# EARLY DETECTION OF PROSTATE CANCER WITH PSA > 4 NG/ML

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## ABSTRACT

*Objective:* To determine whether the prostate specific antigen (PSA), abnormal DRE, family history, age, and prostate volume could increase the specificity and sensitivity of screening for prostate cancer. ***Material & methods:*** We analyzed 92 patients with PSA > 4 ng/ml between January and December 2011 in Sardjito General Hospital Yogyakarta. Patients received prostate biopsy due to having abnormal serum prostate specific antigen (PSA) level. The relationship between the possibility of prostate cancer and the following variables were evaluated including age, PSA level, prostate volume, DRE finding, and family history. By using Chi-square analysis, multiple logistic regression and receiver operating characteristic (ROC) curve were drawn based on the predictive scoring equation to predict the possibility of prostate cancer. All analyses were performed with SPSS, version 18.0. ***Results:*** It showed the relationship between the possibility of prostate cancer and the following variables, including: age (p < 0.001), PSA level (p < 0.001), DRE finding (p < 0.001) family history (p < 0.001) except prostate volume (p = 0.398). Using a predictive equation, P = 1/(1-e-x), where X = -3.821 + 1.846 (if DRE positive) + 2.488 (if family history positive) + 1.718 (when PSA > 10) + 1.414 (when age > 68), followed by ROC curve analysis, it showed the sensitivity 90.4% and specificity 85% in predicting the possibility of prostate cancer. ***Conclusion:*** Age, DRE finding, PSA and family history are factors associated prostate cancer. They can be used as independent predictor to predict prostate cancer.

*Key words:* Logistic regression, early detection, prostate cancer.

## ABSTRAK

*Tujuan:* Menentukan apakah prostate specific antigen (PSA), DRE abnormal, sejarah keluarga, usia, dan volume prostat dapat meningkatkan spesifitas dan sensitifitas screening kanker prostat. ***Bahan & cara:*** Kami menganalisa 92 pasien dengan PSA > 4 ng/ml antara Januari dan Desember 2011 di RSU Sardjito Yogyakarta. Pasien menerima biopsi prostat karena memiliki level serum prostate specific antigen (PSA) abnormal. Hubungan antara kemungkinan kanker prostat dan variabel yg mengikuti termasuk usia, level PSA, volume prostat, temuan DRE, dan sejarah keluarga. Dengan menggunakan analisa Chi-square, multiple logistic regression dan kurva receiver operating characteristic (ROC) dicatat berdasarkan persamaan nilai prediktif untuk memprediksi kemungkinan kanker prostat. Semua analisa menggunakan SPSS versi 18.0. ***Hasil:*** Hasil penelitian menunjukkan hubungan antara kemungkinan kanker prostat dan variabel yang mengikuti termasuk usia (p < 0.001), level PSA (p < 0.001), temuan DRE (p < 0.001) sejarah keluarga (p < 0.001) kecuali volume prostat (p = 0.398). Menggunakan persamaan prediktif P = 1/(1-e-x), dimana X = -3.821 + 1.846 (jika DRE positif) + 2.488 (jika sejarah keluarga positif) + 1.718 (saat PSA > 10) + 1.414 (saat usia > 68), diikuti analisa kurva ROC, menunjukkan sensitifitas 90.4% dan spesifitas 85% dalam memprediksi kemungkinan kanker prostat. ***Simpulan:*** Usia, temuan DRE, PSA dan sejarah keluarga adalah faktor yang berhubungan dengan kanker prostat. Mereka dapat digunakan sebagai prediktor mandiri untuk memprediksi kanker prostat.

*Kata kunci:* Logistic regression, deteksi awal, kanker prostat.

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## INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and the sixth leading cause of death in men, approximately 14% (903.500) of new cancer cases and 6% (258.400) of the total deaths from cancer in men on 2008.[1] Initiation and progression of prostate cancer was still unknown, several studies have shown that genetic, race, diet and environment play an important role.[2,3]

Recently, scientist has found some factors that may help for prostate cancer screening.[4] Prostate

spesific antigen (PSA) is the first prostate cancer indicator. Decreasing prostate cancer incidence between 1992 and 1995 occurred subsequent to PSA as screening.[2] However, PSA as a screening is still controversy because of the cost, high of bias, overdiagnosis and overtreatment.[5,6] Yang JB et al, found that PSA is not effective for prostate cancer screening.[7]

In the last decades, some nomograms have been developed to predict biopsy for prostate cancer patients. Some major predictive factors are total PSA, digital rectal and age, some other predictive factors that can be added are race, family history, previous prostate biopsy, prostate volume, negative prostate biopsy history, number of core biopsy and percentage of free-PSA.[8]

## OBJECTIVE

This study was aimed to assess total PSA, prostate volume, age, digital rectal examination and family history as a predictive factor for prostate cancer.

