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The influence of family history on prostate cancer risk: implications for clinical management

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- The most recent evidence for the link between a family history of prostate cancer and individual risk for future disease was examined, with the aim of understanding what the existence and nature of a family history of prostate cancer does to a man's risk of developing the disease.
- Our findings highlighted the clear association between a family history of prostate cancer and increased risk of developing the disease; with a greater proximity of relatedness, greater number of family members affected and/or earlier age at diagnosis of the family member elevating risk further.
- These findings have important clinical implications for the identification and subsequent management of men deemed to be at increased risk of developing prostate cancer. The evidence for prostate cancer risk reduction with the mono 5α-reductase inhibitor (5ARI) finasteride in a low-risk population and, more recently, with the dual 5ARI dutasteride in a population at increased risk of developing the disease, has potential to expand management options for men at risk of developing prostate cancer beyond more frequent and/or earlier surveillance.
- Given that family history can be easily assessed in routine clinical practice, it should be regarded as an important parameter to consider alongside PSA level for prostate cancer risk assessment.

What's known on the subject? and What does the study add?
A family history of prostate cancer has long been identified as an important risk factor for developing the disease. This risk factor can be easily assessed in clinical practice and current guidelines recommend to initiate prostate cancer early detection 5 years earlier (i.e. around the age of 40 years) than in men without a positive family history.

This review elucidates the close association between the proximity of relatedness, greater number of affected family members and earlier age at diagnosis of the family members and prostate cancer risk. The evidence for prostate cancer risk reduction by 5α-reductase inhibitors has potential to expand management options for men at high risk for developing prostate cancer beyond more frequent and/or earlier surveillance.

KEYWORDS

prostate cancer, family history, hereditary, risk factor, screening, chemoprevention

INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer in men in Europe [1] and in the USA [2]. It is the third leading cause of cancer deaths in Europe [1] and the second leading cause in the USA [2]. Data from the USA, where PSA level testing and subsequent biopsy has become widespread, have shown that the lifetime probability of a man being diagnosed with invasive prostate cancer is 15.9% (1 in 6) [2]. Given the high incidence and mortality associated with the disease, much focus has been placed in recent years on identifying risk factors for developing prostate cancer to help identify men who are at increased risk of being diagnosed with prostate cancer in the future. PSA has been shown to be the single most significant predictive factor for identifying men at increased risk of prostate cancer [3]. Several additional predictive factors can alter risk estimation, including family history of prostate cancer, prostate volume, previous biopsy status and ethnicity, and are important to consider in routine practice [3].

A family history of prostate cancer has long been identified as an important risk factor for developing the disease and it is one that is easily assessed in clinical practice. This article will review the most recent evidence for the link between a family history of prostate cancer and individual risk for future disease, with the aim of understanding what the existence and nature of a family history of prostate cancer does to a man's risk of developing the disease to better aid the identification of higher-risk groups for screening and risk reduction. In light of this,

TABLE 1 Outcomes from meta-analyses of the association between family history and risk of prostate cancer

Reference	No. of studies included	RR (95% CI)					
		Any affected family member	Affected first-degree relative	More than one affected first-degree relative	Affected second-degree relative	Father with prostate cancer	Brother with prostate cancer
Bruner *et al.* 2003 [4]	23 (14 case-control and 9 cohort studies)	1.93 (1.65–2.26)	2.22 (2.06–2.40)	–	1.88 (1.54–2.30)	2.12 (1.82–2.51)	2.87 (2.21–3.73)
Johns and Houlston 2003 [11]	13 (11 case-control and 2 cohort studies)	–	2.5 (2.2–2.8)	3.5 (2.6–4.8)	–	2.5 (2.1–3.1)	3.4 (2.9–4.1)

outcomes from risk reduction studies of 5α-reductase inhibitors (5ARIs) in men with risk factors for prostate cancer that included a family history will be reviewed and their clinical implications discussed.

