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# Estimation of Absolute Risk for Prostate Cancer Using Genetic Markers and Family History

Jianfeng Xu,[1,2]* Jielin Sun,[1,2] A. Karim Kader,[1,3] Sara Lindström,[4] Fredrik Wiklund,[5] Fang-Chi Hsu,[1,2,6] Jan-Erik Johansson,[7] S. Lilly Zheng,[1,2] Gilles Thomas,[8] Richard B. Hayes,[8] Peter Kraft,[8,9] David J. Hunter,[8,9] Stephen J. Chanock,[8] William B. Isaacs,[10]** and Henrik Grönberg[5]

[1]*Center for Cancer Genomics, Wake Forest University School of Medicine, Winston-Salem, North Carolina*
[2]*Center for Human Genomics, Wake Forest University School of Medicine, Winston-Salem, North Carolina*
[3]*Department of Urology, Wake Forest University School of Medicine, Winston-Salem, North Carolina*
[4]*Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts*
[5]*Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*
[6]*Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina*
[7]*Department of Urology, Örebro University Hospital, Örebro, Sweden*
[8]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institute of Health, Bethesda, Maryland*
[9]*Program in Molecular and Genetic Epidemiology, Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts*
[10]*The Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, Maryland*

**BACKGROUND.** Multiple DNA sequence variants in the form of single-nucleotide polymorphisms (SNPs) have been found to be reproducibly associated with prostate cancer (PCa) risk.

**METHODS.** Absolute risk for PCa among men with various numbers of inherited risk alleles and family history of PCa was estimated in a population-based case–control study in Sweden (2,893 cases and 1,781 controls), and a nested case–control study from the Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial in the U.S. (1,172 cases and 1,157 controls).

**RESULTS.** Increased number of risk alleles and positive family history were independently associated with PCa risk. Considering men with 11 risk alleles (mode) and negative family history as having baseline risk, men who had $\geq$14 risk alleles and positive family history had an odds ratio (OR) of 4.92 [95% confidence interval (CI): 3.64–6.64] in the Swedish study. These associations were confirmed in the U.S. population. Once a man's SNP genotypes and family history are known, his absolute risk for PCa can be readily calculated and easily interpreted. For example, 55-year-old men with a family history and $\geq$14 risk alleles have a 52% and 41% risk of being diagnosed with PCa in the next 20 years in the Swedish and U.S. populations, respectively. In comparison, without knowledge of genotype and family history, these men had an average population absolute risk of 13%.

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*Correspondence to: Dr. Jianfeng Xu, Center for Cancer Genomics, Medical Center Blvd, Winston-Salem, NC 27157.
E-mail: jxu@wfubmc.edu

**Correspondence to: Dr. William B. Isaacs, Marburg 115, Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21287.
E-mail: wisaacs@jhmi.edu

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**CONCLUSION.** This risk prediction model may be used to identify men at considerably elevated PCa risk who may be selected for chemoprevention. *Prostate 69: 1565–1572, 2009.*


*KEY WORDS:* **SNPs; association; early detection; chemoprevention**

## INTRODUCTION

Genetic susceptibility to prostate cancer (PCa) is well documented [1]. Recent genome-wide association studies (GWASs) have identified more than a dozen genetic variants that are associated with PCa risk [2–9], supporting the hypothesis of a polygenic inheritance for the disease. Although each of these variants is only moderately associated with PCa risk, collectively, they have a stronger, dose-dependent association with PCa risk as demonstrated in a 5-single-nucleotide polymorphism (SNP) model [10,11]. However, the associations, measured by odds ratio (OR) only, are of limited clinical utility due in part to the need for a comparison group for interpretation [12,13]. Absolute risk, a measurement of probability to develop a disease at a specific age, can be calculated based on an individual's own information and is easier to interpret. Herein, we report a prediction model of absolute risk for PCa using 14 SNPs and family history.

## METHODS

### Study Population

A large population-based PCa case–control study in Sweden named *CA*ncer of the *P*rostate in *S*weden (CAPS) was used to develop a risk prediction model. CAPS has been described in detail elsewhere and includes 2,899 PCa patients and 1,722 control subjects [10]. Positive family history was defined as any first- or second-degree relatives with a diagnosis of PCa. PCa patients who met any of the following criteria were classified as aggressive disease: T3/4, N+, M+, Gleason score sum $\geq$8, or PSA $>$50 ng/ml; otherwise, they were classified as non-aggressive disease. An independent study population in the U.S., which includes 1,172 PCa patients and 1,157 control subjects nested in the Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial, was used for confirmation [8]. The study was approved by the research ethics committees of each involved institute.

