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14. ABSTRACT: The current project seeks to study molecular and clinical predictors of aggressive prostate cancer in two large US cohorts of prostate cancer cases from the Physicians' Health Study (PHS) and the Health Professionals' Follow-up Study (HPFS). We have almost completed review of medical records for the more than 6,000 prostate cancer cases in the cohort, to abstract clinical data, and are assembling a clinical datafile. Among the 900 cases on whom tumor tissue are contained on 8 tissue microarrays, we have undertaken immunohistochemistry to assess protein expression for five genes as part of a recently identified molecular signature associated with lethal prostate cancer. Intensity and percent staining for these five markers has been evaluated by the pathologist for the PHS cases, and statistical analyses are underway to assess the association of the molecular signature to predict poor prostate cancer survival. The statistical team has discussed model building strategies for both sets of markers.

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INTRODUCTION

Upon diagnosis with localized prostate cancer, patients and clinicians are faced with the decision of whether to treat or defer treatment. On one hand, prostate cancer is the second leading cause of cancer death among men in westernized countries (1), and deaths occur even 20 years after diagnosis (2). On the other, treatment has adverse effects (3) and is often unneeded, as most men die with and not from their cancer, and many harbor tumors that remain indolent even in the absence of therapy (2, 4)

Treatment of localized disease can reduce cancer mortality, but in the one randomized trial of radical prostatectomy versus watchful waiting (5, 6), the number needed to treat (NNT) to prevent one cancer death was 19. That trial predated screening by prostate specific antigen (PSA), where 30-60% of PSA-detected cancers may be characterized as overdiagnosed (7, 8) and the NNT may be greater.

There is a clear need for tools to correctly distinguish potentially lethal from indolent disease to guide clinical practice and treatment decisions. The Kattan nomogram characterizes risk of progression using pretreatment clinical markers: PSA levels, biopsy Gleason scores, and clinical stage (9, 10). This and other scoring systems (11, 12) have significant predictive power, but molecular tumor markers hold promise to improve prediction (13). However, few biomarkers studies have assessed their signatures to predict death from prostate cancer.

The current project seeks to examine molecular and clinical predictors of lethal prostate cancer within two large prostate cancer cohorts: the Physicians Health Study (PHS) and the Health Professionals Follow-up Study (HPFS). More than 6,000 men have developed incident prostate cancer in the cohorts, and these men have been followed prospectively for the development of metastases, cancer death, and death from other causes. Archival tumor tissue has been collected from 1,180 of the men, and is currently being constructed into tumor tissue microarrays for semi-quantitative Immunohistochemistry. Using this resource, the following aims will be explored:

1-) To test clinical nomograms to predict development of lethal prostate cancer in the PHS and HPFS cohorts.

2-) To test and validate molecular signatures in tumors to predict development of lethal disease, alone and independent of clinical markers.

BODY

Clinical record review.

We have completed abstraction of clinical parameters from medical records and pathology reports for 2,000 of the 2,240 incident PHS prostate cancers and 3,200 of the 3,800 incident HPFS prostate cancer cases. Data for these records have been scanned and undergone a process of verification to assess quality control of the data entry. Data abstraction should be finalized during the next three months. We have thoroughly reviewed the prostate cancer literature to identify the clinical nomograms that predict PSA relapse after prostatectomy. Once the clinical dataset is finalized, we will test these nomograms to predict lethal disease.

Follow-up data.

We have updated mortality data, including dates and causes of death, for the entire PHS and HPFS prostate cancer cohorts through 2006. These data have been reviewed by an Endpoints Committee and are available for analyses. Information on the development of distant metastases is derived from annual follow-up questionnaires on the cohorts. Participants, who are physicians and health professionals, self-report on site of metastases and date of diagnosis. We have undertaken a small validation study among men who did (N=65) and did not (N=35) report metastases, and have to date found high agreement between self-report and medical records. The follow-up data are finalized and outputted and stored on our UNIX server for analyses.

Tumor block collection.

We have now collected and catalogued archival tumor tissue from 1,100 men in the PHS (biopsy, TURP, prostatectomy tissue) and 780 men in the HPFS (prostatectomy only) prostate cancer cohorts. Our pathologist has undertaken centralized histopathologic review of all cases to confirm cancer, to provide standardized Gleason grading review, and to note other notable histologic features. We have now constructed high density tissue microarrays from the archival prostatectomy TURP and prostatectomy tissue for a total of 1,113 cases in the two cohorts. These TMAs will be used to increase efficiency of immunohistochemical evaluation.

Immunohistochemical evaluation and imaging.