DEFINING FAMILY HISTORY

A family history of prostate cancer represents a complex mix of genetic and environmental factors. It has been estimated that 5–10% of prostate cancer cases are caused by dominantly inherited susceptibility to the disease [4], and autosomal recessive and X-linked modes of inheritance have also been suggested [5]. The influence of genetics on the development of prostate cancer was shown in a study of 44 788 pairs of twins listed in Swedish, Danish and Finnish twin registries [6]. Statistically significant effects of heritable factors were observed for prostate cancer, with inherited genes contributing 42% to the total risk of developing prostate cancer and unshared environmental factors making up the remaining 58% of the risk. More recently, genome-wide association studies have been used to identify genetic risk factors for prostate cancer, with >24 prostate cancer risk-associated single-nucleotide polymorphisms (SNPs) having been discovered and more expected to be discovered from ongoing studies [7,8]. Although each of the SNPs discovered to date are only moderately associated with prostate cancer risk, cumulatively they have a stronger association [8]. In addition, a SNP that is significantly associated with more aggressive prostate cancer risk but not indolent prostate cancer has recently been reported [9].

The term 'hereditary prostate cancer' is generally accepted to include nuclear families with three cases of prostate cancer, families with prostate cancer in each of three generations in the paternal or maternal lineage, and families with two men diagnosed with the disease before the age of 55 years [10]. The aggregation of prostate cancer cases in a family that does not fulfil the criteria for hereditary prostate cancer is called 'familial prostate cancer' and it is defined through a family history and a lack of a definitive genetic basis, reflecting not only shared genes but also shared environment and common behaviours. It is interesting to note that most studies have found no evidence for a significant difference between familial and sporadic forms of prostate cancer for either clinicopathological features, response to treatment, or outcome [11].

In this review, the term 'family history' is used primarily to describe an observed aggregation of cases within a family rather than to imply a demonstrated genetic or hereditary link.

FAMILY HISTORY AND PROSTATE CANCER RISK

The lifetime absolute risk of clinical prostate cancer has been estimated to range from 12% for a man with a father affected at ≥60 years to 35–45% for a man with three or more affected male relatives compared with an 8% absolute risk in men without a family history of the disease [12]. Two meta-analyses, both published in 2003, have shown the association between family history and risk of prostate cancer, with concordant findings in terms of relative risks (RRs) [4,11]. The first of these, by Bruner *et al.* [4] and based on 23 studies, showed a pooled RR estimate of 1.93 for men with a history of prostate cancer in any relative (Table 1) [4,11]. Risk was shown to be impacted by the degree of relatedness, with a RR of 2.22 for those with an affected first-degree relative compared with 1.88 for an affected second-degree relative. Further, risk was significantly higher ($P < 0.03$) for men with a brother with prostate cancer (RR 2.87) than for those with a father with prostate cancer (RR 2.12).

The second meta-analysis of 13 studies showed a pooled RR of 2.5 for men with affected first-degree relatives and also found risk to be higher in men with a brother with prostate cancer vs a father with the disease (RRs 3.4 and 2.5, respectively; Table 1) [11]. Further, for men aged <65 years with an affected first-degree relative, the RR of prostate cancer was 4.3 (95% CI 2.9–6.3), while the RR for those aged >65 years was 2.4 (95% CI 2.0–2.9). It also provided evidence that risk of developing prostate cancer is greater for men with two affected relatives compared with a single affected relative (RR 3.5 vs 2.5).

Since these two meta-analyses were conducted, several additional large-scale studies have been published, providing further insight into the association of family history and risk of developing prostate cancer. The most pertinent of these studies are reviewed below.

THE HEALTH PROFESSIONALS FOLLOW-UP STUDY (HPFS)

Chen *et al.* [13] examined family history and risk of prostate cancer in a study evaluating a subcohort of the HPFS. The HPFS was a health questionnaire-based prospective study initiated in 1986 and involved 51 529 USA male healthcare professionals aged 40–75 years. Family disease history was assessed at the beginning of the study and at intervals throughout the study. From 1990 to the end of January 2004, 3695 cases of prostate cancer were documented in 43 494 eligible participants.