### Selection of SNPs

We selected 14 SNPs discovered in four PCa GWASs and follow-up fine mapping studies [2–9,14,15]. These included three SNPs at 8q24, two at 17q12, and one each at 3p12, 7p15, 7q21, 9q33, 10q11, 11q13, 17q24, 22q13, and Xp11. The SNP rs2735839 in the *KLK3* gene at 19q13 was not included because of a concern with possible PSA detection bias [16]. These 14 SNPs were genotyped in CAPS using a MassARRAY QGE iPLEX system (Sequenom, Inc., San Diego, CA). Two duplicate test samples and two blinded water samples were included in each 96-well plate. The genotype call rate was 98.3% and the concordance rate was 99.8%. For PLCO, 13 SNPs were genotyped and 1 SNP was imputed (rs16901979 at 8q24, call rate = 100%) [17], from the GWAS described elsewhere [8].

### Statistical Analyses

Tests for Hardy–Weinberg equilibrium were performed for each SNP among control subjects in each study using Fisher's exact test. The number of risk alleles of the 14 SNPs, determined from published studies, was counted for each subject. Men were classified into eight approximately equal sized groups based on number of risk alleles ($\leq$7, 8, 9, 10, 11, 12, 13, and $\geq$14). Association of number of risk alleles and family history (yes or no) with PCa risk was tested using a logistic regression model and adjusted for age and geographic region (for CAPS only). Number of risk alleles was modeled as a categorical variable with men who had 11 risk alleles (mode) serving as the baseline group. Multiplicative interaction of number of risk alleles and family history on PCa risk was tested by including additional interaction terms (product of family history and number of risk alleles). ORs for PCa for men with various combinations of number of risk alleles and family history were estimated from regression coefficients of these variables in the logistic regression model. Absolute risk was then estimated based on the OR, calibrated incidence rate of PCa for men with the most common number of risk alleles and negative family history, and mortality rate for all causes excluding PCa in Sweden and the U.S., respectively [18]. The calibrated incidence rates were calculated based on joint attributable risk of number of risk alleles and family history estimated from the data and population incidence rates in Sweden and the U.S. (2006 data) [19,20], as described by Chen et al. [21].

### Role of the Sponsor

The funding organizations had no role in the design and conduct of the study; collection, management,

analysis, and interpretation of the data; and preparation or approval of the manuscript. Drs. Grönberg and Xu had full access to the CAPS study and take responsibility for the integrity of the data and the accuracy of data analysis. Drs. Chanock, Hayes, Hunter, Kraft, and Thomas provided PLCO data.

## RESULTS

The possible number of inherited risk alleles of these 14 SNPs range between 0 and 27 because one of the risk SNPs is on the X chromosome. The observed range was between 0 and 21, with the most common number of risk alleles (mode) being 11 among control subjects of CAPS in Sweden. An increased number of risk alleles of these 14 SNPs and positive family history were independently associated with increased PCa risk in CAPS ($P = 5.9 \times 10^{-19}$ and $1.1 \times 10^{-15}$, respectively). Considering men with 11 risk alleles and negative family history as having baseline risk (OR = 1), men with <11 risk alleles and negative family history had OR <1, while men who had 11 or more and positive family history had OR >1 (Table I, top section). Men who had ≥14 risk alleles and positive family history, found in 4% of cases and 1% of controls, had the highest risk for PCa, with an OR of 4.92 (95% CI: 3.64–6.64). No

**TABLE I. Association of Prostate Cancer Risk With Number of Risk Alleles of 14 Risk SNPs and Family History in CAPS and PLCO**

