Risk prediction of aggressive prostate cancer using baseline PSA during midlife and inherited genetic variants in Caucasian men

Mark A. Preston, Kathryn Penney, Maxine Chen, Adam Kibel, Kathryn Wilson, Lorelei Mucci

Background

A baseline PSA during midlife predicts lethal prostate cancer with good accuracy and can be used for risk-stratified screening. A study published by Witte's group in Nature communications explored how factors other than prostate cancer—such as genetics—can impact PSA level. We sought to investigate that "correction" of baseline PSA levels for single nucleotide polymorphisms (SNPs) related to circulating PSA levels will improve predictive ability for aggressive prostate cancer.

Methods

We used the Physician's Health Study to identify 392 men aged 40-70 years of age and had baseline PSA and SNP data. There were 145 aggressive cancer cases defined as Gleason >6, metastatic or fatal. The comparison group was composed of 247 controls and non-aggressive prostate cancer cases. We excluded those with baseline PSA > 10 ng/ml. Median and percentile PSA groupings were used as established in prior publication (Preston et al, JCO 2016). Median PSA was 1.10 ng/ml and 90th percentile was 3.40 ng/ml. We created both unweighted and weighted genetic risk scores (GRS) based on SNPs identified to be associated with PSA in the Hoffman et al. *Nat Genet.* 2017 GWAS of PSA levels. GRS was used to "adjust" PSA values and then we assessed logistic regression models and AUC results.

Results

Compared to men with a PSA level below the median, the age-adjusted odds ratio for men with PSA > median was OR 2.7 (95% CI 1.6, 4.5), and for those men with PSA >90th percentile, OR 4.3 (95% CI 2.4, 7.9). When including the GRS, the adjusted odds ratio for men with PSA > median improved to OR 2.9 (95% CI 1.7, 4.8), and for those men with PSA >90th percentile, OR 4.8 (95% CI 2.6, 9.1) compared to men with a PSA level below the median. The Area under the curve (AUC) did not change significantly; Age adjusted AUC was 0.64 (95% CI 0.59, 0.70) and SNP adjusted AUC was 0.65 (95% CI 0.59, 0.70).

Conclusion

We found that the GRS adjusted baseline PSA modestly improved prediction of aggressive prostate cancer.

They conducted a GWAS of PSA in 28,503 white men in Kaiser Permanente system and 17,428 men from replication cohorts.

They found:

- Detected 40 genome- wide significant SNPs:
  - 19 novel
  - 15 previously identified for PSA (14 of which were also PCa-associated)
  - 6 previously identified for PCa only
- >50% of the 40 SNPs are PSA-associated independent of PCa.
- 40 SNPs explain 9.5% of PSA variation in non-Hispanic whites, and the remaining GWAS SNPs explain an additional 31.7%;
  - This is higher in younger men, supporting the genetic basis of PSA levels.

We aim to use these well-identified SNPs to adjust PSA values within our cohorts.

a. **Explore whether previously identified germline prostate cancer risk SNPs add to the predictive ability of baseline PSA in predicting advanced prostate cancer in the PHS.**