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Prostate Cancer Prevention

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Jack Cuzick · Mangesh A. Thorat
Editors

Prostate Cancer Prevention

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Editors
Jack Cuzick
Mangesh A. Thorat
Centre for Cancer Prevention
Wolfson Institute of Preventive Medicine
Queen Mary University of London
London
UK

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Preface

Prostate cancer is the most common type of cancer and the third leading cause of cancer death among men in the developed world. Better understanding of factors that modify the risk of prostate cancer and its preventive measures that include pharmacological intervention will help us reduce the burden of this disease. At the same time, a combination of early detection and better discrimination between aggressive and indolent prostate cancer may help reduce treatment-related morbidity and mortality due to prostate cancer.

Recent genome-wide association studies have identified several single nucleotide polymorphisms (SNPs) associated with prostate cancer. These SNPs, in combination as panels, may allow us to identify individuals at high risk of developing prostate cancer. European Prospective Investigation into Cancer and Nutrition and other observational studies are shedding light on dietary and lifestyle factors that modify prostate cancer risk. This information will help in reducing disease risk through lifestyle and dietary modifications and also in better identification of those at high risk, perhaps in tandem with SNP panels.

Screening for prostate cancer by PSA testing remains a very controversial area. Apparently conflicting results from two of the largest screening trials, the ERSPC trial and the PLCO trial, have elicited a strong debate among the experts. Investigators of both these trials present their data and views in this book.

Several agents like 5α-reductase inhibitors aspirin, isoflavonoids, DFMO, and lycopene have been investigated for their role in prostate cancer prevention. This remains an active area of investigation with several ongoing and planned trials. Although the US FDA ruled against the use of 5α-reductase inhibitors in prostate cancer prevention due to an excess of high-grade prostate cancers, recent long-term survival data from the Prostate Cancer Prevention Trial do not support any detriment in survival. Additionally, with a third of low-grade cancers being prevented, use of 5α-reductase inhibitors may be a cost-effective way to reduce prostate cancer burden.

Once diagnosed, distinguishing aggressive prostate cancer from an indolent one is the key question where screening is common. Optimal clinical management of low-risk prostate cancer is also very important in reducing treatment-related morbidity.

The chapters in this book, written by leading researchers and experts in the field, elaborate on these important issues. Each chapter not only discusses the most up-to-date evidence on the topic but also discusses the ongoing research and future directions for research. We believe that scientists and clinicians dealing with prostate cancer will find this book to be a useful companion.

London, UK

Jack Cuzick
Mangesh A. Thorat

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The Biology and Natural History of Prostate Cancer: A Short Introduction

Lars Holmberg and Mieke Van Hemelrijck

Abstract

This chapter aims to serve as a quick glance outlining an overall picture of mainstream thoughts, and to serve as a point of departure for more thorough discussions The introduction of PSA testing has immensely complicated research in prostate cancer epidemiology and biology and added new clinical and biological domains. As for many cancers, age and ethnic origin are the strongest known risk factors. While migrant studies imply that environment and/or personal life style is important, epidemiological studies have failed to establish any strong leads. Despite the known androgen dependence of prostate cancer, there is little to support that circulating levels of androgens, estrogens or 5-alpha-reductase are associated with risk of developing the disease. However, a consistent finding is a positive association with levels of Insulin-like Growth Factor-1 (IGF-1). Prostate cancer is one of the cancers most strongly related to inherited susceptibility, even when taking into account that family history of prostate cancer triggers PSA testing among relatives. A number of somatic genetic alterations (amplifications, deletions, point mutations, translocations) are associated with prostate cancer risk. Findings for alterations in FASN, HPN, AMACR and MYC have been fairly consistent. Recent research shows that the notion of "hormone-independent prostate cancer" has to be revised: most prostate cancers remain dependent on androgen receptor signalling also after progression despite traditional androgen deprivation therapy. Traditional

L. Holmberg (✉)
Department of Surgical Sciences, Uppsala University Regional Cancer Center University Hospital, Uppsala, Sweden
e-mail: lars.holmberg@kcl.ac.uk

L. Holmberg · M. Van Hemelrijck
School of Medicine Division of Cancer Studies, King's College London, London, UK

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markers of stage and type of disease still play a major role for prognostication and treatment decisions. Prostate cancer is one of the few cancers where patients have been recommended watchful waiting or active surveillance. This provides opportunities for studies of natural history of the disease. The understanding of prostate cancer aetiology and natural history has progressed slowly. However, the current situation is positively challenging and opens up possibilities for fruitful research.

Contents

The biology and natural history of prostate cancer is so complex that a short text on the subject cannot include all new emerging ideas, important controversies or nuances in the current debate. This chapter aims to serve as a quick glance to be introduced to the subject by outlining an overall picture of the mainstream thoughts, and to serve as a point of departure for more thorough discussions.

The introduction of PSA testing has immensely complicated the research in prostate cancer epidemiology and biology: we do not know whether the substantial overdiagnosis following screening is due to detection of cancers with malignant potential, but which grow very slowly (a lead time problem), or to diagnosis of truly biologically indolent lesions (adding a new biological domain). Furthermore, high age at diagnosis and long survival times introduce the problem of competing risks in both aetiological and natural history studies.

1 Risk Factors

As for many cancers, age, and ethnic origin (in most studies self-reported) are the strongest known risk factors—in the last decade also the exposure to PSA testing emerges as a 'risk factor' (Wilson et al. 2012). However, while migrant studies clearly imply that environment and/or personal life style is important, a plethora of epidemiological studies have failed to establish any strong leads. Intake of fish, fat, phytoestrogens, tomato products, dairy products, calcium, selenium and vitamins E and D has been extensively studied (Wilson et al. 2012; Alexander et al. 2010; Gilbert et al. 2011; Szymanski et al. 2010; Venkateswaran and Klotz 2010). Tobacco and alcohol use may be emerging, but turn out to be weak or at most modest risk

factors when correcting for competing risks (Wilson et al. 2012). Body mass index (BMI) or indicators of adiposity are also emerging as risk factors or promoters of established disease (Wilson et al. 2012; Davies et al. 2011). In addition, chronic inflammation and/or infections have been implicated as possible risk factors, but no single infectious agent has been identified (Rajarubendra et al. 2011).

Despite the known androgen dependence of prostate cancer, there is little to support that circulating levels of androgens, estrogens or 5-alpha-reductase are associated with risk of developing the disease (Nacusi and Tindall 2011). However, a consistent finding is a positive association with levels of Insulin-like Growth Factor-1 (IGF-1), which is interesting given its link with BMI, adiposity and other metabolic characteristics (Buschemeyer and Freedland 2007).

2 Genetics

Our current knowledge indicates that prostate cancer is one of the cancers most strongly related to inherited susceptibility, even when taking into account that family history of prostate cancer may trigger PSA testing among relatives. Hereditary susceptibility is estimated to explain as much as 40 % of all prostate cancers. Some more uncommon mutations are associated with high risk (e.g. BRCA2, HBOX13, HPC1), however, most hereditary cancers are thought to be associated with low penetrance alleles (Bambury RM et al. 2012). Close to 50 such alleles have already been identified, all with a low risk (i.e. relative risks < 1.5). Several more alleles are currently under study. A combination of these alleles is however thought to increase risk substantially, even though we are yet to understand how these high-risk combinations can be identified as even as little as 50 alleles can already create a very large number of combinations of about 3–5 alleles.

Functional studies have still not been able to establish downstream pathways of germline genetic alterations or variations that could be relevant for prevention. As with many other cancers the MYC and Wnt pathways have been implicated, but interestingly also pathways related to the androgen receptor, as well as pathways related to inflammation (RNASEL, toll-like receptors) and metabolism of vitamin D and IGF-1 have been proposed (Simard et al. 2002).

3 Somatic Genetic Alterations

A number of somatic genetic alterations (amplifications, deletions, point mutations, translocations) have been found to be associated with prostate cancer risk. Examples are alterations in MYC, PTEN, NKx3.1, TMPRSS2-ERG, other translocations in the ETS family of genes, CADM2, PI3K, GSTP1 and FASN (Choudhury et al. 2012; Gurel et al. 2008). Some of these have also been linked to several other cancers, but the TMPRSS2-ERG fusion has attracted much interest since this translocation is both specific for prostate cancer and occurs regularly. Other alterations of interest

are FASN and PI3K (Benedettini et al. 2008; Baca and Garraway 2012): the first due to its relation to fatty acid metabolism and metabolic syndrome and the latter because of the recent development of small molecules that can interfere with PI3K downstream targets. Hitherto, gene expression analyses have only revealed limited overlap and no consistent patterns, but findings for the following four alterations have been fairly consistent: FASN, HPN, AMACR and MYC.

The TMPRSS2-ERG translocation, as well as alterations in MYC and PTEN, has also been associated with prognosis (Choudhury et al. 2012; Attard et al. 2008; Barbieri et al. 2013) but these associations are modest. Immunohistochemical studies of products of PTEN, SMAD4, CyclinD1 and SPP1 and molecular characterisation of PTEN, ERG and ETV1 (Choudhury et al. 2012; Reid et al. 2010) are promising as prognostic profiles. However, none has been shown to discriminate indolent and lethal prostate cancer so well that they have crucially influenced clinical decision-making.

There is a growing understanding of epigenetic changes in prostate cancer, which has the potential to lead to new possible biomarkers for diagnosis and monitoring, and even to new treatment innovations (Perry 2013; Jeronimo et al. 2011).

4 Progression

Understanding the progression of prostate cancer progression is an open field for innovative studies. In autopsy studies, over 50 % of men aged 80 and older have prostate cancer as defined by histopathology. The randomised prostate cancer screening studies show that overdiagnosis is prevalent following PSA testing in asymptomatic men (Klotz 2012). Thus, a substantial proportion of all histopathological lesions today diagnosed as prostate cancers progress either very slowly, not at all and some may even regress. We do not know which of these scenarios is the dominating one and there is currently no coherent theory of a pattern of progression whereby, for instance, the genetic alterations implicated above fit in. For prostate cancer that progresses to metastatic disease it is not established whether clonal expansion, progressive accumulation of malignant properties or stem cell mechanisms is the dominating pathway (Yu et al. 2012).

The knowledge that prostate cancers are heavily dependent on androgen receptor signalling has been utilised effectively to develop treatments. A deeper understanding of the underlying biology now shows that the notion of 'hormone-independent prostate cancer' has to be revised: most prostate cancers remain dependent on androgen receptor signalling also after progression despite traditional androgen deprivation therapy (Alva et al. 2013; Green et al. 2012). Tumours can intrinsically produce androgen receptors, adapt to be sensitive to low levels of androgens, utilise other substrates for receptor activation, synthesise androgen-like substances from, e.g. cholesterol, or activate androgen signalling independently of ligands. 'Castrate resistant prostate cancer' is probably a more relevant terminology. This new understanding is exploited to find new treatments. For example, ligand-independent

activation of AR pathways is hypothesised to be blocked by inhibiting PI3 kinases. Bypass of AR pathways may be associated with the activities downstream of the TMPRSS-ERG fusion, signalling from ERα, ERβ or IGF-1.

5 Natural History

Traditional markers of stage and type of disease still play a major role for prognostication and treatment decisions: tumour size, Gleason score, PSA level at time of diagnosis, presence of regional or distant metastases. For most men, the association between these factors and prognosis will be modified by the treatment given. For instance, surgical removal of clinically localised, low-grade disease will imply a very low risk of disease recurrence.

However, prostate cancer is one of the few cancers where patients have been recommended watchful waiting only, now in a majority of cases replaced by active surveillance. Studies of men with initially untreated prostate cancer show a progression rate to lethal disease of 0.5–1.5 % per year: 18.4 % distant disease progression after 35 years in T0-2 WHO grade 1-2 disease, 20.7 % prostate cancer mortality at 15 years T0-2 Gleason < 8 PSA < 50 ng/ml prostate cancer and 8.4 % prostate cancer mortality at 10 years in T1-2 any grade PSA < 50 ng/ml (Popiolek et al. 2013; Bill-Axelson et al. 2011; Wilt et al. 2012). So far, risk of disease progression has been very low in ongoing series of active surveillance (Tufts Evidence-based Practice Center 2011). The PIVOT trial (Wilt et al. 2012) and the active surveillance series recruited patients from the PSA screening era, while the Orebro natural history study (Popiolek et al. 2013) and the SPCG-4 trial (Bill-Axelson et al. 2011) recruited patients before any widespread screening began. Current cohort studies of patients with deferred primary treatment are difficult to interpret, since most register systems cannot readily differentiate what the intention of the treatment was: active surveillance or watchful waiting. Two quite different patient groups are selected for each treatment and the case mix between these two influences the overall result. Most studies cannot account for secondary androgen deprivation therapy and the drift in Gleason classification system over time complicates the classification of disease.

The median survival time after diagnosis of distant metastatic disease has increased from 22 to 42 months over the last decade. A few investigators believe this is due to the changing natural history, rather than to improved treatment (Alva et al. 2013).

6 Opportunities

The prospects of understanding prostate cancer aetiology and natural history may seem bleak with slow progression. However, one may view the current situation as positively challenging and opening up possibilities for fruitful research:

- If epidemiological study designs circumventing the challenge of PSA-screening can be invented, the current broad research activities in prostate cancer may lead to new etiological understanding.
- Increasingly large biobanks of prostate cancer tissue linked to clinical information and follow-up data have created openings for studies that can study more biological pathways with increasing statistical precision.
- Some potentially modifiable risk factors are emerging and in combination with new knowledge in genetics (e.g. defining risk subsets) and metabolomics (e.g. targeting specific pathways such as IGF-1), a new wave of prevention studies may be feasible.
- Knowledge about important pathways is growing and some of these may be targetable with new drugs.
- For many patients, prostate cancer has a long preclinical phase which may be influenced in secondary prevention strategies.

Taking all of the above into account, it is thus the task of current and future researchers to advance prostate cancer research and improve our knowledge and understanding so that prevention, prediction, treatment choices and management can be ameliorated in the near future.

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Germline Genetic Variants Associated with Prostate Cancer and Potential Relevance to Clinical Practice

Chee Leng Goh and Rosalind Anne Eeles

Abstract

The inherited link of prostate cancer predisposition has been supported using data from early epidemiological studies, as well as from familial and twin studies. Early linkage analyses and candidate gene approaches to identify these variants yielded mixed results. Since then, multiple genetic variants associated with prostate cancer susceptibility have now been found from genome-wide association studies (GWAS). Their clinical utility, however, remains unknown. It is recognised that collaborative efforts are needed to ensure adequate sample sizes are available to definitively investigate the genetic–clinical interactions. These could have important implications for public health as well as individualised prostate cancer management strategies. With the costs of genotyping decreasing and direct-to-consumer testing already offered for these common variants, it is envisaged that a lot of attention will be focussed in this area. These results will enable more refined risk stratification which will be important for targeting screening and prevention to higher risk groups. Ascertaining their clinical role remains an important goal for the GWAS community with international consortia now established, pooling efforts and resources to move this field forward.

C. L. Goh · R. A. Eeles
Oncogenetics Team, Division of Cancer Genetics and Epidemiology, The Institute of Cancer Research, 15 Cotswold Road, Sutton, SM2 5NG, United Kingdom

R. A. Eeles (✉)
Academic Urology and Cancer Genetics Units, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom
e-mail: rosalind.eeles@icr.ac.uk

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1 Introduction

Although prostate cancer (PrCa) remains a significant burden for health services across the world (Ferlay et al. 2010), little is known of its aetiology or triggers. Age, race and family history remain the major risk factors associated with the development of this disease (Crawford 2003). Epidemiological data showing the wide variation of PrCa incidence around the world as well as the cluster patterns observed amongst family members with PrCa imply a potential genetic link within families and/or populations (Center et al. 2012; Goh et al. 2012). Men of African ancestry have nearly twice the incidence rates of Caucasians and Asians, and these differences persist despite accounting for the movement of populations (Jemal et al. 2010).

The clues to a genetic link have been further supported in familial and twin studies. From risk modelling estimates, a positive family history of PrCa increases the risk for an unaffected male relative by two-fold (Lichtenstein et al. 2000). This risk increases the closer the relation is to the man with PrCa, i.e. higher risk if a first versus a second degree relative is affected. The risk also rises with the number of cases affected within the family. Lichtenstein et al. reported that in analyses based on Nordic twin registries, an estimated 42 % of PrCa risk can be explained through germline genetic variants. The higher risks found with monozygotic versus dizygotic twins support the hypothesis that familial aggregation results from shared genetic rather than environmental factors (Lichtenstein et al. 2000). Researchers in this field, therefore, focussed on the discovery of these genetic variants, which could have potentially important clinical utility in public health, both in terms of screening and the tailoring of more effective cancer therapy through personalised medicine.

This chapter aims to provide a brief overview of the evidence for genetic predisposition in PrCa and outline some potential clinical implications for these susceptibility loci as well as the future directions for research in this field.

2 Germline Genetic Models

The initial search for the genetic variants had mixed results. Various analytical methods were used to define this inherited link. Segregation analysis assesses the genetic models of inheritance (Houlston and Peto 2004). Initial studies suggested a major genetic component with an autosomal dominant inheritance, although others have since reported recessive or X-linked modes of inheritance (Carter et al. 1992; Gronberg et al. 1997; Schaid 1998, MacInnis et al. 2010; Cui et al. 2001). This depended heavily on the types of population studied. Nevertheless, these initial results provided further evidence of the inherited link and thus the impetus to search for these high-risk genes. To identify and characterise these genes, molecular analyses in the form of linkage and candidate gene analyses were performed.

Linkage is essentially the co-inheritance of genetic markers with a disease (Easton 2004). The concept of linkage was first described by Mendel who noted the co-inheritance of certain characteristics in his plants. Studies have implicated genes from numerous chromosomes associated with PrCa risk, but many were then refuted by other groups (Lange 2010). In 2005, the International Consortium for PrCa Genetics (ICPCG) reported the largest study to date, combining data from 1,233 families from 10 research groups worldwide (Xu et al. 2005). They identified several promising regions, but the replication of these regions has proved difficult and their status as susceptibility genes remains in doubt. This difficulty suggests that PrCa might be more genetically complex than once thought, involving a polygenic inheritance.

There are, however, genes that have been successfully identified and replicated through candidate studies. Deleterious mutations in both *BRCA1* and *BRCA2* genes have been associated with increased PrCa risk. Both have a moderate to high penetrance, with *BRCA2* conferring an estimated 8.6-fold increased risk in carriers $\leq$65 years (Kote-Jarai et al. 2011a), and *BRCA1* 4.5-fold in carriers $\leq$65 years (Leongamornlert et al. 2012). Consistent evidence is now emerging that *BRCA* mutation carriers who develop PrCa also develop worse disease and have a poorer survival (Castro et al. 2013). More recently, evidence has also emerged for another genetic syndrome, which has been shown to have a moderate effect on PrCa risk. These are the Lynch syndrome mutation carriers who have a germline mutation in the mismatch repair genes; *MLH1*, *MSH2* and *MSH6* (Grindedal et al. 2009; Engel et al. 2012; Barrow et al. 2013). Early data suggest that the risk can be up to 10-fold (Barrow et al. 2013), but further reports are awaited to assess its clinical implications in PrCa and whether all three genes confer an increased PrCa risk when mutated.

Other DNA repair genes have been studied as candidates for PrCa predisposition, and some have been shown to have apparent significant associations, including the *NBS1*, *CHEK2* and *PALB2* genes (Cybulski et al. 2004; Cybulski et al. 2006; Erkko et al. 2007; Thompson et al. 2006; Tischkowitz et al. 2008, Eeles et al. 2010). However, like some of the linkage studies, it has also been

difficult to replicate these results and these may be population origin specific in their risks. More recently, thorough sequencing of a linkage region of interest on 17q has revealed a new locus associated with PrCa risk. Rare germline mutations in *HOXB13*, particularly *G84E,* have been reported to increase the risk of PrCa development of up to 10-fold in early-onset cases from certain populations (Ewing et al. 2012, Shang et al. 2013). Further reports have shown that the RR is nearer 3–4-fold in most populations, but is higher in those of Scandinavian origin (Shang et al. 2013).

Nevertheless, all the genes reported above are rare in the population and are unlikely to account for the vast majority of genetic predisposition for common diseases like PrCa. The difficulty in identifying definitive genes despite epidemiological evidence of the inherited component further supports the hypothesis that PrCa inheritance is unlikely to follow the Mendelian single gene approach, but comprise multiple lower penetrance genes.

Genome-wide association studies (GWAS) were developed to investigate this theory further. Their main advantage is the ability to offer an agnostic approach to identify low risk variants that occur more commonly and are therefore more applicable to a larger proportion of the population (Manolio 2010; Chung et al. 2010). GWAS compares the frequencies of single nucleotide polymorphisms (SNPs), which differ in a single DNA base pair, between cases and controls to look for an association with that particular genetic trait. The SNP is the most common form of genomic variation and the latest estimates for the number of SNPs are 4 million, with a minor-allele frequency of at least 5 % (Abecasis et al. 2012). A typical GWAS would genotype from 0.3 up to 2.5 million SNPs at a single time. Linkage mapping studies lacked power to detect loci that confer low to moderate risks. Given a large enough case–control study, GWAS have the ability to detect multiple loci conferring small risks with odds ratios of ≤ 1.1.

3 Results from Genome-Wide Association Studies

The first PrCa GWAS was published in 2006 (Amundadottir et al. 2006), and currently the National Human Research Genome Institute (NHGRI) catalogue lists over 25 GWAS published with 76 SNPs currently known to be associated with PrCa risk (Hindroff et al. 2009) (see Table 1). Although they individually confer a modest risk of PrCa, collectively they are estimated to explain approximately 30 % of the familial risk (Eeles et al. 2013). The genes identified could prove important in clinical use. Examples are the 8q24 loci, which are the first identified from GWAS and where there is the highest number of independently associated variants (Al Olama et al. 2009). 8q24 is in the vicinity of the *c-MYC* oncogene and chromatin conformation assays have shown that some of these SNPs exert long-range tissue-specific expression of *MYC* expression (Ahmadiyeh et al. 2010). 8q24 is also implicated in many other cancers and would be an important target for cancer management.

Table 1 Common susceptibility loci for PrCa

Locus	SNP	Effect allele frequency[a]	Per allele OR[a]	Nearby genes	References
1q21	rs1218582	0.45	1.06 (1.03–1.09)	*KCNN3*	(Eeles et al. 2013)
1q32	rs4245739	0.25	0.91 (0.88–0.95)	*MDM4, PIK3C2B*	(Eeles et al. 2013)
2p11	rs10187424	0.41	0.92 (0.89–0.94)	*GGCX/VAMP8*	(Kote-Jarai et al. 2011b)
2p15	rs721048	0.19	1.15 (1.10–1.21)	*EHBP1*	(Gudmundsson et al. 2008)
2p21	rs1465618	0.23	1.08 (1.03–1.12)	*THADA*	(Eeles et al. 2009)
2p24	rs13385191	0.56	1.15 (1.10–1.21)	*C2orf43*	(Takata et al. 2010)
2p25	rs11902236	0.27	1.07 (1.03–1.10)	*TAF1B:GRHL1*	(Eeles et al. 2013)
2q31	rs12621278	0.06	0.75 (0.70–0.80)	*ITGA6*	(Eeles et al. 2009)
2q37	rs2292884	0.25	1.14 (1.09–1.19)	*MLPH*	(Kote-Jarai et al. 2011b; Schumacher et al. 2011)
2q37	rs3771570	0.15	1.12 (1.08–1.17)	*FARP2*	(Eeles et al. 2013)
3p11	rs2055109	0.9	1.20 (1.13–1.29)		(Akamatsu et al. 2012)
3p12	rs2660753	0.11	1.18 (1.06–1.31)		(Eeles et al. 2008)
3q13	rs7611694	0.41	0.91 (0.88–0.93)	*SIDT1*	(Eeles et al. 2013)
3q21	rs10934853	0.28	1.12 (1.08–1.16)	*EEFSEC*	(Gudmundsson et al. 2009)
3q23	rs6763931	0.45	1.04 (1.01–1.07)	*ZBTB38*	(Kote-Jarai et al. 2011b)
3q26	rs10936632	0.48	0.90 (0.88–0.93)	*CLDN11/SKIL*	(Kote-Jarai et al. 2011b)
4q13	rs1894292	0.48	0.91 (0.89–0.94)	*AFM, RASSF6*	(Kote-Jarai et al. 2013)
4q22	rs17021918	0.34	0.90 (0.87–0.93)	*PDLIM5*	(Eeles et al. 2009)
4q22	rs12500426	0.46	1.08 (1.05–1.12)	*PDLIM5*	(Eeles et al. 2009)
4q24	rs7679673	0.45	0.91 (0.88–0.94)	*TET2*	(Eeles et al. 2009)

(continued)

Table 1 (continued)

Locus	SNP	Effect allele frequency[a]	Per allele OR[a]	Nearby genes	References
5p12	rs2121875	0.34	1.05 (1.02–1.08)	*FGF10*	(Kote-Jarai et al. 2011b)
5p15	rs2242652	0.19	0.87 (0.84–0.90)	*TERT*	(Kote-Jarai et al. 2011b)
5p15	rs12653946	0.44	1.26 (1.20–1.33)	*IRX4*	(Takata et al. 2010)
5q35	rs6869841	0.21	1.07 (1.04–1.11)	*FAM44B (BOD1)*	(Eeles et al. 2013)
6p21	rs130067	0.21	1.05 (1.02–1.09)	*CCHCR1*	(Kote-Jarai et al. 2011b)
6p21	rs1983891	0.41	1.15 (1.09–1.21)	*FOXP4*	(Takata et al. 2010)
6p21	rs3096702	0.4	1.07 (1.04–1.10)	*NOTCH4*	(Eeles et al. 2013)
6p21	rs2273669	0.15	1.07 (1.03–1.11)	*ARMC2, SESN1*	(Eeles et al. 2013)
6q22	rs339331	0.63	1.22 (1.15–1.28)	*RFX6*	(Takata et al. 2010)
6q25	rs9364554	0.29	1.17 (1.08–1.26)	*SLC22A3*	(Eeles et al. 2008)
6q25	rs1933488	0.41	0.89 (0.87–0.92)	*RSG17*	(Eeles et al. 2013)
7p15	rs10486567	0.77	0.74 (0.66–0.83)	*JAZF1*	(Thomas et al. 2008)
7p21	rs12155172	0.23	1.11 (1.07–1.15)	*SP8*	(Eeles et al. 2013)
7q21	rs6465657	0.46	1.12 (1.05–1.20)	*LMTK2*	(Eeles et al. 2008)
8p21	rs2928679	0.42	1.05 (1.01–1.09)	*SLC25A37*	(Eeles et al. 2009)
8p21	rs1512268	0.45	1.18 (1.14–1.22)	*NKX3.1*	(Eeles et al. 2009)
8p21	rs11135910	0.16	1.11 (1.07–1.16)	*EBF2*	(Eeles et al. 2013)
8q24	rs1447295	0.13	1.62		(Amundadottir et al. 2006)
8q24	rs6983267	0.5	1.26 (1.13–1.41)		(Yeager et al. 2007)
8q24	rs16901979	0.09	1.79 (1.36–2.34)		(Gudmundsson et al. 2007a)

(continued)

Table 1 (continued)

Locus	SNP	Effect allele frequency[a]	Per allele OR[a]	Nearby genes	References
8q24	rs10086908	0.3	0.87 (0.81–0.94)		(Al Olama et al. 2009)
8q24	rs12543663	0.31	1.08 (1.00–1.16)		(Al Olama et al. 2009)
8q24	rs620861	0.39	0.90 (0.84–0.96)		(Al Olama et al. 2009)
9q31	rs817826	0.08	1.41 (1.29–1.54)	*RAD23B-KLF4*	(Xu et al. 2012)
9q33	rs1571801	0.25	1.27 (1.10–1.48)	*DAB21P*	(Duggan et al. 2007)
10q11	rs10993994	0.4	1.25 (1.17–1.34)	*MSMB*	(Eeles et al. 2008; Thomas et al. 2008)
10q24	rs3850699	0.29	0.91 (0.89–0.94)	*TRIM8*	(Eeles et al. 2013)
10q26	rs4962416	0.27	1.20 (1.07–1.34)	*CTBP2*	(Thomas et al. 2008)
10q26	rs2252004	0.77	1.16 (1.10–1.22)		(Akamatsu et al. 2012)
11p15	rs7127900	0.2	1.22 (1.17–1.27)		(Eeles et al. 2009)
11q12	rs1938781	0.3	1.16 (1.11–1.21)	*FAM111A*	(Akamatsu et al. 2012)
11q13	rs7931342	0.49	0.84 (0.79–0.90)		(Eeles et al. 2008; Thomas et al. 2008)
11q22	rs11568818	0.44	0.91 (0.88–0.94)	*MMP7*	(Eeles et al. 2013)
12q13	rs10875943	0.31	1.07 (1.04–1.10)	*TUBA1C/ PRPH*	(Kote-Jarai et al. 2011b)
12q13	rs902774	0.15	1.17 (1.11–1.24)	*KRT8*	(Schumacher et al. 2011)
12q24	rs1270884	0.49	1.07 (1.04–1.10)	*TBX5*	(Eeles et al. 2013)
13q22	rs9600079	0.38	1.18 (1.12–1.24)		(Takata et al. 2010)
14q22	rs8008270	0.18	0.89 (0.86–0.93)	*FERMT2*	(Eeles et al. 2013)
14q24	rs7141529	0.5	1.09 (1.06–1.12)	*RAD51L1*	(Eeles et al. 2013)
17p13	rs684232	0.36	1.10 (1.07–1.14)	*VPS53, FAM57A*	(Eeles et al. 2013)

(continued)

Table 1 (continued)

Locus	SNP	Effect allele frequency[a]	Per allele OR[a]	Nearby genes	References
17q12	rs4430796	0.49	1.22 (1.15–1.30)	*HNF1B*	(Gudmundsson et al. 2007b)
17q12	rs11649743	0.8	1.28 (1.07–1.52)	*HNF1B*	(Sun et al. 2008)
17q21	rs7210100	0.05	1.51 (1.35–1.69)	*ZNF652*	(Haiman et al. 2011)
17q21	rs11650494	0.08	1.15 (1.09–1.22)	*HOXB13, SPOP*	(Eeles et al. 2013)
17q24	rs1859962	0.46	1.20 (1.14–1.27)		(Gudmundsson et al. 2007b)
18q23	rs7241993	0.3	0.92 (0.89–0.95)	*SALL3*	(Eeles et al. 2013)
19q13	rs2735839	0.15	0.83 (0.75–0.91)	*KLK2/KLK3*	(Eeles et al. 2008)
19q13	rs8102476	0.54	1.12 (1.08–1.15)		(Gudmundsson et al. 2009)
19q13	rs11672691	0.76	1.12 (1.03–1.21)		(Amin Al Olama et al. 2013)
19q13	rs103294	0.24	1.28 (1.21–1.36)	*LILRA3*	(Xu et al. 2012)
20q13	rs2427345	0.37	0.94 (0.91–0.97)	*GATAS, CABLES2*	(Eeles et al. 2013)
20q13	rs6062509	0.3	0.89 (0.66–0.92)	*ZGPAT*	(Eeles et al.,2013)
22q13	rs5759167	0.47	0.86 (0.83–0.88)	*BIL/TTLL1*	(Eeles et al. 2009)
Xp11	rs5945619	0.36	1.19 (1.07–1.31)	*NUDT11*	(Gudmundsson et al. 2008; Eeles et al. 2008)
Xp22	rs2405942	0.21	0.88 (0.83–0.92)	*SHROOM2*	(Eeles et al. 2013)
Xq12	rs5919432	0.19	0.94 (0.89–0.98)	*AR*	(Kote-Jarai et al. 2011b)

[a]Data for effect allele frequency and per allele OR (odds ratio) are taken from the original publications. 95 % confidence intervals are given in brackets where available. Modified and updated from Goh et al. (2012)

Other sites of potential clinical significance are the SNP rs4245739 on chromosome 1 near the *MDM4* gene, which is a negative regulator of *TP53*, or rs11568818, which is in linkage disequilibrium with the gene *MMP7*, encoding a matrix metalloproteinase. *MMP7* has been reported to be associated with metastasis and poor prognosis (Eeles et al. 2013). These variants could perhaps play a role in the ability to differentiate low- and high-risk disease. Further work is needed in this area.

The SNP rs10993994, located upstream of the microseminoprotein beta (*MSMB*) gene could potentially play a role in screening (Eeles et al. 2008). *MSMB* is a seminal fluid protein and has been shown to be either lost or decreased in PrCa (Whitaker et al. 2010). The association between a reduced level of *MSMB* and PrCa risk has also been consistently replicated in multi-ethnic cohorts, indicating a potential utility in screening, which is applicable across different populations and is independent of serum PSA level (Haiman et al. 2013). SNPs within the kallikrein regions have also been associated with PSA level (Eeles et al. 2008). These could be incorporated in risk prediction models and would warrant further testing.

Other SNPs have been found in regions of interest including the androgen receptor gene (Kote-Jarai et al. 2011b), DNA repair *RAD51B* (Eeles et al. 2013) and the *CCHCR1* (coding for coiled-coil alpha-helical rod protein 1), which is also associated with psoriasis (Kote-Jarai et al. 2011b). All these could suggest potential targets for therapy.

Nevertheless, despite some evidence of coding SNPs, the majority of these SNPs are non-coding, lying in intronic or intergenic regions. Freedman et al. presented a hypothesis that these trait-associated alleles exert their effects by influencing transcriptional output, for example transcript levels and splicing, through multiple mechanisms. They further emphasise that appropriate assays and models are needed to test the functional effects of these SNPs (Freedman et al. 2011). A better understanding of their functional effects would improve our understanding of the pathogenesis of this disease and potentially lead to better clinical application and utility.

4 Potential Clinical Implications

PrCa mortality has decreased steadily over the past few decades. Over the past 25 years, the 5-year survival rate for all stages combined has increased from 68.3 to 99 % (Siegel et al. 2012). Nevertheless, there are still a large number of men who die from this disease. In the US, it is the second commonest cause of male cancer-related death (Jemal et al. 2010). The ability to differentiate men who are likely to succumb to this disease is therefore of major public health interest. Research is now underway to investigate the use of common germline genetic variants as potential biomarkers.

4.1 Individual Risk Profiling

One of the potential roles for the GWAS risk SNPs is risk profiling. As mentioned before, the SNPs individually exert a modest effect. However, these SNPs act multiplicatively. Antoniou et al. in the paper by Eeles et al., proposed a risk model using the currently known SNPs, where men at the top 1 % of the highest risk distribution have a 4.7-fold relative risk compared with the population average and the top 10 % of men have a 2.7-fold increased risk in comparison (Eeles et al. 2013). MacInnis et al. presented a model that incorporated SNPs and family history, which could stratify men better with regard to their risk of developing PrCa (Macinnis et al. 2011). These models could be used to counsel patients with regard to their individual risk of developing PrCa and have public health implications in terms of targeted screening. Those at higher risk could also be targeted for chemoprevention. Nevertheless, these models do not address the potential interaction between genetic variants and environmental factors. The question that needs to be answered is: do certain genotypes increase the susceptibility risk when exposed to certain environmental stimuli, and vice versa? The BPC3 (Breast PrCa Cohort Consortium) did not report any significant association between 36 GWAS risk SNPs and environmental factors including alcohol, BMI and smoking (Lindstrom et al. 2011). Potential limitations of their study include the low power to detect modest differences. Large consortia are needed to potentially power these sorts of analyses, and until then the gene–environmental interaction question remains unanswered.