| # of risk alleles | Family history | Number (%) of risk alleles | | OR (95% Cl)[a] |
|---|---|---|---|---|
| | | Controls | Cases | |
| CAPS | | | | |
| 0–7 | No | 171 (9.94) | 164 (5.66) | 0.71 (0.55–0.91) |
| 8 | No | 167 (9.70) | 174 (6.00) | 0.78 (0.61–1.01) |
| 9 | No | 191 (11.10) | 250 (8.63) | 0.95 (0.76–1.21) |
| 10 | No | 251 (14.58) | 334 (11.53) | 0.99 (0.80–1.24) |
| 11 | No | 259 (15.05) | 346 (11.94) | 1.00 (baseline) |
| 12 | No | 223 (12.96) | 353 (12.18) | 1.13 (0.91–1.41) |
| 13 | No | 147 (8.54) | 281 (9.70) | 1.41 (1.10–1.79) |
| ≥14 | No | 149 (8.66) | 446 (15.39) | 2.26 (1.79–2.86) |
| 0–7 | Yes | 17 (0.99) | 30 (1.04) | 1.54 (1.12–2.12) |
| 8 | Yes | 16 (0.93) | 37 (1.28) | 1.70 (1.24–2.33) |
| 9 | Yes | 23 (1.34) | 57 (1.97) | 2.07 (1.54–2.80) |
| 10 | Yes | 19 (1.10) | 65 (2.24) | 2.16 (1.61–2.89) |
| 11 | Yes | 26 (1.51) | 71 (2.45) | 2.17 (1.80–2.63) |
| 12 | Yes | 31 (1.80) | 88 (3.04) | 2.45 (1.84–3.27) |
| 13 | Yes | 16 (0.93) | 82 (2.83) | 3.06 (2.25–4.15) |
| ≥14 | Yes | 15 (0.87) | 120 (4.14) | 4.92 (3.64–6.64) |
| PLCO | | | | |
| 0–7 | No | 111 (10.08) | 53 (4.51) | 0.56 (0.38–0.81) |
| 8 | No | 111 (10.08) | 78 (6.63) | 0.76 (0.54–1.07) |
| 9 | No | 146 (13.26) | 94 (7.99) | 0.73 (0.53–1.00) |
| 10 | No | 181 (16.44) | 155 (13.18) | 0.93 (0.69–1.24) |
| 11 | No | 185 (16.80) | 163 (13.86) | 1.00 (baseline) |
| 12 | No | 121 (10.99) | 180 (15.31) | 1.63 (1.21–2.20) |
| 13 | No | 82 (7.45) | 150 (12.76) | 1.98 (1.42–2.74) |
| ≥14 | No | 97 (8.81) | 167 (14.2) | 2.02 (1.48–2.78) |
| 0–7 | Yes | 5 (0.45) | 8 (0.68) | 1.07 (0.74–1.55) |
| 8 | Yes | 9 (0.82) | 9 (0.77) | 1.46 (1.03–2.06) |
| 9 | Yes | 7 (0.64) | 10 (0.85) | 1.39 (1.01–1.92) |
| 10 | Yes | 14 (1.27) | 16 (1.36) | 1.78 (1.33–2.37) |
| 11 | Yes | 8 (0.73) | 18 (1.53) | 1.92 (1.41–2.62) |
| 12 | Yes | 12 (1.09) | 28 (2.38) | 3.13 (2.32–4.22) |
| 13 | Yes | 8 (0.73) | 20 (1.70) | 3.79 (2.73–5.26) |
| ≥14 | Yes | 4 (0.36) | 27 (2.30) | 3.88 (2.83–5.33) |

CAPS, *CA*ncer of the *P*rostate in *S*weden; PLCO, Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial.
[a]Odds ratio (OR) was adjusted for age and geographic region (CAPS only).

evidence of a multiplicative interaction effect on PCa risk between number of risk alleles and family history was found ($P = 0.89$, degrees of freedom = 7). The OR of each increasing number of risk alleles on aggressive and non-aggressive was 1.11 (95% CI: 1.09–1.15) and 1.16 (95% CI: 1.13–1.20), respectively. The difference was not statistically significant between these two types of PCa, $P = 0.82$. Men with higher numbers of inherited risk alleles of these 14 SNPs and positive family history had similar OR estimates for aggressive and non-aggressive PCa. For example, men who had ≥14 risk alleles and positive family history were found in 3.52% and 4.62% of aggressive and non-aggressive PCa. Compared with men who had 11 risk alleles and negative family history, men who had ≥14 risk alleles and positive family history had an OR of 4.77 (95% CI: 3.41–6.69) and 5.05 (95% CI: 3.66–6.96) for aggressive and non-aggressive PCa, respectively.

We performed a confirmation study of these 14 SNPs and family history on PCa risk in the U.S. PLCO population. The most common number of risk alleles of these 14 SNPs was also 11 in control subjects of PLCO. We confirmed that the increased number of risk alleles of these 14 SNPs and positive family history were independently associated with increased PCa risk in PLCO ($P = 1.3 \times 10^{-18}$ and $4.2 \times 10^{-5}$, respectively). Considering men with 11 risk alleles and negative family history as having baseline risk (OR = 1), men with <11 risk alleles and negative family history had OR <1, while men who had 11 or more and positive family history had OR >1 (Table I, bottom section). For example, men who had ≥14 risk alleles and positive family history also had the highest risk for PCa; OR = 3.88 (95% CI: 2.83–5.33).

