RELATIONSHIP BETWEEN P53 EXPRESSION AND PSA SERUM

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ABSTRACT

Objective: *To know the relationship between p53 expression and prostate specific antigen (PSA) serum level in prostate cancer patients.* ***Material & method:*** *Specimens were studied from patients with pathological diagnosis of prostate cancer in Sardjito Hospital Yogyakarta during 2007 to 2008. The p53 expression was measured by immunohistochemical staining. The stains were done in Department of Anatomical Pathology and examined by a pathologist. The relationship between p53 mutated expression and PSA serum level were analyzed with correlation coefficient (rs).* ***Results:*** *There were 29 patients included in this study. The mean age was 66,34 ± 8,15 (50 - 83) years old. The mean PSA serum level was 165,98 ± 269,208 (1,4 – 1051) ng/ml. The mean number of p53 expression was 111,38 ± 94,30 (16 – 396). There was positive correlation between p53 expression and increasing PSA serum level in the prostate cancer patients (rs + 0,497; p = 0,006).* ***Conclusion:*** *P53 expression was positively correlated with increasing PSA serum level.*

Keywords: *Prostate cancer, p53 expression, PSA serum level.*

ABSTRAK

Tujuan Penelitian: *Mengetahui hubungan antara ekspresi p53 dengan kadar serum prostate specific antigen (PSA) pada pasien kanker prostat.* ***Bahan & Cara:*** *Sampel penelitian berasal dari pasien yang terdiagnosis secara klinis dan histopatologis menderita kanker prostat di RS Dr. Sardjito Yogyakarta periode 2007–2008. Ekspresi p53 diketahui dengan pengecatan imunohistokimia. Pengecatan dilakukandi Departemen Patologi Anatomi dan diperiksa oleh seorang Patolog. Hubungan antara ekspresi p53 dan kadar serum PSA dianalisa dengan koefisien korelasi Spearman (rs).* ***Hasil Penelitian:*** *Terdapat 29 pasien dalam penelitian ini. Usia rerata pasien adalah 66,34 + 8,15 (50-83) years old. Rerata kadar serum PSA adalah 165,98 + 269,208 (1,4–1051) ng/ml. Rerata ekspresi p53 adalah 111,38 + 94,30 (16–396). Terdapat hubungan positif antara ekspresi p53 dengan kadar PSA serum (rs + 0,497; p = 0,006).* ***Simpulan:*** *Terdapat hubungan positif antara ekspresi p53 dengan kadar serum PSA.*

Kata Kunci: *Kanker prostat, ekspresi p53, kadar serum PSA.*

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INTRODUCTION

Prostate specific antigen (PSA) is a 34 kD glycoprotein produced by the prostate gland. PSA is produced by the secretory glands and epithelial cells lining the periurethral glands. In normal prostate tissue PSA is secreted into the lumen of secretory duct of the gland and only a small amount that enters the systemic circulation. PSA serves for semen liquefaction so that spermatozoa can move easily and also serves to shed mucosal layer of uterine cervix.[1]

Increased PSA serum occurs in benign prostate enlargement, prostatitis, other benign prostatic disorders and prostate cancer. Elevated levels of serum PSA is a good predictor of prostate cancer.[2] Prostate cancer does not produce more PSA than normal prostate gland cells but elevated levels of PSA serum in prostate cancer is caused by the damage in normal architecture of the prostate gland.[3] However, an increase in PSA production is found in metastatic prostate cancer. Increased PSA production was not yet clearly known but it is believed to be related to the gene p53 suppression by

mutant p53 gene.[4]

P53 is a protein with a molecular weight of 53 kD produced by a gene on chromosome 17p, which is essential in multicellular organisms because p53 plays a role in the regulation and control of cell proliferation.[3] Under conditions of DNA damage in a cell, the functional p53 stops cell division in G1 phase or stimulates cell intrinsic mechanism for the occurrence of cell apoptosis. Because of this role, p53 is known as a tumor suppressor. The loss of p53 function will result in uncontrolled growth of cells with damaged genetic material.[5] In normal cells p53 binds to DNA that would stimulate other genes in the DNA to produce p21 protein, and p21 protein will bind to the cell division booster protein (cdk2 protein). When the p21 protein and cdk2 complex is formed, it will stop cell division. If p53 gene mutation occurs, then p53 will not bind to DNA. The consequences are the loss of p21 protein formation and the loss of control of cell division.[6]