4.2 Public Health Screening Implications

There currently exist controversies in the US and Europe with regard to the benefits of population-based PSA screening for PrCa (Chou et al. 2011; Basch et al. 2012). Whether the harms of screening are justified by the benefits in terms of the reports of reduction in PrCa mortality remain hotly debated. The recent publication of the Prostate Cancer Intervention Versus Observational Trial (PIVOT) casts further doubt, since men with PSA screen-detected localised PrCa who underwent radical prostatectomy did not have a significantly improved PrCa specific survival (Wilt Chou et al. 2012). It is without doubt that PSA screening may identify cancer earlier, but we need better screening approaches that can identify clinically significant disease. The usage of the GWAS risk SNPs to potentially individualise PrCa risk and identify men at higher risk for targeted screening should be evaluated further. Several groups have reported the use of varying numbers of GWAS risk SNPs, incorporating these in screening models using PSA and family history. These methods could improve the positive predictive value of PSA screening but further validation is needed. Pashayan et al. proposed a screening model utilising 31 PrCa risk SNPs to stratify men into risk groups according to their genetic profiles. If a polygenic risk score was generated and screening the bottom 1 % of the genetic risk distribution was avoided, 16 % of

men who would currently be offered screening based on an age threshold of >55 years would avoid screening (Pashayan et al. 2011). Importantly their model estimates that only 3 % of cases will be missed, but it is unknown if these would be clinically significant tumours. Further investigation is needed in this area also.

4.3 Disease Aggressiveness and Prostate Cancer Treatment Outcomes

As mentioned before, rare mutations like *BRCA1/2* have been associated with worse prognosis. It is therefore becoming increasing recognised that mutation carriers with PrCa should be treated more aggressively and early screening studies are currently under investigation, e.g. the IMPACT (The Identification of Men with a genetic Predisposition to Prostate Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls) trial (Mitra et al. 2011). However, the clinical utility of the more common GWAS variants to predict aggressive disease is not yet clear.

Like the screening approach, the ability to stratify men into more refined risk groups for treatment is needed. Staging information and nomograms currently in existence do give some indication of prognosis but these do not predict accurately the response to particular treatment or toxicity. There are also unexpected early deaths and long-term survivors that remain unexplained in good and poor prognosis groups, respectively (Mac Manus et al. 2006). If we can use germline genetic variants to predict men with poorer prognosis or those who respond better/worse to different treatment modalities, we might be better able to tailor treatment. Several groups have reported some association of the GWAS variants with disease aggressiveness including the 8q24 region (Cussenot et al. 2008), 15q13 (Fitzgerald et al. 2011), and the androgen receptor gene (Kote-Jarai et al. 2011b). However, these have not been consistently replicated (Xu et al. 2008). Szulkin et al. published a study looking at association of the GWAS SNPs with disease progression in men with clinically localised PrCa regardless of treatment administered (Szulkin et al. 2012). No significant association was found in the 23 SNPs studied. Further work is still needed to incorporate the updated list of SNPs in analyses of cohorts of patients with treatment outcome data.

Other groups have investigated the utility of genetic variants in specific PrCa treatment cohorts. Prostatectomy cohorts have been the most investigated. Different groups have reported in single centre studies, several candidate genes that are associated with disease aggressiveness. These include, amongst others, the *MMP* (Matrix Metallo-proteinases) (Jaboin et al. 2011), *KLK* (kallikrein) (Morote et al. 2010), *RNASEL* (encoding ribonuclease L) (Larson et al. 2008), *Wnt* signalling pathway genes (Huang et al. 2010), *IGF1 (Insulin-like growth factor-1)* (Chang et al. 2013), *cyclin D1 (*Yu et al. 2013*), SRD5A* (steroid 5-alpha reductase polypeptide) (Audet-Walsh et al. 2011), *IL10* (Interleukin-10) (Dluzniewski et al. 2012), androgen pathway (Strom et al. 2004) and *EGFR* (epidermal growth factor receptor) genes (Perez et al. 2010). For some of these genes, conflicting results

have been reported and further validation is needed to ascertain their true utility. The utility of some of the GWAS risk SNPs have also been reported by different groups in surgical cohorts. SNPs in chromosome 8q24 and the *MSMB* SNP have been reported to be associated with worse pathological tumour stage and biochemical relapse post-prostatectomy, respectively (Huang et al. 2009; Whitman et al. 2010). However, some groups reported no associations (Kader et al. 2009). The true impact of the risk SNPs in this cohort is, therefore, still unclear.

With regard to androgen deprivation therapy, variants in candidate genes like the androgen transporter genes (*SLCO2B1* and *SLCO1B3*) (Yang et al. 2011), *MEGALIN* (low density lipoprotein-related protein 2) (Holt et al. 2008), *SRC* (sarcoma) (Maki et al. 2006) and genes involved in the steroid hormone pathway (Kohli et al. 2012), have been linked with treatment resistance. Bao et al. in 2011 investigated the association of 19 GWAS risk SNPs with PrCa survival in an androgen deprivation therapy cohort (Bao et al. 2012). They reported that only the risk SNP rs169001979 was associated with survival. However, further validation is needed. The same group also published the association of genetic variations in oestrogen and androgen-binding sites as well as microRNA and microRNA target sites (Huang et al. 2012a; Bao et al. 2011; Huang et al. 2012b). These results are encouraging, but again further confirmatory studies are needed.

There have been no published studies to date analysing the impact of risk SNPs in radiotherapy outcomes. However, four genome-wide association studies have been published investigating the association between genotypes and the development of radiation toxicity. Kerns et al. reported the first GWAS, which found an SNP on the *FSHR* (Follicle Stimulating Hormone Receptor) gene associated with increased rates of erectile dysfunction in African-American men post-radiotherapy (Kerns et al. 2010). Two further GWAS reported by the same group published several SNPs in chromosome 9p21 associated with the development of urinary toxicity, and several SNPs approaching GWAS significance associated with erectile dysfunction, but these need to be validated (Kerns et al. 2013a, Kerns et al. 2013b). Another GWAS by Barnett et al. did not report any SNP that was significantly associated with radiotoxicity (Barnett et al. 2012). It was acknowledged that the low number of patients could have resulted in reduced power to detect any significant difference. These groups are in the radiogenomics consortium and we await further results (West et al. 2010).

To investigate the clinical utility of the risk SNPs in PrCa active surveillance cohorts, a recent study investigated the use of risk scores in predicting adverse outcomes (Goh et al. 2013). No significant association was found but low patient numbers is the main limitation of this good prognosis cohort. For PrCa chemotherapy outcomes, groups have investigated the association of genetic variations in drug metabolism pathways. They report that some polymorphisms are associated with treatment resistance (Sissung et al. 2008). Another gene of interest in this area is the chromosome 8p21 *CLUSTERIN* gene (Chi et al. 2010). Increased expression is thought to predict chemotherapy resistance. There have been as yet no published chemotherapy studies utilising the risk SNPs and this remains an unmet need.

5 Future Directions

The clinical utility of the GWAS risk SNPs remains unclear and needs to be established. It has been clear that despite encouraging results from groups reporting some clinical associations, further validation is needed for most studies. Small numbers currently existing in single centre cohorts worldwide will limit the power to detect true differences. It is clear that collaborations are needed to establish larger sample sizes to answer both genetic-clinical and genetic-environmental questions.

International consortia have now been established to not only address these questions but to potentially validate published results. An example is the NIH (National Institute of Health) funded post-GWAS initiatives with the establishment of ELLIPSE (ELucidating Loci Involved in Prostate cancer SuscEptibility) (National Institute of Health 2010). As part of this, the Clinical ELLIPSE Consortium (CEC) was formed to develop risk models, analyse risk profiles and investigate clinical application. Other consortia include The PRACTICAL (Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome) Consortium. PRACTICAL, which interacts with ELLIPSE, bringing together researchers interested in the genetic predisposition of PrCa to discover and validate these genetic variants (PRACTICAL 2008).

Efforts are also underway to fully discover the functional aspects of these SNPs within these consortia. A better understanding of this would in turn bring about a better understanding of the pathogenesis and could potentially lead to therapeutic targets and drug discovery as well as chemoprevention options.

6 Conclusions

Technological advancements with improved high-throughput genome sequencing and better analytical as well as computational tools have escalated our discovery of genes associated with PrCa. The common variants could potentially play a major public health role in many different aspects of management. These include better risk stratification in the general population to identify men for targeted screening or to counsel individuals better regarding their own personal risk of cancer. Determining their effect in predicting treatment outcomes or toxicity would also enable clinicians to personalise and tailor specific treatments according to their genetic profile. With the costs of genotyping decreasing and direct-to-consumer testing already offered for the common variants, it is envisaged that a lot of attention will be focussed on this in the coming years. Ascertaining their clinical role remains an important goal for the GWAS community with consortia now established, pooling efforts and resources to move this field forward.

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Lifestyle and Dietary Factors in Prostate Cancer Prevention

Andrea Discacciati and Alicja Wolk

Abstract

The etiology of prostate cancer (PCa) is still largely unknown and the only well-established risk factors are those that are non-modifiable (age, race, and family history). Therefore, the identification of lifestyle and dietary factors which might prevent PCa development and progression is of paramount importance from a public health point of view. Accumulating evidence indicates that obesity may have a dual effect on PCa: an increased risk of aggressive PCa and a decreased risk of localized PCa. Both occupational and leisure time physical activity have been observed to be associated with a reduced PCa risk. Different dietary factors including coffee have been examined in several epidemiological studies, but results have been mostly inconsistent. However, these inconsistencies can be, at least partly, explained by the fact that the majority of those studies examined total PCa risk only and, in addition, they did not take into account the different genetic characteristics within the study populations. Therefore, the future epidemiological studies should focus on the analysis of PCa subtypes separately in order to examine possible etiological heterogeneity of PCa in relation to some exposures. In addition, differences in the genetic characteristics of the study participants should be taken into account to explore the possibility of gene–environment interactions.

A. Discacciati · A. Wolk (✉)
Unit of Nutritional Epidemiology, Division of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Box 210, 17177, Stockholm, Sweden
e-mail: Alicja.Wolk@ki.se

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Contents

1 Introduction

There is a great need to identify modifiable lifestyle and dietary factors that are related to both prostate cancer (PCa) development and progression. Although not firmly established, protective modifiable factors may include life-long avoidance of obesity and being physically active. There is also accumulating evidence from observational studies that some dietary factors may decrease PCa risk while others may increase risk. However, large unexplained heterogeneities of findings reported for the consumption of specific foods, nutrients, phytochemicals, as well as their biomarkers in different study populations do not allow the results to be summarized to give robust conclusions.

2 Obesity

A recent dose–response meta-analysis of 13 prospective studies observed a possible dual effect of obesity during middle-late adulthood, as measured by body mass index (BMI), on the incidence of localized and advanced PCa (Discacciati et al. 2012). In particular, the authors observed a 6 % reduced risk of localized PCa [Relative Risk (RR) (95 % Confidence Interval (CI)) = 0.94 (0.91–0.97)] and a 9 % increased risk of advanced PCa [RR (95 % CI) = 1.09 (1.02–1.16)], for every 5 kg/m^2 increase in BMI (Fig. 1). Heterogeneity statistics (I^2) for localized and advanced PCa analyses were 18 % ($p_{heterogeneity} = 0.27$) and 38 % ($p_{heterogeneity} = 0.08$), respectively. This dichotomous effect is a possible explanation for why a previous meta-analysis of 27 prospective studies focusing on the incidence of total PCa observed a non-statistically significant association with BMI and a high between-study heterogeneity ($I^2 = 73$ %) (Renehan et al. 2008). These findings support the hypothesis of etiological heterogeneity of PCa related to obesity.

The dual effect of obesity on PCa incidence might be explained partly by detection bias and partly by underlying biological mechanisms. Obese men were observed to have lower prostate-specific antigen blood concentrations compared to normal-weight men (Banez et al. 2007; Baillargeon et al. 2005; Grubb et al. 2009; Price et al. 2008) and additionally obesity could make it more difficult to perform a

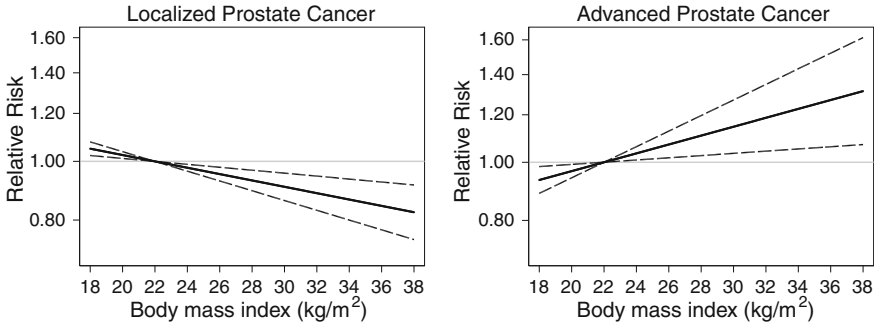

Fig. 1 Dose–response relationships between body mass index (kg/m^2) and relative risk of localized and advanced prostate cancer (*continuous line*) in a meta-analysis of 13 prospective studies (Discacciati et al. 2012). *Long-dashed lines* represent 95 % confidence intervals. The *vertical axes* are on a log scale

thorough digital rectal examination (Chu et al. 2011), resulting in lower biopsy rates. Furthermore, obese men have on average larger prostates (Freedland et al. 2006), which could reduce the odds of detecting a cancer at biopsy. PCa in obese men is therefore more likely to be detected at a later, more advanced stage, possibly following clinical symptoms, rather than at an early, more indolent stage. Detection bias alone, however, is unlikely to completely explain this dichotomous effect (Allott et al. 2013). The biological mechanisms behind these opposite associations between obesity and PCa remain unclear, but testosterone might play an important role in the pathway. In fact, obese men were observed to have lower free testosterone concentrations (Lima et al. 2000), which in turn were shown to be associated with a lower risk of nonaggressive PCa and a higher risk of aggressive PCa in two cohort studies (Platz et al. 2005; Severi et al. 2006). Additionally, more aggressive cancers at diagnosis were observed to be associated with decreased levels of testosterone (Hoffman et al. 2000; Massengill et al. 2003; Schatzl et al. 2001). Several other possible mechanisms could explain the association between obesity and PCa risk, including the sex hormone-binding globulin, insulin-like growth factor I, and inflammation pathways (Hsing et al. 2007).

The role of obesity in earlier stages of life has also been examined by epidemiological studies. Two large cohort studies and a case–control study observed evidence of an inverse association of BMI during early adulthood with incidence of advanced PCa and risk of PCa mortality (Discacciati et al. 2011; Giovannucci et al. 1997; Robinson et al. 2005). Furthermore, a cohort study observed an inverse association with localized PCa incidence (Wright et al. 2007). However, lack of association was observed by other cohort studies (Schuurman et al. 2000; Littman et al. 2007). The observed inverse relationship with PCa risk suggests that early adulthood might be a critical window in which obesity affects sex hormone levels and other physiologic changes that could be important for future PCa risk.

Whether weight change in a time window around the diagnosis of PCa is associated with its prognosis has been less studied. However, two cohort studies carried out among men undergoing radical prostatectomy have addressed this issue. The first study observed a 94 % increased risk of biochemical recurrence (BR) among men who gained more than 2.2 kg 1 year after surgery [RR (95 % CI) = 1.94 (1.14–3.32)], compared to those who maintained their weight before and after prostatectomy (Joshu et al. 2011). The second study observed a 65 % increased risk of BR among men who gained more than 2.5 kg in the year preceding the surgical operation [RR (95 % CI) = 1.65 (1.03–2.64)], compared to all other men (Whitley et al. 2011).

3 Physical Activity

Physical activity, a modifiable lifestyle factor, has been recognized to play an important role in the prevention of several chronic diseases (Samitz et al. 2011; Moore et al. 2012; Woodcock et al. 2011). However, the accumulating evidence from observational epidemiologic studies on physical activity and PCa risk has been mixed. Recently published, the first meta-analysis of available studies on total, occupational, and recreational physical activity and PCa risk that took into account multiple characteristics of the summarized studies (study quality, study design, population sources, assessment methods for physical activity, length of the follow-up in cohort studies) appears to indicate an inverse association, albeit a small one (Liu et al. 2011). More specifically, this meta-analysis showed a statistically significant total PCa risk reduction related to occupational activity [RR (95 % CI) = 0.86 (0.78–0.94); based on results from seven higher quality cohort studies and six higher quality case–control studies; $I^2 = 16$ %, $p_{heterogeneity} = 0.28$]. A summary of higher quality cohort studies indicated that modifiable leisure time activity (recreational physical activity) may be associated with a slightly decreased risk [RR (95 % CI) = 0.95 (0.90–1.00)] based on 16 studies of total PCa ($I^2 = 14$ %, $p_{heterogeneity} = 0.29$).

Based on the summary results, presented above from a meta-analysis of relative body weight, that show an increased risk of advanced PCa among obese men, and in contrast show a decreasing risk of localized cancer, it would be expected that the protective effect of physical activity should be more pronounced for advanced PCa. Furthermore, an experimental study in transgenic mouse model has shown that physical activity can delay PCa progression in a dose–response manner (Esser et al. 2009). However, results from the meta-analysis stratified by PCa subtype did not indicate any difference. Evidence of heterogeneity was observed among studies of both localized cancer ($I^2 = 59$ %, $p_{heterogeneity} = 0.003$; 14 studies) and advanced cancer ($I^2 = 63$ %, $p_{heterogeneity} = 0.001$; 14 studies), which in principle does not allow one to summarize the results. Thus, the question of whether physical activity is especially favorable for the prevention of advanced PCa cannot be answered with these data. There are also other methodological aspects related to

these results making their interpretation difficult. Therefore, there is a need for further well-designed studies to address this urgent issue. This is especially important in the broader context that physical activity may play a role in preventing obesity and so far no other modifiable lifestyle risk factors of significance for PCa prevention have been identified.

Nevertheless, given mounting evidence that physical activity has numerous other health benefits, men should be encouraged to increase their daily physical activity both during work-time (e.g., taking stairs instead of escalator, communicating with coworkers in person instead of sending e-mails) and during leisure time (exchange hours of sitting and watching TV with some physical activities) to improve their overall health and potentially decrease their risk for PCa.

4 Dietary Factors

An approximately 6-fold higher PCa incidence in Western countries as compared with non-Western countries has led to a quite obvious hypothesis that such environmental differences such as dietary factors may contribute to at least a part of the documented incidence differences. Although the first studies of association between diet and PCa risk are dated almost five decades ago there are still no clear conclusions.

The number of accumulated scientific publications linking foods, macro- and micronutrients, and other phytochemicals with PCa risk is impressive, as summarized in recent review (Masko et al. 2013). The most studied nutrient (through July 1, 2012) is calcium (824 publications), followed by vitamin D (676 reports), cholesterol (594), protein (486), selenium (463), vitamin E (361), vitamin A (115), and B-vitamins (109). Among phytochemicals the most studied have been lycopene (295 publications), curcumin (121), and resveratrol (100). Regarding consumption of foods the most investigated has been soy (364 publications), dairy products (159), and meats (125). Association with fat has been reported in large number of publications (191 about total fat, 146 about omega-6 and 123 about omega-3 fatty acids, and 81 about saturated fat, specifically). Despite this very broad and extensive research results are mixed and the evidence is not yet fully convincing for any of the dietary factors.

It should be kept in mind that this apparent lack of consistency among published studies might be, at least in part, ascribed to differences in etiology between localized and more aggressive PCa subtypes. Unfortunately, the majority of published studies so far is limited to analyses of total PCa. As with the above-presented dual association with obesity, the literature for dietary factors can be confusing because effects may differ between localized and aggressive PCa. Indeed, there are some examples showing a lack of association between consumption of vegetables and total PCa incidence and, in the same study population, a substantially reduced risk of advanced cancer (Kirsh et al. 2007).

5 Coffee

Coffee has recently been receiving increasing attention with regard to PCa. However, existing epidemiological evidence for a possible association between coffee consumption and PCa risk is inconsistent, with two meta-analyses published 1 year apart observing different results. The meta-analysis by Park et al., including four cohort studies, observed some evidence of an increased total PCa risk [RR (95 % CI) = 1.06 (0.83–1.35)], when comparing high with low drinkers (Park et al. 2010). On the other hand, the meta-analysis by Yu et al., which included five cohort studies, observed a 21 % decreased total PCa risk [RR (95 % CI) = 0.79 (0.61–0.98)] among high drinkers compared to low or nondrinkers (Yu et al. 2011). Noteworthy, those two meta-analyses have only two cohort studies in common; differences between the two meta-analyses in terms of the literature search strategies and inclusion criteria of the single studies could explain the different results.

Only three cohort studies, not included in the aforementioned meta-analyses, have been carried out by subtype of the disease and their results suggest a protective effect of coffee on PCa risk (Wilson et al. 2011; Shafique et al. 2012; Discacciati et al. 2013). However, two of those three studies observed a decreased PCa risk especially for advanced (Wilson et al. 2011) and high-grade cancers (Shafique et al. 2012), while the third one observed an inverse association principally for localized PCa risk (Discacciati et al. 2013). In particular, the authors of the Health Professionals Follow-Up Study observed a 53 % decreased risk of advanced PCa [RR (95 % CI) = 0.47 (0.28–0.77)] among high coffee consumers (≥6 cups/day) as compared with nondrinkers, while the authors of a small study carried out in Scotland observed a 53 % decreased risk of high-grade PCa [RR (95 % CI) = 0.47 (0.22–1.01)] among men who consumed three or more cups per day compared with nondrinkers. In a large population-based cohort of Swedish men, Discacciati et al. observed a 19 % decreased risk of localized PCa risk [RR (95 % CI) = 0.81 (0.69–0.96)], comparing high coffee drinkers (≥6 cups/day) with regular drinkers (1–3 cups/day) (Fig. 2). Differences in the observed findings could be due, at least partially, to differences in coffee preparation, which could influence its composition (Lee and Binns 2011).

Results from case–control studies summarized in a meta-analysis were also mixed, with hospital-based studies observing a 61 % increased PCa risk [RR (95 % CI) = 1.61 (1.20–2.15); four studies] and population-based studies observing a non-statistically significant 5 % increased risk [RR (95 % CI) = 1.05 (0.86–1.28); six studies], both comparing high versus low coffee drinkers (Park et al. 2010). A recent population-based case–control study conducted in the United States, not included in the aforementioned meta-analysis, did not observe an association between coffee consumption and localized or advanced PCa risk (Geybels et al. 2013).

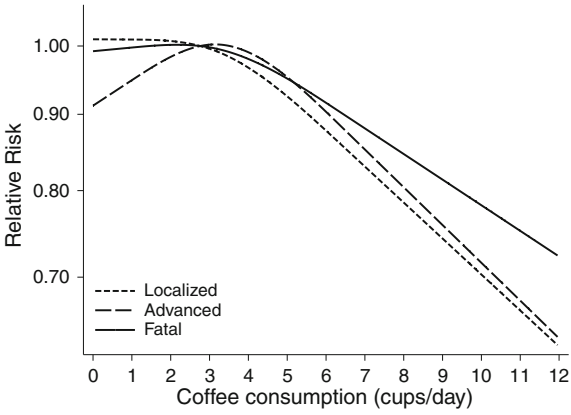

Fig. 2 Dose–response relationships between coffee consumption (cups/day) and relative risk of localized (*short-dashed line*), advanced (*long-dashed line*), and fatal prostate cancer (*continuous line*) in a prospective cohort study of 44,613 Swedish men followed up from 1998 to 2010 (Discacciati et al. 2013). The *vertical axis* is on a log scale

An inverse relationship between coffee consumption and risk of PCa is, however, biologically plausible (Discacciati et al. 2013). Briefly, coffee consumption was observed to be associated with higher adiponectin plasma levels (Imatoh et al. 2011; Kempf et al. 2010; Wedick et al. 2011; Williams et al. 2008), which in turn were associated to both increased SHBG levels (Yasui et al. 2007) and decreased concentrations of blood plasma insulin and IGF-1 (Nakajima et al. 2010). Given the inverse relationship observed between SHBG and PCa risk (Roddam et al. 2008a), as well as the direct associations between risk of PCa and both plasma insulin (Hammarsten and Hogstedt 2005; Ma et al. 2008) and IGF-1 (Roddam et al. 2008b), coffee consumption might be a protective factor against PCa incidence.

Existing epidemiological evidence is still too limited and inconsistent to start recommending that men increase coffee consumption in order to reduce their PCa risk.

6 Summary

Accumulating evidence indicates that obesity may have a dual effect on PCa: an increased risk of aggressive PCa and a decreased risk of localized PCa. Both occupational and leisure time physical activity have been observed to be associated with a reduced PCa risk. On the other hand, results from epidemiological studies on possible associations between PCa risk and dietary factors have been mostly inconsistent. However, the majority of these studies focused on total PCa only, instead of examining its subtypes separately. Furthermore, they did not take into account genetic differences among the study participants. Therefore, the aforementioned inconsistencies can be at least partly explained by etiological heterogeneity between indolent and aggressive subtypes of PCa and by possible gene-environment interactions.

Etiological heterogeneity of PCa in relation to some specific factors can be observed by analyzing localized (or low-grade) and advanced (or high-grade) PCa separately, which can allow the detection of associations that differ in magnitude or direction. The lack of evidence of associations reported in many epidemiological studies that analyzed only total PCa risk might be partially ascribed to this phenomenon. On the other hand, gene–environment interactions might explain the inconsistent results because small genetic differences between men can lead them to respond differently to the same environmental exposures.

The complex nature of this disease warrants considerable further research efforts in order to disentangle the genetic and environmental components and understand how they interact. In particular, future well-designed epidemiological studies on lifestyle, diet, and other environmental factors should focus on the analysis of PCa separately by its aggressiveness and should take into account the genetic characteristics of the study populations.

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Nutrition, Hormones and Prostate Cancer Risk: Results from the European Prospective Investigation into Cancer and Nutrition

Timothy J. Key

Abstract

Nutritional factors may influence the risk of developing prostate cancer, but understanding of this topic is poor. This chapter discusses research on this subject, mostly from the European Prospective Investigation into Cancer and Nutrition (EPIC), a cohort which includes 150,000 men recruited in the 1990s in eight European countries. So far the EPIC collaborators have published analyses of the relationship of prostate cancer risk with the intake of a range of foods and nutrients, and with blood-based markers of nutritional factors, on up to nearly 3,000 incident cases of prostate cancer. Most of the results of these analyses have been null, with no clear indication that the risk for prostate cancer is related to intakes of meat, fish, fruit, vegetables, fibre, fat or alcohol or with blood levels of fatty acids, carotenoids, tocopherols, B vitamins, vitamin D, or selenium. There is some evidence from EPIC that risk may be increased in men with a high intake of protein from dairy products, and analyses of hormone levels have shown that risk is higher in men with relatively high blood levels of insulin-like growth factor-I (IGF-I). More research is needed to better describe the relationships of prostate cancer risk with IGF-I and related hormones, and to better understand whether nutritional factors may influence risk through hormones or perhaps by other mechanisms.

T. J. Key (✉)
Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Roosevelt Drive, Oxford, OX3 7LF, United Kingdom
e-mail: tim.key@ceu.ox.ac.uk

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Contents

1 Introduction

The incidence of prostate cancer varies substantially between different countries, suggesting that there may be modifiable risk factors associated with lifestyle and environment. Currently, the only well-established risk factors for prostate cancer are age, family history, ethnic origin, family history and various genetic factors (Chan et al. 2005; Eeles et al. 2013). Over the last 30 years, many studies have investigated whether dietary and nutritional factors may influence risk, but the results of these studies have been generally inconsistent and inconclusive. Here, we summarise the results from a large prospective study in Europe, in which prostate cancer risk has been examined in relation to the intake of a range of foods and macronutrients, and to circulating biomarkers of nutritional factors. We also discuss the findings from EPIC and other studies on the relationship of prostate cancer risk with circulating concentrations of endogenous hormones.

2 Methods

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a prospective study of approximately 500,000 men and women in ten European countries, recruited between 1992 and 2000. Full details of the study design have been published (Riboli 2002). Briefly, 150,000 of the participants recruited were men, living in eight countries: Denmark, Germany, Greece, Italy, the Netherlands, Spain, Sweden and the United Kingdom. At recruitment participants completed questionnaires on their diet and lifestyle, and most also provided blood samples from which serum, plasma, red blood cells and white blood cells were separated and stored at −80 °C or below. Participants have been followed to ascertain incident cancers and death; in most countries follow-up for cancer was through cancer registries, whereas for Germany and Greece follow-up for cancer was based on self-reported cancer diagnosis followed by confirmation through review of medical records.

For prostate cancer, analyses in EPIC have been planned to examine a range of hypotheses concerning the possible roles of nutritional, lifestyle and hormonal factors (Key et al. 2002). For potential risk factors assessed by questionnaire, such as dietary and lifestyle factors, analyses were conducted using Cox regression for the full cohort of men, with analyses stratified by recruitment centre (so that men

who developed prostate cancer were compared with men recruited in the same place in Europe, who had not developed prostate cancer during the same follow-up period). For risk factors measured in the blood samples, such as nutritional biomarkers and endogenous hormones, analyses were conducted using a nested case–control design, such that for each case one control was selected matched on study centre, age at blood collection and follow-up period; laboratory analyses were conducted blind to case–control status and were planned so that, in general, cases and their matched controls were assayed in the same batch, thus largely eliminating inter-assay variation from the case–control comparisons. Statistical analysis of these nested case–control studies was by conditional logistic regression on matched sets, so that men who developed prostate cancer were compared with men recruited in the same place in Europe, who had not developed prostate cancer during the same follow-up period.

3 Results

Analyses of the relationships of intake of major food groups with prostate cancer risk in EPIC have been generally null (Table 1); the only significant association observed was a positive association with intake of yogurt, with an odds ratio of 1.17 (1.04–1.31) for men with a high intake of yogurt compared to men with a low intake of yogurt (Allen et al. 2008a). Sub-group analyses showed no significant differences in these associations by stage or grade of disease at diagnosis.

For macronutrients, no association was observed between prostate cancer risk and intakes of total protein, fat, fibre or alcohol, but risk was higher in men with a high intake of dairy protein than in men with a low intake (odds ratio 1.22 (1.07–1.41); Allen et al. 2008a, Table 2). Sub-group analyses showed no significant differences in these associations by stage or grade of disease at diagnosis.

For nutritional biomarkers, no association was observed between prostate cancer risk and blood levels of carotenoids, B vitamins, vitamin D, selenium or genistein (Table 3). There was a positive association between prostate cancer risk and the percentage of palmitic acid in plasma phospholipids and an inverse association between prostate cancer risk and the percentage of stearic acid in plasma phospholipids (Crowe et al. 2008b), but no association with the branched chain fatty acid phytanic acid (Price et al. 2010, Table 3) or other fatty acids (results not shown). Sub-group analyses showed some evidence of heterogeneity for the association of fatty acids with risk by grade of disease, such that high levels of myristic acid and α-linolenic acid were associated with a higher risk for high grade disease but not for low grade disease (Crowe et al. 2008b). There was evidence of heterogeneity for the association of lycopene with risk by stage of disease, such that high levels of lycopene were associated with a lower risk for advanced disease but not for localised disease (Key et al. 2007). There was also some evidence of heterogeneity by stage for vitamin B12, such that high levels of vitamin B12 were associated with a higher risk for advanced disease but not for

Table 1 Food groups and prostate cancer risk (Allen et al. 2008a; Key et al. 2004)

Food group	Odds ratio (95 % CI) high versus low intake	Test for trend
Red meat	0.96 (0.82–1.12)	NS
Processed meat	0.93 (0.79–1.09)	NS
White fish	1.03 (0.90–1.18)	NS
Fatty fish	1.07 (0.95–1.21)	NS
Milk	1.01 (0.89–1.16)	NS
Cheese	1.04 (0.90–1.20)	NS
Yogurt	1.17 (1.04–1.31)	0.02
Fruit and vegetables	1.00 (0.79–1.26)	NS

CI confidence interval

Table 2 Macronutrients and prostate cancer risk (Allen et al. 2008a; Crowe et al. 2008a; Suzuki et al. 2009; Rohrmann et al. 2008)

Macronutrient	Odds ratio (95 % CI) high versus low intake	Test for trend
Protein	1.17 (0.96–1.44)	NS
Dairy protein	1.22 (1.07–1.41)	0.02
Fat	0.96 (0.84–1.09)	NS
Fibre	1.02 (0.87–1.19)	NS
Alcohol	0.88 (0.72–1.08)	NS

CI confidence interval

localised disease (Johansson et al. 2008). There was no evidence of heterogeneity by stage or grade for the other nutritional biomarkers.

For endogenous hormones, prostate cancer risk was not associated with serum concentrations of testosterone or free testosterone (Travis et al. 2007). Risk was higher in men with high levels of IGF-I than in men with low levels (odds ratio 1.69 (1.35–2.13); Fig. 1), with no evidence of heterogeneity by stage or grade of disease at diagnosis (Price et al. 2012), and prostate cancer risk was not associated with IGF binding protein 3 (Allen et al. 2007).

4 Discussion

In EPIC, we have examined a range of nutritional and hormonal factors in relation to the risk for prostate cancer. The strongest association we have observed is with IGF-I, and this finding is consistent with a pooled analysis of individual participant data from 12 prospective studies (including EPIC; Roddam et al. 2008). IGF-I is affected by nutritional factors such as energy and protein intake (Ketelslegers et al. 1995) and there is evidence that men with high intakes of animal protein (or

Table 3 Nutritional biomarkers and prostate cancer risk (Crowe et al. 2008b; Price et al. 2010; Key et al. 2007; Johansson et al. 2008; Travis et al. 2009; Allen et al. 2008b; Travis et al. 2012)

Biomarker	Odds ratio (95 % CI) high versus low concentration	Test for trend
Palmitic acid	1.47 (0.97–2.23)	0.03
Stearic acid	0.77 (0.56–1.06)	0.03
Phytanic acid	1.13 (0.76–1.68)	NS
β-carotene	0.92 (0.66–1.28)	NS
Lycopene	0.97 (0.70–1.34)	NS
Folate	1.30 (0.88–1.93)	NS
Vitamin B12	1.19 (0.87–1.63)	NS
Vitamin D	1.28 (0.88–1.88)	NS
Selenium	0.96 (0.70–1.31)	NS
Genistein	1.00 (0.79–1.27)	NS

CI confidence interval

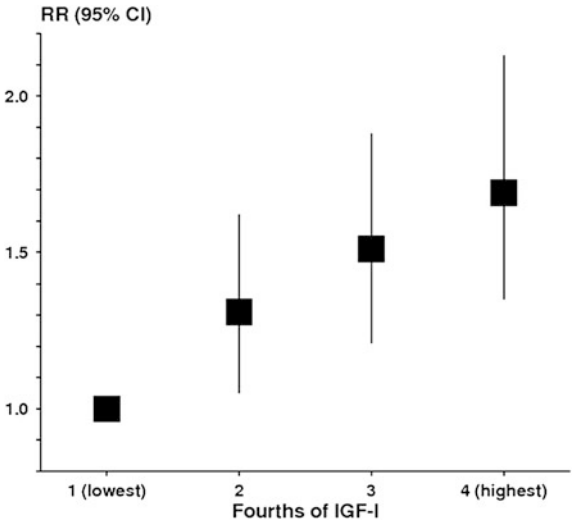

Fig. 1 Insulin-like growth factor-I and risk of prostate cancer in EPIC (figure adapted from results in Price et al. 2012)

particularly dairy protein) have relatively high circulating IGF-I (Giovannucci et al. 2003; Young et al. 2012), but more research is needed to better understand the nature of the effect of nutrition on IGF-I and on whether this effect is likely to have a material impact on the risk of prostate cancer (Key 2011). In EPIC, we observed a weak positive association of dairy protein with prostate cancer risk, and other studies have reported positive associations of risk with dairy foods (Qin et al. 2007; WCRF 2007), but this topic requires further study before firm conclusions can be drawn. In EPIC, we also observed that men with the lactase genotype

associated with lactase persistence have a higher intake of dairy products than men with the wild-type genotype for lactase (Travis et al. 2013), and the possibility that the lactase genotype is associated with prostate cancer risk should be examined in very large datasets.