Absolute risk for PCa at a specific age conditional on survival to that age can be estimated based on the OR estimates described above (Table II). Assuming men with 11 risk alleles and negative family history to be at a baseline risk, men who have a higher number of risk alleles and/or positive family history had an elevated absolute risk. For example, 55-year-old men with a family history and ≥14 risk alleles have a 52% and 41% risk of being diagnosed with PCa in the next 20 years in Sweden and the U.S., respectively. In contrast, their risk is 8% and 6% risk, respectively, in Sweden and in the U.S. if they have 0–7 risk alleles and do not have family history. Without knowledge of these SNPs and family history, these men would have an absolute risk of 13% due to their general population risk.

## DISCUSSION

We found that the number of risk alleles of the 14 SNPs and family history were independently associated with PCa risk in a Swedish population and confirmed these findings in a U.S. population. We further developed a risk prediction model, measured by absolute risk, based on genotypes at 14 SNPs and family history. This risk prediction model is simple to use and easy to interpret. The number of risk alleles of these SNPs can be accurately measured from blood or saliva specimens in a single assay. The absolute risk for PCa measures the likelihood of an individual's risk to develop PCa at a specific age and can be easily estimated once his number of risk alleles and family history are known. The result of absolute risk is specific for men who have the same characteristics in terms of number of risk alleles and family history, and can be easily interpreted by physicians and patients without a need for a reference group. Another major feature of this risk prediction model is the fact that it is informative across a range of risk strata. It can distinguish the absolute risk of an individual from as low as 6–8% to as high as 41–52% in the next 20 years for 55-year-old men in these two populations.

There are several major limitations of this risk prediction model. First, it is recognized that the vast majority of men will fall into risk categories that are at or close to average. This limitation reflects the underlying complexity of this disease where multiple genes and environmental exposures may contribute to its development. A risk prediction model that considerably separates risk to PCa for all men in the population requires predictors that have extraordinarily high OR for the disease (greater than 350), and is unlikely to be found for PCa [22]. However, it is important to note that the primary utility of this risk prediction model is not to assess PCa risk for all men but to identify a small subset of men at highest risk for PCa. For this reason, we did not provide an estimate of area under curve (AUC) of the receiver operating characteristic of this prediction model which is an indication of its usefulness for the former purpose. It is striking to note that this model identifies about 0.5–1% of men (those having ≥14 risk alleles and a positive family history) at greatest risk (41% and 52% risk) for developing PCa between ages 55 and 74 years in the U.S. and Sweden, respectively. This frequency and magnitude of risk are comparable to breast cancer among women who have *BRCA1* and *BRCA2* mutations in the general population [23].

Information on PCa risk has clinical and public health relevance. Men with a higher likelihood of PCa may choose to begin PSA-based PCa screening at an earlier age. Men with greater risk may also pursue preventative measures, including diet/lifestyle intervention and chemoprevention. It is particularly important to note its potential utility in identifying a subset of men who are at greatest risk for PCa for targeted chemoprevention. For example, finasteride is a chemopreventive agent for PCa which has been shown to

**TABLE II. Estimates of Absolute Risk for Prostate Cancer Based on Number of Risk Alleles and Family History in CAPS and PLCO**