In addition to DNA damage, p53 activation can occur in a state of stress on cells caused by exposure to chemicals, ultraviolet and radioactive. In normal cells p53 is kept low due to the process of p53 degradation. A protein called MDM2 binds to p53. This protein will carry the p53 protein into the cytosol and be degraded by the proteosome enzyme.[4]

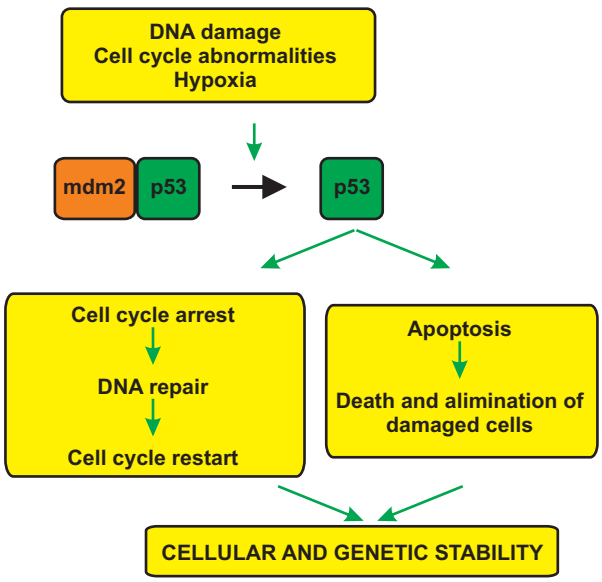

Figure 1. Physiology of p53 in the regulation of normal cell division.

Mutation of the p53 gene is the most frequent changes found in malignant prostate cancer in human organs. In prostate cancer the expression of mutant p53 is increasing in advanced stage. P53 mutations are associated with resistance to chemotherapy, gene instability, increased angiogenesis and rapid tumor progression. P53 mutation is rare in localized prostate cancer. In a research conducted by Gurova et al (2002) on mutant p53 gene, the PSA-expressing gene had increased 6-8 fold, so it was suspected that elevated PSA levels is associated with mutant p53 expression.[7]

OBJECTIVE

This study aimed to explore the relationship between the expression of p53 mutants with increased PSA serum levels in patients with prostate cancer.

MATERIAL & METHOD

Subjects of this study were all patients with prostate adenocarcinoma who were diagnosed clinically and histopathologically in the period between January 1, 2007 and December 31, 2008 at Dr. Sadjito Hospital, Yogyakarta.

The patients must meet the following inclusion criteria (1) Patients with prostate adenocarcinoma that had been established based on histopathologic examination, (2) The clinical staging of patients had been recognized and confirmed by a urologist (AJCC-TNM, 1992), (3) preoperative serum PSA levels was examined, and (4) the degree of tumor differentiation had been recognized (Gleason score).

The exclusion criteria in this study were incomplete preoperative PSA serum data and clinical staging of patients in the medical record.

PSA serum level was checked in the Laboratory of Clinical Pathology, Dr. Sardjito Hospital, and data may be found in the patient's medical record.

P53 staining procedure was performed in the Laboratory of Anatomic Pathology, Dr. Sardjito Hospital, using anti-p53 monoclonal antibodies D-07. This antibody binds to normal p53 protein and p53 mutants, but because normal p53 protein will be degraded, so that only mutant p53 will bind to this antibody and will be microscopically visible. P53 expression is examined by one anatomic pathologist by counting the number of nuclei containing p53 in

each preparation. Examination of each preparation was carried out in five visual fields and the result was the mean of those five visual fields.

Correlation between p53 expression with preoperative PSA serum levels was statistically analyzed by means of bivariate analysis. Prior to analysis, data normality test was performed with the technique of one-sample Kolmogorov-Smirnov. If the obtained data were normally distributed, bivariate analysis was performed with Pearson correlation test, but if the data were not normally distributed, Spearman correlation test would be used. Data analyses were performed with statistical analysis program SPSS version 16.0.