We did not observe an association of endogenous sex hormones with prostate cancer risk, and this is consistent with the results of a pooled analysis of individual participant data from 18 prospective studies (Endogenous Hormones and Prostate cancer Collaborative Group 2008). These results indicate that androgen levels in the normal range are not associated with prostate cancer risk, but more research is needed to determine whether there may be a reduction in risk in men with particularly low androgen levels.

For the other nutritional factors examined in EPIC we have not found any strong associations. This is compatible with other studies worldwide, which have suggested that several nutritional factors may increase or decrease the risk for prostate cancer, but which have not established any definite effects (Chan et al. 2005; WCRF 2007). Further research is needed, because there may be real effects of moderate magnitude which could have major implications for disease prevention. Future studies need to collect data for very large numbers of men with prostate cancer and to collect detailed information on the characteristics of the tumour such as stage and grade, and on survival, to enable analyses of risk factors for aggressive prostate cancer (Wilson et al. 2012).

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Screening for Prostate Cancer: Current Status of ERSPC and Screening-Related Issues

Fritz H. Schröder

Abstract

The "European Randomized Study of Screening for Prostate Cancer" (ERSPC) was initiated in 1993 and up to 1998 six other European countries were joined. The main goal is to establish the effect of Prostate Specific Antigen (PSA)-based screening on prostate cancer (PCa) mortality with morbidity as secondary end point. At present, with 11 and 12 years of follow-up significant relative reductions of 21 % and 31 % relating to both end points have been reported. The diagnosis of non-life threatening PCA (over diagnosis) is estimated to be in the range of 50 % and represents the main "harm", which prevents the introduction of population-based screening. As a result, the prevention of over diagnosis is now given top research priority. PSA as a screening test has poor performance characteristics including a low specificity. With the cut-off value of 3.0 ng/ml chosen within ERSPC, about 25 % of men aged 55–69 test positively, 75 % have "negative" test results, which do not definitely exclude the presence of PCa. Research to establish empirical schemes of follow-up based on PSA levels and other parameters are ongoing worldwide. In the meantime, we are, by approximation, capable to identify over diagnosed PCa detected by screening. Active surveillance can be applied to avoid side effects and expenses of treatment and is, among others, based on the grade of differentiation determined on biopsies. The assignment of the most favorable "Gleason score 6" is a crucial decision element. Unfortunately, biopsy pathology underestimates the true degree of PC aggressiveness by 25–30 % which establishes the need of careful follow-up.

F. H. Schröder (✉)
Department of Urology, Erasmus University Medical Center, Room NH-224 3000, 2040, CA, Rotterdam, Netherlands
e-mail: secr.schroder@erasmusmc.nl

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Screening for prostate cancer remains controversial in spite of increasing evidence of effectiveness in terms of mortality reduction of prostate cancer and of metastatic disease (Schröder et al. 2012a, b). These issues will be addressed in this brief chapter based on the European Randomized study of Screening for Prostate Cancer (ERSPC) and data reporting on 11- and 12-year follow-up periods (mortality and metastatic disease, respectively). In spite of the described effects on mortality and morbidity of prostate cancer the authors are, in line with healthcare providers and officials, convinced that the time for introducing population-based screening has not arrived because of harms of screening which only recently have been addressed and which will also be briefly reviewed within this chapter. In addition to that, the contribution aims to address a number of predefined questions related to the authors prior to the Prostate Cancer Prevention Consensus Conference held in connection with the annual meeting of the European Association of Urology (EAU) in Milano, March 2013.

1 Current Status of ERSPC

The ERSPC study is being conducted in eight European countries. All methodological details and results can be found in (Schröder et al. 2012a). The study was initiated in 1993. France was excluded from the most recent analysis because of a short follow-up period. All rules of participation including the common assignment of a core age group, age 55–69, the minimal dataset and the decision to contract an external data centre in a non-participating country were taken in 1995 and are documented in the criteria for participation which have been published (Schröder et al. 2012a, appendix). A total of 240,000 men age 55–74 were randomised to an upfront agreed core age group of ages 55–69. Of these, after the exclusion of France, 162, 160 men were included in the most recent analysis. The screen interval was 4 years for all centres, except Sweden where a 2-year screening interval was used (13 % of all participants). During the year of 1997 a common screening procedure was introduced indicating a lateralized sextant prostate biopsy in men who had a PSA $\geq$ 3.0 ng/ml. Our data showed a rate ratio of prostate cancer death of 0.79, a 21 % relative risk reduction, $p = 0.001$. The data translated into an absolute risk reduction of 1.07 prostate cancer deaths per 1,000 men. The numbers needed to identify and the numbers needed to diagnose amounted to 936 and 33 in excess of the control group. After adjustment for non-

compliance in men actually screened a relative prostate cancer mortality reduction of 29 % was found for men who participated and were screened.

The ERSPC study group agreed early to also study quality of life and the effects of screening on prostate cancer morbidity. A subgroup of four ERSPC centres found a relative reduction of M+ disease of 31 % in the intention-to-screen analysis and of 42 % in screened men. This translated into numbers needed to identify and numbers needed to diagnose to prevent one case of metastatic disease within 12 years of 328 and 12.

In conclusion, with a median follow-up of 11 years the ERSPC study shows a modest but significant prostate cancer mortality reduction of 21 % in the intention-to-screen analysis and of 29 % after adjustment for non-compliance. The reduction of metastatic disease amounted to 31 % with a 12-year follow-up. Since more than 70 % of all men randomised to the ERSPC study are still alive and since follow-up continues, our data must be considered as preliminary, analyses of data with a 13-year follow-up is ongoing.

The following sections will address a number of questions which are directly related to the subject of this contribution and which have been pre-assigned by the organisers of the consensus meeting.

2 Do Harms of Screening Outweigh Benefits?

The relative weight of benefits and harms of screening was recently evaluated by Heijnsdijk et al. (2012). A modelling approach was used applying the MISCAN system which allows predictions for populations of men during their whole lifetime. Quality of life adjusted life years (Qaly's) was calculated using weight-estimates of health effects of screening (utilities). The study used the 11-year ERSPC follow-up data. For 1,000 screened men aged 55–69 followed for life, a prostate cancer mortality reduction of 28 % was estimated, which translated into 73 life years gained per 1,000 men. When this was applied to a 4-year screening interval, the adjustment due to loss of quality of life was estimated to be 20 %. This resulted in 52 life years and 41 Qaly's gained by screening. Overdiagnosis and overtreatment had a large negative impact on Qaly's gained. The study was criticised because of uncertain assumptions of weights of utilities, the use of preliminary follow-up data of the ERSPC study and the use of the older literature-based assumptions on side effects of treatment. The authors acknowledge that future updating is needed.

3 How to Deal with High PSA Values After a Negative Biopsy?

This question addresses a situation which is extremely common worldwide. Regional estimates in the United States show that about 75 % of all older men had at least one PSA determination, similar data are in the range of 25–40 % for a number of European countries. With commonly used PSA-driven screening and cut-off

values indicating biopsies cancer is being diagnosed in 25–35 % of cases, depending on whether screening or clinical indications are applied. This means that 65–75 % of men are confronted with this question. A recent study from ERSPC Rotterdam presented at the 2013 EAU meeting (Zhu et al. 2013) addressed the issue by comparing prostate cancer mortality in 654 and 526 men who were diagnosed with prostate cancer in the first and second rounds of screening. After truncating the data at a 7-year follow-up period available from the second round population of men and after adjustment for known prognostic parameters the hazard ratio of prostate cancer death of the first versus second round amounted to 0.51 (95 % CI 0.27–0.95). This suggests an almost two-fold lower chance of death for cancers detected with repeat screening in men who had an elevated PSA 4 years earlier. The information can be used in shared decision taking between men and their physicians.

4 How to Manage Gleason 6 Cancer?

Prostate cancers classified into the most favourable prognostic group, Gleason score ≤ 6 on biopsy are considered to have clinically insignificant disease and are often advised to be managed by active surveillance. This has led to an ongoing discussion whether Gleason ≤ 6 cancers detected on biopsy might not be considered as cancer at all. Available published data, however, suggest to the contrary. Several studies show that 25–45 % of Gleason ≤ 6 prostate cancers are undergraded if biopsy findings are compared to the histological examination of radical prostatectomy specimens. Within the ERSPC study Rotterdam in 23.3, 41.7 and 33.3 % of Gleason ≤ 6 prostate cancers diagnosed during the first, second and third rounds of screening, either metastatic disease or death from prostate cancer occurred (Zhu et al. 2011). Furthermore, in a study modelling the development of screen-detected prostate cancer over time, progression of Gleason six prostate cancer to more aggressive disease was shown (Draisma et al. 2006).

How then should we deal with Gleason ≤ 6 prostate cancer? We cannot assume the presence of insignificant disease if Gleason ≤ 6 prostate cancer is found on biopsy. Major efforts, including risk stratification based on PSA, prostate volume, the amount of cancer on biopsies and other potentially available prognostic factors should be used to rule-out more aggressive disease. Advanced imaging studies applying multi-parametric MRI technology should be considered prior to or during active surveillance if this choice is made.

5 Final Conclusions

Screening for prostate cancer was shown to significantly reduce its mortality in the ERSPC study. Harms and their weights have been identified and quantified. Harms decrease but do not exceed the benefits of screening with presently available data. To reduce the most important harm, overdiagnosis and overtreatment, is a top

clinical and research priority. Men with elevated PSA and negative previous biopsies should be followed carefully and not a priori be considered to have insignificant disease. The time of population-based screening has not (yet) come. In the meantime, shared decision taking for well-informed men who wish to undergo PSA-driven testing cannot be denied.

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Update of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Gerald L. Andriole

Abstract

The prostate portion of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial began in the early 1990s to assess the ability of annual PSA and DRE to reduce prostate cancer specific mortality in men aged 55–74. Approximately 80,000 men have been randomized and followed for a minimum of 13 years. Thus far, annual screening in this study has not been associated with a reduction of prostate cancer specific mortality. The potential explanations for this finding are reviewed.

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The PLCO Cancer Screening Trial is a multicenter randomized two-arm trial designed to evaluate the effects of screening for prostate, lung, colorectal, and ovarian cancer on disease-specific mortality. The trial was initiated in November 1993, and enrollment ended in 2001. The methods of recruitment for the PLCO Trial and randomization techniques have been previously described (Andriole et al. 2012). In brief, 76,685 men aged 55–74 were randomly assigned to the

G. L. Andriole (✉)
Division of Urologic Surgery, Washington University in Saint Louis, St. Louis, MO, USA
e-mail: andrioleg@wustl.edu

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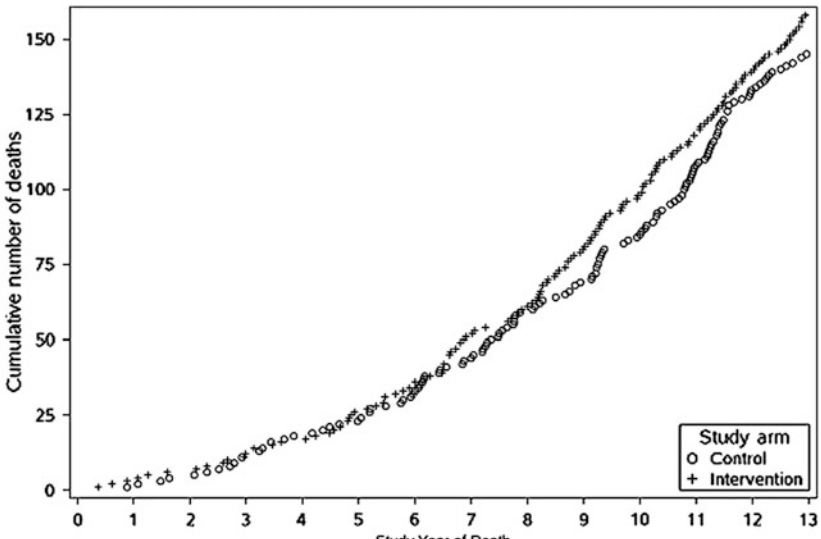

Cumulative deaths - I	3	6	12	16	26	36	51	61	80	98	118	140	158
Cumulative PY - I	38217	76112	113629	150725	187382	223541	259118	294052	328048	359768	387164	409535	426977
Cumulative deaths - C	1	4	11	18	23	33	44	59	69	85	108	133	145
Cumulative PY - C	38223	76132	113635	150689	187278	223329	258811	293631	327455	358904	386109	408262	425439

Fig. 1 Prostate cancer deaths in PLCO

intervention (or "screened") arm (38,240 subjects) or to the control arm (also referred to as the "usual care" arm) (38,345 subjects) at 10 screening centers throughout the United States. Men who were randomized to the screened arm were offered screening with annual serum PSAs for 6 years and digital rectal examination for 4 years. Screening for prostate cancer was completed in 2006. A serum PSA value >4 was considered a positive test as was a suspicious digital rectal examination. In PLCO, the participant and his healthcare provider were informed about the results of the screening tests and subsequent evaluation, such as additional or repeat diagnostic tests, biopsy, and therapy if cancer was discovered was performed outside of the trial. A description of follow-up of men with suspicious prostate screen(s) in PLCO was reported in 2008 (Grubb et al. 2008).

Through 13 years of follow-up, there is an excess of prostate cancer cases in the screened arm (a relative increase of 12 % in comparison to the control arm). After 13 years of follow-up, mortality rates for prostate cancer in the intervention and control arms were not significantly different (see Fig. 1). No statistically significant interactions with respect to prostate cancer mortality were observed between the trial arms when age, the pretrial PSA testing, and comorbidity were considered.

1 Considerations for Interpreting the Results of the Prostate Portion of PLCO

Important considerations when interpreting results of the prostate portion of the PLCO trial are that approximately a third of the patients underwent one or more PSA tests and/or DRE within 3 years of trial entry and 5 % of the patients had a previously negative prostate biopsy (Andriole et al. 2009). Thus to some extent, the population studied was prescreened and rates of subsequent prostate cancer at detection, grade, or stage of cancer detection may differ from those observed in other studies where the enrolled population was not at all or very minimally prescreened.

The compliance of men randomized to the screened arm was approximately 85 %. On the other hand, the contamination (i.e., use of PSA and DRE) in the "usual care arm" was estimated to range from 40 to 52 % over the course of the trial (Pinsky et al. 2010). Therefore, the screening intensity of the "usual care" arm was about half that of the men in the screened arm. This set of circumstances reduces the power of the trial to detect a screening-induced mortality benefit if one were present.

The impact of contamination in the "usual care" arm of PLCO was analyzed by Pinsky et al (2010). During screening, 1,984 and 2,538 cancers were detected in the "usual" care and screened arms, respectively. In the absence of any screening, using SEER incidence rates from 1985 to 1987 (the "pre-PSA era"), 950–960 cancers would have been expected. Using contemporary SEER rates for US men, 1610–1630 cancer would have been expected in each arm. Thus men in the trial had a 2–2.7 fold increased chance of a prostate cancer diagnosis in comparison to men living in the pre-PSA era and men in the "usual care" arm of PLCO had about 20 % more cancers diagnosed than a similar group of contemporary US men not in the trial. It is for these reasons that the results of the prostate portion of the PLCO Cancer Screening Trial should be interpreted as showing that there is no evidence of a mortality benefit from *organized annual PSA-based screening* as compared to *opportunistic screening* that forms part of the "usual care" for many men in the United States.

There is also evidence of a healthy volunteer effect for patients enrolled in the PLCO Cancer Screening Trial (Pinsky et al. 2007). The all cause standardized mortality ratio was 46 % (44–47 %) and the incidence ratio of other cancers, such as bladder, kidney, liver, melanoma, and pancreas, was significantly lower in the PLCO volunteers than in the general population (see Table 1). These standardized mortality ratios and incidence ratios remain significantly lower in the PLCO volunteers even after adjustment for known significant factors such as smoking, education, marital status, body mass index, physical activity, and race.

Similar findings were also present with respect to prostate cancer (Pinsky et al. 2012). There was no significant difference in prostate cancer-specific survival rates between the usual care and the control arms. In both arms, 10-year prostate cancer survival rates were approximately 94 %. The ratio of observed to expected 10-year

Table 1 Evidence of a healthy volunteer effect in the prostate, lung, colorectal, and ovarian cancer screening trial

	Standardized incidence ratio	95 % CI
Bladder	73	70, 76
Kidney	80	70, 91
Liver	60	47, 73
Melanoma	86	76, 97
Pancreas	88	76, 100

Adapted from (Pinsky et al. 2007)

prostate cancer-specific death rates was 0.59 (0.51–0.68) for all prostate cancer cases, 0.66 (0.51–0.81) for Gleason 5–7 cancers, and 1.07 (0.87–1.3) for Gleason 8–10 cases. Within the intervention arm, the small number of men never screened had lower 10-year prostate cancer survival rates (82 %) than men who had screen detected or interval prostate cancer, which were both around 95.5 %.

Prostate cancer-specific survival in PLCO was comparable across both arms and significantly better than expected based on nationwide population data. Whether the improved survival is due to a healthy volunteer effect or to lead time or over-diagnosis biases cannot be definitively known. Finally, it is worthwhile to consider that approximately 40–45 % of the prostate cancers discovered in the PLCO Cancer Screening Trial would be classified as "low risk" (i.e., serum PSA <10 and Gleason Score 6 on biopsy). These cancers in the recently reported PIVOT randomized screening trial (Wilt et al. 2012) have a low likelihood of causing prostate cancer-specific mortality within 10 years whether or not observation or aggressive treatment (radical prostatectomy) is instituted.

2 Further Follow-Up of the PLCO Trial

We plan to update mortality findings from the prostate component of the PLCO Cancer Screening Trial when follow-up data through 15 years are available.

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ERSPC, PLCO Studies and Critique of Cochrane Review 2013

Fritz H. Schröder

Abstract

Screening for prostate cancer by use of serum prostate specific antigen (PSA) remains controversial. In the recent Cochrane analysis, an attempt is made to clarify the issue by conducting a meta analysis of available randomized screening trials. Two large trials are considered to provide data of similar and sufficient quality to conduct a separate meta analysis. However, in the view of this author, this analysis fails because standard Cochrand quality criteria are not observed. Details are given and the outcome suggests that one of the trials, the European Randomized Study of Screening for Prostate Cancer (ERSPC) should be considered superior to the Prostate, Lung, Colon, Ovary screening trial (PLCO) conducted in the USA.

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The most recent review of randomized screening trials of prostate cancer identifies two studies, the European Randomized study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colon and Ovarian screening trial (PLCO) as 'posing a low risk of bias'. The review acknowledges that both studies show

F. H. Schröder (✉)
Department of Urology, Erasmus University Medical Center, Room NH-224, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands
e-mail: secr.schroder@erasmusmc.nl

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contradictory results but fails to present an explanation for this contradiction. In the present document an attempt is made to point out the differences between the two large screening trials which may explain why ERSPC shows a significant advantage in prostate cancer mortality while the PLCO study does not.

This recent Cochrane review (Ilic et al. 2013) is based on the Cochrane criteria for evaluating randomized controlled trials which are part of the 'Cochrane handbook for systematic reviews of interventions' (Higgins and Green 2008) and a more recent summary of the tools of the Cochrane collaboration for assessing risk of bias in randomized trials (Higgins et al. 2011). While the methodology mainly addresses the procedures around meta-analyses, it also provides criteria for including randomized controlled trials (RCT) into meta-analyses. One basic prerequirement is phrased in (Higgins et al. 2011) as "to obtain reliable conclusions, review authors must carefully consider the potential limitations of the included studies". The Cochrane methodology differentiates between risk assessment tools addressing seven different areas of interest and seven risk of bias tools which are clearly formulated in (Higgins et al. 2011). The cited references do not address the question whether the Cochrane tools are equally applicable to treatment trials and to RCTs of screening which essentially study the value of diagnostic tools in the application to define segments of the population (secondary screening).

Figure 1 is derived from (Ilic et al. 2013) and shows the results of the application of six domains of the risk of bias tool to five pre-selected screening trials including ERSPC and PLCO. The authors conclusion that ERSPC and PLCO represent trials at a similar low level of bias is based on this evaluation using the six criteria indicated. Some of these criteria such as allocation concealment may not be applicable to randomized screening trials and other trials which do not allow the use of placebo. Also, while on the first page of (Ilic et al. 2013) the authors claim that the overall judgment on risk basis considers 'the relative importance of domains' such weighting is not found in the manuscript. Also, some of the most important differences between the two studies, such as the upfront use of PSA testing prior to randomization, the contamination by PSA use and the compliance with biopsy indications are included into 'other bias' without specification and weighting with respect to outcomes. In other words, in line with the Cochrane rules, it is not sufficient to state whether a bias is present or absent but also it is also necessary to quantify it and to quantify its possible impact with respect to the overall level of bias assigned. This procedure has not been followed in (Ilic et al. 2013). It can not be replaced by analyses of heterogeneity and sensitivity as carried out and reported in (Ilic et al. 2013). An attempt will therefore be made to compare the occurrence and possible effect of three important parameters between the ERSPC and PLCO study: use of testing prior to randomization, contamination and compliance with biopsy indication.

I. Use of PSA testing prior to randomization
   The PLCO study reports 53.1 and 54.8 % of PSA testing prior to randomization in the screening and control arm populations (Pinsky et al. 2012). Accurate data on the ERSPC study are not available. However, considering the period of randomization in most centers running from 1993 to 2000, the rate of PSA testing can be considered to be below the 20 % assumed in the

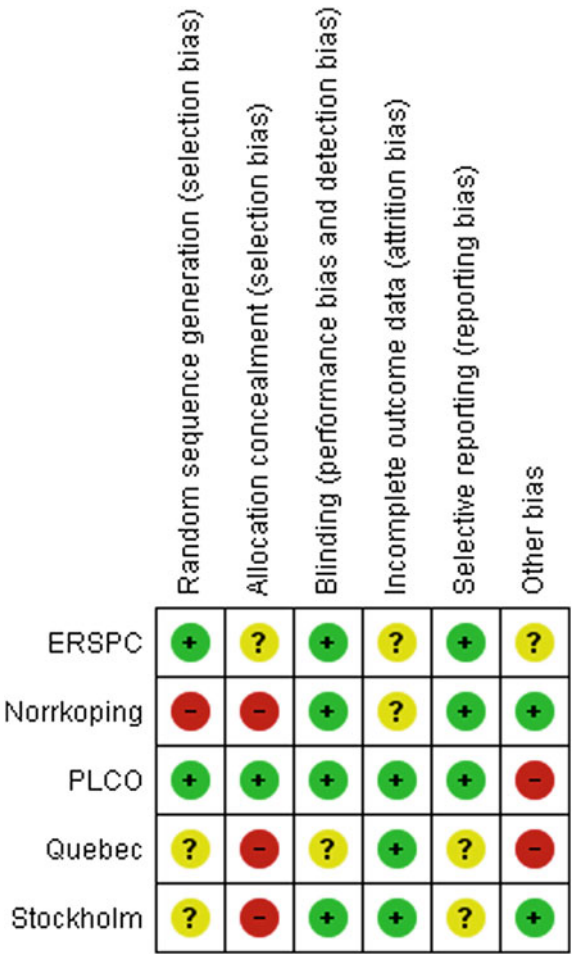

Fig. 1 Risk of bias summary: review authors' judgments about each risk of bias item for each included study (Ilic et al. 2013, doi: 10.1002/14651858.CD004720.pub3). With permission of the Cochrane Collaboration and John Wiley and Sons

power calculation. If the rate of screening had been similar in the ERSPC and PLCO studies, this should be visible in terms of the prostate cancer incidence figures and specifically the incidence of advanced disease, which is effectively classified as Gleason 8–10. Such cancers were found in 10.2 and 13 % in the screen and control arms of PLCO (Pinsky et al. 2012) and in 7.4 versus 12.5 % in the ERSPC study. Overall, the cancer detection rates in the PLCO study amounted to 26.4 versus 23.7 % for the age group 55–64 and to 58.9 and 58.6 % for the age group 65–74 between screening and control. The most recently reported detection rates for the core age group 55–69 years of the ERSPC study amounted to 9.6 and 6.0 % between the screen and control arms. The larger difference in overall detection and specifically in the detection of aggressive disease between the two arms of the ERSPC study is likely to be the result of a lower rate of screening prior to randomization.

II. Contamination
PLCO reported an overall at least one time PSA use of 54.8 % (Pinsky et al. 2012). The estimated contamination rate for ERSPC is reported to be in the range of 30 % in the control arm (Roobol et al. 2009). This figure is the result of extrapolation from Dutch data to the rest of Europe. Large differences per country exist however, and have been documented by Ciatto et al. (2003). Still, even maximizing the contamination rate in ERSPC up to the year of 2005 to 30.7 % reveals a 22 % higher contamination rate in the PLCO study.

III. Compliance with biopsy indication
Non-compliance with biopsy indication is another factor that may reduce the power of a screening trial by decreasing the incidence of cancers in the screen arm which may contribute to the mortality reduction by screening. The PLCO study reported 14–15 % positive tests in the screen arm and a biopsy rate of 40.2 % among these during the first round and 30.1 % during subsequent rounds of screening (Grubb et al. 2008). In the ERSPC trial 16.6 % of all men tested positive and of these at average of all centers 82.7 % were biopsied (Schröder et al. 2012). This very large difference in biopsy compliance is likely to contribute to the lower rate of cancer detection in the screen arm in PLCO and to the lack of a difference in the final outcome, prostate cancer mortality in comparison between the screen and control arms.

1 Conclusion

The author hopes to have shown that in applying the Cochrane criteria and specifically the group summarizing 'other biases' it is necessary to specify and quantify the criteria used. Omission of this procedure may result in misinterpretation of the available data and finally in wrong judgment on biases. Also, it is questionable whether the Cochrane criteria and tools for assessing the risk of bias in randomized trials are applicable without any change to randomized screening trials (Schröder et al. 2012). Quality requirements for screening trials, as the have been designed early during the ERSPC study, are clearly different from quality requirements for randomized treatment studies. A careful evaluation of the effect of the large differences seen with respect to the important diagnostic parameters upfront screening, contamination and compliance with biopsy indications on prostate cancer mortality is needed and is likely to explain why PLCO does not show an absolute and relative reduction of prostate cancer mortality by screening.

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Screening for Prostate Cancer: Reflecting on the Quality of Evidence from the ERSPC and PLCO Studies

Dragan Ilic

Abstract

The first Cochrane systematic review examining the evidence on screening for prostate cancer was first published in 2006. The 2006 version of the Cochrane review identified two randomised controlled trials (RCTs), drawing the conclusion that there was insufficient evidence to either support, or refute, the use of screening versus no screening in reducing prostate cancer-specific morality. The most recent version of the review, published in 2013, assessed evidence from five RCTs. Based on the evidence from the five RCTs, the authors of the 2013 version concluded that screening did not significantly reduce prostate cancer-specific mortality. Of the five trials included in the 2013 Cochrane review, only two were assessed as being a low risk of bias—the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial. This chapter discusses the differences between the ERSPC and PLCO trials, and examines what issues may contribute to their conflicting results. It also aims to contextualise results from this most recent Cochrane systematic review and discuss the critique of the Cochrane systematic review raised by Schroder in the chapter entitled, "ERSPC, PLCO studies and critique of Cochrane review 2013".

D. Ilic (✉)
Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Level 6, The Alfred Centre, Monash University, 99 Commercial Road, Melbourne, VIC 3004, Australia
e-mail: dragan.ilic@monash.edu

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The evidence base informing the merits of screening for prostate cancer has changed significantly since the first Cochrane systematic review was published in 2006 (Ilic et al. 2006). That version of the review identified two randomised controlled trials (RCTs), both assessed as having methodological weaknesses, concluding that there was insufficient evidence to either support or refute the use of screening, compared to no screening, for reducing prostate-specific cancer mortality. The most recent version of this review, published in 2013, identified five RCTs and concluded that a meta-analysis of those five studies did not significantly decrease prostate cancer specific mortality (Ilic et al. 2013). This chapter aims to contextualise results from this most recent Cochrane systematic review and discuss the critique of the Cochrane systematic review raised by Schroder in the chapter entitled, 'ERSPC, PLCO studies and critique of Cochrane review 2013'.

Each of the five studies included in the 2013 version of the Cochrane systematic review were assessed for their risk of bias. Seven domains are available for assessment under Cochrane's 'risk of bias' tool. These domains include selection bias (sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias and other biases (Higgins et al. 2011). All five trials included in the 2013 version of the Cochrane systematic review were assessed against these domains, with the exception of performance bias—since blinding of participants and study personnel to the intervention received is redundant in screening trials.

Three of the studies included in the 2013 Cochrane review were assessed as posing a 'high' risk of bias, whilst the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trials were assessed as posing a 'low' risk of bias. Whilst there is consensus on the rating of the three trials, which were rated as posing a 'high' risk of bias, Schroder raises the point that some of the domains used in assessing this risk of bias, such as allocation concealment, may not be applicable to screening trials. The Cochrane 'risk of bias' tool permits each domain to be assessed and assigned a judgement of 'low', 'high' or 'unclear' risk, with evidence from published data to support this assessment (Table 1). Both the ERSPC and PLCO studies are assessed as 'low' risk of bias for sequence generation (selection bias). The ERSPC study has been assessed as 'unclear' risk of bias for the allocation concealment domain, since information regarding the allocation process itself was not present in published data. If the investigator or patient is able to identify the impending treatment allocation, then the value of the randomisation has been compromised, thereby increasing the chances of imbalances between prognostic factors between the two groups and selection bias upon the trial (Forder et al. 2005).

Table 1 Risk of bias for the ERSPC and PLCO studies as described by the 2013 Cochrane systematic review of screening for prostate cancer (Ilic et al. 2013)

Bias	Authors' judgement	Support for judgement
ERPSC study		
Random sequence generation (selection bias)	Low risk	The study was a multicentre trial across nine European countries that randomly assigned men to screening or control groups 'Within each country, men were assigned to either the screening group or the control group… on the basis of random number generators'
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in the publication '…randomization procedures differed among countries and were developed in accordance with national regulations'
Blinding (performance bias and detection bias)	Low risk	Outcomes were evaluated in a blinded manner 'Causes of death were evaluated in a blinded fashion… or on the basis of official causes of death. The causes were classified by the independent committees'
Incomplete outcome data (attrition bias)	Unclear risk	Data from the Portugal study centre were excluded from all analyses due to discontinuation. Data from the France centre of the trial were not included in mortality analyses due to short duration of follow-up, and were not included in primary analyses of additional outcomes—although data were provided '…the primary analysis was planned at the outset on the basis of follow-up of at least 10 years, which was reached with data through 2008. The current analyses include follow-up data through 2008…regarding the core age group analysis'
Selective reporting (reporting bias)	Low risk	Objectives of the ERSPC include cancer specific mortality and quality of life outcomes. Mortality is reported but quality of life is not descriptively reported in this publication. Measures relating to quality of life are currently being reviewed and will form the basis of future publications '…an evaluation of the effect on quality of life is pending'
Other bias	Unclear risk	Main data analysis is based on the core age group (55–69 years). There are differing age groups across the eight reported sites in the publication 'The benefit of screening was restricted to the core age group of subjects who were between the ages of 55 and 69 years at the time of randomizations'

(continued)

Table 1 (continued)

Bias	Authors' judgement	Support for judgement
PLCO study		
Random sequence generation (selection bias)	Low risk	Individual randomisation was performed within blocks stratified according to centre, age and sex 'The randomization scheme uses blocks of random permutations of varying lengths and is stratified by SC (study centre), gender and age. Random assignment is implemented using compiled software and encrypted files loaded on SC microcomputers'
Allocation concealment (selection bias)	Low risk	Concealment was achieved through a central system 'As each person is successfully randomized into the trial, data including name, gender, date of birth and study arm are automatically stored in encrypted data tables'
Blinding (performance bias and detection bias)	Low risk	Possible cancer specific deaths were reviewed by blinded reviewers 'Reviewers of these deaths were unaware of study-group assignments for deceased subjects'
Incomplete outcome data (attrition bias)	Low risk	Data on mortality and diagnosis are available for the 10-year follow-up, but follow-up data on 13-year outcomes are not complete 'As of December 31, 2009 (the cutoff date for this analysis), the vital status of 92 % of the trial participants was known at 10 years and of 57 % of the participants at 13 years'
Selective reporting (reporting bias)	Low risk	Study protocol is available and the study's pre-specified outcomes have been reported. '…there is evidence of harms, in part associated with the false-positive tests, but also with the overdiagnosis inseparable from PSA screening, especially in older men'
Other bias	High risk	Data on contamination were provided (estimated to be 40–52 %)

There are important differences between the ERSPC and PLCO studies, including contamination and compliance issues. The impact of these biases cannot be addressed under the theme of selection, performance, attrition, detection bias or reporting bias; hence why the category of 'other sources of bias' is available (Higgins et al. 2011). Published data on the PLCO estimated contamination to be 40–52 % between groups; therefore, it was judged to pose a high risk of bias for that domain. Risk of bias for each study is determined by the empirical evidence across these domains. Additionally, the risk of bias across each outcome (prostate cancer specific mortality, all-cause mortality, diagnosis of prostate cancer and prostate tumour stage), with sensitivity analysis demonstrating no meaningful

Table 2 Summary of findings from the Cochrane systematic review on screening for prostate cancer (Ilic et al. 2013)

Outcomes[b]	Illustrative comparative risks[a] (95 % CI)		Relative effect (95 % CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Screening				
All-cause mortality	21 per 100	21 per 100 (20–22)	RR 1 (0.96–1.03)	294,856 (4 studies[c,d])	⊕⊕⊕⊖ moderate[e,f,g]	
Prostate cancer specific mortality	7 per 1,000	7 per 1,000 (6–8)	RR 1 (0.86–1.17)	341,342 (5 studies[c,d])	⊕⊕⊕⊖ moderate[g,h,i,j]	
Prostate cancer diagnosis	68 per 1,000	88 per 1,000 (69–112)	RR 1.3 (1.02–1.65)	294,856 (4 studies[c,d])	⊕⊕⊖⊖ low[e,j,k,l]	
Tumour stage (localised T1-T2, N0, M0)	6 per 100	10 per 100 (7–15)	RR 1.79 (1.19–2.7)	247,954 (3 studies[m,n])	⊕⊕⊖⊖ low[j,o,p,q]	
Tumour stage (advanced T3-4, N1, M1)	11 per 1,000	9 per 1,000 (8–9)	RR 0.8 (0.73–0.87)	247,954 (3 studies[m,n])	⊕⊕⊕⊖ moderate[o,p,r]	

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Patient or population: adult male patients
Settings: primary or secondary care
Intervention: screening for prostate cancer
CI Confidence interval; *RR* vRisk ratio
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate
[a]The basis for the *assumed risk* (e.g. the median control group risk across studies) is provided in footnotes. The *corresponding risk* (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the *relative effect* of the intervention (and its 95 % CI)
[b] Information on costs, quality of life, metastatic disease at follow-up and harms of screening was limited and could not be meta-analysed; available information is summarised in the text
[c] ERSPC study data includes all ages (not just 'core' age group defined by trialists)
[d] PLCO study data is at 10 years of follow-up for this outcome
[e] Risk of bias was 'high' or 'unclear' for allocation concealment in three studies; 'high' or 'unclear' for random sequence generation in two studies; 'low' for blinding in all four studies; 'unclear' for incomplete outcome data in two studies; 'unclear' for selective reporting in 1 study and 'high' or 'unclear' for other bias in two studies
[f] $I^2 = 62$ %; $\text{Chi}^2 = 7.99$ ($P = 0.05$)
[g] Norrkoping study data for this outcome only included men who had been diagnosed with prostate cancer up to 12/31/1999, in whom mortality was then followed until 12/31/2008
[h] Risk of bias was 'high' or 'unclear' for allocation concealment in four studies; 'high' or 'unclear' for random sequence generation in three studies; 'unclear' for blinding of outcome assessment in one study; 'unclear' for incomplete outcome data in two studies; 'unclear' for selective reporting in two studies and 'high' or 'unclear' for other bias in three studies
[i] $I^2 = 46$ %; $\text{Chi}^2 = 7.40$ ($P = 0.12$)
[j] Wide 95 % CI
[k] $I^2 = 98$ %; $\text{Chi}^2 = 162.78$ ($P < 0.00001$)
[l] Screening intervention and screening interval varied between and even within some studies; the method of diagnosis also varied
[m] PLCO study data is provided at 13 years of follow-up for this outcome
[n] ERSPC study data includes only 'core' age group, as defined by trialists
[o] Risk of bias was 'high' or 'unclear' for allocation concealment in two studies; 'high' for random sequence generation in one study; 'low' for blinding in all three studies; 'unclear' for incomplete outcome data in two studies; 'low' for selective reporting in all three studies and 'high' or 'unclear' for other bias in two studies
[p] Tumour stage was unknown for some participants diagnosed with prostate cancer in all 3 studies
[q] $I^2 = 99$ %; $\text{Chi}^2 = 288.85$ ($P < 0.00001$)
[r] $I^2 = 0$ %; $\text{Chi}^2 = 1.34$ ($P = 0.51$)

difference in prostate cancer specific mortality, all-cause mortality and diagnosis of prostate cancer. Sensitivity analysis demonstrated a reduction in effectiveness of detecting localised prostate cancer with the removal of one high risk of bias study (Ilic et al. 2013).