| | | Absolute risk at specific age (year)[a] | | | | |
|---|---|---|---|---|---|---|
| # of risk alleles | Family history | 55–59 | 60–64 | 65–69 | 70–74 | 55–74 |
| CAPS | | | | | | |
| 0–7 | No | 0.01 | 0.02 | 0.02 | 0.03 | 0.08 |
| 8 | No | 0.01 | 0.02 | 0.03 | 0.03 | 0.08 |
| 9 | No | 0.01 | 0.02 | 0.03 | 0.04 | 0.10 |
| 10 | No | 0.01 | 0.02 | 0.03 | 0.04 | 0.11 |
| 11 | No, baseline | 0.01 | 0.02 | 0.03 | 0.04 | 0.11 |
| 12 | No | 0.01 | 0.03 | 0.04 | 0.04 | 0.12 |
| 13 | No | 0.02 | 0.03 | 0.05 | 0.05 | 0.15 |
| ≥14 | No | 0.03 | 0.05 | 0.07 | 0.09 | 0.24 |
| 0–7 | Yes | 0.02 | 0.04 | 0.05 | 0.06 | 0.17 |
| 8 | Yes | 0.02 | 0.04 | 0.06 | 0.07 | 0.18 |
| 9 | Yes | 0.02 | 0.05 | 0.07 | 0.08 | 0.22 |
| 10 | Yes | 0.03 | 0.05 | 0.07 | 0.08 | 0.23 |
| 11 | Yes | 0.03 | 0.05 | 0.07 | 0.08 | 0.23 |
| 12 | Yes | 0.03 | 0.06 | 0.08 | 0.09 | 0.26 |
| 13 | Yes | 0.04 | 0.07 | 0.10 | 0.12 | 0.32 |
| ≥14 | Yes | 0.06 | 0.11 | 0.16 | 0.18 | 0.52 |
| PLCO | | | | | | |
| 0–7 | No | 0.01 | 0.01 | 0.02 | 0.02 | 0.06 |
| 8 | No | 0.01 | 0.02 | 0.03 | 0.03 | 0.08 |
| 9 | No | 0.01 | 0.02 | 0.02 | 0.03 | 0.08 |
| 10 | No | 0.01 | 0.02 | 0.03 | 0.04 | 0.10 |
| 11 | No, baseline | 0.01 | 0.02 | 0.03 | 0.04 | 0.11 |
| 12 | No | 0.02 | 0.04 | 0.06 | 0.06 | 0.18 |
| 13 | No | 0.03 | 0.04 | 0.07 | 0.08 | 0.21 |
| ≥14 | No | 0.03 | 0.05 | 0.07 | 0.08 | 0.22 |
| 0–7 | Yes | 0.01 | 0.02 | 0.04 | 0.04 | 0.12 |
| 8 | Yes | 0.02 | 0.03 | 0.05 | 0.06 | 0.16 |
| 9 | Yes | 0.02 | 0.03 | 0.05 | 0.05 | 0.15 |
| 10 | Yes | 0.02 | 0.04 | 0.06 | 0.07 | 0.19 |
| 11 | Yes | 0.02 | 0.04 | 0.07 | 0.07 | 0.21 |
| 12 | Yes | 0.04 | 0.07 | 0.11 | 0.12 | 0.34 |
| 13 | Yes | 0.05 | 0.09 | 0.13 | 0.14 | 0.40 |
| ≥14 | Yes | 0.05 | 0.09 | 0.13 | 0.15 | 0.41 |

CAPS, *CA*ncer of the *P*rostate in *S*weden; PLCO, Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial.
[a]Absolute risk was estimated based on OR, calibrated incidence of prostate cancer for men without family history, and mortality rate for all causes excluding prostate cancer in Sweden and the U.S., respectively [19,20]. Calibrated incidence rates were calculated based on joint attributable risk of number of risk alleles and family history and incidence rates in general populations of Sweden and the U.S., as described by Chen et al. [21].

reduce PCa risk by 25% [24]. However, targeting all men of age 55 and older is not cost-effective for society, and is estimated to yield a gain of 6 life-years per 1,000 men treated at a cost of ~1,660,000 per life-year gained [25]. An alternative strategy is to target those men who are at elevated risk for PCa for chemoprevention. The preventive effect of chemoprevention might be stronger among men at higher risk under a polygenic model [26]. Even if the chemoprevention effect is the same for men with higher or lower absolute risk for PCa, the net gain would be larger for men at higher risk. For example, assuming a 25% reduction of PCa using finasteride, men at 13% absolute risk (average risk to develop PCa at age 55–74 years in the U.S. and Sweden) would decrease risk by 3% while men at 41–52% risk would decrease risk by 10–13%. Furthermore, men at elevated risk may be more likely to choose and adhere to a chemoprevention regimen. The potential clinical utility of this approach remains to be tested in a clinical trial.

The second major limitation is that this risk prediction model does not distinguish risk of aggressive

from non-aggressive PCa, and therefore may exacerbate the potential problem of over-diagnosis and over-treatment of PCa. This limitation is primarily due to the drawback that these PCa risk-associated SNPs were identified by comparing both types of PCa with unaffected controls using GWAS. A recent large study comparing these risk-associated SNPs among 1,253 aggressive and 4,233 non-aggressive PCa cases using a case–case study design found that none of these 14 SNPs had significant differences in allele and genotype frequencies between the two types of PCa [27]. While this concern needs to be addressed by including yet to be discovered genetic markers that distinguish aggressive from non-aggressive PCa, this risk prediction model, when combined with its utility in promoting chemoprevention among men at elevated risk, may reduce PCa incidence. Despite the inability of this approach to discern aggressive or non-aggressive PCa, if chemoprevention could decrease the number of men developing any PCa, such men would be spared the decisions which burden men diagnosed with PCa. Again, the benefits and risks of this type of risk prediction modeling need to be further evaluated.

There are three additional methodological considerations related to this study. Rather than give each of these SNPs the same weight in assessing their cumulative effect on PCa risk by counting number of risk alleles, an alternative approach is to give different weights for these SNPs based on their OR. Although we believe that this alternative method may provide a slightly better prediction model within any single study where the model is developed, it may be difficult to generalize the results to other studies because an accurate OR estimate of each SNP requires large sample sizes and the point estimate of each SNP may vary by study populations. Furthermore, our approach, by counting number of risk alleles, is less cumbersome for clinicians and patients alike.

