Karolinska Institutet

Institutionen för kliniska vetenskaper vid Danderyds Sjukhus

PREDICTING PROSTATE CANCER

on the use of biomarkers in prostate cancer diagnostics

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i aulan, Danderyds Sjukhus

Fredagen den 30 januari 2015 klockan 9.00

av

Tobias Nordström

Leg. läkare

Huvudhandledare:
Professor Henrik Grönberg
Karolinska Institutet
Institutionen för medicinsk epidemiologi och biostatistik

Bihandledare:
Professor Peter Wiklund
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

Med. Dr. Anders Hallin
Karolinska Institutet
Institutionen för kliniska vetenskaper vid Danderyds Sjukhus

Docent Martin Eklund
Karolinska Institutet
Institutionen för medicinsk epidemiologi och biostatistik

Fakultetsopponent:
Professor Lars Holmberg
King's College, London, UK
Division of Cancer Studies
Cancer Epidemiology and Population Health

Betygsnämnd:
Docent Anna Bill-Axelson
Uppsala Universitet
Institutionen för kirurgiska vetenskaper
Enheten för urologkirurgi

Docent Fredrik Granath
Karolinska Institutet
Institutionen för medicin
Enheten för klinisk epidemiologi

Professor Pär Sparen
Karolinska Institutet
Institutionen för medicinsk epidemiologi och biostatistik

Stockholm 2014

ABSTRACT

Aims
The aims of this thesis were to address the following questions. *Paper I*: How prevalent is testing and re-testing with prostate-specific antigen (PSA)?; *Paper II*: Is a genetic score based on Single Nucleotide Polymorphisms (SNP) informative on the risk of prostate cancer (PCa) among men with low PSA?; *Paper III*: Are the commercially available models PHI and the four-kallikrein panel comparable in aiding biopsy-decisions?; *Paper IV*: Do commonly used medications affect PSA and the risk of PCa?

Methods
In *Paper I* and *Paper IV*, the population-based PSA-cohort STHLM0 was used together with registry-based data. *Paper I* described limited duration-point prevalence of testing and survival-analysis describing re-testing with PSA. *Paper IV* determined differences in PCa risk and PSA level by medication. *Paper II* included 172 men with PSA 1-3ng/ml. Participants were invited by their genetic score and underwent prostate biopsy. Risk of prostate cancer was assessed using logistic regression. *Paper III* included 531 men having undergone a first prostate biopsy. Predictive models were compared using receiver operating characteristics (ROC/AUC) and calculation of saved biopsies.

Results
Paper I: During a 9-yr study period, 46%, 68%, and 77% of men without prior PCa and aged 50–59 years, 60–69 years, and 70–79 years, respectively, had a PSA test. The probability of retesting with PSA was PSA and age dependent, with a 26-mo cumulative incidence of 0.34 if the first PSA value was <1 ng/ml.

Paper II: In men with PSA 1-3ng/ml, PCa was diagnosed in 47 of 172 participants (27%), with Gleason sum ≥7 in 10 of 172 men (5.8%). There was an increase in the odds ratio of 1.60 with increasing genetic risk score. The absolute risk difference of positive biopsy was 19 percentage points, comparing the high and low genetic risk group (37% vs. 18%).

Paper III: The four-kallikrein panel showed AUCs of 69.0 when predicting any-grade PCa and 71.8 when predicting high-grade cancer (Gleason score ≥7). Similar values were found for PHI: 70.4 and 71.1, respectively. Both models had higher AUCs than a base model with PSA value and age. Using 10% predicted risk of high-grade PCa by the four-kallikrein panel or PHI=39 as cut-off for biopsy saved 29% of performed biopsies at a cost of delayed diagnosis for 10% of the men with high-grade cancer.

Paper IV: There were no significant associations between aspirin or any antidiabetic medication and the risk of PCa. Men using any statin had an increased risk of both high-grade PCa and PCa overall (OR 1.25; OR 1.16). Compared to men without the medication, the level of the first PSA was lower among men using aspirin, statin, metformin or insulin.

Conclusions
Although screening for PCa is not recommended in Sweden, PSA testing in Stockholm County was high across men aged over 50 years. A risk score based on SNPs predicts biopsy outcome in previously unbiopsied men with PSA 1–3 ng/ml. Further, we found that two blood tests, the Prostate Health Index and the four-kallikrein panel, performed similarly in predicting prostate biopsy outcome. Introducing such risk stratification tools can increase the proportion of men being classified in line with their true risk of PCa. We found no protective effect of aspirin, statins or antidiabetics in terms of overall risk of prostate cancer or high-grade disease.