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Comparison of two methods for estimating absolute risk of prostate cancer based on SNPs and family history

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Abstract

Disease risk-associated single nucleotide polymorphisms (SNPs) identified from genome-wide association studies have the potential to be used for disease risk prediction. An important feature of these risk-associated SNPs is their weak individual effect but stronger cumulative effect on disease risk. Several approaches are commonly used to model the combined effect in risk prediction but their performance is unclear. We compared two methods to model the combined effect of 14 prostate cancer (PCa) risk-associated SNPs and family history for the estimation of absolute risk for PCa in a population-based case-control study in Sweden (2,899 cases and 1,722 controls). Method 1 weighs each risk allele equally using a simple method of counting the number of risk alleles while Method 2 weighs each risk SNP differently based on their respective Odds Ratios. We found considerable differences between the two methods. Absolute risk estimates from Method 1 were generally higher than that of Method 2, especially among men at higher risk. The difference in the overall discriminative performance, measured by area under the curve (AUC) of the receiver operating characteristic was small between Method 1 (0.614) and Method 2 (0.618), $P = 0.20$. However, the performance of these two methods in identifying high-risk individuals (two-fold or three-fold higher than average risk), measured by positive predictive values (PPV), was higher for Method 2 than Method 1. In conclusion, these results suggest that Method 2 is superior to Method 1 in estimating absolute risk if the purpose of risk prediction is to identify high-risk individuals.

Keywords

Absolute risk; SNPs; association; prostate cancer; genomic medicine

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INTRODUCTION

Genome-wide association studies (GWAS) have led to the discovery of more than two dozen genetic variants that are associated with prostate cancer (PCa) risk (1–12). These genetic variants are common in the general population of European descent, and associations with PCa risk are consistently observed in multiple studies. Although each of these variants is only moderately associated with PCa risk, collectively, they have a stronger, dose-dependent association with PCa risk (13–15). The discovery of a large number of risk-associated genetic variants, compared to only three previously known risk factors for PCa (age, race, and family history), represents a major breakthrough in risk profiling and may improve the ability to predict an individual's risk for PCa. Such risk prediction is an important step towards the overall goals of personalized medicine and allows for the identification of high risk individuals for prevention, screening, and early diagnosis.

Absolute risk is an informative measurement of the probability of developing a disease at a specific age and can be easily interpreted by physicians and patients. Two methods are commonly used to estimate absolute risk when genetic variants are included as predictors. One method treats each risk allele equally and uses a simple method of counting the number of risk alleles. Another method weighs each risk SNP differently based on their individual Odds Ratios (ORs). The relative performance of these two methods in estimating absolute risk of disease is unclear. Herein, we compare the absolute risk estimates of these two methods when the same genetic variants are used.

SUBJECTS AND METHODS

Study population

A large population-based PCa case–control study in Sweden named CAnceR of the Prostate in Sweden (CAPS) was used to develop a risk prediction model. CAPS has been described in detail elsewhere (13). Briefly, PCa patients in CAPS were identified and recruited from regional cancer registries in Sweden (all Caucasians). The inclusion criterion for case subjects was pathologically or cytologically verified adenocarcinoma of the prostate, diagnosed between July 2001 and October 2003. DNA samples from blood and tumor-node-metastasis stage, Gleason grade (biopsy), and prostate-specific antigen (PSA) levels at diagnosis were available for 2,899 patients. Control subjects were recruited concurrently with case subjects. They were randomly selected from the Swedish Population Registry, and matched according to the expected age distribution of cases (groups of 5-y intervals) and geographic region. DNA samples from blood were available for 1,722 control subjects. Positive family history was defined as any first- or second-degree relatives with a diagnosis of PCa. The research ethics committees at Wake Forest University School of Medicine and the Karolinska Institute approved the study.

Selection of SNPs

We selected 14 SNPs discovered in four PCa GWAS and follow-up fine mapping studies reported before June 2009 (1–8,16–18) (Supplemental table 1). All of these SNPs were selected from GWAS that were based on Caucasian populations. These included three SNPs at 8q24 (16–17), two at 17q12 (18), and one each at 3p12, 7p15, 7q21, 9q33, 10q11, 11q13, 17q24, 22q13, and Xp11 (1–8). The SNP rs2735839 in the *KLK3* gene at 19q13 was not included because of a concern for possible PSA detection bias (19). These 14 SNPs were genotyped in CAPS using a Mass ARRAY 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 average genotype call rate was 98.3% and the concordance rate was 99.8%. All SNPs are in Hardy-Weinberg equilibrium. ($P>0.05$).