Schroder highlights that it is not sufficient to state whether a bias is present or absent, but that it is necessary to quantify it and its potential impact with respect to the overall level of bias. The 2013 version of the Cochrane review utilised for the first time the GRADE framework, which was applied to assess the quality of evidence across all outcomes, and reported in a summary of findings Table 2 (Ilic et al. 2013). According to the GRADE framework, RCTs begin the grading process as high-quality evidence, with several factors influencing whether it is ultimately rated as high, medium, low or very low (Guyatt et al. 2011). Evidence may be modified higher if it demonstrates a large magnitude of effect, dose response and/or confounders are likely to minimise the effect. Evidence may be modified lower if there is likely publication bias and serious risk of bias, inconsistency, indirectness and/or imprecision. Risk of bias using the GRADE framework quantified a moderate quality of evidence for prostate cancer specific, all-cause mortality and tumour stage (advanced), with a low quality of evidence for prostate cancer diagnosis and tumour stage (localised).

Overall findings of the Cochrane systematic review determined that four of the five studies did not report a significant benefit in screening for prostate cancer (Ilic et al. 2013). A meta-analysis of the five studies concluded no evidence of benefit in the reduction of prostate cancer specific mortality (RR = 1.00 (95 %CI 0.86, 1.17)), with sensitivity analysis of the ERPSC and PLCO studies (as the only "low" risk of bias studies) resulting in a similar result (RR = 0.96 (95 %CI 0.70, 1.30)) (Ilic et al. 2013). Potential reasons for the contradictory results between the ERSPC and PLCO studies have also been highlighted within the summary of main results and characteristics of included studies table of the 2013 Cochrane systematic review.

Given the clinical and statistical heterogeneity of studies included in the Cochrane systematic review, a meta-analysis may not be appropriate (Ilic et al. 2013); in which case a descriptive analysis may be more suitable. Although the ERSPC study has been designed as a multicentre study, the potential for clinical heterogeneity within the study sites should also be explored. Variation in the recruitment of patients with respect to age and follow-up and between site variation in their use of PSA/DRE and PSA thresholds would be suggestive markers of clinical heterogeneity present in the ERSPC study (Ilic et al. 2013). This clinical heterogeneity within the ERSPC study itself may in part contribute to the variation in results, as only two of the sites (Netherlands and Sweden) demonstrated a statistically significant reduction in the risk of prostate cancer specific mortality.

Several types of systematic reviews are available under the Cochrane framework including reviews of interventions, diagnostic test accuracy, methodology or overview of review. In his concluding remarks, Schroder raises the possibility that the quality requirements for screening trials are different from the quality requirements for treatment trials. Much like other screening reviews (including

screening for breast, lung and colorectal cancer), screening for prostate cancer (be it by prostate-specific antigen (PSA) test and/or digital rectal examination (DRE)), is an intervention study. The potential impact of systematic bias remains constant, regardless of whether the intervention is one of screening or treatment.

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Phase III Prostate Cancer Chemoprevention Trials

Howard L. Parnes, Otis W. Brawley, Lori M. Minasian and Leslie G. Ford

Abstract

Chemoprevention refers to the use of pharmacologic interventions to delay, prevent, or reverse carcinogenesis with the ultimate goal of reducing cancer incidence Two large, population-based, phase 3 prostate cancer prevention trials reported that 5-alpha reductase inhibitors significantly reduce prostate cancer risk. However, this class of agents were also associated with increased detection of high-grade prostate cancer. Another large, phase 3 prostate cancer prevention clinical trial showed no benefit for long-term supplementation with the trace element Se, given in the form of selenomethionine, or vitamin E, either individually or in combination. Paradoxically, a significant increase in prostate cancer was observed among men randomized to receive vitamin E alone. A great deal of progress had been made in the field of prostate cancer prevention over the past decade. Future studies will focus on prevention of disease progression in men on Active Surveillance, immunotherapy, mechanistically based drug combinations, and novel biomarkers of risk and benefit.

Contents

H. L. Parnes (✉) · L. M. Minasian · L. G. Ford
Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, USA
e-mail: parnesh@mail.nih.gov

O. W. Brawley
American Cancer Society, Atlanta, Georgia, USA

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1 The Prostate Cancer Prevention Trial (PCPT)

1.1 Rationale and Study Design

The PCPT was a phase III, double-blind, placebo-controlled trial of finasteride for the primary prevention of prostate cancer. Finasteride belongs to a class of agents (5-alpha-reductase inhibitors, 5-ARIs), which converts testosterone (T) into the more potent androgen, di-hydrotestosterone (DHT) (Bartsch et al. 2000; Tindall and Rittmaster 2008). 18,882 men age 55 and older with a PSA of $\leq$3 ng/ml and a normal digital rectal examination (DRE) were enrolled on this clinical trial between 1993 and 1996 and followed with yearly PSAs and digital rectal examinations. The primary study endpoint was the 7-year period prevalence of biopsy-proven prostate cancer; biopsy Gleason Score was a secondary endpoint.

1.2 Results

The primary finding of the PCPT was a 24.8 % relative reduction in prostate cancer prevalence among men randomized to the finasteride arm (24.4 vs. 18.4 %, $p < 0.001$) among the 9,060 men in whom a prostate biopsy or trans-urethral resection of the prostate had been performed during the study (Thompson et al. 2003). Finasteride was associated with decreased prostate cancer prevalence regardless of a priori risk level based on age, race, family history, and baseline PSA (Thompson et al. 2003). However, despite a clear decrease in the prevalence of prostate cancer, finasteride was associated with a small but statistically significant increase in the prevalence of high-grade prostate cancer. Overall, 43 more cancers with a Gleason score (GS) of 7–10 were diagnosed in men on the finasteride than on the placebo arm (280 vs. 237 men) representing 6.4 and 5.1 % of men on the two study arms, respectively ($p = 0.005$). Among these men, 90 on the finasteride arm and 53 on the placebo arm had a GS 8–10 prostate cancer (Thompson et al. 2003).

1.3 High-Grade Prostate Cancer in PCPT

The observation that the excess of high-grade cancer observed on the finsteride arm of the PCPT occurred early and did not increase over the course of the 7-year trial suggests that the association between finasteride and high-grade prostate cancer may not have been causal (Thompson et al. 2003). Alternatively, finasteride may

have simply increased the detection of previously existing high-grade cancer and, in fact, two forms of detection bias appear to have been operative in the PCPT.

Reliance on biopsies to address the secondary Gleason score endpoint, a practical necessity as not all men diagnosed with prostate cancer undergo prostatectomy, coupled with the effects of finasteride on gland volume, clearly introduced an element of "volume bias." Ultrasound examinations at the time of prostate biopsy confirmed a nearly 25 % decrease in median prostate volume among men treated with finasteride (Thompson et al. 2003). As the extent of biopsy sampling was similar on the two study arms, there was relatively greater sampling of the smaller, finasteride-treated glands, increasing the likelihood of detecting high-grade prostate cancer, if present, among men on finasteride.

A second form of bias is known as "PSA bias." Subsequent analyses of the PCPT showed that finasteride increases the sensitivity of PSA testing for the detection of prostate cancer, in general, and high-grade prostate cancer, in particular (Thompson et al. 2006). As approximately 50 % of the cancers diagnosed in the PCPT were prompted by PSA tests, this finasteride-induced increase in PSA sensitivity would be expected to have resulted in both an overestimate of high-grade prostate cancer and an underestimate in the reduction of nonhigh-grade cancer among men on the finasteride arm. Supporting the hypothesis that detection bias accounted, at least in part, for the observed increase in high-grade cancer on the finasteride arm of the PCPT is the observation that patients in whom high-grade disease was documented at prostatectomy (the gold-standard for determining Gleason score) were significantly more likely to have had their high-grade cancer correctly identified on biopsy *if they had been on finasteride* than if they had been on placebo (70 vs. 51 %, $p = 0.01$) (Lucia et al. 2007).

Another relevant issue is whether reducing a man's risk of being diagnosed with low-risk prostate cancer confers true clinical benefit given the indolent natural history of the majority of such cancers. The answer to this question is related to the aggressiveness with which the disease is treated. As recently as 2004–2006, approximately 85 % of the men in the CaPSURE registry with low-risk prostate cancer received definitive therapy (usually surgery or radiation) with their attendant morbidities, including impotence, urinary incontinence, and rectal injury (Cooperberg et al. 2007). This underscores the substantial burden of disease imposed even by low-risk prostate cancer.

Finally, it is important to consider the degree to which adverse consequences (such as a true increase in high-grade cancer) are acceptable in the cancer prevention setting. The tolerance for such events must be balanced against an individual's risk of being diagnosed with and subsequently treated for cancer in the absence of the preventive intervention. In the case of prostate cancer, a man's risk of diagnosis (and hence treatment) is highly dependent on whether he chooses to undergo regular screening. Therefore, 5-alpha-reductase inhibitors would have a more favorable risk–benefit ratio in men committed to regular screening than in non-screened populations.

2 The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

SELECT was a phase III randomized, placebo-controlled trial of selenium (200 mg/day, *L*-selenomethionine), and/or vitamin E (400 IU/day) supplementation for prostate cancer prevention (Lippman et al. 2005). The rationale for studying selenium and vitamin E was based on secondary endpoints from two earlier phase III, placebo-controlled, randomized, cancer prevention trials: the alpha-Tocopherol beta-Carotene Study (ATBC) and the Nutritional prevention of cancer Study (NPC). Although both studies were negative with regard to their primary endpoints, lung cancer and non-melanoma skin cancer incidence, respectively, men randomized to the vitamin E arm of ATBC had a 40 % reduction in prostate cancer mortality (Heinonen et al. 1998) and men randomized to the selenium arm of NPC had an approximately two-thirds reduction in prostate cancer incidence (Clark et al. 1996).

The major eligibility requirements for SELECT were age $\geq$55 years for non-African American men ($\geq$50 years for African American men), serum PSA $\leq$4 ng/ml, and a non-suspicious DRE. SELECT accrued 35,533 participants between July 2001 and July 2004; participants were seen every 6 months throughout the trial (initially planned for 7–12 years) for adherence and adverse events monitoring (Lippman et al. 2005). The primary endpoint was the clinical incidence of prostate cancer; secondary endpoints included lung, colon, and total cancer incidence, cardiovascular events, death from any cause and toxicity. In addition, four prospectively conducted sub-studies addressing the usefulness of selenium and vitamin E in the prevention of macular degeneration, chronic obstructive lung disease, Alzheimer's disease, and colon polyps were performed in men already accrued to the parent study.

On September 15, 2008, following the second of five planned interim analyses, the Data and Safety Monitoring Committee recommended that the study supplements, vitamin E and selenium, be discontinued due to lack of efficacy. In addition, vitamin E was associated with a nonsignificant 13 % increase in prostate cancer incidence ($p = 0.06$, not corrected for multiple comparisons). This trend was not seen in the combined vitamin E + selenium arm. No significant differences were observed in any of the prespecified secondary endpoints, including lung and colon cancer, overall cancer, cardiovascular events, and toxicity (Lippman et al. 2009). A follow-up analysis including 54,464 additional person-years of follow-up and 521 additional cases of prostate cancer reported a statistically significant 17 % increase in prostate cancer incidence on the vitamin E alone arm, $p = 0.008$ (Klein et al. 2011).

These findings show the importance of conducting adequately powered, controlled, clinical trials to determine the true risks and benefits of products with healthcare claims, including nonprescription nutritional supplements. An important component of SELECT was the creation of a biorepository of prediagnostic specimens (both serum and DNA) from all participants. These biospecimens, which are linked to a clinical database, provide a powerful tool to explore the

biology of prostate cancer and other diseases through the conduct of correlative studies. Details regarding procedures for gaining access to these samples can be found at the Southwest Oncology Group (SWOG) website, http://www.swog.org.

3 Conclusions

While selenium and vitamin E, in the doses and formulations tested, were ineffective for the prevention, and vitamin E appeared to increase the risk of prostate cancer, finasteride was definitively shown to reduce a man's risk of this disease. Whether the potential benefits of 5-alpha-reductase inhibitors, both in terms of overall risk reduction and enhanced detection of high-grade disease, are outweighed by the possibility of a small increase in the risk of high-grade cancer remains controversial and these drugs are currently not FDA approved for prostate cancer prevention. Given the substantial resources needed to conduct large-scale, phase III cancer prevention trials, it is important that the future trials be well supported by mechanistic, preclinical, and phase II clinical data. The National Cancer Institute's division of cancer prevention is committed to supporting chemoprevention agent development research with these goals in mind.

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Risk Adapted Chemoprevention for Prostate Cancer: An Option?

Bernd J. Schmitz-Dräger, Oliver Schöffski, Michael Marberger, Sevim Sahin and Hans-Peter Schmid

Abstract

A high disease prevalence, the presentation in older age, a frequently slowly progressing course of disease, and high costs make diagnosis and therapy of prostate cancer a special challenge for urologists. Effective prevention of the disease may help to resolve some of the problems mentioned above. Two randomised, controlled studies prove that effective chemoprevention of prostate cancer is possible using 5-α reductase inhibitors (finasteride, dutasteride) (LoE 1) both in individuals at low and those at high risk developing prostate cancer. Furthermore, there is evidence that other compounds, e.g. selective estrogen receptor modulators (SERMs), non-steroidal anti-inflammatory drugs (NSAIDs) and statins might also be effective. This review investigates potential risks and benefits of chemoprevention including a consideration of health economic aspects. The authors conclude that chemoprevention in a high risk cohort using

B. J. Schmitz-Dräger (✉) · S. Sahin
Urologie, Schön Klinik Nürnberg/Fürth, Urologie 24, c/o Europa-Allee 1, 90763 Fürth, Germany
e-mail: bernd_sd@yahoo.de

O. Schöffski
Lehrstuhl für Gesundheitsmanagement, Universität Erlangen-Nürnberg, Lange Gasse 20, 90403 Nürnberg, Germany

M. Marberger
Department of Urology, Medical University of Vienna, 1090 Vienna, Austria

H.-P. Schmid
Urologische Klinik, Kantonsspital St. Gallen, 9007 St. Gallen, Switzerland

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5-α reductase inhibitors is a viable option and may even be cost effective. In consequence, the options of chemoprevention in prostate cancer should be further explored in an open and unbiased way.

Contents

1 Introduction

Since the introduction of prostate specific antigen (PSA)-based early detection the number of newly-diagnosed prostate cancer (PCA) cases increased approximately fivefold through the past 25 years. During the same period the number of radical prostatectomies multiplied by the factor of 15. Considering that only 15–20 % of patients will die from PCA it is evident that the vast majority of patients will not die from tumor-related causes. In consequence, overdiagnosis and overtreatment are considered key problems of the current screening debate.

Diagnosis, therapy, and follow-up of prostate cancer imposes not only considerable physiological and psychological burden to the patient but is also related to high costs for the health systems. Through the last decades, economical pressure has further increased through development and introduction of new and expensive therapeutic agents and the consecutive prolonged course of disease and improved survival of PCA patients.

Based upon these facts it is to be expected that PCA prevention would yield considerable benefits to patients and, by saving costs, be also advantageous for the health system. Based upon these considerations primary prevention of PCA could aim at several different end points:

- Reduction of incidence
- Reduction of low risk PCA, not requiring therapy
- Postponing initiation of disease/diagnosis/therapy
- Reduction of the psychological burden for patients due to diagnostic and therapeutic procedures and follow up
- Cost savings.

Life style modification for PCA prevention would be most desirable due to low costs and lack of serious side effects, however, more recent analyses could no longer identify nutritional compounds with evidence-based efficacy to prevent PCA [reviewed in (Schmitz-Dräger et al. 2012) and see chapters by Key TJ and

Table 1 Non-natural agents with potential preventive effects in prostate cancer

• 5α reductase inhibitors
• NSAIDs/COX-2 inhibitors
• SERMs
• SPARMs
• iNOS inhibitors
• Cell cycle blockers
• Apoptosis inducers

Discacciati A et al.]. Although there is still evidence that nutrition is related to prostate cancer development, today physicians should avoid any recommendation for a use of food supplements with the intention to decrease PCA risk.

In contrast, randomized controlled trials clearly demonstrate the efficacy of chemical compounds to decrease the risk of being diagnosed with PCA (Thompson et al. 2003; Andriole et al. 2010; Wilt et al. 2010). The authors acknowledge that within this concept paper the term "chemoprevention" is used for non-natural chemical compounds and does not include a use of (artificial) food supplements. Table 1 provides a summary on agents currently investigated for their efficacy to prevent PCA.

This review just addresses aspects of primary prevention. Secondary or tertiary prevention after being diagnosed with PCA is not considered. To report the current status of this field, the authors aimed at focusing on controlled trials wherever possible.

1.1 5-α-Reductase Inhibitors

Based upon experimental and clinical observations the Prostate Cancer Prevention Trial (PCPT) was initiated in 1993 (Thompson et al. 2003). 18882 healthy men aged 55 years or older with PSA levels less than 3 ng/ml were entered in this prospective randomized double-blinded study comparing the use of 5 mg finasteride versus placebo. Prostate biopsy was performed in patients with increased serum PSA or suspicious finding at digital rectal examination. An end of study biopsy was offered to all other patients.

Thompson and coworkers reported a 24.8 % decrease of men diagnosed with PCA in the treatment arm ($p < 0.0001$) (Thompson et al. 2003). The study was heavily criticized for a significantly increased amount of aggressive cancers (Gleason score 7–10) in men receiving finasteride (Scardino 2003). Subsequently, the PCPT data underwent careful reconsideration and detailed analysis. These investigations strongly suggest that the findings are based upon an improved detection of high grade PCA caused by the decreased prostate volume in the finasteride group (Sarvis and Thompson 2008; Redman et al. 2008).

Similar results were obtained in a further randomized controlled study comparing type I and II 5α reductase inhibitor dutasteride against placebo in 6729 men

at high risk developing PCA with an increased serum PSA and previously negative biopsy findings (REDUCE) (Andriole et al. 2010). Per protocol re-biopsies were performed after 2 and 4 years. After 4 years men receiving dutasteride were found to have 22.8 % less PCA as compared to the placebo group ($p < 0.001$). Again, a higher amount of high grade cancers was observed in the treatment arm; however, in contrast to the PCPT trial this difference did not achieve statistical significance.

In contrast to earlier concerns on the usefulness of PSA for PCA diagnosis REDUCE could confirm the diagnostic relevance of PSA in the treatment arm (Marberger et al. 2012). Furthermore, it was observed that PSA accuracy was even superior in patients with high grade (Gleason score 7–10) PCA taking dutasteride as compared to the control group suggesting that relevant high grade lesions may be detected earlier in patients receiving 5α reductase inhibitors.

A recent meta-analysis of phase III studies by Wilt et al. (2010) reported a 25 % decreased risk of being diagnosed with PCA in men using 5α reductase inhibitors. A comment in a previous analysis dating from 2008 concerning a potentially increased risk of developing high risk prostate cancer was no longer included in the more recent analysis (Wilt et al. 2008).

1.2 Non-Steroidal Anti-Inflammatory Drugs/COX-2 Inhibitors

Experimental and epidemiological evidence suggests a preventive efficacy of NSAIDs. NSAIDs inhibit cyclooxygenase activity (COX), a group of enzymes, involved in the metabolism of arachidonic acid to prostaglandins (PG).

Cyclooxygenase (COX)-2 expression is induced by several stimuli, e.g. inflammatory cytokines or growth factors. COX-2 mediated reactions may, through formation of highly reactive compounds, designated as reactive oxygen species (ROS), induce DNA oxidation. Furthermore, metabolites of the COX-2 dependent arachidonic acid pathway, e.g. prostaglandin E2 are involved into tumor development via different mechanisms. In vitro examinations demonstrate that COX-2 inhibitors decrease cell proliferation, increase apoptosis and modify cell cycle regulation (Roberts et al. 2004).

Two recent meta-analyses have been published on the prevention of PCA by NSAIDs: while Jafari et al. (2009) report a significant decrease of PCA for men taking any NSAID with a specific effect for men taking aspirin. This in contrast to an analysis by Mahmud et al. (2010), who only observed a significantly decreased PCA risk for aspirin but not for other NSAIDs. Both groups conclude that the studies included in these meta-analyses showed a considerable heterogeneity. These conclusions were further confirmed by a recent review by Schmidt et al. (2012).

A randomized controlled double blinded trial investigating the preventive efficacy of the COX-2 inhibitor rofecoxib (ViP-trial) was terminated ahead of schedule due to an increase of cardiovascular events in the treatment arm after more than 1.5 years of treatment (van Adelsberg et al. 2007).

1.3 Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) act as estrogen receptor agonists and thus may exert effects on hormone-sensitive cells. Toremifen is one of the compounds currently under investigation for preventive effects in breast and prostate cancer. In a double blinded phase III trial 514 men with high-grade prostatic intraepithelial neoplasia (PIN) were randomized to either toremifen 20, 40, 60 mg or placebo (Price et al. 2006). Re-biopsy of treatment yielded a significantly lower number of PCA cases in the toremifen 20 mg group. As compared to placebo reduction was 24.4 and 31.2 % ($p < 0.05$) after 6 months and 1 year, respectively. These figures translate into a number needed to treat (NNT) of 15 (= 6.8/100 men undergoing therapy). However, a larger phase III study in 1.590 patients could not confirm the previous findings (Taneja et al. 2013).

2 Statins

Moyad suggested the investigation of the preventive effects of statins in genitourinary tumors (Moyad 2004a, b). He concluded that, in addition to experimental evidence, statins are proven effective in prevention of cardiovascular events. Specifically in prostate cancer the vast majority of patients will not die cancer-related but from intercurrent disease. Statin use will decrease cardiovascular death rate and may even exert further PCA preventive effects through regulation of fatty acid metabolism. This assumption appears further supported by the potential correlation between overweight and PCA incidence (Hsieh et al. 2003).

Several studies have been published on a putative correlation between statin use and PCA incidence: in a recent meta-analysis Esposito and coworkers (2013) did not confirm a preventive effect of statins on PCA risk. This observation is further strengthened by findings made in the REDUCE trial patient cohort (Freedland et al. 2013). However, it remains unclear if different statins may have a different preventive capacity. The authors of the analysis acknowledge heterogeneity of the studies included in particular with regard to consumption interval and follow-up (Solomon and Freeman 2011).

In summary, a diagnostic bias introduced by a reduced PSA level in patients taking statins may account at least for some of the observations reported in the past.

3 Other Compounds

Through the last decade a number of different agents have been suggested to have a potential in preventing prostate cancer. Among others, ligands of the peroxisome proliferator-activated receptor gamma (PPAR-gamma) have been found to suppress breast cancer development in experimental animal models. In analogy to SERMs as mentioned above, selective PPAR modulators (SPARMs) are currently developed aiming at the modulation of genes or gene products related to carcinogenesis.

Table 2 Requirements for primary prevention in prostate cancer

Parameter	PCA
High prevalence (widespread disease)	+
Definition of risk groups possible	+
Expensive diagnosis, therapy, follow-up	+
High psychological burden for patients (cancer)	+
High motivation to undergo prevention measures in patients at risk	+
Prevention strategies	
Effectiveness	+
Side effects	−
Costs	±

Further concepts currently investigated are inhibitors of inducible nitric oxide synthase (iNOS), activation of phase II detoxification enzymes (Glutathion-S tranferases, *N*-acetyl transferases, etc.) or the modulation of regulators of cell cycle and apoptosis. For these purposes both, chemical compounds and natural plant extracts are extensively studied (Malik et al. 2005).

4 Conclusions

In general, PCA appears suitable for implementation of disease prevention strategies (Table 2). In addition to a high disease prevalence making PCA a widespread disease it also appears beneficial to only postpone the onset of disease for several years since this effect will prevent invasive therapeutic measures in many patients.

The review of potential candidate substances for PCA prevention clearly demonstrates that currently only 5α reductase inhibitors have proven efficacy (LoE 1a). For this reason further considerations will focus on the potential risks and benefits of PCA chemoprevention using 5α reductase inhibitors.

The PCPT and REDUCE trials demonstrate that a use of 5α reductase inhibitors for 4 and 7 years, respectively, reduces diagnosis of PCA by approximately 25 % (Thompson et al. 2003; Andriole et al. 2010; Wilt et al. 2010). This reduction is obviously also present in different risk groups. It can be speculated that this impressive effect subsequently translates into an improved cancer-specific survival. However, given the relatively high age of most patients at diagnosis is it not reasonable to expect measurable effects on overall survival.

Unger et al. recalculated the results obtained in the PCPT study using data from the SEER registry comprising nearly 10 % of all US citizens (Unger et al. 2005). For prevention with finasteride on a population basis a gain between 262,567 and 316,760 life years was calculated. Although there is evidence that these figures

rather underestimate the real effect, it is obvious that average life expectancy will not be increased by more than 5 to a maximum of 7 days.

Nevertheless, there are a number of additional effects that should not be neglected: a preferential effect of 5α reductase inhibitors on low risk tumors as suggested by the study results would yield a considerable decrease of costly and invasive therapeutic procedures in those patients, in which the benefit of those interventions is questionable (Albertsen et al. 2011).

Applying preventive strategies requires particular consideration of side effects. In general, side effects will be accepted based upon the expected outcome. This means that in situations with poor patient prognosis higher and more serious side effects are acceptable as compared to less serious conditions (e.g. flu). In consequence, tolerance of side effects in a situation, where no disease is present (prevention) is low. However, even in primary prevention risk ratio and threat will modulate this tolerance as shown for familial breast cancer and carriers of BRCA1 and 2 mutations (Anglian Breast Cancer Study Group 2000). As BRCA2 mutation is linked to a >70 % lifetime risk of developing breast cancer, even drastic prophylactic measures as breast ablation are socially accepted.

Use of 5α reductase inhibitors is correlated with sexual dysfunction and endocrine side effects as shown e.g. in the PCPT trial (Thompson et al. 2003). Table 3 demonstrates that in an asymptomatic low risk cohort side effects are infrequent and mostly mild. Even after long-term use side effects appear not to accumulate (Moinpour et al. 2007). It should be noted that for treatment of patients with benign prostate enlargement (BPE) these side effects appear acceptable (Oelke et al. 2011). In particular, patients with large glands and increased serum PSA could have additional benefit from taking 5α reductase inhibitors since their risk of unnecessarily undergoing prostate biopsies may decrease.

The NNT has evolved as a relevant parameter for social and health economical acceptance of diagnostic or therapeutic measures. NNT gives the number of subjects to be treated in order to prevent one target event. Acceptance derives from the relevance of the target event (e.g. death vs. flu-like symptoms), invasiveness of the procedure (e.g. fecal sample vs. colonoscopy), related costs and finally social acceptance, which can differ in different cultures. In conclusion, a number needed to screen of 503 for healthy subjects and a NNT of 18 for therapy of a screen-detected prostate cancer to prevent 1 prostate cancer death do not appear acceptable in western countries (Loeb et al. 2011).

This is in contrast to the use of aspirin for prevention of cardiovascular events, which appears acceptable socially as well as for health maintenance organizations (HMO). While costs for aspirin-based chemoprevention are low (app. € 0.05/day (100 mg)), however, potential benefits are accompanied by side effects, e.g. gastritis and gastrointestinal bleedings and further compromised by a relatively high NNT 144 (Berger et al. 2006). The use of statins for prevention of cardiovascular events (infarction, apoplexy, consecutive death) is covered by HMOs in many countries. Daily costs, e.g. for simvastatin 40 mg of € 0.30 are balanced by a NNT of 20 (Ridker et al. 2009). Results from PCPT translate into daily costs of approximately € 0.30–0.60 and a NNT of less than 17.

Table 3 Side effects of 5α reductase inhibitor finasteride (modified after ref. Thompson et al. (2003))

Variable	Finasteride ($n = 9423$)	Placebo ($n = 9457$)
	No. (%)	
Sexual functioning/endocrine effects		
Reduce volume of ejaculate	5690 (60.4)	4473 (47.3)
Erectile dysfunction	6349 (67.4)	5816 (61.5)
Loss of libido	6163 (65.4)	5635 (59.6)
Gynecomastia	426 (4.5)	261 (2.8)
Genitourinary effects		
Increased urinary urgency or frequency	1214 (12.9)	1474 (15.6)
Urinary incontinence	183 (1.9)	208 (2.2)
Urinary retention	398 (4.2)	597 (6.3)
Transurethral resection of prostate	96 (1.0)	180 (1.9)
Prostatitis	418 (4.4)	576 (6.1)
Urinary tract infection	90 (1.0)	126 (1.3)

With no doubt, costs of chemoprevention programs are of utmost relevance. Since back in 2003, C. Olsson calculated costs of population-based chemoprevention with Proscar® (finasteride) in US men to be approximately 200 billion $ these figures have dramatically changed. After the end of pending patents, treatment costs dropped significantly. Given daily costs down to $ 0.30 for 5α reductase inhibitor finasteride in 2013 (e.g. www.pharmacychecker.com) and using a similar maximum calculation (all men aged 50 years treated for 7 years) treatment costs of approx. 2 billion $ per year would be expected.

In the current context of discussion concerning PCA screening, we believe that preventive efforts should also focus on high risk groups for several reasons:

- Minimizing population stressed with side effects of therapy
- Improving risk benefit ratio
- Better acceptance of program in high risk group
- Minimizing costs.

Since the risk of being detected with relevant prostate cancer in men with serum PSA levels of less than 3 ng/ml is very low (Thompson et al. 2004; Stephan et al. 2011) and efficacy of 5α reductase inhibitors is also maintained in cohorts at increased risk (Andriole et al. 2010) chemoprevention protocols may be restricted to individuals with increased serum PSA. Cohort studies suggest that between 10–20 % of males between 50–70 years will have PSA levels of >3.0 ng/ml (Luboldt et al. 1999; Moore et al. 2009). In this cohort, approximately 25 % of men will be detected with PCA at a first biopsy leaving a 7.5–15 % of males at an

increased risk of having or developing PCA. Cohort studies suggest that within 2–5 years another 25 % of these men will be diagnosed with the disease (Gann et al. 2010). It can be expected that motivation to participate in this type of program may be high since the potential target population is stressed by the knowledge of an increased PSA value, the potential threat and a previous biopsy.

We tried to translate these considerations to Germany and a cohort of males starting the program at a given age (e.g. 50 years). While in 2013 733,000 men will reach this age (peak of the baby-boom generation) within the next ten years this number will decrease to 468,000 men. In our calculation we assumed an average of ~550,000 men entering this age annually. Based upon the figures provided in the cohort studies mentioned above (Luboldt et al. 1999; Moore et al. 2009). This would yield 55,000–110,000 men annually (with 55,000 men being more likely) based on the assumption of 50–100 % participation. An estimated 13,750–27,500 of these men would be diagnosed with PCA at a first biopsy, leaving the remaining 41,250–82,500 men as potential candidates for a chemoprevention program as suggested above. Approximately 10,000–20,000 of these men would eventually develop PCA. Applying the data from the REDUCE trial it may be expected that between 2,500 and 5,000 PCA diagnoses (or 10 % of all PCA cases in this calculation) could be avoided annually. Based upon a—debatable—length of chemoprevention for 7 years, maximum costs of € 56 million/year (41,250 men, 7 years, 0.53 € daily drug cost (Germany, 2013)) to 112 million/year (82,500 men) may be anticipated. However, it can reasonably be expected that negotiations with pharmaceutical industry will further decrease the costs of the program.

It is obvious that these are theoretical considerations largely modulated by individual and social acceptance of the program but also other factors, e.g. exclusion of men with high comorbidity or men already on 5α reductase inhibitors for treatment of BPE. However, even considering that only a minority of men may participate, it still can be expected that among participants prostate cancer cases may be decreased by approximately 10 %.

The expenses of the program are opposed to cost savings through direct savings in diagnosis (biopsy, prophylactic antibiotics, treatment of complications, pathology, imaging), therapy (surveillance, surgery, radiation therapy), follow up (incl. rehabilitation) and treatment of side effects of therapeutic measures (incontinence, erectile dysfunction, lower urinary tract obstruction, etc.). Based upon the fact that in-patient treatment-related costs for PCA patients sum up to € 300 million/year [Bundesamt für Statistik] and are caused to a vast majority by surgery in patients with local PCA an expected 10 % reduction of cases would translate into savings of app. € 25 million annually. Another € 5–7.5 million may be saved yearly by avoiding radiation therapy procedures. It can be expected that only these savings will cover a significant part of the expenses for medication.

