Incorporation of Detailed Family History from the Swedish Family Cancer Database into the PCPT Risk Calculator

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Abbreviations and Acronyms

DRE = digital rectal examination
FDR = first-degree relative
LR = likelihood ratio
PCPT = Prostate Cancer Prevention Trial
PCPTRC = PCPT Risk Calculator
PSA = prostate specific antigen
SDR = second-degree relative
SFCD = Swedish Family Cancer Database

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Purpose: A detailed family history provides an inexpensive alternative to genetic profiling for individual risk assessment. We updated the PCPT Risk Calculator to include detailed family histories.

Materials and Methods: The study included 55,168 prostate cancer cases and 638,218 controls from the Swedish Family Cancer Database who were 55 years old or older in 1999 and had at least 1 male first-degree relative 40 years old or older and 1 female first-degree relative 30 years old or older. Likelihood ratios, calculated as the ratio of risk of observing a specific family history pattern in a prostate cancer case compared to a control, were used to update the PCPT Risk Calculator.

Results: Having at least 1 relative with prostate cancer increased the risk of prostate cancer. The likelihood ratio was 1.63 for 1 first-degree relative 60 years old or older at diagnosis (10.1% of cancer cases vs 6.2% of controls), 2.47 if the relative was younger than 60 years (1.5% vs 0.6%), 3.46 for 2 or more relatives 60 years old or older (1.2% vs 0.3%) and 5.68 for 2 or more relatives younger than 60 years (0.05% vs 0.009%). Among men with no diagnosed first-degree relatives the likelihood ratio was 1.09 for 1 or more second-degree relatives diagnosed with prostate cancer (12.7% vs 11.7%). Additional first-degree relatives with breast cancer, or first-degree or second-degree relatives with prostate cancer compounded these risks.

Conclusions: A detailed family history is an independent predictor of prostate cancer compared to commonly used risk factors. It should be incorporated into decision making for biopsy. Compared with other costly biomarkers it is inexpensive and universally available.

Key Words: prostatic neoplasms, biopsy, family, likelihood functions, breast neoplasms

As cancer clinical practice moves toward personalized approaches and large-scale data specializing in individual risk factors become increasingly available, the need emerges to synthesize and incorporate this information into existing cancer risk prediction tools. For example, the completion of multiple confirmatory genome-wide association studies identifying common and rare single nucleotide polymorphisms has promoted

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their incorporation into commonly used cancer risk prediction tools.[1–9] To date these markers have had only modest impacts on risk and they are often not widely used due to cost.[10]

A less expensive and more easily implemented alternative to genetic markers is the collection of a detailed family history of cancer. While the commonly used definition of a family history of disease is dichotomous (ie do you have a FDR with a history of the same disease? Yes or no), a detailed family history assesses for the disease in SDRs, the number of relatives diagnosed, ages at diagnosis and information on related diseases. Although a self-reported family history is easier to obtain and far less costly than genetic measures, it is prone to recall error and large sample sizes are needed to appropriately assess the association between rare family history patterns and disease outcomes.

The SFCD, which includes data on the entire population of Sweden (those born after 1931 plus their biological parents), is the largest comprehensive family cancer registry in the world.[11] Data housed in the registry are not self-reported but rather assimilated from a nationwide linked network of death and hospital registries. The latest SFCD update occurred in 2010 and it now includes more than 12.2 million individuals and more than 1.1 million first primary cancers.[11] Analogous to the large genome-wide consortiums that maximize sample numbers for clinical outcome predictions based on genetic markers, the SFCD provides the large sample numbers needed to accurately identify the association between a detailed family history and cancer risk prediction.

After a large-scale twin study in Sweden, Denmark and Finland estimated the heritability of prostate cancer at 42%, a SFCD study identified the key detailed family history risk factors associated with the risk of prostate cancer in the next 10 years.[12,13] These factors included prostate cancer detected in a FDR younger than 60 vs 60 years old or older, prostate cancer in a SDR, breast cancer in a FDR and esophageal carcinoma in situ in the index man or in a FDR. A comprehensive risk score based only on these factors was proposed for use in prostate cancer screening. This risk assessment score can be easily implemented in clinical practice, requiring that the patient only complete a short questionnaire.

An ideal method to implement a detailed family history into prostate cancer risk assessment would be to use a comprehensive tool that incorporates other validated measures of risk. The PCPTRC (http://myprostatecancerrisk.com/), the most commonly used tool for this assessment, includes PSA, DRE, family history of prostate cancer, prior negative biopsy (if done), age and race/ethnicity.[14] Based on these risk factors a simple display of individualized predicted outcomes (negative biopsy and low vs high grade cancer) enables physicians to provide a context to counsel patients on their preference of whether to proceed to biopsy. The PCPTRC was externally validated in dozens of international diverse populations.[15–25] Since its development, the calculator has been modified to incorporate newly discovered and FDA (Food and Drug Administration) approved markers for prostate cancer, including *PCA3* and percent free PSA, using a Bayesian technique to update a risk tool called the LR.[26,27] As these updated PCPTRC calculators became available online, they have also undergone validation studies.[28,29] We provide an updated online PCPTRC to incorporate a detailed family history into contemporary clinical prostate cancer risk assessment based on the established risk factors.

MATERIALS AND METHODS

Data on men with at least 1 FDR recorded in the 2010 version of the SFCD were extracted. The men were alive, 55 years old or older and free from prostate cancer at the beginning of the study period (1999 to 2010). The SFCD was collected under approval by the Lund University regional ethics committee in Sweden with an anonymous version used for this analysis. To establish prostate cancer cases and controls the men who met study eligibility requirements were segregated into those in whom prostate cancer did and did not develop, respectively, during the subsequent 11 years until 2010.

Based on the study by Roudgari et al[13] FDR and SDR prostate cancer history, and FDR breast cancer history were selected as the detailed family history patterns relevant to prostate cancer risk. FDR prostate cancer history was stratified by whether cancer was diagnosed before vs at or after age 60 years as well as by whether zero, 1, or 2 or more FDRs were diagnosed. SDR prostate cancer and FDR breast cancer history were only stratified by no vs 1 or more respective relatives diagnosed. Roudgari et al used the cutoff point of 60 years as the age most commonly serving as a discriminator for prostate cancer at younger ages, comparable to other published studies. Esophageal carcinoma in a FDR, which was included in the score of Roudgari et al, was not included due to its low incidence.

The LR was defined as the ratio of the proportion of prostate cancer cases with a specific family history pattern vs the corresponding proportion of controls with the pattern. Thus, a LR greater than 1 means that a specific family history pattern was more common in cancer cases, a LR less than 1 means that the pattern was more common in controls and a LR of 1 means that the pattern was equally common in cases and controls.[30] No adjustment was made for age or race to preserve sample size and