Statistical analyses

Two methods were used to estimate absolute risk for PCa for each individual based on their genotypes at these 14 risk-associated SNPs and family history. They differed primarily in the form of estimating the combined effect of these 14 SNPs and family history. In the first method (Method 1), the combined effect of these 14 SNPs was modeled cumulatively by treating each risk allele equally and simply counting the number of risk alleles (14). We first counted the number of risk alleles of these 14 SNPs of each subject and then classified them into eight approximately equally sized groups (≤ 7 , 8, 9, 10, 11, 12, 13, and ≥ 14 number of risk alleles). Thus, only one variable with eight categories was created for the cumulative effect of the SNPs. ORs for the number of risk alleles (8 categorical variables) and family history (yes or no) were estimated from a logistic regression model with men who had 11 risk alleles (mode) and negative family history of PCa serving as the reference group. OR is a measure describing the strength of association between two binary data values. Here it was used to explore the association between PCa and number of risk alleles (each categorized group vs. the reference group) and family history. The absolute risk of developing PCa between age 55 and 74 years old was then estimated for each man based on the OR of their respective status of number of risk alleles and family history, calibrated incidence rate of PCa, and mortality rate for all causes excluding PCa in Sweden (20). The calibrated incidence rate was needed to infer the incidence rate estimate for men without a family history based on the population incidence rate in Sweden (21) which includes men with and without family history. It was calculated based on the attributable risk of family history that was estimated from the CAPS and population incidence rates in Sweden, using a method described by Chen et al. (22).

In the second method (Method 2), the combined effect of these 14 SNPs and family history was modeled by multiplying the OR of each individual risk SNP and family history, as described in a simple multiplicative (log-additive) model by Pharoah et al. (23). We briefly described how the absolute risk was obtained in the following four steps: 1) the allelic OR assuming an additive model for each SNP was first estimated in CAPS using a logistic regression model, 2) a multiplicative model assuming no interaction was used to derive genotype relative risks from the allelic OR, 3) for each of the three genotypes at each SNP, we converted the genotype relative risk to the risk relative to the average risk in the population (23), and 4) we derived the overall risk relative to the population by multiplying the risks relative to the population of all SNPs as well as the family history of the individual. The absolute risk for each man was then estimated based on the overall risk relative to the population, the incidence rate of PCa in the general population, and the mortality rate for all causes excluding PCa in Sweden.

We used two methods to compare the absolute risk estimates from Methods 1 and 2. We used the Spearman's rank correlation coefficient to assess the consistency of estimated absolute risk among study subjects between the two methods. We also used Kappa statistics to compare agreement between the two methods and to correct for chance agreement.

We used area under the curve (AUC) statistics of the receiver operating characteristic (ROC) to assess the overall performance of estimated absolute risk in discriminating PCa cases and controls. ROC is a plot of the sensitivity vs. (1-specificity) of classifying PCa at various thresholds. AUC quantifies the overall ability to discriminate between those who have the disease and those who do not have the disease and ranges from 0.5 (useless) to 1 (perfect). A nonparametric approach developed by Delong and colleagues was used to test for equality of the AUCs (24). The analysis was performed using Stata software, version 8.2. We also assessed the performance of estimated absolute risk at specific cutoff values using sensitivity, specificity, and positive predictive value (PPV), where PPV was calculated based on sensitivity, specificity, and prevalence using Bayes' theorem. A range of prevalences, 0.1, 0.15, and 0.2 were used (25).

RESULTS AND DISCUSSION

The absolute risk of developing PCa between age 55 and 74 years old was estimated for each subject in CAPS using Method 1 and Method 2, respectively, and is presented in Figure 1. There were 16 distinct values of absolute risk estimates derived from Method 1 because subjects fall in 16 risk groups: 8 groups of number of risk alleles (≤ 7 , 8, 9, 10, 11, 12, 13, and ≥ 14) and 2 groups of family history (yes or no) (Figure 1a). The estimated absolute risks ranged from as low as 0.08 to as high as 0.52. Although the vast majority of subjects had an absolute risk at or near the average risk of 0.11, 26% of men had an absolute risk that was more than two-fold the average risk. The absolute risk estimates derived from Method 2 were continuous (Figure 1b). Again, while the vast majority of men had an absolute risk that was at or near the average risk, 10% of subjects had absolute risk that was more than two-fold the average risk. Interestingly, one subject had an absolute risk estimate of 1.42 using Method 2. Although the actual risk (probability) for PCa cannot exceed 1, it is numerically possible to have an absolute risk estimate of greater than 1 in Method 2 in rare situations when subjects have many risk alleles. For example, only one subject in our study had an absolute risk estimate larger than 1 (he inherited 19 risk alleles of these 14 SNPs) and no other subjects had absolute risk estimate greater than 0.8. This outlier was removed from further analysis in this study. In addition, we have provided the relative risks and corresponding absolute risks in Supplemental table 2. For example, the relative risk is approximately 4 when the absolute risk is higher than 0.5.