## MATERIAL & METHOD

This study was a retrospective study. It was a case-control design with 92 patients who underwent transurethral resection of prostate (TURP) and prostate biopsy with PSA ≥ 4 ng/ml and/or abnormal digital rectal at Sardjito General Hospital Yogyakarta, from January to December 2012. Risk factors in this study were age, prostate specific antigen (PSA) level, prostate volume, digital rectal and family history. Inclusion criteria in this study were prostate cancer patients and benign prostate enlargement who had complete medical records, performed TURP or prostate biopsy with PSA ≥ 4 ng/ml and/or abnormal digital rectal. Patients with no anatomical pathology results were excluded.

Predictive factors of prostate cancer and the prediction formula were obtained using Chi-square analysis, multiple logistic regression and receiver operating characteristic (ROC) curve. The entire analysis was done using SPSS version 18.

## RESULT

**Tabel 1.** Variable characteristics.

| Variable | Mean (median) | 95% CI | p* |
|---|---|---|---|
| Age | 69.39 (71) | 67.51-71.28 | 0.053 |
| PSA | 35.97 (16) | 26.7-45.2 | < 0.001 |
| Prostate Volume | 51.86 (48.8) | 46.99-56.73 | 0.005 |
| IPSS | 21.04 (21) | 20.50-21.59 | < 0.001 |

*Kolmogorov-Smirnov

**Tabel 2.** Bivariate analysis.

| Variable | Prostate cancer | | p* |
|---|---|---|---|
| | Yes | No | |
| Age (years) | | | |
| < 68 | 10 | 25 | < 0.001 |
| ≥ 68 | 42 | 15 | |
| Total PSA | | | |
| < 10 ng/ml | 6 | 22 | < 0.001 |
| ≥ 10 ng/ml | 46 | 18 | |
| Digital Rectal Examination | | | |
| Abnormal | 36 | 4 | < 0.001 |
| Normal | 16 | 36 | |
| Family history | | | |
| Positive | 46 | 7 | < 0.001 |
| Negative | 6 | 33 | |
| Prostate volume | | | |
| < 40 ml | 20 | 12 | 0.398 |
| ≥ 40 ml | 32 | 28 | |

* Chi-square test

**Table 3.** Multivariate analysis.

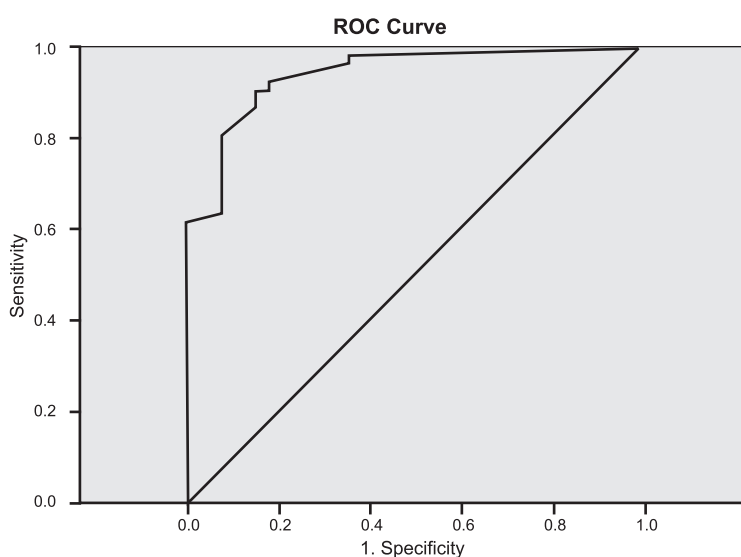| Variables | B | Sig | Exp (B) | 95% Confidence Interval (CI) | |
|---|---|---|---|---|---|
| | | | | Minimum | Maximum |
| Family history | 2.488 | 0.001 | 12.032 | 3.087 | 46.895 |
| Digital rectal examination | 1.846 | 0.019 | 6.334 | 1.358 | 29.541 |
| PSA level | 1.718 | 0.032 | 5.571 | 1.160 | 26.756 |
| Age | 1.414 | 0.046 | 4.111 | 1.025 | 16.489 |
| Constants | -3.821 | 0001 | 0.022 | | |



**Diagram 1.** ROC curve.

Average of age, PSA, prostate volume and IPSS from 92 patients in this study were 69.39, 35.97, 51.86, and 21.04 respectively. Age had a normal data distribution ($p > 0.05$), while the PSA, prostate volume, and IPSS had an abnormal data distribution ($p < 0.05$), tested using Kolmogorov-Smirnov test (Table 1).

Bivariate analysis was performed using Chi-square test (Table 2). This study found that age ($p < 0.001$), total PSA levels ($p < 0.001$), digital rectal examination ($p < 0.001$) and family history ($p < 0.001$) had relationship with prostate cancer. However, prostate volume had no relationship with prostate cancer ($p = 0.398$).

Multivariate analysis was performed for variables that had significance value ($p < 0.2$). From this analysis, age, PSA levels, digital rectal and family history can be used as predictive factors of prostate cancer (Table 3).

Family history was a strong predictive factor for prostate cancer, followed by digital rectal examination, PSA levels and age. This analysis obtained a predictor formula as follows: $P = 1/(1-e-X)$, $X = -3.821 + 1846$ (if digital rectal abnormal) + 2.488 (if family history positive) + 1.718 (if PSA > 10) + 1.414 (if age > 68).