The results showed a strong association between family history and risk of prostate cancer (Table 2) [13-15]. Prostate cancer in a father only (RR 1.78, 95% CI 1.62–1.95), brother(s) only (RR 1.84, 95% CI 1.59–2.12), a father or brother(s) (RR 1.83, 95% CI 1.69–1.98), or a father and brother(s) (RR 2.34, 95% CI 1.76–3.12) was significantly associated with elevated risk of prostate cancer. These findings were consistent with the risk estimates in the previous meta-analyses [4,11]. The increased risk was similar whether it was a father or brother(s) who was affected. When a father or brother had been diagnosed with the disease before 60 years of age, the RR was 2.16 (95% CI 1.70–2.73); if either the father or a brother was diagnosed at ≥60 years, the RR was 1.95 (95% CI 1.77–2.15). For men with a family history of prostate cancer, the risk of early-onset prostate cancer (age <65 years) was significantly elevated (RR 2.25, 95% CI 1.95–2.60) compared with men with no family history. This finding may indicate a difference in the natural history of familial vs sporadic prostate cancer, but greater use of screening and investigative procedures in men with a positive family history could also contribute, at least in part, to diagnosis at an earlier point in the natural history [16], and indeed this should be considered as a potential source of bias for any estimate of familial risk.

THE SWEDISH FAMILY-CANCER DATABASE

Brandt *et al.* [14] used the nationwide Swedish Family-Cancer Database to estimate age-specific risks of prostate cancer according to the number and type (father or brother) of affected first-degree relatives and according to the relative's age at diagnosis (Table 2). The Swedish Family-Cancer Database includes a record of >11.8 million individuals and their cancers from 1958 to 2006, including >3.9 million with identified parents; the study included 26 651 patients with prostate cancer, of whom 5623 were familial. This represents the largest study of familial prostate cancer published to date.

The hazard ratios (HRs) of prostate cancer diagnosis increased with the number of affected relatives and decreased with increasing age. The highest HRs were for men aged <65 years with three affected brothers (HR ≈ 23) and the lowest for men aged between 65–74 years with an affected father (HR ≈ 1.8). An affected brother conferred a higher risk than an affected father. In general, the HRs increased with decreasing paternal or fraternal diagnostic age. For men aged <55 years, the HRs ranged from 1.5 for those with a father affected aged >83 years to 6.6 for those with a brother affected before 60 years of age.

THE α-TOCOPHEROL, β-CAROTENE CANCER PREVENTION (ATBC) STUDY

The ATBC study was a placebo-controlled, primary prevention trial to determine whether α-tocopherol or β-carotene supplementation reduced the incidence of lung or other cancers in Finnish male smokers [15]. Between 1985 and 1988, 29 133 men aged 50–69 years were enrolled; family history of common cancers, including prostate cancer, was assessed once during the study in 1991. The study ended in 1993 but follow-up continued until 2003; among 19 562 men with complete data, 1111 prostate cancer cases were identified during the follow-up period, allowing prospective investigation of the association between family history and prostate cancer risk.

A family history of prostate cancer in first-degree relatives vs no family history was associated with almost a doubling of prostate cancer risk. A first-degree family history of prostate cancer was associated with an overall RR of 1.91 (95% CI 1.49–2.47). Men whose fathers had been diagnosed with prostate cancer showed a slightly greater risk increase (RR 1.99, 95% CI 1.48–2.67) than men who had brother(s) with the disease (RR 1.70, 95% CI 1.05–2.75). This finding is not consistent with other studies that showed greater risk with an affected brother vs father. However, as family history was only recorded once during the study, history of prostate

TABLE 2 Outcomes from recent large-scale studies examining the association between family history and risk of prostate cancer by degree of relationship

Study, reference	Eligible participants, n	Documented cases of prostate cancer, n	Risk of prostate cancer (95% CI)			
			Father affected	Brother(s) affected	Father or brother(s) affected	Father and brother(s) affected
HPFS, Chen *et al.* 2008 [13]	43 494	3 695	RR 1.78 (1.62–1.95)	RR 1.84 (1.59–2.12)	RR 1.83 (1.69–1.98)	RR 2.34 (1.76–3.12)
The Swedish Family-Cancer Database, Brandt *et al.* 2010 [14]	>3.9 million	26 651	HR 2.12 (2.05–2.20)	One brother: HR 2.96 (2.80–3.13); two brothers: HR 7.71 (6.54–9.08); three brothers: HR 17.74 (12.26–25.67)	-	Father and one brother: HR 5.51 (5.00–6.09); father and two brothers: HR 8.51 (6.13–11.80)
The ATBC study, Ahn *et al.* 2008 [15]	19 562	1 111	RR 1.99 (1.48–2.67)	RR 1.70 (1.05–2.75)	RR 1.91 (1.49–2.47)	-

FIG. 1. Proportion of men with prostate cancer (PCa) detected, according to family history status in the PCPT [17].