The absolute risks for the same subject estimated from these two different methods are presented in a scatter plot (Figure 2). The correlation coefficient (r^2) of absolute risk between the two methods was estimated to be 0.941 (95% confidence interval: 0.938–0.944). For men in each of the 16 risk groups based on Method 1, a large amount of variation was observed in the absolute risk estimates from Method 2. The mean absolute risk estimates were all higher in Method 1 than Method 2 for each of the 16 risk groups (Table 1). Assuming Method 2 is more accurate because exact estimates of OR of each predictor was used in the prediction model, this comparison suggests an upward bias in estimating absolute risk using Method 1 in this specific example. When we examined the categorical concordance of men classified as having high risk of PCa, defined by absolute risk of more than two-fold (≥ 0.22) or three-fold (≥ 0.33) of average risk, the Kappa statistics was estimated to be 0.56 and 0.74, respectively. Overall, these results suggest considerable differences in estimating absolute risk and in defining high risk individuals for PCa between the two methods.

Finally, we assessed the performance of these two risk prediction methods in discriminating cases and controls in CAPS. We first compared the overall performance of these two methods in correctly discriminating case and control status using the AUC statistics. The AUC for Method 2 (0.618) was slightly higher than Method 1 (0.614), although the difference was not statistically significant, $P = 0.20$. Furthermore, considering the primary utility of the risk prediction model is to identify men at considerably elevated risk for PCa, we then compared the predictive performance of these two methods at two specific cutoff values of absolute risk: twofold and three-fold of average risk. The sensitivity, specificity, and PPV of these two methods are presented in Table 2. Method 2 had 0.03 to 0.04 higher PPV when using two-fold or threefold as the cutoff value, suggesting this method is more accurate in predicting PCa than Method 1.

There are a number of limitations in these analyses. First, several newly reported PCa risk associated SNPs were not included in the risk prediction model (9–12). The omission of these SNPs may affect the estimates of absolute values of risk. Second, although we excluded the SNP (rs2735839) in the *KLK3* gene, other reported PCa-risk associated SNPs that were included in the risk prediction model may also be influenced by PSA detection bias (19,26). The inclusion of SNPs influenced by PSA-detection bias may affect the validity of risk

prediction. Note that for sensitivity analysis, we included SNP rs2735839 in the analysis and the result was similar. Third, we used the OR estimated from the CAPS study population in risk prediction of CAPS subjects and then assessed the performance of risk prediction in the same study population. This circular approach likely led to an upward bias in the estimates of predictive performance. Finally, we used PPV to assess prediction performance in this case-control study. It is well known that PPV should be estimated from cohort studies because PPV is sensitive to the prevalence of diseases. Here we overcome this issue by using Bayes's theorem and assuming a range of reasonable prevalences in the calculation. In addition, the emphasis in this study is to compare the PPVs between the two methods, not the absolute values of the PPVs. Altogether, these limitations will likely affect the absolute values of PCa risk estimates and statistics of predictive performance. However, they are not likely to have a substantial impact on the interpretation of these results because the primary focus of this study is to compare the difference between the two risk prediction methods, where both suffered from these limitations.

With these caveats, results from this study provide needed information on the differences of these two commonly used methods in the estimation of PCa absolute risk and in predictive and discriminative performance. These results indicated considerable differences between the two methods in terms of absolute risk estimates for the same individuals, even though the same SNPs are included in both methods. It is particularly interesting to find that absolute risk estimates from Method 1 (weighing each risk allele equally) were generally higher than that of Method 2 (weighing each risk SNP differently), especially for men at higher risk. However, results from this study indicated that the difference in overall discriminative performance between the two methods was small. The AUC statistics of these two methods were not statistically different and were in essence the same. These seemingly contradictory observations may be explained by the generally low discriminative ability of both risk prediction methods for the vast majority of men because they are at or near the average risk for PCa. The predictive performance of these two methods in identifying high-risk individuals, on the other hand, differed considerably. For example, the predictive performance, measured by PPV, was 0.03 to 0.04 higher for Method 2 than Method 1 among men who had two-fold or three-fold higher than average risk. Overall, these results suggest that Method 2 is superior to Method 1 in estimating absolute risk, especially if the purpose of risk prediction is to identify high-risk individuals. However, it is noted that the point estimate of absolute risk from Method 2 may not be reliable among men with an extremely elevated risk. For example, we found one subject who had an estimated absolute risk of over 1 using Method 2, because he carried most of the risk alleles of these SNPs. This problem may be more pronounced when larger number of SNPs is included in the risk prediction model.