The absolute risk in CAPS may be overestimated because ORs from the case–control study were used to approximate relative risk (RR) in CAPS. It is known that ORs tend to overestimate RRs when a disease incidence is high, especially when the ORs are farther away from the null (OR = 1). Estimates of absolute risk in PLCO are more reliable because the ORs are equivalent to RR due to the use of an incidence density sampling method for case/control selection. Differences in designs between the two studies may account for the slightly lower estimates of absolute risk in the U.S. population.

Finally, although we did not include the SNP rs2735839 in *KLK3* gene at 19q13 because of a concern with possible PSA detection bias [16], several of the 14 SNPs we did include may also be susceptible to this bias because they are associated with PSA levels among men without PCa [28]. If men inherit alleles that are associated with higher PSA levels, they will be more likely to have higher PSA levels, thus increasing the frequency of biopsy for PCa, which in turn increases the chance of being diagnosed with PCa. The potential bias of these SNPs in PCa risk prediction models should be tested in studies, such as Prostate Cancer Prevention Trial [24], where all men are biopsied for PCa regardless of PSA levels.

The current risk prediction model was based on 14 risk SNPs that were discovered in the past 2 years [2–9,14,15]. More risk SNPs will most likely be discovered from ongoing and combined GWASs because these 14 risk SNPs account for less than 6% of genetic variation in PCa risk in this Swedish population [14]. The ability to differentiate men's risk to PCa may be further improved using additional risk SNPs for this polygenic disease [29], although diminishing returns in prediction may be encountered [13]. However, it is important to stress that the potential benefit of using risk SNPs in predicting disease risk may be stronger in PCa than other diseases because only three risk factors (age, race, and family history) have been consistently shown to be associated with PCa [1].

In conclusion, genetic markers have the potential to identify men at greater risk for PCa. Larger cohort studies are warranted to obtain more accurate estimates of absolute risk. Geneticists, epidemiologists, clinicians, and genetic counselors need to work together to continue to improve the performance and implementation of these markers, and assess the risks and benefits of this information, to further improve the care of men at risk for PCa.