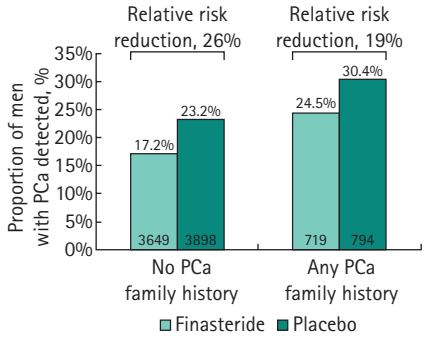
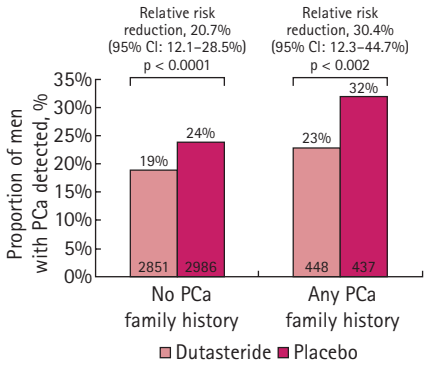


FIG. 2. Proportion of men with a positive biopsy for prostate cancer (PCa), according to family history status in the REDUCE study [21].



cancer among brothers may not have been fully manifested, as compared with that for fathers. For cases with early onset of disease (aged <65 years) a family history of prostate cancer was associated with a RR of 2.40, but this finding was based on only a few patients.

THE PROSTATE CANCER PREVENTION TRIAL (PCPT)

The PCPT was the first large-scale randomized clinical trial of a 5ARI in prostate cancer risk reduction. In all, 18 882 men aged ≥55 years and with PSA levels of ≤3.0 ng/mL and a normal DRE were randomized to finasteride or placebo for 7 years [17]. Prostate biopsy was recommended if the annual PSA level, adjusted for the effect of finasteride, was >4.0 ng/mL or if the DRE was abnormal; all men who had not been given a prostate cancer diagnosis during the study were offered an end-of-study biopsy. An analysis of risk factors for developing prostate cancer, including family history, was conducted based on 5519 men from the placebo group who underwent prostate biopsy, had a PSA test and DRE ≤1 year of the biopsy and an additional PSA test during the 3 years before the biopsy [18]. Family history was defined as either positive or negative; 920 of the 5519 men (16.7%) had a family history of prostate cancer. In a multivariable analysis, a positive family history of prostate cancer was statistically significantly associated with an increased risk of prostate cancer (odds ratio 1.31, 95% CI 1.11–1.55, $P = 0.002$).

Based on the previously published meta-analyses and the findings from more recent large-scale studies, it is clear that any family history of prostate cancer places a man at increased risk of developing the disease himself. The degree of relatedness affects the risk for developing prostate cancer, with it being increased in men with an affected first-degree vs second-degree relative. Further, there is evidence that an earlier age at diagnosis of the family member elevates risk, as does a greater number of family members affected.

POTENTIAL MANAGEMENT APPROACHES FOR MEN WITH A FAMILY HISTORY OF PROSTATE CANCER

Given that men with a family history of prostate cancer are at increased risk of developing the disease, they may warrant enhanced surveillance. This could take the form of earlier and/or more frequent surveillance with the aim of detecting prostate cancer at an early, organ-confined stage and facilitating appropriate onward monitoring and/or treatment. Current guidelines from the National Comprehensive Cancer Network state that focusing on early detection in young men with a strong family history of prostate cancer may be the key to improving the survival rate [19].

Looking further ahead, a future potential option for men with a family history of prostate cancer is the implementation of an active risk reduction strategy [3]. To date, two large-scale randomized clinical trials of 5ARIs in prostate cancer risk reduction have been conducted, the PCPT and the REduction by DUtasteride of prostate Cancer Events (REDUCE) study. In the following section, we will examine what evidence exists from these studies for prostate cancer risk reduction in men with a family history.