Our group recently identified a five gene model that predicted death from prostate cancer in a Swedish Watchful Waiting Cohort. We seek to validate the signature in the HPFS and PHS prostate cancer cohorts. We have undertaken immunohistochemistry using antibodies against the five genes – cIAP, p63, MTA1, Jagged1, ABP280—on the PHS and HPFS TMAs. These images have been digitally scanned for imaging. The pathologist has reviewed the images for the first three PHS cases, digitally circling areas of tumor tissue. The intensity and percent staining for these three TMAs have been read by the Chromavision system, and we are about to begin preliminary data analysis to assess the predictive value of the molecular signature on development of lethal prostate cancer. The remaining six TMAs are now scheduled to be digitally reviewed by the pathologist in order for imaging to take place.

KEY RESEARCH ACCOMPLISHMENTS

- We have abstracted clinical data for 5,200 men with incident prostate cancer diagnosed in the PHS and HPFS cohorts.
- We have achieve long-term and complete clinical follow-up of the cohort with respect to development of metastases and cancer death, without loss to follow-up.
- We have assembled a large, population-based biorepository of archival tumor tissue, which has been catalogued and undergone histopathologic review.
- We have constructed nine high-density tissue microarrays (TMAs) from the tumor tissue.
- We have identified a five gene signature associated with lethal prostate cancer, and which we will validate in the PHS and HPFS cohorts. We have undertaken Immunohistochemistry to assess protein expression of the five genes across the nine TMAs.
- We will present preliminary data on the five gene model as a poster presentation at the upcoming Active Surveillance of Early Stage Prostate Cancer Meeting in San Francisco in January 2007.

REPORTABLE OUTCOMES

- Development of a prostate tumor biorepository for 1,800 men with incident prostate cancer, on whom there is long-term and complete clinical follow-up for development of distant metastases and cancer death.
- Preliminary results from the molecular signature will be presented as a poster presentation at a prostate cancer meeting:
    - Mucci LA, Stampfer M, Pawitan P, Demichelis F, Fall K, Adami HO, Andersson SO, Kantoff PW, Stark JR, Johannson JE, Rubin MA. Molecular signatures to predict lethal prostate cancer, Active Surveillance of Early Stage Prostate Cancer Meeting in San Francisco, January 2007
- Funding of this grant was instrumental in promoting the study PI to Assistant Professor in Medicine.

CONCLUSIONS

While the work for this project is ongoing, the preliminary data demonstrate our ability to undertake a large, population-based study of clinical and molecular predictors of aggressive prostate cancer. We have made significant progress on the data collection phase of the project, and have already successfully immunostained for five molecular markers of significant interest. This preliminary work with ensure that the project achieves the study aims by the end of the project period.

REFERENCES

1. Ferlay J BF, Pisani P, Parkin DM. GLOBOCAN 2002: Cancer Incidence, Mortality, and Prevalence Worldwide IARC CancerBase No. 5 version 2.0. In: IARC*Press*, Lyon; 2004.

2. Johansson JE, Andren O, Andersson SO, et al. Natural history of early, localized prostate cancer. JAMA 2004;291(22):2713-9.

3. Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002;347(11):790-6.

4. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. Jama 2005;293(17):2095-101.

5. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005;352(19):1977-84.

6. Holmberg L, Bill-Axelson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med 2002;347(11):781-9.

7. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. J Natl Cancer Inst 2002;94(13):981-90.

8. Ciatto S, Gervasi G, Bonardi R, et al. Determining overdiagnosis by screening with DRE/TRUS or PSA (Florence pilot studies, 1991-1994). Eur J Cancer 2005;41(3):411-5.

9. Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. J Natl Cancer Inst 1998;90(10):766-71.

10. Stephenson AJ, Scardino PT, Eastham JA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst 2006;98(10):715-7.

11. Partin AW, Piantadosi S, Sanda MG, et al. Selection of men at high risk for disease recurrence for experimental adjuvant therapy following radical prostatectomy. Urology 1995;45(5):831-8.

12. Blute ML, Bergstralh EJ, Iocca A, Scherer B, Zincke H. Use of Gleason score, prostate specific antigen, seminal vesicle and margin status to predict biochemical failure after radical prostatectomy. J Urol 2001;165(1):119-25.

13. Kattan MW, Shariat SF, Andrews B, et al. The addition of interleukin-6 soluble receptor and transforming growth factor beta1 improves a preoperative nomogram for predicting biochemical progression in patients with clinically localized prostate cancer. J Clin Oncol 2003;21(19):3573-9.