This analysis has 90.4% sensitivity and 85% specificity which can be seen through the ROC curve on diagram 1.

**DISCUSSION**

Risk factor assessment in prostate cancer patients is very useful for determining treatment, consultation and diagnosis. Hernandez et al, showed that increasing age, increasing total PSA, low PSA, abnormal digital rectal examination, African-American race, positive family history, number of

positive biopsy cores and positive previous biopsy increased the risk for prostate cancer and high-grade biopsy results.[8]

Bivariate analysis performed in this study used Chi-square test. It found that age (p < 0.001), total PSA levels (p < 0.001), digital rectal (p < 0.001) and family history (p < 0.001) had a relationship with the incidence of prostate cancer. However, prostate volume had no relationship with prostate cancer incidence (p = 0.398).

The relationship between age and the risk of PCa is very strong. However, due to the narrow age range in the screening process, age may not be an independent predictive factor. Schroder et al showed that age (per year or per decade) is not statistically significant for predicting prostate cancer in men aged 55-70 years in early screening.[1,2]

Family history of PCa is an important risk factor. Two meta-analysis reported that relative risk (RR) of family history is 2-3.5. Risk depends on the degree of relatedness and degree affected. Among first-degree relatives, the risk was significantly higher for men with affected relatives compared to those with affected father. Study was conducted on 26651 PCa patients who 5623 of them are familial.[1,4,9]

Hazard Ratio (HR) of PCa increased with the number of affected relatives and decreased with increasing age. The highest HR found in men aged < 65 years old with three affected siblings (HR: about 23) and lowest in men aged between 65 and 74 years with affected father (HR: approximately 1.8). Patterns of PCa family death similar to incidence data, with the highest risk of death in men with a father and two brothers were affected (HR: 9.7).[1,4,9]

Initial observations was made by Stenman et al. Forty four men with PCa were selected from 21172 Finnish men, the author reported a relationship between the range of PSA values and cancer risk in 6-10 years. Gann et al, measured PSA level in Physicians' Health Study blood samples and 366 people who were diagnosed with PCa and 1.098 as controls. PCa was found increased 5-6 years before diagnosis.[1]

Data from Baltimore Longitudinal Study of Aging showed that PSA was greater than the average age of men 40-60 years old was associated with an RR 3.6 for diagnosed with PCa with an average follow-up of 13 years.[1] Data from Indonesian Society of Urologic Oncology (ISUO) in 2011 showed that there were 971 prostate cancer patients during 2006-2010. Mean age was 68.3 years and the highest was at 70-79 years (37.6%).[10]

Prostate cancer mostly located in peripheral zone and can be detected with digital rectal examination if the volume is ≥ 0.2 ml. If there is an abnormality such as hard nodules, asymmetry and bumpy surface, it can be an indication for prostate biopsy. Eighteen percent of all prostate cancer patients were detected only by digital rectal alone. Patients with abnormal digital rectal accompanied with PSA levels > 2 ng/ml have predictive value of 5-30%.[10]

Catalona et al, reported that DRE with PSA measurement improved early detection of PCa. Men with positive DRE tend to have poorly differentiated biopsy results. Therefore, men with abnormal DRE should undergo prostate biopsy.[2,4]

Some studies suggested that there was a relationship between prostate cancer and smaller prostate volume. Prostate volume less than 40 cm$^3$ had an increased risk for PCa incidence. However, prostate volume is difficult to measure and has limitations in screening.[1,6,7] Therefore, in this study it found that prostate volume is not related to the incidence of prostate cancer.

From the multivariate analysis we found that family history is a strong predictive factor for prostate cancer, followed by digital rectal examination, PSA levels, and age. The analysis obtained a predictor formula as follows: P = 1/(1-e-x), where x = -3.821 + 1846 (if abnormal digital rectal) + 2.488 (if positive family history) + 1.718 (if PSA > 10) + 1.414 (if age > 68), with sensitivity 90.4% and specificity 85%.

Hernandez et al, conducted a multivariate analysis on several predictive factors. They found that increasing age, elevated PSA level, abnormal digital rectal examination, African-American race and positive family history increased prostate cancer risk.[8] The result was consistent with this study, in which age, family history, digital rectal examination and PSA levels were predictive factor for prostate cancer.

Early-stage prostate cancer is always asymptomatic. Suspicion will increase with the presence of other symptoms such as bone pain, pathologic fractures or bone marrow suppression. PSA examination is recommended for men older than 50 years old whereas if they have positive family history, it is recommended for early examination at 40 years. Examinations to diagnose prostate cancer are disease history, digital rectal examination, PSA and transrectal/transabdominal ultrasonography. Definitive diagnosis of prostate

biopsy is obtained by biopsy result or surgery specimen in form of adenocarcinoma.[10,11]

## CONCLUSION

Family history, digital rectal examination, PSA levels, and age are factors related to prostate cancer incidence and can be used as independent factors for predicting prostate cancer incidence.

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