Considering the additional cost savings for diagnostic measures, follow-up, therapy of side effects and complications (as mentioned above), for secondary therapies (e.g. adjuvant hormonal/radiation therapy, therapy of biochemical recurrence), and avoided costs for treatment of BPE, which are difficult to

quantitate, it can be assumed that expenditures of a chemoprevention program with 5α reductase inhibitors will be largely balanced by respective savings.

Also not included in the calculation are socioeconomic costs, e.g. the loss of working hours during therapy and costs imposed by premature retirement of some patients. Finally, psychosocial effects of avoiding diagnosis and therapy by saving 10 % patients from a cancer diagnosis will be difficult to convert into financial revenues.

There are no recommendations supporting chemoprevention in current guidelines. This aspect is even not addressed in the EAU guideline (Heidenreich et al. 2011). Chemoprevention using 5α reductase inhibitors is included in the recent German S3 guideline with at statement summarizing the results from PCPT and REDUCE (Wirth et al. 2011). However, it is explicitly stated that FDA and EMEA approval is lacking. Only the AUA/ASCO guideline recommends discussing risks and benefits of 5α reductase inhibitors with men undergoing early detection examination and men already taking 5α reductase inhibitors for BPE treatment (Kramer et al. 2009).

In summary, chemoprevention remains a controversial issue. With this contribution the authors would like to stress the fact that in particular the complex current situation in screening, diagnosis and therapy of PCA warrants intensive consideration of cancer prevention strategies. In contrast to earlier statements the authors come to the conclusion that PCA chemoprevention using 5α reductase inhibitors in a high risk cohort could be cost-effective. While the economic dimension of this type of program deserves thorough consideration the lack of drug approval in this indication must not prohibit scientific thinking and discussion. It is recommended that conclusions on the significance of chemoprevention should be based on scientific evidence, plausibility and patient's wellbeing. In consequence, emotional statements as published sometimes are not considered helpful and should be avoided.

Further investigation of chemoprevention includes development of risk-adapted chemoprevention programs, a search for more effective and less toxic compounds as well as further efforts in identification of individual risk factors (risk tables). Finally, based upon the respective information every man must personally balance the risk of eventually being diagnosed with PCA against risks and side effects of a preventive measure.

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Aspirin and Prostate Cancer Prevention

Cristina Bosetti, Valentina Rosato, Silvano Gallus and Carlo La Vecchia

Abstract

Aspirin has been associated to a reduced risk of colorectal, and possibly of other cancers. Data from at least 25 observational studies also suggest a modest reduced risk of prostate cancer in regular aspirin users, with a summary relative risk, RR, of 0.91 (95 % confidence interval, CI, 0.86–0.96) overall, 0.87 (95 % CI 0.74–1.02) from nine case–control studies, and 0.92 (95 % CI 0.87–0.97) from 16 cohort studies. However, risk estimates are heterogeneous and there is no relation with frequency, dose, or duration of aspirin use. Data from randomized controlled trials of aspirin for the prevention of vascular events showed a nonsignificant reduced risk of death from prostate cancer after a latent period of five or more years (RR 0.52, 95 % CI 0.20–1.24) based on 37 deaths from prostate cancer from seven trials. The RR was 0.81 (95 % CI 0.61–1.06) after 20 years of follow-up, based on 210 cases from three trials with long-term follow-up. Thus, data from observational studies and clinical trials are compatible with a modest favorable effect of aspirin on prostate cancer. Inference for causality and public health implications are, however, far from conclusive given the heterogeneity of results and the lack of dose and duration-risk relationships. Data on prostate cancer survival are still limited and inconsistent.

C. Bosetti (✉) · V. Rosato · S. Gallus · C. La Vecchia
Department of Epidemiology, IRCCS—Istituto di Ricerche Farmacologiche "Mario Negri", Via La Masa 19, 20156 Milan, Italy
e-mail: cristina.bosetti@marionegri.it

C. La Vecchia
Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy

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Contents

1 Introduction

Aspirin has been related to a reduced risk of colorectal cancer, and possibly of other neoplasms, particularly of the digestive tract (Cuzick et al. 2009; Bosetti et al. 2012a; Rothwell et al. 2012a; Algra and Rothwell 2012).

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may exert their favorable effect against cancer by inhibiting the enzymes cyclooxygenases, particularly prostaglandin-endoperoxide synthase 2, also known as COX-2 (Taketo 1998a, b; Elwood et al. 2009; Langley et al. 2011). These are abnormally expressed in many cancer cell lines—including prostate ones (Yoshimura et al. 2000; Gupta et al. 2000)—and have been implicated in cell proliferation, tumor growth, apoptosis, and angiogenesis. Additional mechanisms of the anticarcinogenic effect of aspirin and other NSAIDs on (prostate) cancer include the induction of apoptosis through COX-independent pathways, the inhibition of NF$\kappa\beta$ factor, and the upregulation of tumor suppression genes (Elwood et al. 2009; Langley et al. 2011).

At least three recent meta-analysis of observational studies have been published on aspirin and prostate cancer (Bosetti et al. 2012a, b; Algra and Rothwell 2012; Mahmud et al. 2010). We summarize here the results of the most recent meta-analysis (updated to September 2011) (Bosetti et al. 2012a, b), and consider a few epidemiological studies that have been subsequently published up to March 2013 (Jacobs et al. 2012; Veitonmäki et al. 2013). We will also consider data from pooled analyses of randomized clinical trials of aspirin for the prevention of cardiovascular disease which included information on prostate cancer risk, and a few studies on aspirin and prostate cancer survival.

2 Meta-Analysis of Observational Studies

In the last meta-analysis, there were data from 24 observational studies on aspirin and prostate cancer incidence (or death) (nine case–control and 15 cohort studies) on a total of 37,452 prostate cases (5,795 from case–control and 31,657 from cohort studies) (Bosetti et al. 2012a, b). Seventeen out of 24 studies reported risk estimates below unity, of which only eight were significant. When considering case–control studies only, significant 20–50 % inverse associations between

aspirin use and prostate cancer risk were reported in three US investigations (Liu et al. 2006; Harris et al. 2007; Salinas et al. 2010); however, two large case–control studies from the USA (Menezes et al. 2006) and from Italy (Bosetti et al. 2006) respectively, reported relative risks (RRs) close to unity, even for the most frequent and longer duration of aspirin use. Among cohort studies, significant 10–30 % reductions in the risk of prostate cancer was reported in a cohort from the USA (Habel et al. 2002), in the US Health Professionals Follow-up Study (Dhillon et al. 2011), in two case–control studies nested within the Quebec Health Insurance Database (Perron et al. 2003; Dasgupta et al. 2006), and in one nested case–control within the UK General Practice Database (Garcia Rodriguez LA 2004). RRs close to unity were reported in other cohort studies, including a large case–control study nested within a Canadian Prescription database (Mahmud et al. 2011) and the American Cancer Society/Cancer Prevention Study (ACS/CPS) II Nutrition cohort (Jacobs et al. 2007). However, in the latter cohort, a significant RR of 0.81 was reported for five or more years of aspirin use.

Two additional reports have been published after the meta-analysis by Bosetti et al. (2012a, b). A case–control study within a population-based Cancer Registry from Finland, including 24,657 prostate cancer cases diagnosed during 1995–2002, reported a RR of 0.95 (95 % CI, confidence interval, 0.88–1.00) for ever aspirin use (based on 2003 cases) and of 0.83 (95 % CI 0.73–0.94) for the highest level of aspirin use (based on 489 cases) (Veitonmäki et al. 2013). It reported no association for any of the other NSAIDS nor for COX-2 selective NSAIDs. In an analysis of mortality from cancer in the ACS-CPS study II (Jacobs et al. 2012)—whose data have partially been included in the previous meta-analysis (Bosetti et al. 2012a, b)—the RR of prostate cancer death was 0.77 (95 % CI 0.53–1.12) for current daily use of aspirin at baseline, based on 68 deaths and 0.57 (95 % CI 0.32–1.03) for updated information on current daily use of aspirin, based on 26 deaths, with no trend in risk for duration of use.

When all the available data from observational studies were pooled, the summary RR of prostate cancer for regular aspirin use was 0.91 (95 % CI 0.86–0.96), 0.87 (95 % CI 0.74–1.02) from nine case–control studies, and 0.92 (95 % CI 0.87–0.97) from 16 cohort studies (Fig. 1). The RRs were similar for low (0.81; 95 % CI 0.69–0.95) and regular/high (0.83; 95 % CI 0.70–0.97) dose, and no trend in risk was found with frequency (0.88; 95 % CI 0.81–0.95, for daily use) or duration (0.92; 95 % CI 0.83–1.01, for $\geq$5 years) of use. Risk estimates were also similar for low-grade/less aggressive cancers (RR 0.97; 95 % CI 0.85–1.10) and high-grade/more aggressive cancers (RR 0.88; 95 % CI 0.82–0.95).

3 Evidence from Randomized Clinical Trials

Cancer incidence and mortality was considered using data from randomized controlled trials of aspirin for the prevention of vascular events.

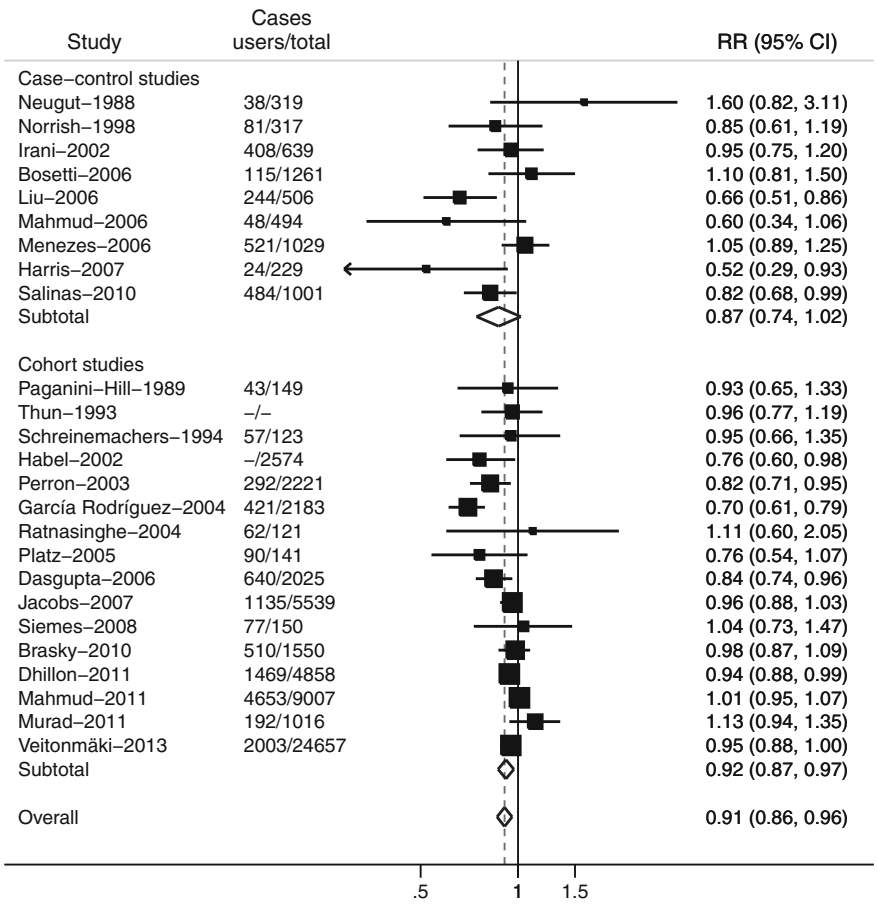

Fig. 1 Summary relative risk (RR) and corresponding 95 % confidence interval (CI) of prostate cancer for regular aspirin use versus never use from case–control and cohort studies, and overall

In a pooled analysis of individual data from clinical trials, allocation to aspirin reduced cancer mortality (RR 0.85, 95 % CI 0.76–0.96, based on 34 trials), particularly from 5 years onwards (RR 0.63, 95 % CI 0.49–0.82) (Rothwell et al. 2012a).

The effect of daily aspirin on long-term risk of cancer death was considered among data from eight trials, including 25,570 patients and 647 cancer deaths (Rothwell et al. 2011). There was a nonsignificant reduced risk of death from prostate cancer after a latent period of ≥5 years (RR 0.52, 95 % CI 0.20–1.24) based, however, on 37 deaths from prostate cancer only from seven trials. The RR was 0.81 (95 % CI 0.61–1.06) after 20 years of follow-up, based on 210 cases from three trials with long-term follow-up. That study showed a significant and

strong effect of aspirin on long-term risk of colorectal and other digestive tract cancers, and a less strong—and nonsignificant—effect for prostate cancer.

An analysis of the effect of daily aspirin on cancer metastasis, based on five clinical trials, showed an overall RR of 0.64 (95 % CI 0.48–0.84) for incidence of distant metastasis, with a stronger effect for adenocarcinomas (RR 0.54, 95 % CI 0.38–0.77) (Rothwell et al. 2012b).

In another meta-analysis comparing evidence from observational studies versus randomized trials (Algra and Rothwell 2012), regular use of aspirin was associated with a reduced proportion of prostate cancers with distant metastases (RR 0.69, 95 % CI 0.31–1.51, based on 102 prostate cancers and 43 metastatic cases).

The findings of relevant clinical trials with reference to prostate cancer are therefore consistent with the considerably larger evidence from observational studies (Algra and Rothwell 2012).

4 Studies on Prostate Cancer Survival

A longitudinal, observational study based on a registry database of 5,955 men with biopsy-proven prostate cancer—the Cancer at the Prostate Strategic Urologic Research Endeavor (CaPSURE) Study (Choe et al. 2012)—analyzed the subsequent prostate cancer-specific mortality. Ten-year death from prostate cancer was registered in 2 % of the 1,796 aspirin users versus 6 % of 350 other anticoagulant non-aspirin users, and 8 % of 3,726 nonusers of anticoagulants. The multivariate hazard ratio (HR), after allowance for initial prostate-specific antigen (PSA) level, Gleason score, tumor stage, and other treatment modalities was 0.43 (95 % CI 0.21–0.87) for aspirin use and 1.30 (95 % CI 0.55–3.06) for other anticoagulant use.

The apparently strong relationship between aspirin use and prostate cancer death has been related to the antiplatelet pathway, which has a role in cancer progression and metastasis (Bambace and Holmes 2011; Gay and Felding-Habermann 2011). A role of platelets in metastasis has long been recognized in mice (Camerer et al. 2004), and in several cancer patients thrombocytosis occurs frequently and is related to poor prognosis (Cuzick et al. 2009; Rothwell et al. 2012b; Bambace and Holmes 2011; Gay and Felding-Habermann 2011). Additional mechanisms may, however, may explain the specific favorable effects of aspirin as compared to other anticoagulants, including the inhibition of the COX-2, as prostate cancer progression can occur through pathways that include COX-2 (Thun et al. 2002; Brown and DuBois 2005).

The inverse association between prostate cancer mortality and aspirin use in the CaPSURE study (Choe et al. 2012) is apparently stronger than that between aspirin use and prostate cancer risk reported in the meta-analyses of observational studies. The CaPSURE study (Choe et al. 2012) therefore suggested that the favorable effect of aspirin on prostate cancer may be larger in the phases of prostate cancer metastasis and progression to death than prostate cancer initiation.

The role of aspirin on prostate cancer progression and survival has been also investigated within the Health Professionals Follow-up Study (Dhillon et al. 2012), with contrasting results. This prospective study included 3,986 participants with a prostate cancer diagnosis between January 1, 1990, and December 31, 2005. In total, 265 men developed bony or other organ metastases or fatal prostate cancer during 18 years of follow-up. No association between updated aspirin use after diagnosis and lethal prostate cancer was observed after adjusting for risk factors associated with incidence and mortality in this cohort, prediagnostic aspirin use, Gleason score, tumor-node-metastasis stage, and primary treatment (HR 1.12, 95 % CI 0.72–1.72 for <2 tablets/week, 1.05, 95 % CI 0.62–1.80 for 2–5 tablets/week and 1.08, 95 % CI 0.76–1.54 for ≥6 tablets/week, p for trend = 0.99). Likewise, there was no association with frequency of use, nor when aspirin use at baseline or fatal prostate cancer only were considered. Thus, this study does not support an association between aspirin use after a prostate cancer diagnosis and subsequent death from prostate cancer.

5 Conclusion

Evidence from both observational epidemiological studies and clinical trials indicates a modest favorable effect of aspirin on prostate cancer risk. Overall, prostate cancer is reduced by 10 % in regular aspirin users, with similar risk reductions in both case–control and cohort studies, and for both less aggressive and more aggressive cancers. However, there is some heterogeneity across observational studies, and there is no evidence of a relationship with frequency, dose, or duration of use. Studies which examined the effect of non-aspirin NSAIDs or all NSAIDs combined also suggest a reduced risk of prostate cancer, although their results are even less consistent than for aspirin (Mahmud et al. 2010).

Epidemiological studies on aspirin use may have the inherent limitations of observational studies, related in particular to measurement errors in the exposure to aspirin. An inherent limitation of summarizing results from several studies is the high variability of aspirin use definitions across studies, which may partly explain the heterogeneity in risk estimates across observational studies. Estimates from cohort studies are considered more reliable than those from case-control studies, since they are generally less prone to (differential) information or selection bias. No meaningful differences in risk estimates are, however, found between study designs. Prospective studies based on prescription databases might be biased by the lack of accounting for over-the-counter medication use. The data from clinical trials, which are less subject to those sources of bias, point, if anything, to a stronger effect of aspirin on prostate cancer incidence and mortality, but are based on small numbers of cases and in several instances are not significant. Detection bias is also possible in the case of prostate cancer since aspirin users may have had more frequent medical contacts and consequently PSA measurements, thus increasing their probability of being diagnosed with prostate cancer. This would

have tended to bias the estimates toward the null, as suggested by a few studies which have tried to adjust for the possible confounding effect of PSA (Mahmud et al. 2010).

Thus, epidemiologic studies available to date indicate a modest protective effect for prostate cancer risk. Inference for causality and public health implications are, however, far from conclusive given the heterogeneity of results and the lack of evidence of dose and duration-risk relationships. Data on prostate cancer survival are still limited and inconsistent.

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Chemoprevention of Prostate Cancer by Isoflavonoids

Stefan Aufderklamm, Florian Miller, Anastasia Galasso, Arnulf Stenzl and Georgios Gakis

Abstract

In Europe, prostate cancer (PC) is the most common malignancy in males. There are three known risk factors strongly coherent to the development of PC: heredity, ethnical origin, and age. Migration studies have shown that environmental factors may influence the development of PC. In this context, specific nutritional components may exert an influence on the tumorigenesis of PC. Primary prevention of PC is still an important issue due to its high prevalence, treatment-associated morbidities, and long-term complications. Phytoestrogenes as flavonoids seem to play an essential role in the chemoprevention of PC which is possibly due to their hormonal function and antioxidative capability. Flavonoids and their subgroups are naturally existent in traditional asian and vegetarian nutrients as coverings of plants, fruits, and vegetables. Two of the most frequently investigated flavonoids are genistein and quercetin. These nutritional components may have therapeutic potential and may impact the development of PC. Even though these flavonoids show promising results in the chemoprevention of PC, the literature is almost experimental, epidemiological, and retrospective with a missing long-term follow-up. Therefore, randomized clinical trials are urgently needed to evaluate in depth its oncologic effects in PC.

S. Aufderklamm (✉) · F. Miller · A. Stenzl · G. Gakis
Department of Urology, Eberhard-Karls University, Tübingen, Germany
e-mail: stefan.aufderklamm@gmail.com

A. Galasso
Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany

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1 Introduction

Prostate cancer (PC) is the most common malignant tumor in Europe and has an incidence of 214 cases per 1,000 men (Boyle and Ferlay 2005). In addition, PC is the second most common cause of cancer death in men (Jemal et al. 2008). There are three known risk factors strongly coherent to the development of PC: heredity, ethnical origin, and age (Schultz et al. 2011). Due to geographic differences verified in migration studies environmental factors may play an important role in the development of PC (Schultz et al. 2011). This hypothesis is supported by a study which reported that Asian Americans, who live in second generation in the U.S., have the same risk of PC as white Americans (Adams et al. 2004). Due to these observations, various environmental factors have been investigated during the last decades. Especially, men with classical Asian food pattern and vegetarians have a significant lower risk of developing PC (Key et al. 2009a, b).

In conclusion, specific nutritional components may exert an influence on the tumorigenesis of PC. For this, in vivo and in vitro studies have been set up to investigate the effects of nutritional components for the development of PC.

High amounts of calcium and milk product intake as well as meat and fatty acids have consistently shown to cause to a higher oxidative cell stress and contribute to an increased risk of PC (Butler et al. 2010; Miyanaga et al. 2012). Conversely, there are studies which suggest that specific nutrients exert potentially chemopreventive effects on PC. Among phytoestrogens, flavonoids seem to play an essential role in the chemoprevention of PC (Aalinkeel et al. 2010) which is possibly due to their hormonal function and antioxidative capability (Tarkowski et al. 2013).

2 Flavonoids: General Overview

Flavonoids and their subgroups (flavones, flavanones, flavanols, flavan-3-ols, flavonols, anthocyanidines, isoflavonoids, and neoflavonoids (Czaplinska et al. 2012)) are naturally existent in traditional, especially Asian and vegetarian, nutrients (Czaplinska et al. 2012; Gibellini et al. 2011). Highest concentrations can be found in the coverings of plants, fruits, and vegetables (Czaplinska et al. 2012).

Due to their similar biochemical structure to estrogens, flavonoids are also named phytoestrogens (Pendleton et al. 2008). Two of the most frequently investigated flavonoids are genistein and quercetin. In the following, their chemopreventive effects on PC development are outlined.

3 Genistein: General Aspects

Genistein is a natural component with an extraordinarily high concentration in soy products with 30–92 mg/100 g (Tarkowski et al. 2013; Kumar et al. 2004, 2007). In the Japanese population, the mean intake of genistein is approximately 60–80 mg per day (Kumar et al. 2007). In contrast, the daily intake of genistein in the Western population does not exceed 1 mg per day (Kumar et al. 2007). These data underpin one of the major differences between eastern and Western nutritional patterns and explain the hypothesis that a higher daily intake of isoflavonoids is likely associated with a lower PC risk (Ferris-Tortajada et al. 2012). Genistein has a large spectrum of activity: it protects cells from malignant processes, inhibits proliferation of malignant cells, and stimulates apoptosis (Tarkowski et al. 2013).

4 Chemoprevention of PC by Genistein

Several studies have been conducted to investigate the chemopreventive properties of genistein in malignant diseases. Prostatic tissue strongly depends on hormonal regulation (Magee and Rowland 2004). It is well known that PC growth which is subjected to distinct hormonal stimulation (Cheng and Balk 2003; Jenster 1999) due to its molecular characteristics genistein exerts estrogenous but also anti-estrogenous effects on tissues thereby influencing the development of hormonally dependent cancers (Kumar et al. 2004). Importantly, in vitro tests have shown that genistein influences and inhibits PC-cells due to the activation of NF-kappa B and Akt signaling pathways (Banerjee et al. 2008). In addition, genistein may antagonize estrogen- and also androgen-mediated signaling pathways in malignant processes. Moreover, genistein has shown antioxidant potential and is a potent inhibitor of angiogenesis and metastasis (Banerjee et al. 2008).

5 Quercetin: General Remarks

Quercetin is a flavonoid which is predominantly existent in nutrients like apples, onions, broccoli, citrus fruits, and tea (Williamson and Manach 2005; Bischoff 2008). The concentration of quercetin which is reabsorbed by the intestine depends strongly on the sort and the type of food preparation. There are less data about the mean daily intake of quercetin in Western countries. Bhagwat et al. (USDA Database for the Flavonoid Content of Selected Foods, 2012) calculated a mean dietary intake of quercetin in Western regions of about 10–20 mg per day.

6 Chemopreventive Effects of Quercetin

Quercetin may influence carcinogenesis based on its strong antioxidative potential (Bischoff 2008). Similar to genistein, quercetin exerts its chemopreventive properties based on a similar biochemical structure to estrogens (Bischoff 2008). In vitro and in vivo studies have confirmed the androgen-independent effect on PC (Bischoff 2008; Cimino et al. 2012). In fact, quercetin has also pro-apoptotic effects as it is capable of enhancing the activity of Caspase-9 and Caspase-3, and causing cell cyclus arrest in the G1 phase. Furthermore, it downregulates the PI3K/AKT signaling pathway and decreases the expression of the antiproliferative proteins Cdc2/Cdk-1 and Cyclin B1. In addition, quercetin has androgen-dependent effects by deregulating the formation of the protein complex c-Jun, Sp1, and the androgen receptor (Bischoff 2008; Cimino et al. 2012).

7 Discussion

Until now, up to 400 substances have been attributed to exert chemopreventive effects on PC (Cimino et al. 2012). Especially, the two polyphenols genistein and quercetin have been found to act as protective factors. Due to its high concentration in Asian food, genistein may have a strong influence on the development of PC. This might explain the significantly lower PC rates in Asian compared to Western countries (Perabo et al. 2008; Travis et al. 2009). In vivo and in vitro studies demonstrate that these polyphenols are capable of inhibiting carcinogenesis (Miyanaga et al. 2012; Kumar et al. 2007; Perabo et al. 2008; Barnes 1995; Zhao et al. 2009; Lazarevic et al. 2011). However, in order to clinically establish their chemopreventive effects randomized placebo-controlled trials are urgently needed.

Different studies have investigated the pharmacological characteristics of quercetin. Increased dietary supplementation results in a dosage-dependent increase of serum quercetin levels (Egert et al. 2008; Jin et al. 2010). The differences in quercetin uptake between Caucasian and Asian people could possibly be due to genetic polymorphisms of intestinal enzymes. In addition, the dietary uptake of quercetin depends also on daily nutritional habits (Egert et al. 2008) as quercetin concentration is highest in vegetables and fruits (Liu 2013).

Likewise to dietary intake, supplementation of genistein has been investigated in clinical trials. However, the results for genistein were divergent compared to those for quercetin. In some studies, serum levels of genistein were surprisingly higher before supplementation, whereas other groups reported opposite effects. Interestingly, while in all of these studies plasma or serum probes have been used to quantify genistein concentrations (Kumar et al. 2007; Travis et al. 2012: Hussain et al. 2003; deVere White et al. 2010), the underlying analytical method (i.e., high-performance liquid chromatography (HPLC), mass spectroscopy-based HPLC, and ultra performance liquid chromatography (UPLC) (Travis et al. 2009; deVere White et al. 2010)) might have biased the final results.

A total of 53 men with localized PC, a maximum Gleason score of 6 received 80 mg isoflavones or placebo for 12 weeks (Kumar et al. 2007). Compared to the serum levels of genistein at the beginning of the study, genistein levels were 9 times higher at the end of treatment (Kumar et al. 2007). These results were confirmed by Hussein et al. who showed that during supplementation with 100 mg soy isoflavones serum levels of genistein and daidzein increased significantly from 0.11 to 0.65 microM (Hussain et al. 2003).

It is well known that soy products which are commonly consumed in Asian regions contain high concentrations of genistein. Interestingly, people of Asian origin living in Western countries who preserve their nutritional habits have 7–110-fold higher genistein plasma levels compared to individuals with less intake of soy products (National Cancer Institute 1996).

Various studies have investigated the chemopreventive properties of flavonoids on PC incidence and PSA dynamics. McCann et al. showed that a daily intake of 26 μg quercetin is associated with a relative risk reduction of 27 % in PC development of PC (2005). However, data regarding the question of how quercetin concentration enriches in prostate tissue during supplementation are rare as this has only been investigated in in vitro models with PC cell lines (Vijayababu et al. 2005, 2006; Lee et al. 2008; Tang et al. 2010) and within epidemiological studies (McCann et al. 2005).

Gardner et al. showed that genistein supplementation before radical prostatectomy leads to a significant enrichment of this isoflavonoid in prostatic tissue (2009). This might offer an explanation for the direct anticancerogenic properties of genistein in prostatic tissues.

In terms of the effects of dietary genistein supplementation on PSA dynamics there is divergent data. Pendleton et al. investigated within a 12-month intervention study, the impact of isoflavones (141 mg daily) on total PSA dynamics but failed to demonstrate changes in PSA values before and after the intervention (2008). Also, Kumar et al. reported a slight tendency of PSA decrease after an intervention period of 3 months with 70 mg of isoflavonoids (Maskarinec et al. 2006). These results were confirmed by Hussain et al. and Schröder et al. demonstrating a significant decrease in PSA kinetics during dietary supplementation with isoflavones (Hussain et al. 2003; Dalais et al. 2004; Schroder et al. 2005). Hussein et al. conducted a pilot study in patients with diagnosed PC and rising serum PSA levels (2003). All patients had a newly diagnosed and untreated disease and were under watchful waiting with rising PSA or increasing serum PSA following local therapy or receiving hormonal treatment. They were supplemented 100 mg of isoflavone orally twice a day for at least 3 months. A significant effect on PSA stabilization was observed in the group of patients undergoing local therapy and in those with hormone-refractory disease following antihormonal treatment (83 % and 35 %, respectively). In addition, a decrease in the rise of serum PSA was obseved in the whole group ($P = 0.01$) following the soy isoflavone intervention (Hussain et al. 2003). Serum genistein and daidzein levels increased significantly during supplementation (genistein, $P = 0.00002$ and daidzein, $P = 0.00001$) (Hussain et al. 2003).

Schröder et al. included 49 patients with PC and rising PSA levels after radical prostatectomy or radiotherapy with curative intent in a randomized, double-blind, placebo-controlled crossover study investigating the effects of dietary supplements as soy, isoflavones, or lycopenes (Schroder et al. 2005). Changes in PSA kinetics (PSA slope and doubling time) were the primary endpoints of this study. Results showed a significant decrease in PSA slope ($p = 0.030$) and (2)log PSA slope ($p = 0.041$) (Schroder et al. 2005). The authors concluded that soy-based dietary supplements significantly delayed PSA progression after treatment with curative intent (Schroder et al. 2005).

In contrast, other similar studies did not observe a relation between isoflavonoids and PSA dynamics (Adams et al. 2004; deVere White et al. 2010). However, as PSA is only a surrogate marker, the results of the above-mentioned studies on the chemopreventive properties of isoflavonoids need to be carefully interpreted. In 2011, Miyanaga et al. performed a randomized placebo-controlled, double-blind study with a dietary supplementation of 60 mg isolavonoids per day over a period of 12 months. This study demonstrated a significant lower PC incidence in the intervention arm compared to the control group. Notably, the substitution with isoflavonoids did not influence PSA kinetics in both groups (2012). This study supports the hypothesis that genistein exerts chemopreventive effects on PC incidence. Moreover, the fact that patients included in this study had an elevated risk of PC as suggested by elevated PSA levels (2, 5–10 ng/ml) and negative prostate biopsies underlines that patients in the intervention arm presumably benefitted from the chemopreventive properties of genistein (Miyanaga et al. 2012). Finally, these results support a potential role of isoflavones in the prevention of PC and their possible benefit in case of histologically confirmed disease.

8 Conclusions

Primary prevention of PC is still an important goal due to its high prevalence, treatment-associated morbidities, and long-term complications. Nutritional components as genistein and quercetin have therapeutic potential and may strongly impact the development of this malignant disease. However, the evidence investigating genistein and quercetin and their relation to PC is almost solely based on experimental, epidemiological and retrospective studies with missing data on long-term follow-up. Future prospective and randomized clinical trials are strongly needed in this field.

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Lycopene for the Prevention and Treatment of Prostate Disease

Dragan Ilic

Abstract

Benign prostatic hyperplasia (BPH) and prostate cancer are common diseases of the prostate gland. BPH is commonly treated by pharmaceutical products, which commonly improve symptoms but are often off-set by adverse events including erectile dysfunction, which affect quality of life. Similarly, a variety of treatment options exist for the treatment of prostate cancer. The applicability of these prostate cancer treatments is reliant on stage of disease. Whilst effectiveness of prostate cancer treatments may vary, common adverse effects include erectile dysfunction, incontinence and lower quality of life. Early evidence from systematic reviews has suggested that diet and lifestyle factors may be beneficial in reducing the risk of cancer. Lycopene, a member of the carotenoid family, found commonly in red pigmented fruit and vegetables has been established as having strong antioxidant and pro-oxidant properties. This chapter examines the current evidence on the use of lycopene as a preventive agent for prostate disease.

Contents

D. Ilic (✉)
Department of Epidemiology and Preventive Medicine,
School of Public Health and Preventive Medicine, Monash University, Level 6,
The Alfred Centre, 99 Commercial Road, Melbourne, VIC 3004, Australia
e-mail: dragan.ilic@monash.edu

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1 What is Prostate Disease?

Benign prostatic hyperplasia (BPH) and prostate cancer are common diseases of the prostate gland. Both BPH and prostate cancer are generally recognised as common diseases that affect men as they age. BPH is defined as a non-malignant enlargement of the prostate gland that causes resistance and obstruction of the urethra, leading to lower urinary tract symptoms (LUTS) (Wilt and Ishani 1998; McVary et al. 2011). Symptoms commonly include increased urinary frequency, nocturia, urinary incontinence, and trouble with voiding (slow and/or weak stream and sense of incomplete emptying of the bladder) (Coyne et al. 2009).

Approximately 50 % of men aged over 50 years of age will experience BPH-related symptoms, rising to 90 % of men aged over 80 years (Berry et al. 1984; Schwarz et al. 2008). After lung cancer, prostate cancer is the most commonly diagnosed cancer in men worldwide, and a leading cause of mortality in men (Jemal et al. 2011). Prostate cancer incidence varies worldwide, with prostate cancer incidence the highest in developed countries across Europe, North American and Australia (Jemal et al. 2011). Greater uptake of prostate cancer screening and dietary intake have been postulated as potential reasons for this geographical variability, although limited evidence currently exists to substantiate these suggestions (Ilic et al. 2013).

2 How is Prostate Disease Treated?

BPH is primarily treated by pharmaceutical products such as alpha-blockers and 5-alpha reductase inhibitors. Evidence from systematic reviews indicates that when used in combination, or alone, such pharmaceutical interventions may improve urine flow, nocturia and quality of life (Tacklind et al. 2010; Wilt et al. 2008). These benefits are offset by adverse events associated with these pharmaceutical interventions including increased rates of erectile dysfunction, decrease in libido, hypotension and dizziness (Tacklind et al. 2010; Wilt et al. 2008). Surgical intervention via a transurethral resection of the prostate (TURP) is successful in treating BPH and LUTS in 75 % of men, but is also associated with greater morbidity than pharmaceutical intervention including blood loss, infection and erectile dysfunction (Hoffman et al. 2000).

A variety of prostate cancer treatments are available including radical prostatectomy (robotic assisted or laparoscopic), radiotherapy (external beam or brachytherapy), androgen therapy or active surveillance or observation alone (Heidenreich et al. 2011). However, the applicability of each therapy is reliant upon the stage of disease—for example, active surveillance may be utilised when the cancer is localised to the prostate gland and is assessed as non-aggressive, but not in more aggressive tumours (i.e. Gleason 8+). Common adverse events associated with these treatments (apart from active surveillance) include erectile dysfunction, urinary incontinence, blood loss, infection and negative impact upon quality of life through psychosocial aspects (Heidenreich et al. 2011).

