with prostate cancer, a significant proportion present with high-risk features. Patterns of practice have suggested substantial variation in the treatment of high-risk disease, and raise the concern for under-treatment in many cases. Multiple contemporary studies favor more multimodal management in these men, and as newer systemic agents have come to the market, their role in combination with more established primary curative therapies are being investigated.

Men who present with high-risk prostate cancer are those most likely to progress to metastasis and die of their disease, thereby making them the most likely to benefit from treatment. Screening has effected a significant decrease in the incidence of high-risk prostate cancer, and if more focus is directed towards the detection and selective treatment of men with high-risk features, ongoing decline might be expected in the burden of high-risk disease.

Acknowledgements
None.

Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 381).

1. Siegel R, Naishadham D, Jemal A. Cancer statistics. CA Cancer J Clin 2013; 63:11–30.
2. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality in a randomized European Study. N Engl J Med 2009; 360:1320–1328.
3. Cooperberg MR, Cowan J, Broering JM, Carroll PR. High-risk prostate cancer in the United States, 1990–2007. World J Urol 2008; 26:211–218.
4. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2011; 364:1708–1717.
5. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus
■■ observation for localized prostate cancer. N Engl J Med 2012; 367:203–213.
This study reports a randomized trial of surgery vs. watchful waiting for men with prostate cancer in the Veterans Affairs system. The study showed no survival benefit for surgery for men with low-risk disease, but nonetheless importantly documented a substantial, early benefit for surgery for men with high-risk disease.
6. Zhu X, Albertsen PC, Andriole GL, et al. Risk-based prostate cancer screen-
■ ing. Eur Urol 2012; 61:652–661.
An excellent review of the data and rationale supporting a risk-based approach to PSA screening.
7. Moyer VA. U.S. Preventive Services Task Force. Screening for prostate
■ cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012; 157:120–134.
This review misinterprets much critical evidence regarding screening, and is based on an incomplete evidence review that overstates the harms of screening and understates the benefits. Nonetheless, it raises important concerns regarding overtreatment of low-risk disease, and it is important to be familiar with the rationale behind the USPSTF's recommendation.
8. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol 2010; 28:1117–1123.
9. Carroll PR, Whitson JM, Cooperberg MR. Serum prostate-specific antigen for the early detection of prostate cancer: always, never, or only sometimes? J Clin Oncol 2011; 29:345–347.
10. Bastian PJ, Boorjian SA, Bossi A, et al. High-risk prostate cancer: from definition to contemporary management. Eur Urol 2012; 61:1096–1106.
11. Cooperberg MR, Vickers AJ, Broering JM, Carroll PR, for the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) Investigators. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. Cancer 2010; 116:5226–5234.
12. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. J Am Med Assoc 2005; 294:433–439.
13. Brawley OW. Trends in prostate cancer in the United States. J Natl Cancer Inst Monographs 2012; 2012:152–156.
14. Shao YH, Demissie K, Shih W, et al. Contemporary risk profile of prostate cancer in the United States. J Natl Cancer Inst 2009; 101:1280–1283.
15. Cooperberg MR, Broering JM, Kantoff PW, Carroll PR. Contemporary trends in low risk prostate cancer: risk assessment and treatment. J Urol 2007; 178:S14–S19.
16. Schröder FH, Hugosson J, Roobol MJ, et al. Prostate cancer mortality at
■■ 11 years of follow-up. N Engl J Med 2012; 366:981–990.
The primary study updating results from the ERSPC screening study showing a significant mortality reduction with PSA-based screening.
17. Andriole GL, Crawford ED, Grubb RL III, et al. Mortality results from a randomized prostate cancer screening trial. N Engl J Med 2009; 360:1310–1319.
18. Pinsky PF, Blacka A, Kramer BS, et al. Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Clin Trials 2010; 7:303–311.
19. Cooperberg MR, Carroll PR. Prostate-cancer screening. N Engl J Med 2009; 361:203; author reply 204–205.
20. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61:69–90.
21. Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol 2012; 61:1079–1092.
22. Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. J Clin Oncol 2011; 29:235–241.
23. Virnig BA, Baxter NN, Habermann EB, et al. A matter of race: early-versus late-stage cancer diagnosis. Health Aff (Millwood) 2009; 28:160–168.

24. Carpenter WR, Howard DL, Taylor YJ, *et al.* Racial differences in PSA screening interval and stage at diagnosis. Cancer Causes Control 2010; 21:1071–1080.

25. Miller DC, Litwin MS, Bergman J, *et al.* Prostate cancer severity among low income, uninsured men. J Urol 2009; 181:579–584.

26. Porten SP, Richardson DA, Odisho AY, *et al.* Disproportionate presentation of high risk prostate cancer in a safety net health system. J Urol 2010; 184:1931–1936.

27. Taksler GB, Keating NL, Cutler DM. Explaining racial differences in prostate cancer mortality. Cancer 2012; 118:4280–4289.

28. Fedewa SA, Jemal A. Prostate cancer disease severity and country of origin among black men in the United States. Prostate Cancer Prostatic Dis 2013 [Epub ahead of print]. doi: 10.1038/pcan.2012.53.

29. Madersbacher S, Alcaraz A, Emberton M, *et al.* The influence of family history on prostate cancer risk: implications for clinical management. BJU Int 2010; 107:716–721.

30. Sun J, Na R, Hsu F-C, *et al.* Genetic score is an objective and better measurement of inherited risk of prostate cancer than family history. Eur Urol 2013; 63:585–587.

31. Nakagawa H, Akamatsu S, Takata R, *et al.* Prostate cancer genomics, biology, and risk assessment through genome-wide association studies. Cancer Sci 2012; 103:607–613.

32. Choudhury AD, Eeles R, Freedland SJ, *et al.* The role of genetic markers in the management of prostate cancer. Eur Urol 2012; 62:577–587.

33. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. Eur Urol 2013; 63:800–809.

34. Masko EM, Allott EH, Freedland SJ. The relationship between nutrition and prostate cancer: is more always better? Eur Urol 2013; 63:810–820.

35. Punnen S, Cooperberg MR, Sadetsky N, Carroll PR. Among potent men post radical prostatectomy, does the need for phosphodiesterase inhibitors have an impact on sexual bother scores? BJU Int 2012; 109:1520–1524.

36. Hamilton AS, Albertsen PC, Johnson TK, *et al.* Trends in the treatment of localized prostate cancer using supplemented cancer registry data. BJU Int 2011; 107:576–584.

37. Loblaw DA, Virgo KS, Nam R, *et al.* Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2007 update of an American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2007; 25:1596–1605.

38. Silberstein JL, Vickers AJ, Power NE, *et al.* Reverse stage shift at a tertiary care center: escalating risk in men undergoing radical prostatectomy. Cancer 2011; 117:4855–4860.

39. Cooperberg MR, Ramakrishna NR, Duff SB, *et al.* Primary treatments for
■ clinically localised prostate cancer: a comprehensive lifetime cost-utility analysis. BJU Int 2013; 111:437–450.
A comprehensive cost-effectiveness study supporting a greater role for surgery, especially in the management of high-risk prostate cancer.