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

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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

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J. Cuzick and M. A. Thorat (eds.), *Prostate Cancer Prevention*,
Recent Results in Cancer Research 202, DOI: 10.1007/978-3-642-45195-9_1,
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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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