3 Can Diet and Lifestyle Changes Prevent Prostate Disease?

The World Cancer Research Fund (WCRF) reported in 2007 that a high fruit and vegetable intake may be beneficial in reducing the risk of cancer (World Cancer Research Fund/American Institute for Cancer Research 2007). This recommendation was based on the assumption that most cancers will only become identifiable years after the initial DNA damage has occurred; with diet and nutrition possible modifying factors (World Cancer Research Fund/American Institute for Cancer Research 2007). The WCRF expert panel concluded that foods that contain lycopene, selenium, vitamin E and soy have a potential protective role against cancer (World Cancer Research Fund/American Institute for Cancer Research 2007). Current evidence from systematic reviews of randomised controlled trials investigating the anti-neoplastic effects of selenium, vitamin E, zinc and beta-carotenes concludes that there is no conclusive evidence to support the claim that these products prevent or decrease the incidence of prostate disease (Dennert et al. 2011; Stratton and Godwin 2011).

Lycopene is a member of the carotenoid family, found most commonly in fruit and vegetables that contain red pigmentation, such as tomatoes, strawberries and watermelon (Chan et al. 2005). Unlike beta-carotene, another member of the carotenoid family, lycopene has been established as having strong antioxidant and pro-oxidant properties that may be useful in protecting DNA from oxidation and cancer-related mutations (Wertz et al. 2004; Wang 2012).

Several pathways in which lycopene may prevent cancer have been postulated. It has been suggested that lycopene inhibits the propagation of cancer cells at the G0-G1 cell cycle phase (Matsushima et al. 1995). Inhibition of prostate cancer cell growth has been linked with the interaction of androgen steroid hormones promoting the biological action of lycopene in reducing the expression of 5-alpha reductase-1 (Wang 2012). It has also been suggested that prevention may occur through the upregulation of tumour suppressor proteins and increased gap-junctional intercellular communication through the insulin-like growth factor (IGF) 1 pathway (Karas et al. 2000).

4 Can Lycopene Assist in the Prevention and Treatment of Prostate Disease?

A number of systematic reviews on before and after, case–control, cohort and RCTs have been performed—all with varying conclusions about the efficacy of lycopene in the prevention of prostate disease (Haseen et al. 2009; Etminan et al. 2004; Ilic et al. 2011; Ilic and Misso 2012). A systematic review reporting the results of five before and after studies on lycopene for the prevention and treatment of prostate disease identified that three out of the five studies reported a significant decrease in prostate-specific antigen (PSA) levels post-intervention (Haseen et al. 2009). Only one of the before and after studies reported a significant reduction in

Table 1 Results from pooled analysis of case–control and cohort studies for lycopene supplementation in the prevention of prostate cancer

Study type	Number of studies	Pooled relative risk (95 % confidence intervals)
Case–control	7	RR = 0.97 (0.86, 1.09) (low or moderate intake of lycopene) RR = 0.98 (0.83, 1.16) (high intake of lycopene)
Cohort studies	3	RR = 1.00 (0.92, 1.08) (low or moderate intake of lycopene) RR = 0.84 (0.75, 0.95) (high intake of lycopene)
All studies	10	RR = 0.99 (0.93, 1.06) (low or moderate intake of lycopene) RR = 0.89 (0.81, 0.98) (high intake of lycopene)

Data in table adapted from Etminan (Etminan et al. 2004)

pain—with the same study reporting a significant improvement in LUTS (Haseen et al. 2009; Ansari and Gupta 2003).

A systematic review of observational studies identified 11 case–control and 10 cohort studies investigating lycopene as a preventive agent for prostate disease (Etminan et al. 2004). Pooled analysis of the case–control and cohort studies demonstrated little benefit from lycopene supplementation in the prevention of prostate cancer (Table 1) (Etminan et al. 2004). However, a pooled analysis of all observational studies identified in that systematic review suggests a potential benefit in the consumption of high concentrations of lycopene for potentially preventing prostate cancer.

Systematic reviews of RCTs in 2011 and 2012 identified eight RCTs that have investigated the merits of lycopene in the prevention and treatment of BPH and/or prostate cancer (Ilic et al. 2011; Ilic and Misso 2012). Meta-analysis of two studies identified a significant decrease in PSA levels in men allocated to receive lycopene Mean difference (MD) = −1.58 (95 %CI −2.61, −0.55) (Ilic and Misso 2012). Further meta-analysis of two studies within the review identified no significant reduction in the incidence of BPH (RR = 0.92 (95 %CI 0.66, 1.29)) or prostate cancer diagnosis (RR = 0.95 (95 %CI 0.63, 1.44)) between men receiving lycopene supplementation or placebo (Ilic and Misso 2012). No adverse events were reported across the systematic reviews regarding ingestion of lycopene (Haseen et al. 2009; Etminan et al. 2004; Ilic et al. 2011; Ilic and Misso 2012).

5 What is the Future of Lycopene?

Based on evidence from observational and experimental studies, it is apparent that there is no substantial evidence to either support, or refute, the claim that lycopene is effective in the prevention and treatment of prostate disease (be it BPH or prostate cancer). A high intake of lycopene has been associated with a significant decrease in prostate cancer incidence in a pooled analysis of observational studies (Etminan et al. 2004).

The ideal daily intake or lycopene is unknown, although it has been suggested that a daily intake of 6 mg is sufficient to achieve its antioxidant properties (Porrini and Riso 2005). The common dose of lycopene in published RCTs has ranged from 15 to 30 mg, and yet this higher dose of lycopene was not associated with a decrease in the incidence of BPH or prostate cancer. However, the evidence base on this issue is limited as the meta-analysis is based on only two studies. Furthermore, the follow-up period of RCTs to date has been short, ranging from 4 weeks to 2 year follow-up periods (Ilic and Misso 2012). Conversely, the pooled evidence from observational studies would suggest a small, but significant, decrease in the incidence of prostate cancer in men with a high intake of lycopene. However, drawing such positive inferences observational data should be cautiously given the potential for recall and response bias, as well as confounding effects, in case–control and cohort studies.

In the USA, it has been estimated that more than 50 % of consumers regularly consume dietary supplements, with this figure rising to over 70 % of consumers aged above 70 years (Bailey et al. 2011). The evidence would currently suggest that lycopene supplementation does no harm, but it also has limited benefits. Although it could be argued that with the large amounts of consumers buying such supplements, the hidden harm is the cost associated with purchasing a therapy that has no proven benefit. Studies that have investigated the merits of lycopene for the prevention and treatment of prostate disease vary in their methodological quality and dosage. Given the lack of clinical evidence, there is an urgent need for a well-designed RCT, with long-term follow-up of participants, to determine the efficacy of lycopene for the prevention and treatment of prostate disease.

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Chemoprevention of Prostate Cancer with the Polyamine Synthesis Inhibitor Difluoromethylornithine

Frank L. Meyskens Jr., Anne R. Simoneau and Eugene W. Gerner

Abstract

In vitro and in vivo preclinical results suggest that inhibition of polyamine synthesis inhibits the progression of prostate cancer. These findings has led to two clinical trials in patients at risk for invasive prostate cancer with difluoromethylornithine which specifically and irreversibly inhibits ornithine decarboxylase which catalyses the conversion of ornithine to putrescine the rate limiting step in polyamines synthesis. We have conducted a phase IIa one month and placebo randomized phase IIb 12 months trials in patients at increased risk for invasive prostate cancer. Favorable reduction in prostate polyamine levels and prostate volume was documented with no difference in clinical hearing changes. Patients with Gleason's VI lesions in a surveillance cohort would be appropriate candidates for a definitive risk reduction trial although the unavailability of validated biomarkers for invasive progression would require a large and lengthy study.

F. L. Meyskens Jr. (✉) · A. R. Simoneau
Chao Family Comprehensive Cancer Center, University of California Irvine, Irvine, CA, USA
e-mail: flmeyske@uci.edu

F. L. Meyskens Jr.
Departments of Medicine, Biological Chemistry and Public Health, University of California Irvine, Irvine, CA, USA

A. R. Simoneau
Departmentof Urology, University of California Irvine, Irvine, CA, USA

E. W. Gerner
BIO5 Institute and Arizona Cancer Center, University of Arizona, 1580 E. Hanley Blvd., Tucson, AZ 85737, USA

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Contents

1 Introduction

Polyamines are small cationic molecules that have diverse roles in the cellular management of normal and malignant cells (Nowotarski et al. 2013). The biochemical pathways which intersect with polyamine metabolism are complex and a simplified version is shown in Fig. 1. Extensive discussions of the polyamine network of synthetic and catabolic enzymes and transport systems are available elsewhere (Gerner et al. 2004).

A key regulatory step involves the decarboxylation of ornithine to yield putrescine by the rate-limiting enzyme ornithine decarboxylase (ODC). This gene contains several single nucleotide polymorphisms (SNPs); under certain circumstances, one ODC SNP at +316 from the transcription start site is associated with cancer prognosis and response to certain therapies (Zell et al. 2010). In 1976 difluoromethylornithine (DFMO), a specific irreversible inhibitor of ODC, was synthesized. It is important to note that inhibition of ODC by DFMO results in a rapid decrease in changes in the levels of putrescine, while a decrease in the Spd/Spm ratio reflects long-term alterations. Therapeutic studies of DFMO in hematopoetic malignancies and solid tumors were negative (Seiler 2003), but a series of preclinical prevention studies in the late 1980s were positive, particularly in colon and prostate cancers, which led us to explore the activity of DFMO in patients with these organ site malignancies. A summary of the early findings particularly relevant to prostate cancer are summarized in Table 1 and include in vitro and animal model findings (Kadmon 1992). Based on these encouraging preclinical results, we began a series of trials involving patients at significant risk for progression of low-grade (Gleason's VI) prostate cancer. Until recently selection of at-risk patients were driven by clinical parameters, Gleason scores, and prostate-specific antigen (PSA) levels. We began our studies of prostate cancer chemoprevention in 1995 and have reported results from a 1-month phase IIa trial in 2001 and a 12-month phase IIb trial in 2008 (Simoneau et al. 2001, 2008).

The phase IIa trial (1 month duration) was designed as follows:

- Objective: to evaluate the effects of DFMO on polyamine levels in the prostate.
- Methodology:
  - Prospective nonrandomized study of men aged 50–85 who required prostate needle biopsy. Four additional cores were taken at time of initial contact.
  - If surgery or rebiopsy was indicated, subjects started DFMO 0.5 gm/m^2 orally each day for 28 days prior to a second procedure. Four additional cores were taken for analysis and analyzed for polyamine levels.

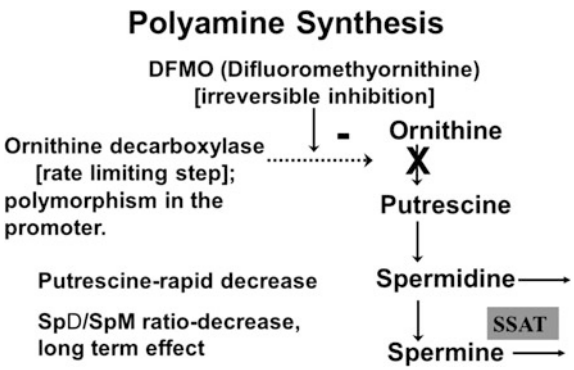

Fig. 1 Synthesis of Polyamine: Major Pathway. The amino acid ornithine is rapidly converted by ornithine decarboxylase into the polyamine putrescine and its levels are a reliable measure of short-term changes in tissue polyamines. A series of enzymatic steps lead to formation of spermidine and the terminal polyamine spermine. Changes in the spermidine/spermine ratio reflect long-term effects. Acetylation (SSAT) of the polymines occurs which enhances export; some NSAIDs (such as Sulindac) enhance this step

Table 1 Historical perspective of preclinical studies of polyamines and the prostate (1978–1992)[a]

• ODC activity and polyamines are higher in prostatic tissue compared to other tissues
• Rats given DFMO had reduction of ODC activity to 10 % of controls by 4 h
• The prostate was more sensitive than other tissues to DFMO polyamine suppression
• DFMO can affect rat prostate weight
• ODC activity is higher in hormone unresponsive prostate cancer cell lines (G_3)
• DFMO inhibited prostate cancer cell lines in vitro and in vivo

[a]Adapted from Kadmon (1992)

- Participants: 49 signed consent, 18 who did not have extra biopsies; 22 with first biopsy only; 10 who took DFMO; and 9 who completed pre- and post-biopsy.

The major features of the phase IIb trial (12 months) included:

- Objective: to evaluate the effects of DFMO on polyamine levels in the prostate, prostate volume, PSA levels, and toxicity.
- Methodology:
  - Men diagnosed with prostate cancer before the age of 70 who also had a first-degree relative with prostate cancer, or men diagnosed before the age of 55 designated as a proband. Their brothers and first cousins under 70 years were eligible for the study.
  - Participants had an AUA history, PSA determination, prostate ultrasound, and prostate biopsies.

Table 2 Major findings in phase IIa and phase IIb chemoprevention trials of DFMO for prostate cancer[a]

Phase IIa (1 month, pre–post comparison)
Marked reduction of putrescine, spermidine, and spermine levels in all nine participants and decreased Sp/Spm ratio in eight of nine patients
Phase IIb (12 month, pre–post comparison, randomized)
• Prostate volume: DFMO (↑ 0.14 cm^3), placebo (↑ 2.95 cm^3); $p = 0.03$
• Prostate putrescine: DFMO (↓ 60.8 %), placebo (↑ 139 %); $p = 0.001$ The changes in volume and putrescine levels occurred in the AA and AG but not the GG ODC genotype
• Clinical ototoxicities: no difference between arms, but subclinical changes documented by audiometry in the AA/AG group (Zell et al. 2010)

[a]Summarized from Simoneau (2001, 2008)

  - Prostate tissue examined for histology, polyamine content, and tissue markers.
  - Participants received placebo or 500 mg/day of DFMO.
  - One year later repeat studies were performed. Analysis of differences before and after DFMO, each man served as his own control.
- Participants: 140 men enrolled (consented); 81 underwent an initial biopsy, 76 men were randomized; 66 completed two sets of biopsies of which 62 finished within 12 months of study drug and an end of study biopsy.

The overall results of both trials are summarized in Table 2. The results from these trials clearly demonstrated that a low nontoxic dose of DFMO suppressed putrescine levels in the prostate rapidly and long term led to a significant decrease in prostate size that was more pronounced in patients with the AA/GA ODC allele. There was also a trend in decreasing PSA doubling time.

We and others have gained extensive clinical experience with DFMO in the prevention of colorectal (Meyskens et al. 2008) and nonmelanoma skin cancers (Kreul et al. 2012). At the doses used, this drug was nontoxic, although subclinical changes in hearing in a few patients were detectable by audiometry (McLaren et al. 2008).

2 The Future

The results from these trials and the increasing recognition of the important role that polyamines play in cellular regulation (Agostinelli et al. 2010) have encouraged us to re-examine a potential role for DFMO in the chemoprevention of prostate cancer. Exciting new work with polyamine transport inhibitors has also refocused attention on the polyamine pathway (Samal et al. 2013). Negative results in the large PCPT and SELECT trials (Thompson et al. 2003; Algotar et al. 2013) as well as the failure of toremifine and 1 α—hydroxyvitamin D2) (Gee et al. 2013; Taneja et al. 2013) in HGPIN has also refocused attention on DFMO. A wide

range of preclinical studies are examining the role of natural compounds in prostate cancer prevention (Horie 2012; Ozten-Kandaş and Bosland 2011; Cimino et al. 2012; Thapa and Ghosh 2012), but to date the results have been unconvincing and clinical trials have not been forthcoming (Horie 2012).

The major question then about expanding studies with DFMO is: Which group of patients should be the targeted population? Only about 20 % of patients with Gleason's 6 tumors progress to aggressive cancers. Until biomarkers are developed that can identify these patients with considerable accuracy, large definitive trials are unlikely to be undertaken. Alternatively, one might consider a trial in patients with Gleason's 7 or even 8/9 tumors, but ethical considerations might limit such a trial. Overall, definitive trials of DFMO as a chemopreventive agent await more accurate classification of risk based on a better understanding of the natural history of low-grade prostate cancer (e.g., see Earnshaw et al. 2013; Pan et al. 2012).

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Prostate Cancer Prevention: Agent Development Strategies

Howard L. Parnes, Margaret G. House and Joseph A. Tangrea

Abstract

Despite advances in surgery, radiation, and medical therapy over the past decade and the widespread adoption of PSA screening, prostate cancer continues to be the second leading cause of cancer death in men in the United States. Invasive cancer is the end result of carcinogenesis, a chronic process occurring over many years driven by genetic and epigenetic alterations. The protracted nature of this transformation to the malignant phenotype provides an opportunity to intervene pharmacologically to prevent, reverse, or delay carcinogenesis, i.e. chemoprevention. Herein, we describe the unique features of cancer prevention, as opposed to cancer treatment, agent development clinical trials, and provide a summary of the ongoing research in this field being supported by the National Cancer Institute.

Contents

H. L. Parnes (✉)
Division of Cancer Prevention, 9609 Medical Center Drive, National Cancer Institute, Bethesda, MD 20892-9783, USA
e-mail: parnesh@mail.nih.gov

M. G. House · J. A. Tangrea
Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, USA

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1 Introduction

Prostate cancer remains the second leading cause of cancer death among U.S. males despite recent advances in treatment and screening. The length of time (decades) required for transformation to the malignant phenotype, a process referred to as carcinogenesis, (Schulman et al. 2000) coupled with the non-modifiable nature of the major prostate cancer risk factors (age, race, and family history) (Thompson et al. 2006) suggest that primary prevention may be the best way to reduce the morbidity and mortality associated with this disease (Sporn and Suh 2000; Lippman and Hong 2002; Kinzler and Vogelstein 1996; Jones and Baylin 2002; Renan 1993; Sporn and Suh 2002). Cancer prevention agents must be safe, convenient, and inexpensive given their intended long-term use in people without overt disease. For this reason, bioactive food components, such as vitamins (e.g., C, D, and E), soy isoflavones (e.g., genistein), green tea catechins (e.g., epigallocatechin gallate or EGCG), phytonutrients from cruciferous vegetables (e.g., diindolylmethane or DIM), and the trace element selenium (e.g., high-selenium yeast and selenomethionine) have generated much interest as potential cancer prevention agents (Parnes et al. 2004). Drugs targeting the androgen pathways represent the other major category of prostate cancer prevention agents. For example, both finasteride and dutasteride, which inhibit the conversion of testosterone to dihydrotestosterone, have been shown to decrease the risk of prostate cancer in large Phase III, randomized, placebo-controlled clinical trials (Thompson et al. 2003; Andriole et al. 2010).

2 Trial Endpoints

An important consequence of the long natural history of prostate cancer is that many years would be required to demonstrate a reduction in cancer incidence. Therefore, Phase II efficacy trials of candidate cancer prevention agents must rely on intermediate biomarker endpoints, rather than clinical endpoints. While serum-based biomarkers can be informative at this stage, tissue is required to determine whether an agent (1) gets to the prostate gland and (2) modulates processes important to carcinogenesis, such as cellular proliferation and apoptosis, at the tissue level (Bostwick and Qian 2001; De Marzo et al. 1999). In addition to the need for tissue, early phase prevention trials benefit greatly from randomized, placebo-controlled study designs, as comparisons of biomarker expression levels before and after an intervention can otherwise be difficult to interpret.

3 Study Cohorts

Cohort selection for prevention agent development clinical trials is driven to a large extent by the need for tissue. Several cohorts in whom prostate tissue is obtained as part of the standard of care have been identified: (1) men with prostate

cancer scheduled for prostatectomy, (2) men with low-risk prostate cancer being followed on active surveillance, (3) men with high-grade prostatic intraepithelial neoplasia (HGPIN) or severe atypia, and (4) men with an elevated PSA levels and a negative prostate biopsy. The NCI has supported prostate cancer prevention agent development studies in each of these cohorts (Table 1).

3.1 Preprostatectomy Cohort

Men with localized prostate cancer planning to undergo definitive surgery represent a potentially informative cohort for prostate cancer prevention agent development. Study agents are generally administered during the 3–6 week window of opportunity between the diagnostic biopsy and prostatectomy. The preprostatectomy model has the potential to provide valuable information regarding distribution of the candidate agent in prostate tissue and the effect of the study drug on tissue-based biomarkers, as the entire gland will become available following prostatectomy. Most of the drugs that have undergone Phase II testing in the NCI prostate cancer chemoprevention agent development program over the past decade have been evaluated in this cohort.

In a recently completed preprostatectomy trial, investigators at the University of Arizona randomized 52 men with biopsy-confirmed prostate cancer to Polyphenol E (PPE), a proprietary mixture of epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC) or a matching placebo, for 3–6 weeks before surgery (Nguyen et al. 2012). The primary objective was to determine the bioavailability of these catechins in prostate tissue. Secondary endpoints included tissue biomarkers of proliferation (Ki-67), apoptosis (cleaved caspase-3), and angiogenesis (microvessel density) as well as several serum biomarkers, e.g., prostate specific antigen (PSA), insulin-like growth factor, oxidative DNA damage, and plasma catechin concentrations.

Forty-eight men (24 in each group) met all inclusion criteria and completed the intervention. The two groups were balanced for baseline characteristics such as age, race, body mass, pre-study PSA levels, and biopsy Gleason score. PPE was well tolerated and there were no withdrawals from the study due to adverse events. Although plasma catechin concentrations were low, detectable levels in the picogram range were observed among men on the PPE arm. None of the subjects on the placebo arm had detectable plasma levels. Fresh–frozen prostate tissue was available from 15 men receiving PPE and from 19 subjects receiving placebo. The tissue analyses revealed very poor tissue bioavailability with 10 of the 15 men on the PPE arm having no detectable catechin levels and only 1 of 15 having detectable levels of all 3 catechins analyzed. Not surprisingly, no significant differences were seen between the treatment and control arms in serum-based or tissue biomarker endpoints.

These findings highlight an important shortcoming of the inherently short-duration preprostatectomy window of opportunity studies for chemoprevention

Table 1 NCI-sponsored prostate cancer prevention trials[a]

Cohort	Agent	Endpoints	Actual accrual/ goal	Results
Preprostatectomy	Toremifene (40 mg QD) 3–6 weeks	HGPIN index	52/78	No effect on either HGPIN or biomarkers (Nelson, Personal communication, 2006)
Preprostatectomy	Metformin ER (500 mg/day 1 week, 1,000/day 2 weeks, then 1,500 mg/day) 4–12 weeks	Tissue bioavailability; proliferation, apoptosis, angiogenesis; mTOR; fasting glucose; fasting insulin; insulin-like growth factor	16/50	Ongoing
Preprostatectomy	Sulindac sulfone (375 mg/ day) 4 weeks	Apoptosis	105/ 130	No significant changes in biomarkers of apoptosis (Weight et al. 2012)
Preprostatectomy	Celecoxib (400 mg BID) 4–6 weeks	Tissue prostaglandin levels; PSA; proliferation; cyclooxygenase-2 expression; DNA oxidation	64/65	Celecoxib was not associated with significant alterations in any of the examined biomarkers (Carducci et al. 2007)
Preprostatectomy	Genistein (150, 300, 600 mg/ day) 2–6 weeks	Oxidative stress; plasma; and tissue genistein levels	34/80	No change in oxidative stress biomarkers; paradoxical increase in IGF-1 in 600 mg group; increase in plasma and tissue genistein levels in treated patients (Kucuk, Personal communication, 2006)
Preprostatectomy	Genistein (2 mg/kg/day) 1–2 months	Morphology; PSA; gene expression profiles; testosterone; proliferation; apoptosis	37/80	Altered expression of motility genes (Huang et al. 2005)
Preprostatectomy	Cholecalciferol (Vit D3) (200,000 IU) X 1 dose and Genistein (600 mg/day) 21–28 days	Cholecalciferol (Vit D3) serum and tissue bioavailability; vitamin D receptor levels; insulin-like growth factor	5/50	Ongoing

(continued)

Table 1 (continued)

Cohort	Agent	Endpoints	Actual accrual/ goal	Results
Preprostatectomy	Hecterol (10 ug/day) 4–6 weeks	Proliferation; apoptosis; angiogenesis; HGPIN	31/60	No significant changes in proliferation, apoptosis, microvessel density; Nonsignificant decrease in HGPIN (50 vs. 23.1 %, $P = 0.148$) (Wilding, Personal communication, 2008)
Preprostatectomy	Se–met (400 ug/day), Finasteride (5 mg/day) 8–9 weeks (factorial design)	PSA gene expression; apoptosis	33/164	Ongoing (Ip, Personal communication, 2008)
Preprostatectomy	Se–met (200 ug/day) 14–31 days	Prostate selenium concentration; PSA	68/68	22 % increase in prostate selenium concentration; no significant change in PSA levels (Nguyen et al. 2012; Sabichi et al. 2006)
Preprostatectomy	Green Tea Catechins (800 mg PPE/day) 3–6 weeks	Tissue catechin levels; insulin-like growth factor; DNA oxidation; clusterin	50/50	Low to undetectable green tea catechin prostate tissue levels; tissue biomarkers of proliferation, apoptosis, and angiogenesis in prostate tissue did not differ between treatment arms (Nguyen et al. 2012)
Preprostatectomy	Diindolylmethane (DIM) (100, 200 mg/day) 3–4 weeks	Tissue DIM levels Testosterone; PSA; insulin-like growth factor; androgen receptor localization; apoptosis; proliferation	45/45	Low to undetectable DIM prostate tissue levels; manuscript in preparation (Bailey, Personal communication, 2013)
Active surveillance	Lycopene (30 mg/day) v Omega-3 fatty acids (1 gm/ day) 3 months	Gene expression; insulin-like growth factor; cyclooxygenase-2 expression	85/180	No change in IGF-1 or COX-2 gene expression in prostate biopsy tissue (Chan et al. 2011)
Active surveillance	Isoflavones (80 mg/day) 3 months	Isoflavone levels, PSA; testosterone; estrogen.	53/148	Increase in plasma isoflavone levels; no effect on PSA, T, E, or SHBG (Kumar et al. 2007)

(continued)

Table 1 (continued)

Cohort	Agent	Endpoints	Actual accrual/ goal	Results
Active surveillance	Pomegranate Fruit Extract 1000 mg PO qd × 12 months	Insulin-like growth factor; compliance and toxicity; PSA; testosterone; angiogenesis; apoptosis; proliferation; Gleason grade; and tumor volume	0/30	Ongoing
Active surveillance	Se–yeast (200, 800 ug/day) Average duration 45 months 800 arm dropped in 2000 due to toxicity	PSA; prostate cancer progression; apoptosis; proliferation	159/ 220	No significant change in PSA velocity overall for 200 ug/day or 800 ug/day Se versus placebo (Stratton et al. 2010)
Active surveillance	Dietary intervention via telephone counseling	PSA; Gleason score; tumor extension; telephone intervention effects on treatment seeking, anxiety, and coronary heart disease	159/ 400	Ongoing
High-risk, post-radical prostatectomy	Soy protein 20 g × 24 months	Two year PSA failure rate; time to PSA failure	169/ 284	No effect on PSA (Ozten-Kandas and Bosland 2011)
HGPIN	Se–met (200 ug/day) 3 years	Prostate cancer incidence; apoptosis; proliferation	440/ 465	No difference in prostate cancer risk (Marshall et al. 2011)
HGPIN or ASAP	Green Tea Catechins (400 mg PPE/day) 12 months	Compliance, toxicity, quality of life; prostate cancer incidence	96/240	Ongoing (Kumar 2011)
Elevated PSA with negative biopsy	Se–yeast (200, 400 ug/day) Up to 57 months	Prostate cancer; PSA kinetics	612/ 700	No significant decrease in prostate cancer risk for selenium 200 ug/day or 400 ug/day. No significant change in PSA velocity (Algotar et al. 2013)

(continued)

Table 1 (continued)

Cohort	Agent	Endpoints	Actual accrual/ goal	Results
Positive family history with negative biopsy	DFMO (500 mg QD) 1 year	Prostate polyamines levels; PSA	81/100	Decreased putrescine levels noted; no significant effect on other polyamines or PSA (Simoneau et al. 2008)
Healthy men	Se–yeast (240, 350 ug/day) Se–met (200 ug/day) 9 months	Plasma and urine selenium concentration; PSA; dihydrotestosterone; testosterone	56/300	Ongoing (El-Bayoumy, Personal communication, 2012)

[a]All trials are placebo-controlled with the exception of sulindac sulfone, which used historical and concurrent controls

agent development. A 3–6 week intervention may provide insufficient time for adequate tissue accumulation of the agent and/or for measurable changes in traditional tissue-based biomarkers to occur. In an effort to address the latter issue, we are currently exploring whether changes in microRNA might provide a more sensitive indicator of an anticancer drug effect than changes at the gene or protein level. Another way to circumvent this issue is by studying patients in whom a longer duration of drug exposure is possible. A potentially promising approach in this regard is to evaluate putative prostate cancer chemoprevention agents in men who choose to be followed on active surveillance for low-risk prostate cancer (see below).

3.2 Active Surveillance Cohort

PSA screening results in the diagnosis and subsequent treatment of many cancers that would never have otherwise become apparent during a man's lifetime (Cooperberg et al. 2007). Recognition of this problem has led to greater acceptance of expectant management with curative intent (also known as active surveillance) as an alternative to immediate definitive therapy with surgery or radiation (Carter et al. 2007; Klotz et al. 2010; Singer et al. 2012). Men on active surveillance protocols for low-risk prostate cancer are excellent candidates for chemoprevention agent development trials with tissue biomarker endpoints, as follow-up prostate biopsies are usually recommended to monitor for disease progression (Singer et al. 2012). This population may also provide a useful cohort in which to evaluate the usefulness of genomics and proteomics to predict the natural history of this heterogeneous disease. Pilot studies of soy isoflavones, lycopene, omega-3 fatty acids, and selenium have recently been completed in men with low-risk prostate cancer being followed with active surveillance (Chan et al. 2011; Kumar et al. 2007; Stratton et al. 2010). An NCI-supported randomized clinical trial of pomegranate fruit extract in this population is currently pending activation.

3.3 HGPIN Cohort

Several small studies in the late 1990s suggested that the presence of high-grade prostatic intraepithelial neoplasia (HGPIN) in a prostate biopsy was associated with a high risk of cancer (as much as 40–50 %), and that patients with HGPIN required close monitoring with repeat biopsies. For example, in a study from Johns Hopkins, repeat biopsies identified cancer in 32.2 % of 245 men with a prior diagnosis of HGPIN. The number of cores with HGPIN proved to be the only independent predictor of a cancer diagnosis: 30.2 % with 1 or 2 cores, 40 % with 3 cores, and 75 % with >3 cores (Kronz et al. 2001). The close surveillance recommended for men with HGPIN made this group a potentially informative cohort for chemoprevention agent development.

A Phase III, randomized, placebo-controlled trial of selenomethionine in men with HGPIN was recently completed by the Southwest Oncology Group (SWOG) (Marshall et al. 2011; Marshall, Personal communication, 2008) and a Phase II, randomized, placebo-controlled study of polyphenon E in men with HGPIN or Atypical Small Acinar Proliferation (ASAP) is nearing completion (Kumar, Personal communication, 2011). In the SWOG trial, 452 men with HGPIN confirmed by central pathology review were randomized to receive selenomethionine, 200 μg/day, or a matching placebo for 3 years. An end-of-study biopsy was planned for all patients not previously diagnosed with prostate cancer during the trial. The 3-year period prevalence of prostate cancer, the primary study endpoint, was about 35 % in both arms, confirming that HGPIN is associated with a modest increase in prostate cancer risk.

3.4 Elevated PSA, Negative Biopsy Cohort

Men with an elevated PSA and a negative biopsy represent another potentially informative cohort for chemoprevention agent development, as most men in this category will undergo repeat biopsies over the course of a year or more. This cohort, therefore, provides an opportunity to assess intermediate tissue biomarker endpoints following a prolonged exposure to a drug intervention. An NCI-sponsored clinical trial of high-selenium yeast in this cohort was recently completed at the University of Arizona.

This Phase III randomized, double blind, placebo-controlled clinical trial was conducted in 875 men with PSA >4 ng/ml and/or a suspicious digital rectal examination and/or a PSA velocity >0.75 ng/ml/year, but with a negative prostate biopsy. Participants were randomized to receive a daily oral placebo versus 200 or 400 μg/day of selenium (as high-selenium yeast) for up to 5 years. With a median follow-up of 36 months no significant differences were seen in prostate cancer incidence: 11.3 % (placebo), 10.3 % (200 ug/day), and 10.0 % (400 ug/day), $p = 0.86$. In addition, the time to study endpoint was not different in the two selenium groups compared to the placebo group and the intervention had no effect on PSA velocity (Algotar et al. 2013). These findings were compatible with the data from SELECT, the largest prostate cancer prevention trial conducted to date, in which selenium was administered in the form of selenomethionine rather than as high-selenium yeast (Lippman et al. 2009; Klein et al. 2011).

4 Conclusions

The National Cancer Institute has supported a wide range of early phase prostate cancer prevention agent development trials over the past decade. Although significant work remains to be done to fully realize the potential of chemoprevention in this disease, this early phase clinical trials program has provided important insights regarding tissue bioavailability and modulation of intermediate endpoint

biomarkers. In an effort to address the most important limitation of the preprostatectomy model, i.e., the short duration of exposure to the putative chemoprevention agent, future studies will place greater emphasis on preventing disease progression in men with newly diagnosed prostate cancer being followed on active surveillance protocols. The future studies will explore the potential role of vaccines (immunotherapy) in this cohort and will seek to develop improved biomarkers of risk and benefit.

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Prognostic Value of a Cell Cycle Progression Score for Men with Prostate Cancer

Jack Cuzick

Abstract

A new prognostic score called the cell cycle progression or CCP score has been evaluated for predicting outcome in men with prostate cancer. The score is based on 31 cell cycle progression genes and 15 housekeeper control genes. Results on 5 cohorts have been reported. In all cases the CCP score was strongly predictive of outcome both in univariate models and in multvariate models incorporating standard factors such as Gleason grade, PSA levels and extent of disease. Two cohorts evaluated patients managed by active surveillance where the outcome was death from prostate cancer, two cohorts examined patients treated by radical prostatectomy where biochemical recurrence was the primary endpoint, and one smaller cohort looked at patients treated with radiotherapy where again biochemical recurrence was used as the endpoint. In all cases a unit change in CCP score was associated with an approximate doubling of risk of an event. These data provide strong event to support use of the CCP score to help guide clinical management.

Contents

J. Cuzick (✉)
Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine,
Queen Mary University of London, London, EC1M 6BQ, UK
e-mail: j.cuzick@qmul.ac.uk

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Table 1 Summary of the five prostate cancer cohorts in which the cell cycle progression (CCP) score has been evaluated

Study	Sample type	Number of patients (events)	Endpoint	Reference
TURP conservatively managed	Biopsy	337 (76)	Death from prostate cancer	Cuzick et al. (2011)
Needle biopsy conservatively managed	Biopsy	349 (90)	Death from prostate cancer	Cuzick et al. (2012)
Radical prostatectomy 1	Surgical tumor	353 (132)	Biochemical recurrence	Cuzick et al. (2011)
Radical prostatectomy 2	Surgical tumor	413 (83)	Biochemical recurrence	Cooperberg et al. (2013)
External beam XRT	Biopsy	141 (19)	Biochemical recurrence	Freedland et al. (2013)

The natural history of prostate cancer is highly variable and accurately assessing a tumor's aggressiveness based on currently available clinical and pathologic features is challenging. Useful prognostic information is contained in Gleason score, PSA level, extent of disease (including clinical stage) (Cuzick et al. 2006; Kattan et al. 1998), and a minor gain is seen with some immunohistochemical markers such as Ki-67 and PTEN (Berney et al. 2009; Cuzick et al. 2013), but much room for improvement remains. Other expression profile and methylation markers show some promise (Vasiljević et al. 2011; Erho et al. 2013; Chao et al. 2013; Wu et al. 2013; Penney et al. 2011; Markert et al. 2011; Wang et al. 2012), but are still at an early stage of development.