Risk prediction for common diseases using risk-associated SNPs identified from GWAS has received a great deal attention recently. An important feature of these SNPs is their weak individual effect but stronger cumulative effect on disease risk. Currently, two approaches are commonly used to model the combined effect, but their performance in estimating absolute risk of disease is unclear. Results from this study provide important information to address this question. It is important to note that the conclusions of this study may be influenced by the prevalence of disease under study, the number of SNPs used in the model, as well as the characteristics of SNPs such as frequency and OR of each risk allele. Therefore, additional studies, especially large population-based cohort studies, are needed to further evaluate the performance of risk prediction using SNPs and the method used to assess their cumulative effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Amundadottir LT, Sulem P, Gudmundsson J, et al. A common variant associated with prostate cancer in European and African populations. *Nat Genet* 2006;38:652–8. [PubMed: 16682969]
2. Gudmundsson J, Sulem P, Manolescu A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet* 2007;39:631–7. [PubMed: 17401366]
3. Yeager M, Orr N, Hayes RB, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nat Genet* 2007;39:645–9. [PubMed: 17401363]
4. Gudmundsson J, Sulem P, Steinthorsdottir V, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. *Nat Genet* 2007;39:977–83. [PubMed: 17603485]
5. Duggan D, Zheng SL, Knowlton M, et al. Two genome-wide association studies of aggressive prostate cancer implicate putative prostate tumor suppressor gene DAB2IP. *J Natl Cancer Inst* 2007;99:1836–44. [PubMed: 18073375]
6. Thomas G, Jacobs KB, Yeager M, et al. Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet* 2008;40:310–5. [PubMed: 18264096]
7. Gudmundsson J, Sulem P, Rafnar T, et al. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. *Nat Genet* 2008;40:281–3. [PubMed: 18264098]
8. Eeles RA, Kote-Jarai Z, Giles GG, et al. Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet* 2008;40:316–21. [PubMed: 18264097]
9. Yeager M, Chatterjee N, Ciampa J, et al. Identification of a new prostate cancer susceptibility locus on chromosome 8q24. *Nat Genet* 2009;41:1055–7. [PubMed: 19767755]
10. Gudmundsson J, Sulem P, Gudbjartsson DF, et al. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. *Nat Genet* 2009;41:1122–6. [PubMed: 19767754]
11. Eeles RA, Kote-Jarai Z, Al Olama AA, et al. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. *Nat Genet* 2009;41:1116–21. [PubMed: 19767753]
12. Al Olama AA, Kote-Jarai Z, Giles GG, et al. Multiple loci on 8q24 associated with prostate cancer susceptibility. *Nat Genet* 2009;41:1058–60. [PubMed: 19767752]
13. Zheng SL, Sun J, Wiklund F, et al. Cumulative association of five genetic variants with prostate cancer. *N Engl J Med* 2008;358:910–9. [PubMed: 18199855]
14. Xu J, Sun J, Kader AK, et al. Estimation of absolute risk for prostate cancer using genetic markers and family history. *Prostate*. 2009
15. Fitzgerald LM, Kwon EM, Koopmeiners JS, Salinas CA, Stanford JL, Ostrander EA. Analysis of recently identified prostate cancer susceptibility loci in a population-based study: associations with family history and clinical features. *Clin Cancer Res* 2009;15:3231–7. [PubMed: 19366831]
16. Haiman CA, Patterson N, Freedman ML, et al. Multiple regions within 8q24 independently affect risk for prostate cancer. *Nat Genet* 2007;39:638–44. [PubMed: 17401364]
17. Zheng SL, Sun J, Cheng Y, et al. Association between two unlinked loci at 8q24 and prostate cancer risk among European Americans. *J Natl Cancer Inst* 2007;99:1525–33. [PubMed: 17925536]
18. Sun J, Zheng SL, Wiklund F, et al. Evidence for two independent prostate cancer risk associated loci in the HNF1B gene at 17q12. *Nat Genet* 2008;40:1153–5. [PubMed: 18758462]
19. Ahn J, Berndt SI, Wacholder S, et al. Variation in KLK genes, prostate-specific antigen and risk of prostate cancer. *Nat Genet* 2008;40:1032–4. [PubMed: 19165914]
20. Dupont WD. Converting relative risks to absolute risks: A graphical approach. *Stat Med* 1989;8:641–51. [PubMed: 2749072]