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## REFERENCES

1. Gronberg H. Prostate cancer epidemiology. Lancet 2003;361: 859–864.
2. Amundadottir LT, Sulem P, Gudmundsson J, Helgason A, Baker A, Agnarsson BA, Sigurdsson A, Benediktsdottir KR, Cazier JB, Sainz J, Jakobsdottir M, Kostic J, Magnusdottir DN, Ghosh S, Agnarsson K, Birgisdottir B, Le Roux L, Olafsdottir A, Blondal T, Andresdottir M, Gretarsdottir OS, Bergthorsson JT, Gudbjartsson D, Gylfason A, Thorleifsson G, Manolescu A, Kristjansson K, Geirsson G, Isaksson H, Douglas J, Johansson JE, Bälter K, Wiklund F, Montie JE, Yu X, Suarez BK, Ober C, Cooney KA, Gronberg H, Catalona WJ, Einarsson GV, Barkardottir RB, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. A common variant associated with prostate cancer in European and African populations. Nat Genet 2006;38:652–658.
3. Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, Helgason A, Rafnar T, Bergthorsson JT, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Xu J, Blondal T, Kostic J, Sun J, Ghosh S, Stacey SN, Mouy M, Saemundsdottir J, Backman VM, Kristjansson K, Tres A, Partin AW, Albers-Akkers MT, Godino-Ivan Marcos J, Walsh PC, Swinkels DW, Navarrete S, Isaacs SD, Aben KK, Graif T, Cashy J, Ruiz-Echarri M, Wiley KE, Suarez BK, Witjes JA, Frigge M, Ober C, Jonsson E, Einarsson GV, Mayordomo JI, Kiemeney LA, Isaacs WB, Catalona WJ, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. Nat Genet 2007;39:631–637.
4. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, Minichiello MJ, Fearnhead P, Yu K, Chatterjee N, Wang Z, Welch R, Staats BJ, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Gelmann EP, Tucker M, Gerhard DS, Fraumeni JF, Jr., Hoover R, Hunter DJ, Chanock SJ, Thomas G. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet 2007;39:645–649.
5. Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, Rafnar T, Gudbjartsson D, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Blondal T, Stacey SN, Helgason A, Gunnarsdottir S, Olafsdottir A, Kristinsson KT, Birgisdottir B, Ghosh S, Thorlacius S, Magnusdottir D, Stefansdottir G, Kristjansson K, Bagger Y, Wilensky RL, Reilly MP, Morris AD, Kimber CH, Adeyemo A, Chen Y, Zhou J, So WY, Tong PC, Ng MC, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Tres A, Fuertes F, Ruiz-Echarri M, Asin L, Saez B, van Boven E, Klaver S, Swinkels DW, Aben KK, Graif T, Cashy J, Suarez BK, van Vierssen Trip O, Frigge ML, Ober C, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Palmer CN, Rotimi C, Chan JC, Pedersen O, Sigurdsson G, Benediktsson R, Jonsson E, Einarsson GV, Mayordomo JI, Catalona WJ, Kiemeney LA, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet 2007; 39:977–983.
6. Duggan D, Zheng SL, Knowlton M, Benitez D, Dimitrov L, Wiklund F, Robbins C, Isaacs SD, Cheng Y, Li G, Sun J, Chang BL, Marovich L, Wiley KE, Bälter K, Stattin P, Adami HO, Gielzak M, Yan G, Sauvageot J, Liu W, Kim JW, Bleecker ER, Meyers DA, Trock BJ, Partin AW, Walsh PC, Isaacs WB, Grönberg H, Xu J, Carpten JD. Two genome-wide association studies of aggressive prostate cancer implicate putative prostate tumor suppressor gene DAB2IP. J Natl Cancer Inst 2007;99:1836–1844.
7. Gudmundsson J, Sulem P, Rafnar T, Bergthorsson JT, Manolescu A, Gudbjartsson D, Agnarsson BA, Sigurdsson A, Benediktsdottir KR, Blondal T, Jakobsdottir M, Stacey SN, Kostic J, Kristinsson KT, Birgisdottir B, Ghosh S, Magnusdottir DN, Thorlacius S, Thorleifsson G, Zheng SL, Sun J, Chang BL, Elmore JB, Breyer JP, McReynolds KM, Bradley KM, Yaspan BL, Wiklund F, Stattin P, Lindström S, Adami HO, McDonnell SK, Schaid DJ, Cunningham JM, Wang L, Cerhan JR, St Sauver JL, Isaacs SD, Wiley KE, Partin AW, Walsh PC, Polo S, Ruiz-Echarri M, Navarrete S, Fuertes F, Saez B, Godino J, Weijerman PC, Swinkels DW, Aben KK, Witjes JA, Suarez BK, Helfand BT, Frigge ML, Kristjansson K, Ober C, Jonsson E, Einarsson GV, Xu J, Gronberg H, Smith JR, Thibodeau SN, Isaacs WB, Catalona WJ, Mayordomo JI, Kiemeney LA, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. Nat Genet 2008;40:281–283.
8. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, Yu K, Chatterjee N, Welch R, Hutchinson A, Crenshaw A, Cancel-Tassin G, Staats BJ, Wang Z, Gonzalez-Bosquet J, Fang J, Deng X, Berndt SI, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cussenot O, Valeri A, Andriole GL, Crawford ED, Tucker M, Gerhard DS, Fraumeni JF, Jr., Hoover R, Hayes RB, Hunter DJ, Chanock SJ. Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet 2008; 40:310–315.
9. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, Mulholland S, Leongamornlert DA, Edwards SM, Morrison J, Field HI, Southey MC, Severi G, Donovan JL, Hamdy FC, Dearnaley DP, Muir KR, Smith C, Bagnato M, Ardern-Jones AT, Hall AL, O'Brien LT, Gehr-Swain BN, Wilkinson RA, Cox A, Lewis S, Brown PM, Jhavar SG, Tymrakiewicz M, Lophatananon A, Bryant SL, UK Genetic Prostate Cancer Study Collaborators, British Association of Urological Surgeons' Section of Oncology, UK ProtecT Study Collaborators. Horwich A, Huddart RA, Khoo VS, Parker CC, Woodhouse CJ, Thompson A, Christmas T, Ogden C, Fisher C, Jamieson C, Cooper CS, English DR, Hopper JL, Neal DE, Easton DF, Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet 2008;40:316–321.
10. Zheng SL, Sun J, Wiklund F, Smith S, Stattin P, Li G, Adami HO, Hsu FC, Zhu Y, Bälter K, Kader AK, Turner AR, Liu W, Bleecker ER, Meyers DA, Duggan D, Carpten JD, Chang BL, Isaacs WB, Xu J, Grönberg H. Cumulative association of five genetic variants with prostate cancer. N Engl J Med 2008;358:910–919.
11. Sun J, Chang BL, Isaacs SD, Wiley KE, Wiklund F, Stattin P, Duggan D, Carpten JD, Trock BJ, Partin AW, Walsh PC, Grönberg H, Xu J, Isaacs WB, Zheng SL. Cumulative effect of five genetic variants on prostate cancer risk in multiple study populations. Prostate 2008;68:1257–1262.
12. Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? Br Med J 1999;319:1562–1565.