Novel prognostic markers are needed to more precisely guide therapeutic decisions. The cell cycle progression (CCP) score measures the expression levels of 31 CCP genes in prostate cancer tissue and offers a new approach to dealing with this problem. To date, the CCP score has been evaluated in five independent cohorts. The study characteristics are summarized in Table 1.

All studies were retrospective and analyzed formalin-fixed paraffin imbedded prostate tissue from men diagnosed with adenocarcinoma. The CCP score was calculated by measuring the average RNA expression level of 31 CCP genes normalized by the average expression of 15 housekeeping genes as quantified by RT-PCR. The specific genes involved are given in Table 2 and further details are given elsewhere (Cuzick et al. 2011). Hazard ratios (HR) are given for a one-unit change in CCP score. The median size of the interquartile range (IQR) of the CCP score in these studies was 1.1, so a one-unit change is a good measure of the population variability and the extent to which the risk of progression or death in these populations that can be accounted for by the CCP score. A histogram of the spread of CCP score for the needle biopsy cohort is shown in Fig. 1 and is representative of that seen in the other cohorts.

Table 2 CCP gene list

FOXM1	ASPM	TK1	PRC1
CDC20	BUB1B	PBK	DTL
CDKN3	RRM2	ASF1B	CEP55
CDC2	DLGAP5	C18orf24	RAD51
KIF11	BIRC5	RAD54L	CENPM
KIAA0101	KIF20A	PTTG1	CDCA8
NUSAP1	PLK1	CDCA3	ORC6L
CENPF	TOP2A	MCM10	

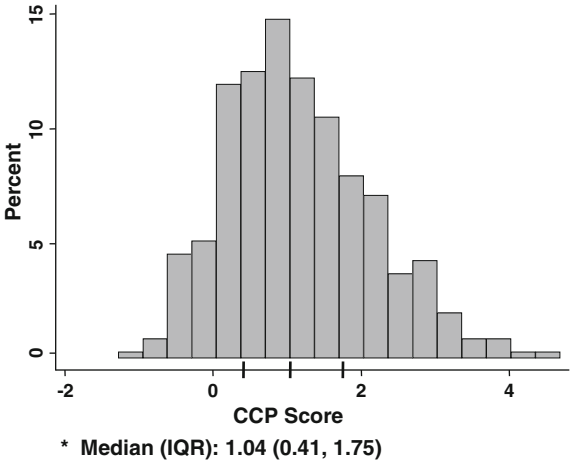

Fig. 1 Histogram for CCP scores in the needle biopsy cohort (Cuzick et al. 2012)

Two cohorts (Cuzick et al. 2011, 2012) examined conservatively managed patients with clinically localized disease—one consisted of patients diagnosed by TURP ($n = 337$), and in the other they were diagnosed by needle biopsy ($n = 349$). In both cohorts the outcome was death from prostate cancer. Both were from the United Kingdom and were cancer registry based. Cancers were diagnosed between 1990 and 1996 and median follow-up exceeded 10 years.

Two additional studies from the United States looked at patients treated by radical prostatectomy, where biochemical recurrence was the primary endpoint (Cuzick et al. 2011; Cooperberg et al. 2013). Here, the CCP score was performed on material taken from the prostatectomy specimen. Median follow-up for these studies is 9.4 and 7.1 year, respectively. A fifth cohort examined 141 men treated by external beam radiotherapy. The CCP score was assayed from the diagnostic needle biopsy and outcome was biochemical recurrence (Freedland et al. 2013). Follow-up was censored at 5 years in this study.

Table 3 Prognostic value of the CCP score in univariate and multivariate PH models for multivariate model, P-values are from the addition of specified variable in a model where the other variables are included

Study	Endpoint		CCP score		PSA	Gleason score
			Hazard ratio (95 % CI)	p-value	p-value	p-value
TURP conservatively managed (Cuzick et al. 2011)	CaP death	Univariate	2.9 (2.4, 3.6)	$<10^{-21}$	$<10^{-13}$	$<10^{-18}$
		Multivariate	2.6 (1.9, 3.4)	$<10^{-10}$	$<10^{-7}$	0.028
Needle biopsy conservatively managed (Cuzick et al. 2012)	CaP death	Univariate	2.0 (1.6, 2.5)	$<10^{-9}$	$<10^{-4}$	$<10^{-7}$
		Multivariate	1.7 (1.3, 2.1)	$<10^{-4}$	0.017	0.0022
Radical prostatectomy A (Cuzick et al. 2011)	BCR	Univariate	2.0 (1.6, 2.4)	$<10^{-8}$	$<10^{-17}$	$<10^{-9}$
		Multivariate	1.7 (1.4, 2.2)	$<10^{-5}$	$<10^{-8}$	0.015
Rad prostatectomy B (Cooperberg et al. 2013)	BCR	Univariate	2.1 (1.6, 2.9)	$<10^{-5}$	0.0035	$<10^{-5}$
		Multivariate	2.0 (1.4, 2.8)	$<10^{-4}$	0.12	0.17
External beam XRT (Freedland et al. 2013)	BCR	Univariate	2.6 (1.4, 4.6)	0.0017	$<10^{-3}$	0.051
		Multivariate	2.1 (1.0, 4.2)	0.035	0.054	0.20

The main results are summarized both for univariate and multivariate proportional hazard models in Table 3. In all cases except for one radical prostatectomy cohort the CCP score was the strongest predictor of failure, and in all cases significant prognostic information was obtained from the CCP score.

In univariate analyses (Table 3) the risk of an event was increased more than two-fold for every unit increase in CCP score (range 2.0–2.9). Kaplan–Meier survival curves for different CCP values in the cohorts are shown in Fig. 2a–e. In all cases there is a clear gradient of increased risk for each unit change in CCP score, across a wide spectrum of values. A unit change in score is equivalent to a doubling in normalized expression level. Multivariate models, adjusted for Gleason score, PSA level, and other clinical variables gave only slightly attenuated HR for the CCP score, ranging from 1.7 to 2.6 (Table 3). This was due to the weak positive correlation between the CCP score and other variables such as Gleason grade and PSA level. This is given in Table 4, where correlations were typically in the 0.10–0.40 range; the one exception being the TURP cohort where the correlation with Gleason score was 0.57.

The added value of CCP score to Gleason score and PSA level is shown in Fig. 3 for the conservatively managed needle biopsy cohort. Here, the prognostic value of Gleason score and PSA was determined by a model developed in the same cohort. Similar discrimination is seen when the CAPRA score (Cooperberg et al. 2011)

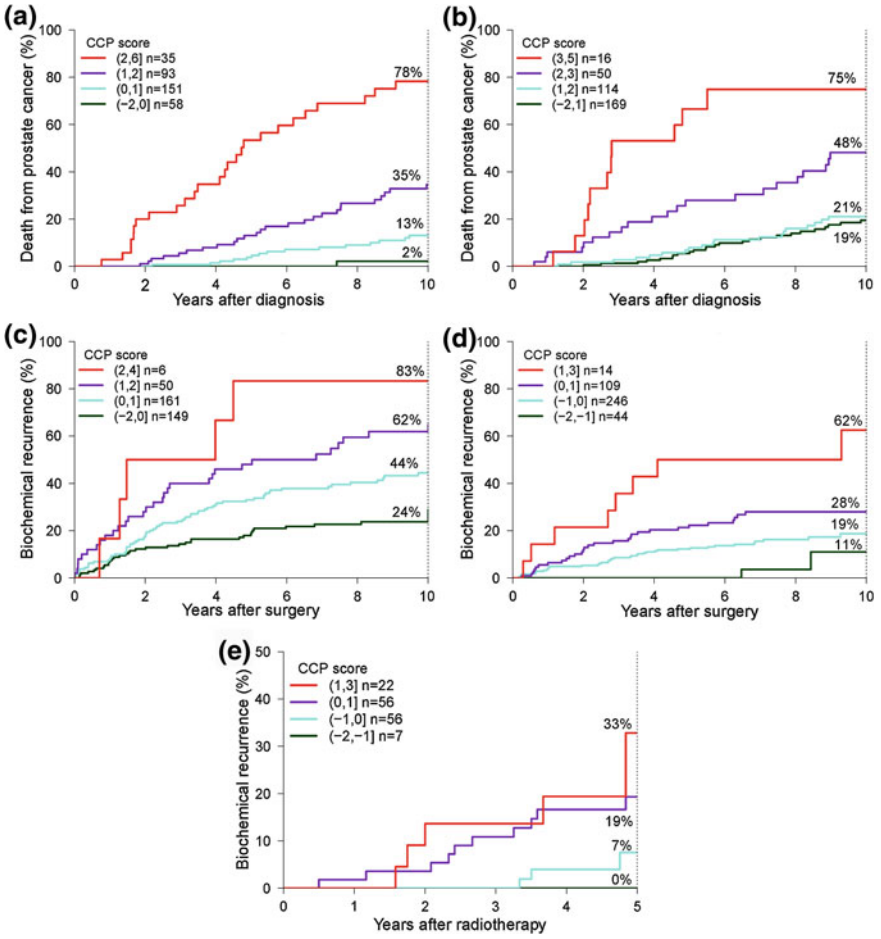

Fig. 2 Time to event curves for 5 cohorts examining the CCP score: **a** Conservatively managed TURP cohort, **b** conservatively managed needle biopsy cohort, **c** radical prostatectomy cohort A, **d** radical prostatectomy cohort B, and **e** radiotherapy cohort

is used to estimate the contribution from clinical variables, but this was available from only 60 % of the needle biopsy cohort.

The CCP score appears to give good added discrimination across all Gleason grades and PSA levels. In particular, this was seen for patients with low-risk cancers as judged by Gleason score 6, PSA <10 ng/ml, or low CAPRA score.

Table 4 Pearson correlation coefficient between the CCP score and Gleason score or PSA in the five cohorts

Study	CCP score versus Gleason score	CCP score versus PSA
TURP conservatively managed (Cuzick et al. 2011)	0.57	0.27
Needle biopsy conservatively managed (Cuzick et al. 2012)	0.37	0.14
Radical prostatectomy A (Cuzick et al. 2011)	0.22	0.21
Radical prostatectomy B (Cooperberg et al. 2013)	0.18	0.11
External beam XRT (Freedland et al. 2013)	0.23	0.31

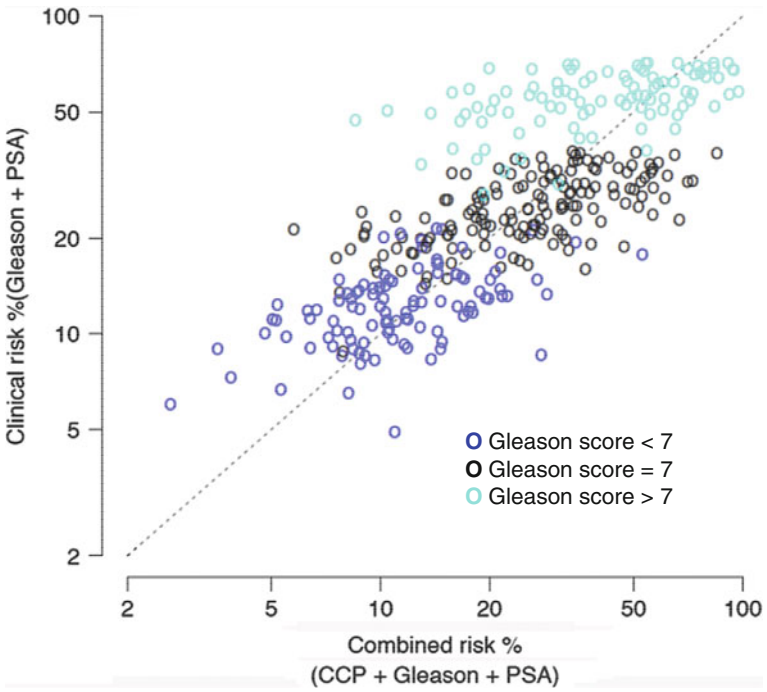

Fig. 3 Ten year predicted risk of death from prostate cancer in the needle biopsy cohort (cuzick et al. 2012) for combined CCPscore with Gleason and PSA (*horizontal axis*) vs Gleason and PSA alone (*vertical axis*). Each circle represents a person is the study and the colour of the circle indicates predicted risk using Gleason only

1 Conclusions

In conclusion, the CCP score predicts prostate cancer outcome in multiple patient cohorts and in diverse clinical settings. The CCP score provides independent information beyond that available from clinicopathologic variables such as Gleason score, PSA level, and extent of disease, and helps to further differentiate aggressive prostate cancer from indolent cancer.

There are several potential roles for this test which remain to be fully elucidated. The most obvious and potentially largest role is to help with the decision as to whether apparently low-risk patients can be safely managed by active surveillance, or whether radical prostatectomy or radiotherapy is needed. This is an important question especially in places where PSA testing is common. In the USA, for example, incidence is about eight times higher than mortality, and many patients are overtreated. Identifying a larger and more accurately assessed cohort which could be safely watched after diagnosis is an important goal. In such patients, the role of the CCP score in repeat biopsies is also an important question and studies in this area are needed to see if the CCP score can more rapidly anticipate the need for radical surgery before metastases have occurred. Other roles include determining the need for adjuvant hormonal treatment or chemotherapy in men who have been treated by radical prostatectomy or radiation.

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Distinguishing Indolent from Aggressive Prostate Cancer

Zoran Culig

Abstract

Prostate cancer natural course is variable and it is difficult to determine prognosis on the basis of limited clinical information. In order to distinguish between aggressive and indolent tumors, genomic analysis, proteomic studies, and biomarker measurement were applied. Identification of single nucleotide polymorphisms may help to assess prostate cancer risk, however, it is questionable whether single nucleotide polymorphisms may predict a good or bad prognosis. Results of genomic and proteomic analyses between different laboratories may be difficult to compare because of non-standardized procedures which may be responsible for variant results. One of the early changes in prostate tumor tissues which may indicate a bad prognosis is high phosphorylation of Akt. A biomarker which is specific for prostate cancer is the TMPRSS2-ERG fusion which occurs in about 50% of tumors. Experimental studies indicate that this gene fusion may promote malignant phenotype. Biomarkers which could distinguish between latent and aggressive tumors may be detected in prostate tissue, serum, and urine. In summary, there is a limited progress in the field of prognostic biomarkers because of prostate cancer heterogeneity and missing unification of diagnostic procedures.

Z. Culig (✉)
Experimental Urology, Department of Urology, Innsbruck Medical University, Anichstrasse 35, A-6020, Innsbruck, Austria
e-mail: zoran.culig@i-med.ac.at

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Contents

1 Introduction

An increase in incidence of prostate cancer in Western countries could be explained by improved diagnostic procedures, in particular by implementation of prostate-specific antigen screening in the male population. There is a large number of prostate tumors detected in an early stage which may be very small histologically. Some of these tumors are represented by a low-Gleason grade. In the urological community, there is an intensive debate about modalities for treatment of these cancers. Many very small prostate cancer do not cause clinical symptoms and may be subjected to active surveillance. The policies on prostate cancer management are different in various regions and depend in part on financial resources of social security systems. Obviously, one of the most important issues in prostate cancer research is how to distinguish between indolent and potentially life-threatening prostate cancers. If researchers would be able to predict with confidence which prostate cancers are indolent, this may cause considerable savings for public health systems. This is particularly important for "intermediate" Gleason scores for which it is very difficult to establish the prognosis solely on the basis of histopathological findings. However, there is a legitimate question whether very small prostate cancers could cause dramatic changes in the composition of body fluids which would be indicative of an aggressive character of the disease.

With the advent of novel technologies and improvement of genomic and proteomic approaches there is an increasing expectation in identification of novel markers that may distinguish between indolent and aggressive tumors. This article will therefore focus on common approaches proposed to distinguish between indolent and aggressive prostate cancers: genomic analyses, proteomic studies, and biomarker measurement.

2 Prostate Cancer Family History and Aggressiveness

Prostate cancer family history is a well-established risk factor for the disease. Genome-wide association studies (GWAS) allowed identification of single nucleotide polymorphisms SNPs which are associated with prostate cancer risk (Amundadottir et al. 2006; Gudmundsson et al. 2007). However, it is questionable whether SNPs may predict a good or bad prognosis of prostate cancer. Xu et al.

(2010) have investigated the association between the disease severity and SNPs in three independent populations from the United States and Sweden. They found that there was a higher frequency of the TT genotype of SNP rs4054823 at 17p12 in patients with more aggressive disease. The authors studied 4,829 and 12,205 patients with more and less aggressive prostate cancer, respectively, and evaluated ca. 27,000 SNPs. The frequency of this genotype has increased with a higher Gleason grade. There have been also limitations of the study of Xu and associates, in particular the follow-up information about tumor progression and the TT genotype was not available. There is a consensus among researchers that difficulties in interpretation of GWAS occur because of relatively small sample sizes, heterogeneous definition of aggressive disease across multiple study populations, and reliance on clinical grading and staging. Genetic variants at chromosomes 3p12, 6q25, 7q21, 10q11, 11q13, 19q13, and Xp11 were evaluated as a part of the PRACTICAL study (Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome) (Kote-Jarai et al. 2008). That study included 7,370 prostate cancer cases and 5,742 controls and no association with tumor grade was reported. The question whether risk variants in the KLK3 gene coding for prostate-specific antigen and in the microseminoprotein gene are universal remain to be answered in the future (Kader et al. 2009). In addition, the possibility to change the design of GWAS in the future may be discussed. Future studies may also examine an impact of combination of risk variants for identification of aggressive cancers.

3 Potential and Limitation of Genomic and Proteomic Analyses in Prediction of Tumor Aggressiveness

With advent of novel technologies, scientists hoped that it will be possible to establish molecular subclassification of prostate cancers and identify more aggressive ones. However, there have been difficulties in comparing data from multiple laboratories obtained for various reasons. It is important to standardize the procedures from the time of obtaining tissue at surgery, including transportation and storage to the analyses. Differences in experimental protocols are likely reasons for difficulties in evaluation and interpretation of data. Nanni et al. have analyzed the expression of 22,500 transcripts in cultures from normal and hyperplastic tissues (2006). They showed that Akt1 is highly expressed in cultures derived from prostate cancer, consistent with most findings obtained with clinical prostate cancer samples (Kreisberg et al. 2004). Hyperactivation of the Akt pathway is one of the early changes in prostate cancer which explains reduced sensitivity to pro-apoptotic agents. According to that study, the downregulation of phosphorylated histone H2AX involved in DNA repair was discriminating for the prognosis of patients. Those patients were found to have a bad prognosis thus indicating that perturbations in DNA repair contribute to prostate carcinogenesis. In cultures from patients with bad prognosis, expression of genes involved in the

activation of cellular response to hypoxia, such as HIF1alpha, HIF2alpha, and HIF1beta was upregulated. This upregulation may be associated with reduced sensitivity to prostate cancer therapies. Importantly, androgen receptor (AR) is expressed in the majority of prostate cancers and its expression may be upregulated during tumor progression (Culig and Bartsch 2006). However, AR is implicated in multiple cellular processes including proliferation, apoptosis, angiogenesis, migration, and differentiation. Thus, targeting the AR in advanced prostate cancer is therapeutically justified. However, the drug effect may be associated with AR-mediated dedifferentiation. For this reason, it is difficult to estimate prostate cancer prognosis on the basis of AR expression. Androgen ablation therapy for non-organ-confined prostate cancer is a treatment which leads to tumor regression; however, this response is only palliative. Interruption in the use of an anti-androgen (hydroxyflutamide, bicalutamide)may lead to a temporary improvement in clinical symptoms, most probably because anti-androgens in these cases cause mutations of the AR which are responsible for acquisition of agonistic properties of the drugs (Hara et al. 2003). Recent improvements in the survival of patients with prostate cancer have been achieved by use of abiraterone acetate and enzalutamide. AR coactivators are implicated in regulation of specific cellular functions in prostate cancer and may be upregulated in localized or metastatic disease. Expression of some of the co-regulatory proteins may increase with a higher Gleason grade (Agoulnik et al. 2005). Thus, identification of overexpressed coactivators in association with other tumor-related proteins may be helpful in improved molecular classification of prostate cancer. It is assumed that novel therapies which interfere with androgen signaling will also consider down-regulation of coactivators overexpressed in tumor tissue. The appearance of AR variants may be also important in prostate cancer and should be investigated in the context of determination of aggressiveness of a tumor. These truncated receptors are constitutively active and have a distinct transcription program compared to the wild-type receptor. Another biomarker which is specific for prostate cancer is the TMPRSS2-ERG gene fusion which occurs in about 50 % of prostate cancers. Although it was demonstrated that the cell lines which overexpress the fusion migrate faster, there are open questions regarding clinical significance of the fusion. Publications according to which the fusion is a good or bad prognostic factor, respectively, are available in the literature (Demichelis and Rubin 2007; Saramaki et al. 2008).

Proteomic analyses may be potentially useful of identification of aggressive prostate cancers. The application of laser capture microdissection (LCM) and surface-enhanced laser desorption/ionization time could confirm prostate cancer diagnosis (Zheng Y et al. 2003). Another proteomic study revealed that GDF15 protein may be an early marker in prostate carcinogenesis (Cheung et al. 2004). There is a consensus that proteomic analyses may be useful in the diagnosis of prostate cancer, however, they do not allow the researchers and clinicians do distinguish between indolent and aggressive prostate cancer. It is useful to confirm the proteomic findings by immunohistochemistry, especially in biomarker studies. In future studies, in order to determine the aggressive potential of prostate cancer,

it may be reasonable to investigate the expression of multiple markers to better reflect the heterogeneity of the disease. It is unlikely that a single marker will be useful in the determination of malignant potential of a large group of tumors with Gleason score of 6 or 7. It is also important to determine the purity of prostate tissue samples investigated since sample contamination with stromal elements may affect interpretation of data. These procedures are improved by LCM in the laboratory practice. The discovery and validation of biomarkers could be performed in tumor tissue and biological fluids (reviewed by Pin et al. 2013). Determination of tumor characteristics on the basis of proteomic analysis may be of advantage if biopsy material is used. These analyses may yield comprehensive information about the tumor protein profile and help in stratification of patients who will respond or not respond to therapy. However, the procedure is invasive, the quantity of the sample limited, and the success of the analysis is dependent on freezing of the sample not later than 30 min after surgical intervention. An analysis in serum and plasma is in contrast minimally invasive and cheap. It could be used for an early diagnosis and prognosis. However, the concentration of a biomarker of interest may be low and there may be considerable intra- and inter-patient variability. Similarly, the determination of a biomarker in urine is a non-invasive procedure which does not cause excessive costs but the interpretation is limited due to a low biomarker concentration. Biomarkers for identification of aggressive prostate cancer may be determined also in prostate fluid and seminal plasma. Determination of markers of aggressiveness in biological fluids may be accurate because they are released into the circulation from the tumor cells. Again, the procedure is not invasive but the problems may occur because of low biomarker concentration and variability.

In addition to oncogenes and tumor suppressors whose expression is investigated in prostate cancer for diagnostic or prognostic purposes, current research is focused on miRNA which regulates many processes in prostate oncogenesis. Some of the miRNAs are regulated by androgens and AR activation; however, the effects of miRNA on AR have also been described. Future studies are needed to examine whether changes in miRNA expression which lead to identification of aggressive prostate cancer occur in independent patients' collectives. For example, the microRNA -23b/-27b cluster suppresses the metastatic phenotype and may be investigated as a potential marker for a less aggressive prostate cancer (Ishteiwy et al. 2012).

One of the consequences of improved classification of subtypes of prostate cancer and identification of aggressive subtypes could be a more personalized approach to therapy. For example, chemotherapy selection, which should be improved in prostate cancer, could be applied to patients whose biomarker profile indicates disease aggressiveness or response to a specific treatment. By doing so, other individuals at low risk need not be subjected to a treatment which does not have many side effects. The studies in this field are particularly difficult because of intra-patient variability.

Future studies with aim to identify markers of the aggressive prostate malignant disease should take into account the presence of tumor-initiating cells in cancer tissue. These cells are AR-negative and do not respond to endocrine therapies or to chemotherapy (Puhr et al. 2012). It is assumed that they are responsible for tumor recurrence. Because of their low presence in tumor tissue, quantitative analyses of tumor-initiating markers are technically challenging.

4 Directions for Future Research

In summary, although multiple methodological approaches have been developed to distinguish between indolent and aggressive tumors of the prostate, there is a very limited progress in the field. The main reason for problems with reproducibility of the data is tumor heterogeneity which is reflected in different profiles between primary and metastatic lesions of the same patient. Several markers proposed in explorative studies may be also implicated in regulation of inflammatory processes in the prostate. Disease classification studies should consider an appropriate sample size and statistical evaluation. Any influence of age of study population and specific demographics should be taken into account. Establishment of standard laboratory operating procedures which will be followed should improve evaluation of data from different centers. It is particularly important to consider sample collection and storage as well as protein extraction methodologies. Use of archival samples may be problematic because of possible protein degradation. At this stage, it is not possible to provide guidelines for practicing urologists how to identify life-threatening prostate cancer. The diagnostic procedures therefore cannot avoid classic pathology procedures in prostate cancer classification. Similarly, the use of prostate-specific antigen in laboratory medicine is useful in diagnosis and treatment monitoring but is of a lesser help in identification of the aggressive disease.

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Management of Low Risk and Low PSA Prostate Cancer: Long Term Results from the Prostate Cancer Intervention Versus Observation Trial

Timothy J. Wilt

Abstract

Management of localized prostate cancer is controversial due in part to the lack of randomized controlled trial information in men diagnosed with prostate specific antigen (PSA) testing. Men with low risk or low PSA ($\leq$10 ng/ml) prostate cancer comprise up to 70 % of men currently diagnosed. Evidence suggests an excellent long-term prognosis with observation though nearly 90 % are treated with surgery (radical prostatectomy), external beam radiation, or brachytherapy. Results from the Prostate cancer Intervention Versus Observation Trial (PIVOT) provide high quality Level 1 evidence that observation compared to surgery results in similar long-term overall and prostate cancer survival, prevention of bone metastases and avoidance of surgery related harms. Combined with emerging evidence from screening, natural history, decision analysis and cost-effectiveness modeling studies, these data demonstrate that observation is the preferred treatment option for men with low risk and possibly low PSA prostate cancer. Recommending against PSA testing or, in men who still desire testing, raising thresholds of PSA values used to define abnormal, lengthening intervals between PSA tests and discontinuing testing in men with a life expectancy less than 15 years will reduce diagnostic and treatment related harms without adversely impacting overall or disease specific mortality and morbidity.

T. J. Wilt (✉)
Minneapolis VA Center for Chronic Diseases Outcomes Research,
1 Veterans Drive (111-0), Minneapolis, MN 55417, USA
e-mail: tim.wilt@va.gov

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Contents

1 Introduction

Treatment of early prostate cancer remains controversial, especially for tumors detected with prostate specific antigen (PSA) testing (Cooperberg et al. 2010). While the lifetime risk of being diagnosed with prostate cancer is about 17 %, the risk of dying from the disease is approximately 3 %, suggesting that conservative management may be appropriate for many men (2012, http://consensus.nih.gov/2011/docs/prostate/ASPC%20Final%20Draft%20Statement.pdf 2011). During the PSA era, observational studies have documented high 10 year cancer survival among men treated conservatively especially for men with low risk disease (Lu-Yao et al. 2009; Hayes et al. 2013; Daskivich et al. 2013; Ganz et al. 2012). Despite excellent long-term disease-specific survival with observation, more than 90 % of men with low risk disease are treated with surgery (radical prostatectomy), external beam radiation or brachytherapy. Observation is rarely used, in part due to lack of randomized trial evidence comparing observation to attempted curative treatment in men with prostate cancer detected since PSA testing became common practice (Graham et al. 2008).

"Active surveillance" is another conservative management treatment option whereby patients are monitored with periodic PSA tests and prostate biopsies. Monitoring protocols differ but delayed surgical or radiation treatment is typically recommended if these tests reveal evidence of disease progression that places a patient in a higher tumor risk category. Approximately 30 % of men may be ultimately treated with a prostate cancer specific survival exceeding 95 % (Klotz et al. 2010). No randomized trials of active surveillance have been completed. The decision to intervene with surgery or radiation is influenced by patient and provider preferences or the findings on the intermediate measures of tumor size, histology and PSA values rather than patient signs or symptoms or evidence of clinical necessity or benefit. Nonetheless, this option has become a common form of treatment for men with low risk disease not undergoing immediate "definitive

therapy" and was recommended in a U.S. State of the Science conference (Ganz et al. 2012).

Two randomized trials compared radical prostatectomy (RP) to observation, but were conducted before widespread PSA testing (Iversen et al. 1995; Bill-Axelson et al. 2011). One failed to find a difference in overall mortality after more than 20 years (Iversen et al. 1995). Another demonstrated absolute differences in all-cause and prostate cancer mortality at 15 years of 6.6 % and 6.1 %, respectively, favoring surgery (Widmark 2011). A randomized trial comparing external beam radiotherapy to observation, also among men diagnosed before PSA testing, reported no mortality differences through at least 16 years (Widmark 2011).

The Prostate cancer Intervention Versus Observation Trial (PIVOT) is a multicenter randomized controlled trial conducted at over 50 medical centers in the United States. Main results have previously been reported (Klotz et al. 2010). This paper focuses on findings from the subgroup of enrolled men with low PSA and low risk disease.

2 Study Design

We previously reported PIVOT design and participant baseline characteristics (Klotz et al. 2010). Enrollment began in November 1994 and ended in January 2002 with follow-up through January 2010. Patients were medically fit for RP and had biopsy proven clinically localized prostate cancer (T1–T2, Nx, M0) of any grade diagnosed within the past 12 months, PSA value <50 nanograms (ng) per milliliter (mL), age ≤75 years, bone scan negative for metastatic disease and a life expectancy of at least 10 years. Sites assessed eligibility based on local PSA values and biopsy readings. Following randomization, a central pathologist reviewed biopsy and radical prostatectomy specimens and a central laboratory measured PSA.

3 Treatment Protocol

Radical prostatectomy technique was at the surgeon's discretion. Additional interventions were determined by the participant and his physician. Men randomized to observation were offered palliative treatment or chemotherapies for symptomatic or metastatic progression.

4 Follow-Up and Definition of Clinical Outcomes

We scheduled study visits every 6 months for a minimum of 8 years, maximum of 15 years or patient death. We obtained bone scans at year 5, 10, 15, end-of-study and clinician discretion. The primary outcome was all-cause mortality. Our

secondary outcome was prostate-cancer mortality defined by a three member endpoints committee blinded to treatment assignment as "definitely or probably due to prostate cancer or definitely or probably due to prostate cancer treatment". Bone metastases were defined as a bone scan or skeletal radiograph positive for metastases. We assessed 30 day perioperative harms and 2 year prevalence of urinary incontinence, erectile and bowel dysfunction self-reported by men as at least moderate in severity.

5 Results

5.1 Participant Characteristics

Among 13,022 men with prostate cancer, 5023 were considered eligible. 731 men (14.6 %) agreed to participate and were randomized to radical prostatectomy ($n = 364$) or observation ($n = 367$). The mean age was 67 years. Nearly one-third were black; 85 % reported full activities of daily living. The median PSA was 7.8 ng/mL (mean = 10.1). One-half had stage T1c disease (not palpable, PSA detected). Specific to the focus of this paper [low PSA, low D'Amico tumor risk category (D'Amico et al. 1998) and Gleason scores of 6 or less (Gleason 1977)]: 479 men (65.5 %) had PSA ≤10, 296 (40.4 %) had low risk disease and 515 (70.4 %) had Gleason biopsy scores of 6 or less. Based on central pathology review, 52 % had Gleason 6 or lower histological scores and 34 % had low risk categories.

5.2 All-Cause Mortality

Among all men randomized in PIVOT RP did not reduce all-cause mortality compared to observation (hazard ratio, 0.88; 95 % confidence interval [CI], 0.71–1.08; $P = 0.22$; absolute risk reduction, 2.9 % points). The effect did not differ according to age, Gleason score, race, self-reported performance status or Charlson comorbidity categories. We identified a significant interaction between treatment group and baseline PSA (P for interaction = 0.04) and a borderline interaction ($P = 0.07$) for tumor risk categories (Fig. 1, Table 1).

Compared to observation, surgery did not reduce all-cause mortality in men with PSA ≤ 10 ng/mL (median PSA = 6.0) (HR = 1.03; 95 % CI, 0.79–1.35). Radical prostatectomy did not reduce all-cause mortality compared to observation at 4, 8, or 12 years. Risk differences were always less than 3 % and became smaller over time and favored observation from 12 years onward. At study close-out absolute risk differences favored, but not significantly, observation (ARD = −2.7 (95 % CI, −11.5–6.2).