In the PCPT, the primary endpoint was the prevalence of prostate cancer during the 7 years of the study and the primary intention-to-treat analysis included men who received a diagnosis of prostate cancer during the study or who underwent an end-of-study biopsy. Overall, a reduction of 24.8% in the risk of prostate cancer detection was shown for finasteride vs placebo ($P < 0.001$) [17]. At randomization, the study included 2913 men with a first-degree family history of prostate cancer. In this group, prostate cancer was detected in 176 of the 719 men in the finasteride group who had data for the final analysis (24.5%) and 241 of the 794 men in the placebo group (30.4%); the relative risk of prostate cancer for the finasteride group was 0.81 vs the placebo group (Fig. 1) [17]. The risk reduction with finasteride vs placebo in men with a family history of prostate cancer was similar to that in men without a family history.

Further evidence for 5ARI prostate cancer risk reduction is provided by the REDUCE study, a 4-year trial exploring the effect of the dual 5ARI dutasteride vs placebo on the risk of biopsy-detectable prostate cancer [20]. In contrast to the PCPT, the REDUCE study was specifically designed to enrol men at increased risk for developing prostate cancer by including the PSA level range of 2.5–10.0 ng/mL at enrolment. Eligible men aged 50–75 years were required to have a negative biopsy of 6–12 cores ≤6 months before enrolment; TRUS-guided biopsies (10 cores) were performed at 2 and 4 years.

Overall, the REDUCE study showed a 23% RR reduction in biopsy-detectable prostate cancer in men who received dutasteride vs placebo [20]. Among men biopsied, 13% had a family history of prostate cancer; most had only one relative affected, most commonly the father [21]. Dutasteride significantly reduced the risk of prostate cancer in men with ($P < 0.002$) or with no family history of prostate cancer ($P < 0.0001$) and the effect was homogeneous across regions (Fig. 2) [21]. The RR reduction for dutasteride vs placebo for any prostate cancer in men with a family history of prostate cancer was 30.4% and 20.7% in men with no family history (Fig. 2).

Of course, in the absence of a qualitative marker for prostate cancer, the findings from the PCPT and the REDUCE study are unable to indicate what proportion of the cancers prevented would have become clinically

significant. Such uncertainty will remain until a genotype associated specifically with aggressive disease is identified. However, a reduction in the incidence of biopsy-detectable prostate cancer of ≈25% can be considered to be a clinically relevant benefit in itself, due to what this may represent for patients in terms of reducing over diagnosis, overtreatment and treatment-related morbidity.

IMPLICATIONS FOR CLINICAL PRACTICE

The identification of men at increased risk of prostate cancer in clinical practice is important to determine subsequent surveillance and potentially risk reduction interventions. PSA has been shown to be the single most significant predictive factor for identifying men at increased risk of prostate cancer [3]. However, family history is one of several additional predictive factors for developing prostate cancer that can alter risk estimation [3]. There is a large body of evidence to show that men with a family history of prostate cancer are at increased risk of developing the disease compared with those with no family history. Moreover, a man's risk can be affected further according to the degree of relatedness to the affected family member(s), the age of the affected family member at prostate cancer diagnosis, and the total number of family members affected. Given that family history is a simple factor to assess in routine clinical practice through basic patient questioning, it should be regarded as an important parameter to consider next to PSA for prostate cancer risk assessment. Further, family history can be assessed from a relatively early age (≈40 years if a father is affected), potentially offering the opportunity for earlier intervention for men at increased risk of prostate cancer through enhanced surveillance and, in the future, active risk reduction strategies if they become available.

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CONFLICT OF INTEREST

Stephan Madersbacher is a Consultant for GSK. Mark Emberton is an Investigator for GSK and is on the Advisory Board, and has received honoraria for lectures for GSK. Fritz H. Schröder is a Paid Consultant. Andrea Tubaro is a Study Investigator for Astellas, Ipsen, Ferring and Novartis.

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Abbreviations: **5ARI**, 5α-reductase inhibitor; **SNP**, single-nucleotide polymorphism; **RR**, relative risk; **HPFS**, Health Professionals Follow-up Study; **HR**, hazard ratio; **ATBC**, α-Tocopherol, β-Carotene Cancer Prevention Study; **PCPT**, Prostate Cancer Prevention Trial; **REDUCE**, REduction by DUtasteride of prostate Cancer Events study.