13. Janssens AC, van Duijn CM. Genome-based prediction of common diseases: Advances and prospects. Hum Mol Genet 2008;17(R2):R166–R173 (review).
14. Sun J, Zheng SL, Wiklund F, Isaacs SD, Purcell LD, Gao Z, Hsu FC, Kim ST, Liu W, Zhu Y, Stattin P, Adami HO, Wiley KE, Dimitrov L, Sun J, Li T, Turner AR, Adams TS, Adolfsson J, Johansson JE, Lowey J, Trock BJ, Partin AW, Walsh PC, Trent JM, Duggan D, Carpten J, Chang BL, Grönberg H, Isaacs WB, Xu J. Evidence for two independent prostate cancer risk-associated loci in the HNF1B gene at 17q12. Nat Genet 2008;40:1153–1155.
15. Sun J, Zheng SL, Wiklund F, Isaacs SD, Li G, Wiley KE, Kim ST, Zhu Y, Zhang Z, Hsu FC, Turner AR, Stattin P, Liu W, Kim JW, Duggan D, Carpten J, Grönberg H, Isaacs WB, Xu J, Chang B-L. Sequence variants at 22q13 are associated with prostate cancer risk. Cancer Res 2009;69:10–15.
16. Ahn J, Berndt SI, Wacholder S, Kraft P, Kibel AS, Yeager M, Albanes D, Giovannucci E, Stampfer MJ, Virtamo J, Thun MJ, Feigelson HS, Cancel-Tassin G, Cussenot O, Thomas G, Hunter DJ, Fraumeni JF Jr, Hoover RN, Chanock SJ, Hayes RB. Variation in KLK genes, prostate-specific antigen and risk of prostate cancer. Nat Genet 2008;40:1032–1034.
17. Marchini J, Howie B, Myers S, McVean G, Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. Nat Genet 2007;39:906–913.
18. Dupont WD. Converting relative risks to absolute risks: A graphical approach. Stat Med 1989;8:641–651.
19. The National Board of Health, Welfare of Sweden. Statistical databases [documents on the Internet]. Socialstyrelsen online; Sept 27, 2007 [cited Apr 26, 2009]. Available from: http://www.socialstyrelsen.se/en/Statistics/Statistical_databases.htm.
20. Surveillance Research Program, NCI. Surveillance, epidemiology and end results (SEER) [documents on the Internet]. National Cancer Institute online [cited Apr 26, 2009] http://seer.cancer.gov/.
21. Chen J, Pee D, Ayyagari R, Graubard B, Schairer C, Byrne C, Benichou J, Gail MH. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. J Natl Cancer Inst 2006;98:1215–1226.
22. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. Am J Epidemiol 2004;159:882–890.
23. Fackenthal JD, Olopade OI. Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. Nat Rev Cancer 2007;7:937–948 (review).
24. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA Jr. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215–224.
25. Zeliadt SB, Etzioni RD, Penson DF, Thompson IM, Ramsey SD. Lifetime implications and cost-effectiveness of using finasteride to prevent prostate cancer. Am J Med 2005;118:850–857.
26. Wray NR, Goddard ME, Visscher PM. Prediction of individual genetic risk of complex disease. Curr Opin Genet Dev 2008; 18:257–263 (review).
27. Kader AK, Sun J, Isaacs SD, Wiley KE, Yan G, Kim S, Fedor H, DeMarzo AM, Epstein JI, Walsh PC, Partin AW, Trock B, Zheng SL, Xu J, Isaacs W. Individual and cumulative effect of prostate cancer risk-associated variants on clinicopathologic variables in 5,895 prostate cancer patients. Prostate 2009 [Epub ahead of print].
28. Wiklund F, Zheng SL, Sun J, Adami HO, Lilja H, Hsu FC, Stattin P, Adolfsson J, Cramer SD, Duggan D, Carpten JD, Chang BL, Isaacs WB, Grönberg H, Xu J. Association of reported prostate cancer risk alleles with PSA levels among men without a diagnosis of prostate cancer. Prostate 2009;69:419–427.
29. Janssens AC, Aulchenko YS, Elefante S, Borsboom GJ, Steyerberg EW, van Duijn CM. Predictive testing for complex diseases using multiple genes: Fact or fiction? Genet Med 2006;8:395–400.