21. 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
22. Chen J, Pee D, Ayyagari R, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. *J Natl Cancer Inst* 2006;98:1215–26. [PubMed: 16954474]
23. Pharoah PD, Antoniou AC, Easton DF, Ponder BA. Polygenes, risk prediction, and targeted prevention of breast cancer. *N Engl J Med* 2008;358:2796–803. [PubMed: 18579814]
24. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45. [PubMed: 3203132]
25. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, Minasian LM, Ford LG, Lippman SM, Crawford ED, Crowley JJ, Coltman CA Jr. Prevalence of prostate cancer among men with a prostate-specific antigen level $\leq$ 4.0 ng per milliliter. *N Engl J Med* 2004;350:2239–46. [PubMed: 15163773]
26. Wiklund F, Zheng SL, Sun J, et al. Association of reported prostate cancer risk alleles with PSA levels among men without a diagnosis of prostate cancer. *Prostate* 2009;69:419–27. [PubMed: 19116992]

Figure 1.

Percentage of men in CAPS with estimated absolute risk for prostate cancer derived from two methods based on: a) treating each risk allele equally using a simple method of counting the number of risk alleles, and b) weighing each risk SNP differently based on their respective Odds Ratio. Red and blue bars represent cases and controls, respectively.

Figure 2. Scatter plot of absolute risk for prostate cancer in CAPS estimated using two different methods. Method 1 treats each risk allele equally, using a simple method of counting the number of risk alleles, while Method 2 weighs each risk SNP differently based on their respective Odds Ratio.

Table 1

Absolute risk estimated from two methods

Group	# of subjects	Absolute risk		
		Method 1	Method 2	
			Mean (SD)	Range
FH-, # of alleles ≤ 7	336	0.08	0.05 (0.01)	0.02 ~ 0.11
FH-, # of alleles = 8	341	0.08	0.06 (0.01)	0.05 ~ 0.15
FH-, # of alleles = 9	441	0.10	0.07 (0.01)	0.06 ~ 0.13
FH-, # of alleles = 10	585	0.11	0.09 (0.01)	0.08 ~ 0.17
FH-, # of alleles = 11	605	0.11	0.10 (0.01)	0.07 ~ 0.2
FH-, # of alleles = 12	577	0.12	0.12 (0.02)	0.09 ~ 0.28
FH-, # of alleles = 13	428	0.15	0.14 (0.02)	0.1 ~ 0.32
FH-, # of alleles ≥ 14	595	0.24	0.19 (0.06)	0.11 ~ 0.84
FH+, # of alleles ≤ 7	48	0.17	0.10 (0.02)	0.05 ~ 0.19
FH+, # of alleles = 8	53	0.18	0.13 (0.02)	0.1 ~ 0.24
FH+, # of alleles = 9	80	0.22	0.15 (0.02)	0.13 ~ 0.22
FH+, # of alleles = 10	84	0.23	0.18 (0.02)	0.15 ~ 0.35
FH+, # of alleles = 11	97	0.23	0.21 (0.03)	0.16 ~ 0.32
FH+, # of alleles = 12	119	0.26	0.24 (0.04)	0.17 ~ 0.39
FH+, # of alleles = 13	98	0.32	0.28 (0.04)	0.21 ~ 0.45
FH+, # of alleles ≥ 14	135	0.52	0.37 (0.12)	0.24 ~ 1.42

Table 2

Comparison of discriminative performance of two methods

a) Method 1					
Absolute risk	Sensitivity	Specificity	PPV (0.10)*	PPV (0.15)*	PPV (0.20)*
0.11	0.56	0.60	0.14	0.20	0.26
0.22	0.32	0.84	0.18	0.26	0.33
0.33	0.04	0.99	0.35	0.46	0.54
b) Method 2					
Absolute risk	Sensitivity	Specificity	PPV (0.10)*	PPV (0.15)*	PPV (0.20)*
0.11	0.61	0.54	0.13	0.19	0.25
0.22	0.16	0.93	0.21	0.30	0.37
0.33	0.05	0.99	0.38	0.49	0.58

* PPV (assumed prevalence)