Among men with low risk cancers (PSA ≤ 10 ng/m; Gleason score ≤6;Stage T1a-c or T2a), there was a 15 % increase in death among men randomized to RP versus observation that was not statistically significant; HR = 1.15 (95 % CI,

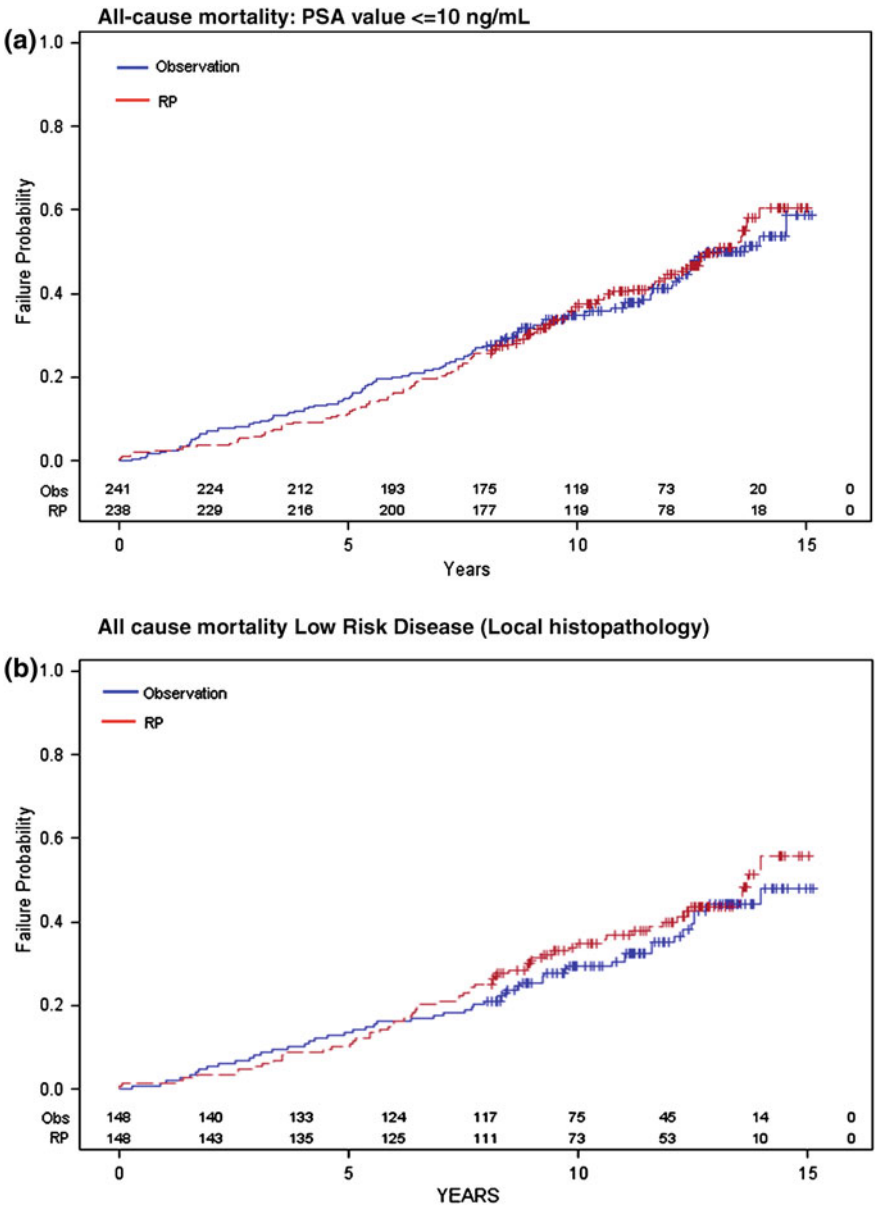

Fig. 1 **a**, **b**: Cumulative incidence of all-cause mortality in the two study groups according to tumor subgroups: *Panel A*: PSA <= 10 (HR = 1.03; 95 % CI, 0.79–1.35); *Panel B*: Low D'Amico Tumor Risk Category; (HR = 1.15; 95 % CI, 0.80–1.66)

Table 1 All-cause mortality: cumulative incidence: overall and low PSA/Low risk tumor subgroup findings

All-cause mortality	Cumulative incidence				Absolute risk reduction % (95 % CI)	Relative risk (95 % CI)	p-value
	Radical prostatectomy		Observation				
	No.	% (95 % CI)	No.	% (95 % CI)			
Overall	171	47.0 (41.9–52.1)	183	49.9 (44.8–55.0)	2.9 (−4.3–10.1)	0.94 (0.81–1.09)	0.22
All ages, 4 year		9.6 (7.0–13.1)		14.2 (11.0–18.1)	4.6 (−0.2–9.3)	0.68 (0.45–1.02)	
All ages, 8 year		26.7 (22.4−31.4)		29.7 (25.3−34.6)	3.1 (-3.5−9.5)	0.90 (0.71−1.13)	
All ages, 12 year		40.9 (36.0−46.1)		43.9 (38.9–49.0)	2.9 (−4.2–10.0)	0.93 (0.79–1.11)	
Tumor characteristic derived subgroups							
PSA ≤ 10	110	46.2 (40.0–52.6)	105	43.6 (37.5–49.9)	−2.7 (−11.5–6.2)	1.06 (0.87–1.29)	0.82
PSA ≤ 10, 4 year		9.4 (6.2−13.6)		12.0 (8.5–16.8)	2.8 (−2.8–8.4)	0.77 (0.45–1.30)	
PSA ≤ 10, 8 year		25.6 (20.5−31.5)		27.4 (22.1–33.3)	1.8 (−6.1–9.6)	0.94 (0.69–1.26)	
PSA ≤ 10, 12 year		40.8 (34.7−47.1)		38.2 (32.3–44.5)	−2.6 (−11.3–6.1)	1.07 (0.86–1.33)	
Risk—Low (Local)	62	41.9 (34.3−50.0)	54	36.5 (29.2–44.5)	−5.4 (−16.3–5.7)	1.15 (0.86–1.53)	0.45
Risk—Low, 4 year		8.8 (5.2−14.4)		10.1 (6.2–16.1)	1.4 (−5.5–8.3)	0.87 (0.43–1.76)	
Risk—Low, 8 year		25.0 (18.7−32.6)		21.0 (15.2–28.2)	−4.1 (−13.6–5.5)	1.19 (0.78–1.82)	
Risk—Low, 12 year		37.2 (29.8−45.2)		31.8 (24.8–39.6)	−5.4 (−16.0–5.4)	1.17 (0.85–1.60)	
Risk—Low (Central)	45	40.5 (31.9−49.8)	47	38.5 (30.4–47.4)	−2.0 (−14.4–10.4)	1.05 (0.77–1.45)	0.72
Risk—Low, 4 year		8.1 (4.3−14.7)		9.8 (5.7–16.4)	1.7 (−6.0–9.3)	0.82 (0.36–1.88)	
Risk—Low, 8 year		26.1 (18.9−35.0)		23.0 (16.4–31.2)	−3.2 (−14.2–7.8)	1.14 (0.73–1.79)	
Risk—Low, 12 year		35.1 (26.9−44.4)		32.8 (25.1–41.5)	−2.4 (−14.4–9.7)	1.07 (0.75–1.53)	
Gleason (Local) <7	113	44.5 (38.5−50.6)	125	47.9 (41.9–53.9)	3.4 (−5.2–11.9)	0.93 (0.77–1.12)	0.26

(continued)

Table 1 (continued)

All-cause mortality	Cumulative incidence				Absolute risk reduction % (95 % CI)	Relative risk (95 % CI)	p-value
	Radical prostatectomy		Observation				
	No.	% (95 % CI)	No.	% (95 % CI)			
Gleason <7, 4 year		8.7 (5.8−12.8)		13.8 (10.1–18.5)	5.1 (−0.4–10.7)	0.63 (0.38–1.04)	
Gleason < 7, 8 year		25.2 (20.3−30.9)		28.4 (23.2–34.1)	3.2 (−4.5–10.7)	0.89 (0.67–1.18)	
Gleason < 7, 12 year		38.6 (32.8−44.7)		42.2 (36.3–48.2)	3.6 (−4.9–11.9)	0.92 (0.74–1.13)	
Gleason < 7, 4 year		7.7 (4.6−12.8)		12.2 (8.4–17.6)	4.5 (−1.9–10.7)	0.63 (0.33–1.20)	
Gleason < 7, 8 year		27.4 (21.2−34.6)		25.0 (19.5−31.5)	−2.4 (−11.5–6.6)	1.10 (0.78–1.55)	
Gleason < 7, 12 year		35.7 (28.9−43.2)		37.8 (31.3−44.7)	2.0 (−7.9–11.8)	0.95 (0.72–1.24)	

0.80–1.66). The absolute difference at 12 years was 5.4 % favoring observation (37.2 % vs. 31.8 %). Sensitivity analyses using central biopsy readings found no significant differences in all-cause mortality between RP and observation according to Gleason or tumor risk categories ($P > 0.13$ for all categories).We found no significant effect of RP on all-cause mortality in men with Gleason scores of 6 or less. Death from any cause occurred in 47.9 % of men randomized to observation and 44.5 % of men randomized to surgery (ARD = 3.4 (95 % CI, −5.2–11.9). Results were similar when using central histopathology readings.

We also addressed all-cause mortality in men frequently diagnosed by current PSA screening, i.e. men with T1c (non-palpable) disease ($n = 368$). Radical prostatectomy did not reduce all-cause mortality compared to observation (HR = 1.01; 95 % CI, 0.74–1.39; $P = 0.93$). RP also did not reduce all-cause mortality compared to observation in the subgroup of men with T1c tumors and a PSA value of ≤10 (HR = 1.05; 95 % CI, 0.71–1.55; $P = 0.82$; all-cause mortality = 40.2 RP vs. 39.8 % observation).

5.3 Prostate-Cancer Mortality

Among all randomized men compared to radical prostatectomy did not reduce prostate cancer mortality compared to observation (hazard ratio, 0.63; 95 % CI, 0.36–1.09; $P = 0.09$); absolute risk reduction, 2.6 % points). The effect of RP on prostate cancer mortality did not differ according to age, race, Charlson comorbidity or health status categories. We found borderline evidence for treatment interaction for subgroups defined by PSA and tumor risk categories (P for interaction = 0.11 for both groups) (Table 2, Fig. 2).

Prostate cancer mortality was not reduced by surgery compared to observation among men with PSA ≤10 ng/mL ($P = 0.82$). Absolute risk differences remained less than 1 % through study conclusion. The cumulative prostate cancer mortality incidence at study close-out was 6.2 % (95 % CI, 3.8–10.0 %) in men randomized to observation versus 5.9 % (95 % CI, 3.5–9.6 %) in men randomized to surgery (ARD = 0.3 (95 % CI, 4.1–4.8 %)).

In men with low risk disease death due to prostate cancer was rare occurring in less than 3 % in men randomized to observation. Radical prostatectomy did not reduce prostate cancer mortality at 4, 8 or 12 years or at study close out. Risk differences were small throughout the study and remained stable over time. The cumulative incidence of prostate cancer mortality at study close out was 2.7 % in men randomized to observation versus 4.1 % in men randomized to surgery. ($P = 0.54$; RR = 1.50 (95 % CI, 0.43–5.21; ARD = −1.4 (95 % CI, −6.2–3.2)). Results were similar when substituting central for local PSA measures and histopathology. In men with Gleason scores of 6 or less surgery also did not reduce prostate cancer specific mortality. The absolute difference was 1.4 % (95 % CI, −2.5–5.4 %), not statistically significant and similar when using central

Table 2 Prostate cancer mortality-cumulative incidence

CAP-specific mortality	Cumulative incidence				Absolute risk reduction % (95 % CI)	Relative risk (95 % CI)	p-value
	Radical prostatectomy		Observation				
	No.	% (95 % CI)	No.	% (95 % CI)			
Overall	21	5.8 (3.8–8.7)	31	8.5 (6.0–11.7)	2.7 (−1.1–6.5)	0.68 (0.40–1.17)	0.09
All ages, 4 year		1.7 (0.8–3.6)		1.6 (0.8–3.5)	0 (−2.1–2.1)	1.0 (0.33–3.10)	
All ages, 8 year		3.0 (1.7–5.3)		4.9 (3.1–7.6)	1.9 (−1.0–4.9)	0.62 (0.30–1.29)	
All ages, 12 year		4.4 (2.7–7.0)		7.4 (5.1–10.5)	3.0 (−0.5–6.5)	0.60 (0.33–1.09)	
Tumor characteristic derived subgroups							
PSA $\leq$ 10	14	5.9 (3.5–9.6)	15	6.2 (3.8–10.0)	0.3 (−4.1–4.8)	0.95 (0.47–1.91)	0.82
PSA $\leq$ 10, 4 year		2.1 (0.9–4.8)		2.1 (0.9–4.8)	−0.0 (−3.0–2.9)	1.01 (0.30–3.45)	
PSA $\leq$ 10, 8 year		3.4 (1.7–6.5)		3.7 (2.0–6.9)	0.4 (−3.2–4.0)	0.90 (0.35–2.29)	
PSA $\leq$ 10, 12 year		4.6 (2.6–8.1)		5.4 (3.2–9.0)	0.8 (−3.3–4.9)	0.86 (0.39–1.87)	
Risk—Low (Local)	6	4.1 (1.9–8.6)	4	2.7 (1.1–6.7)	−1.4 (−6.2–3.2)	1.50 (0.43–5.21)	0.54
Risk—Low, 4 year		0.7 (0.1–3.7)		1.4 (0.4–4.8)	0.7 (−2.5–4.2)	0.50 (0.05–5.45)	
Risk—Low, 8 year		1.4 (0.4–4.8)		2.0 (0.7–5.8)	0.7 (−3.0–4.6)	0.67 (0.11–3.93)	
Risk—Low, 12 year		2.7 (1.1–6.7)		2.7 (1.1–6.7)	0.0 (−4.4–4.4)	1.00 (0.25–3.92)	
Risk—Low (Central)	1	0.9 (0.2–4.9)	5	4.1 (1.8–9.2)	3.2 (−1.5–8.4)	0.22 (0.03–1.85)	0.13
Risk—Low, 4 year		0.0 (0.0–3.4)		1.6 (0.5–5.8)	1.6 (−1.9–5.8)	–	
Risk—Low, 8 year		0.9 (0.2–4.9)		3.3 (1.3–8.1)	2.4 (−2.1–7.3)	0.27 (0.03–2.42)	
Risk—Low, 12 year		0.9 (0.2–4.9)		4.1 (1.8–9.2)	3.2 (−1.5–8.4)	0.22 (0.03–1.85)	
Gleason (Local) < 7	11	4.3 (2.4–7.6)	15	5.8 (3.5–9.3)	1.4 (−2.5–5.4)	0.75 (0.35–1.61)	0.34

(continued)

Table 2 (continued)

CAP-specific mortality	Cumulative incidence				Absolute risk reduction % (95 % CI)	Relative risk (95 % CI)	p-value
	Radical prostatectomy		Observation				
	No.	% (95 % CI)	No.	% (95 % CI)			
Gleason < 7, 4 year		0.8 (0.2–2.8)		1.5 (0.6–3.9)	0.8 (−1.5–3.2)	0.51 (0.09–2.78)	
Gleason < 7, 8 year		1.6 (0.6–4.0)		3.5 (1.8–6.4)	1.9 (−1.0–5.0)	0.46 (0.14–1.46)	
Gleason < 7, 12 year		2.8 (1.3–5.6)		5.0 (2.9–8.3)	2.2 (−1.3–5.9)	0.55 (0.22–1.36)	
Gleason (central) < 7	2	1.2 (0.3–4.2)	9	4.6 (2.4–8.5)	3.4 (−0.3–7.4)	0.26 (0.06–1.18)	0.07
Gleason < 7, 4 year		0.0 (0.0–2.2)		1.0 (0.3–3.6)	1.0 (−1.3–3.6)	–	
Gleason < 7, 8 year		0.6 (0.1–3.3)		3.1 (1.4–6.5)	2.5 (−0.7–6.0)	0.19 (0.02–1.60)	
Gleason < 7, 12 year		0.6 (0.1–3.3)		4.1 (2.1–7.9)	3.5 (0.1–7.3)	0.15 (0.02–1.15)	

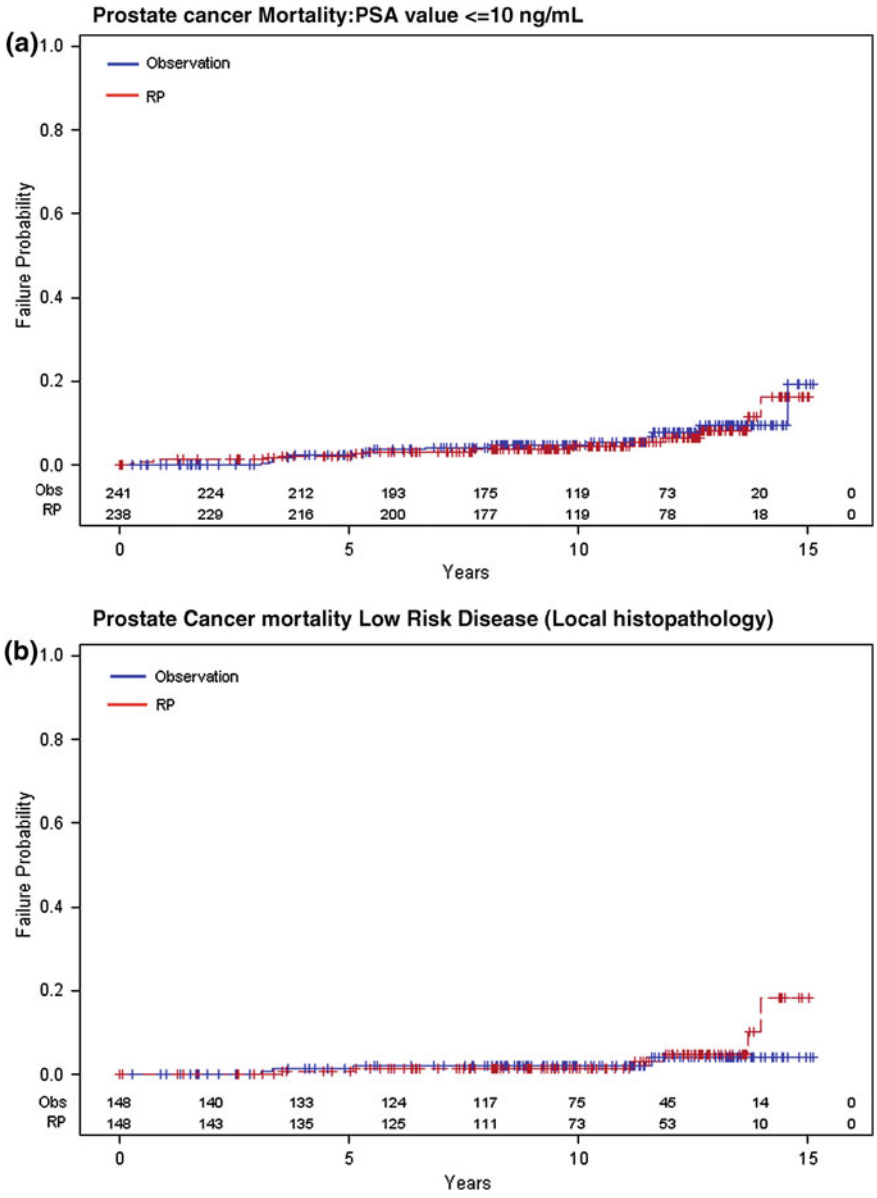

Fig. 2 **a**, **b**: Cumulative incidence of prostate cancer mortality in the two study groups according to tumor subgroups: *Panel A*: PSA <= 10; *Panel B*: Low D'Amico Tumor

histopathology readings. Results were fairly stable after 8 years of follow-up. Radical prostatectomy did not significantly reduce prostate cancer mortality in the 368 men with non-palpable (T1c) disease with differences favoring RP (2.2 vs.

5.5 %; ARD = 3.3 %; HR = 0.43; 95 % CI, 0.14–1.38; $p = 0.15$) or the subgroup of men with T1c tumors that had a PSA value of ≤10 (HR = 0.58; 95 % CI, 0.14−2.33; $P = 0.44$; prostate cancer mortality = 2.4 % RP vs. 4.8 % observation). Events in both subgroups were infrequent, confidence intervals wide and absolute risk differences of approximately 3 % or less.

6 Bone Metastases

Bone metastases were infrequent in men with PSA ≤10 ng/mL and in men with low-risk disease and not significantly reduced by surgery compared to observation with absolute risk differences of less than 4 %.

In men with PSA values of 10 or less the cumulative incidence of bone metastases was 8.7 % in men randomized to observation versus 5.0 % in those randomized to surgery (RR 0.58 (95 % CI, 0.29–1.15); ARD 3.7 % (95 % CI, −1.0–8.4)).

In men with low risk disease bone metastases was infrequent in men randomized to observation (6.1 %) and not significantly reduced by surgery (4.1 %); (RR = 0.67 (95 % CI, 0.24–1.83); ARD = 2.0 (95 % CI, −3.3–11.2)). Similar to overall and prostate cancer mortality any cumulative incidence subgroup differences were small, not significant at 4, 8 or 12 years and remained stable after about 8 years (Table 3).

In all men with Gleason scores of 6 or less there was a statistically significant reduction in bone metastases in men randomized to surgery versus surgery based on local but not central histopathology. For example, based on local histopathology readings, bone metastases occurred in 3.5 % of men randomized to RP versus 8.1 % randomized to observation (ARD = 4.5 (95 % CI, 0.4–8.9)). This difference was smaller and not statistically significant when using central rather than local histopathology. 1.2 % (RP) versus 4.1 % (Observation) (ARD = 2.9 (95 % CI, −0.8–6.8)).

7 Surgical Morbidity

Among all men randomized to RP and undergoing surgery thirty-day perioperative complications occurred in 21.4 % of men and included 1 death. Data are not available for men with low PSA, low risk or low Gleason disease. The most common complication was wound infection in 4.3 %. Complications occurring in greater than 2 % included urinary infection, surgical repair, bleeding requiring transfusion and urinary catheter present greater than 30 days post-operatively. Two year patient reported urinary incontinence and erectile dysfunction but not bowel dysfunction was more common among men randomized to RP then observation (Klotz et al. 2010).

Table 3 Bone metastases: cumulative incidence

Bone metastasis	Cumulative incidence				Absolute risk reduction % (95 % CI)	Relative risk (95 % CI)	p-value
	Radical prostatectomy		Expectant management				
	No.	% (95 % CI)	No.	% (95 % CI)			
Overall	17	4.7 (2.9–7.4)	39	10.6 (7.9–14.2)	6.0 (2.1–9.9)	0.44 (0.25–0.76)	0.001
All ages, 4 year		1.4 (0.6–3.2)		3.3 (1.9–5.6)	1.9 (−0.4–4.4)	0.42 (0.15–1.18)	
All ages, 8 year		1.9 (0.9–3.9)		7.1 (4.9–10.2)	5.2 (2.2–8.4)	0.27 (0.12–0.62)	
All ages, 12 year		3.9 (2.3–6.4)		9.5 (6.9–13.0)	5.7 (2.1–9.5)	0.40 (0.22–0.74)	
PSA $\leq$ 10	12	5.0 (2.9–8.6)	21	8.7 (5.8–13.0)	3.7 (−1.0–8.4)	0.58 (0.29–1.15)	0.09
PSA $\leq$ 10, 4 year		1.7 (0.7–4.2)		2.9 (1.4–5.9)	1.2 (−1.7–4.4)	0.58 (0.17–1.95)	
PSA $\leq$ 10, 8 year		2.5 (1.2–5.4)		5.4 (3.2–9.0)	2.9 (−0.8–6.7)	0.47 (0.18–1.21)	
PSA $\leq$ 10, 12 year		4.2 (2.3–7.6)		7.9 (5.1–12.0)	3.7 (−0.7–8.2)	0.53 (0.25–1.12)	
Risk—Low (Local)	6	4.1 (1.9–8.6)	9	6.1 (3.2–11.2)	2.0 (−3.3–7.6)	0.67 (0.24–1.83)	0.39
Risk—Low, 4 year		0.7 (0.1–3.7)		2.7 (1.1–6.7)	2.0 (−1.4–6.1)	0.25 (0.03–2.21)	
Risk—Low, 8 year		1.4 (0.4–4.8)		4.1 (1.9–8.6)	2.7 (−1.4–7.3)	0.33 (0.07–1.62)	
Risk—Low, 12 year		2.7 (1.1–6.7)		6.1 (3.2–11.2)	3.4 (−1.6–8.7)	0.44 (0.14–1.41)	
Risk—Low (Central)	1	0.9 (0.2–4.9)	6	4.9 (2.3–10.3)	4.0 (−0.8–9.5)	0.18 (0.02–1.50)	0.08
Risk—Low, 4 year		0.0 (0.0–3.4)		2.5 (0.8–7.0)	2.5 (−1.3–7.0)	–	

(continued)

Table 3 (continued)

Bone metastasis	Cumulative incidence				Absolute risk reduction % (95 % CI)	Relative risk (95 % CI)	p-value
	Radical prostatectomy		Expectant management				
	No.	% (95 % CI)	No.	% (95 % CI)			
Risk—Low, 8 year		0.0 (0.0–3.4)		4.1 (1.8–9.2)	4.1 (0.0–9.2)	–	
Risk—Low, 12 year		0.0 (0.0–3.4)		4.9 (2.3–10.3)	4.9 (0.7–10.3)	–	
Gleason (Local) < 7	9	3.5 (1.9–6.6)	21	8.1 (5.3–12.0)	4.5 (0.4–8.9)	0.44 (0.21–0.94)	0.02
Gleason < 7, 4 year		0.4 (0.1–2.2)		2.7 (1.3–5.4)	2.3 (0.0–5.1)	0.15 (0.02–1.18)	
Gleason < 7, 8 year		1.2 (0.4–3.4)		5.4 (3.2–8.8)	4.2 (1.1–7.7)	0.22 (0.06–0.76)	
Gleason < 7, 12 year		2.4 (1.1–5.1)		7.7 (5.0–11.5)	5.3 (1.5–9.4)	0.31 (0.13–0.76)	
Gleason (Central) < 7	2	1.2 (0.3–4.2)	8	4.1 (2.1–7.9)	2.9 (−0.8–6.8)	0.29 (0.06–1.35)	0.10
Gleason < 7, 4 year		0.0 (0.0–2.2)		1.5 (0.5–4.4)	1.5 (−0.9–4.4)	–	
Gleason < 7, 8 year		0.0 (0.0–2.2)		2.6 (1.1–5.8)	2.6 (−0.1–5.8)	–	
Gleason < 7, 12 year		0.6 (0.1–3.3)		3.6 (1.7–7.2)	3.0 (−0.3–6.6)	0.17 (0.02–1.34)	

P value: from log-rank test for survival analysis **Risk status:** Low risk = PSA ≤ 10; Gleason histological score ≤ 6; tumor stage T1, T2a; **Y =** year

8 Discussion

Among men with clinically localized prostate cancer diagnosed after PSA testing came into practice, PIVOT found that radical prostatectomy did not reduce all-cause or prostate cancer mortality compared to observation through at least 12 years of follow-up. All-cause mortality differences decreased over time. Both prostate cancer mortality and bone metastases changed little after about 8 years suggesting that longer follow-up would not alter these findings Table 3.

In the subgroups of men most frequently diagnosed during the PSA screening era, i.e. men with non-palpable (T1c) and low risk disease and men with PSA values of 10 or less we found strong evidence that early intervention with radical prostatectomy did not reduce all-cause or prostate cancer mortality through more than 12 years. These results include men with long life expectancy including men less than 65 years of age, men with 1 or fewer comorbid conditions and men reporting independence in activities of daily life. Therefore, our findings have broad applicability and add to evidence supporting observation, and possibly active surveillance, for many men currently diagnosed with PSA screen detected prostate cancer especially men with low PSA or low-risk disease Wilt et al. (2008; 2012, http://consensus.nih.gov/2011/docs/prostate/ASPC%20Final%20Draft%20Statement.pdf; Widmark 2011; Lu-Yao et al. 2009; Hayes et al. 2013; Daskivich et al. 2013; Ganz et al. 2012; Graham et al. 2008; Klotz et al. 2010; Gleason 1977; Cooperberg et al. 2007; Fleming et al. 1993; Djulbegovic et al. 2010).

The attained sample size and follow-up duration have led to concerns about the statistical power of PIVOT to detect clinically important mortality differences. However, our findings through at least 10 years are robust based on point estimates, confidence intervals, inspection of mortality and metastases curves and cumulative incidence trends. This is especially true among men with PSA values $\leq$10 ng/mL (including men with Gleason $\geq$7 histology) and low-risk tumors. These subgroups: (1) were relatively large in size; (2) had point estimates that either favored observation or resulted in absolute reductions of 3 % or less that were not significant; (3) demonstrated stable findings after 8 years of follow-up. For example among men with PSA $\leq$10 ng/mL, all-cause mortality was slightly lower with observation at 12 years; prostate cancer mortality with observation was 6 % with a non-significant absolute reduction due to RP of less than 1 % and no significant reduction in bone metastases. In men with low-risk disease, observation led to a non-significant lower all-cause and prostate cancer mortality and no difference in bone metastases compared to surgery.

PIVOT has strengths that enhance clinical applicability. Age, health status, PSA and tumor risk characteristics of PIVOT enrollees were similar to eligible men declining randomization (Klotz et al. 2010) and population estimates of men diagnosed with prostate cancer (Cooperberg et al. 2010; Wilt et al. 2008; 2012, http://consensus.nih.gov/2011/docs/prostate/ASPC%20Final%20Draft%20Statement.pdf; Hayes et al. 2013; Vis et al. 2006). Perioperative morbidity and mortality were similar to previous reports (Wilt et al. 2008; Eastham et al. 2003;

Obek et al. 1999). Percentage of positive surgical margins were comparable to earlier reports and lower than SPCG-4 (Obek et al. 1999). While higher than some contemporary series (Vis et al. 2006; Ohori et al. 1995), our findings likely reflect tumor volume and PSA values among men diagnosed during PIVOT enrollment. Our choice of all-cause mortality as the primary outcome emphasizes the importance of improving life expectancy with cancer treatment and avoids the possibility of biased cause-of-death ascertainment (Ohori et al. 1995; Dubben 2009; Schellhammer et al. 1997; Newschaffer et al. 2000).

PIVOT enrolled men diagnosed in the early era of PSA testing. The current practice of: repeated PSA testing, lower PSA thresholds triggering biopsies, obtaining more tissue biopsy cores and repeating biopsies after initial negative findings increases detection of smaller volume indolent cancers (Newschaffer et al. 2000; Thompson and Klotz 2010; Albertsen et al. 2005; Ghani et al. 2005; Stamey et al. 2002; Welch and Albertsen 2009). Along with histologic upgrading, these factors enhance over-diagnosis and overtreatment. Among men currently diagnosed, absolute reductions due to RP in metastases, or should they occur, in mortality, will likely be smaller, and the time required to identify a reduction, longer than reported in our study or SPCG-4 (Obek et al. 1999).

Our findings strongly support observation for low PSA and low-risk clinically localized prostate cancer especially men age 60 and older with non-palpable disease. Up to two-thirds of men diagnosed with prostate cancer have low PSA or low-risk category disease but nearly 90 % receive early intervention, typically surgery or radiation therapy (Cooperberg et al. 2010; Hayes et al. 2013; Welch and Albertsen 2009). In the United States alone the cost of prostate cancer diagnosis and treatment care go beyond physical harms with the financial direct health care costs exceeding $1.3 billion (Hayes et al. 2013). In contrast to observation, active surveillance initiates therapy with curative intent for suspected disease progression or risk status reclassification , digital rectal examinations and prostate biopsies (2012, http://consensus.nih.gov/2011/docs/prostate/ASPC%20Final%20Draft%20Statement.pdf). Active surveillance is being compared to surgery or radiotherapy in a randomized trial (Welch and Albertsen 2009). Informing men of the favorable long-term effects on mortality, bone metastases, urinary and erectile function achieved with observation and increasing utilization of observation may avoid the harms of unnecessary biopsies and interventions (Rosario et al. 2012; Moyer VA on behalf of the 2012; Qaseem et al. 2013; Basch et al. 2012) while still achieving excellent long-term disease specific survival.

Recent findings from a cost-effectiveness modeling study demonstrate that among men aged 65–75 years who are newly diagnosed with low-risk prostate cancer observation is more effective, results in superior quality of life and costs less than initial treatment (Hayes et al. 2013). Furthermore, even under a wide range of clinical scenarios, watchful waiting is most effective and least expensive including when compared to active surveillance. Given the robustness of these data the results likely extend to men younger than age 65. Therefore, for the majority of men currently diagnosed with prostate cancer observation should be recommended as the preferred treatment option. Such an approach would also

result in considerable cost savings. If the number of newly diagnosed men with low risk prostate cancer who selected observation would increase from 10 % to 50 % it would result in a cost savings of more than $1 billion in the U.S. alone (Hayes et al. 2013).

Given the current controversy regarding PSA testing and early treatment of screen detected cancer PIVOT results provide guidance on diagnostic and management approaches to favorably improve the balance of screening and treatment benefits and harms. Our results support recent results from randomized screening trials demonstrating that If a mortality benefit exists from PSA screening it is small in magnitude through at least 15 years, confined to men age 55–69 years, and associated with considerable diagnostic and treatment related harms (Djulbegovic et al. 2010; Moyer VA on behalf of the 2012; Qaseem et al. 2013; Basch et al. 2012; Schroder et al. 2012; Andriole et al. 2012). Furthermore, PIVOT data add to evidence indicating that screening and early treatment are expensive for any possible care benefits and considered low value. For example, a recent analysis estimated that the cost of diagnosis and treatment is slightly more than $5 million to prevent 1 prostate cancer death even when based on assumptions highly favorable to screening and treatment (Shteynshlyuger and Andriole 2011).

Therefore, not undergoing PSA screening is a wise health choice for most men and high value care recommendation by clinicians. For men deciding to receive PSA screening after receiving information about the known harms and limited (if benefits exists) clinicians can improve the balance of benefits and harms by raising the threshold of PSA values designated as abnormal and prompting a biopsy to between 6 and 10 (Welch et al. 2005). Widening between PSA testing intervals, for those desiring testing, from annually to every 2–4 years would markedly reduce false positives and subsequent diagnostic biopsies and over diagnosis without adversely impacting cancer mortality (Moyer VA on behalf of the 2012; Qaseem et al. 2013; Basch et al. 2012; Gulati et al. 2013; Welch and Black 2010).

Recommending and choosing observation rather than immediate definitive treatment or active surveillance is a preferred option for many men with non-palpable, low risk, low PSA prostate cancer based on clinical and cost outcomes. Such an option will result in excellent disease specific survival, freedom from metastatic disease and similar length of life while avoiding diagnostic and treatment related harms. Observation is more effective and costs less than initial treatment for these men and is superior to active surveillance. Initiating definitive therapy based on changes in monitored PSA or biopsy values (active surveillance) has not been proven beneficial, subjects men to the harms of monitoring and delayed intervention as well as the financial costs.

Clinicians and patients are reluctant to utilize observation due to concerns about the presence or development of higher grade disease that might progress and result in morbidity and mortality unless treated aggressively initially or monitored closely with PSA and prostate biopsies leading to deferred intervention. However, our findings and other data provide support for observation among men with low PSA and low risk disease at the time of initial diagnosis. Given PIVOT results, other randomized data and findings from natural history and decision analysis studies,

AS or early intervention are very unlikely to have a favorable impact on mortality and metastases yet result in monitoring and treatment harms.

It is well known that many men with biopsy detected low risk disease harbor undetected pathologic evidence of higher grade disease. Similarly men with baseline PSA values of ≤10 had increases in PSA values over time that exceeded 10 ng/mL. Yet these men comprised the cohort of individuals enrolled in PIVOT with an initial diagnosis of low risk and low PSA disease in whom an excellent prognosis occurred with observation and in whom surgery did not improve outcomes These individuals are likely similar to men frequently defined as having progressed to "higher PSA or higher risk disease" based on monitoring PSA values or prostate biopsy findings in active surveillance programs (Ganz et al. 2012; Coen et al. 2011). Findings from PIVOT as well as recent observational and modeling studies indicate that the majority of these men can be treated more effectively, with better health outcomes and lower costs with observation than active surveillance or early intervention (Shao et al. 2009). In comparison long-term mortality and metastatic disease benefits from early intervention may positively affect a small subgroup of men currently diagnosed with clinically localized prostate cancer radical prostatectomy who have palpable tumors or PSA values of 10 or greater on initial biopsy. These results should be confirmed in future trials including studies comparing active surveillance to early intervention for men with intermediate and high risk disease.

In conclusion, PIVOT demonstrated that compared to observation, radical prostatectomy did not reduce all-cause or prostate cancer mortality through at least 12 years in men with clinically localized prostate cancer diagnosed in the PSA era. In the subgroup of men with PSA values of 10 or less or low risk disease our findings are particularly strong with mortality outcomes either favoring observation or showing effects of 1 % or less. The results from PIVOT are supported by recent observational and modeling studies demonstrating that observation should be recommended as a preferred treatment option. Observation is more effective, has fewer harms and costs less than initial treatment or active surveillance.

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