RESULTS

There were 29 males involved as subjects, with mean age of 66,34 ± 8,15 (50-83) years. They met the criteria and were included as research subjects. Characteristics of the subjects can be seen in Table 1. The mean preoperative PSA serum levels were 165,98 ± 269,2 (1,4 to 1051) ng/ml and the mean number of p53 expression was 111,38 ± 94,3 (16-396)/LPB.

Table 1. Characteristics of patients (n = 29).

Age (year), mean ± SD (interval)	66,34 ± 8,15
PSA serum value (ng/ml)	
0 - 9	2 (6,9%)
10 - 19	1 (3,4%)
20 - 49	4 (13,8%)
> 49	22 (75,9%)

Table 2. Staging of prostate cancer patients.

Staging	Total
Localized prostate cancer (T1-2, N_X -N_0,M0)	14 (48,3%)
Locally advanced prostate cancer (T3 -T4, N_x -N_0,M0)	0 (0%)
Metastatic prostate cancer (M1)	15 (51,7%)

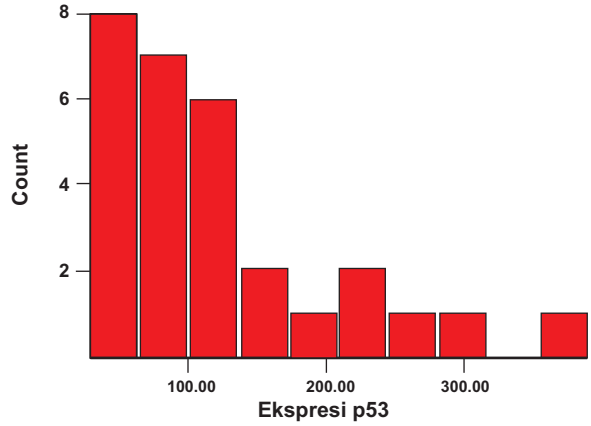

Figure 1. Expression of p53 in the study sample.

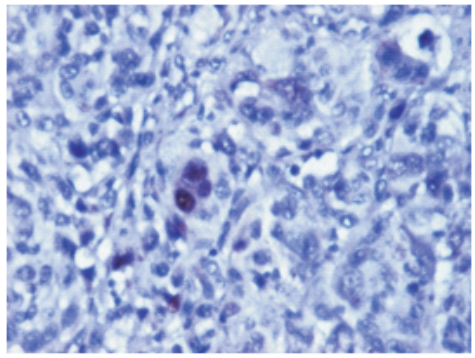

Figure 2. Results of pathological examination of samples with low p53 expression.

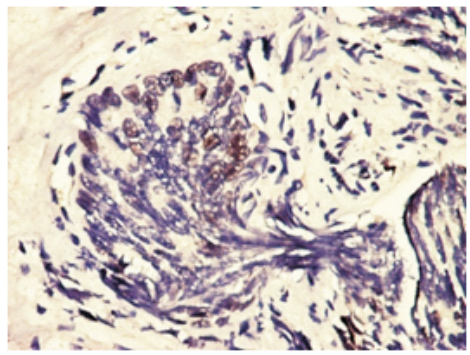

Figure 3. Results of pathological examination of samples with high p53 expression.

Table 3. Correlation analysis.

			P53 expression	t-PSA serum value (ng/ml)
Spearman's rho	P53 Expression	Correlation Coefficient	1,000	,497(**)
		Sig. (2-tailed)	,	,006
		N	29	29
	t-PSA serum value (ng/ml)	Correlation Coefficient	,497(**)	1,000
		Sig. (2-tailed)	,006	,
		N	29	29

Because the results of normality test with Kolmogorov-Smirnov showed that the data were not normally distributed (r = 0,000), Spearman correlation test was carried out. The analysis showed that there was a significant positive correlation between p53 expression with increased levels of preoperative PSA serum (Spearman r = + ,497; p = 0,006).

DISCUSSION

Mutation of the p53 tumor suppressor gene is the most frequent genetic alterations found in human malignant tumors and its presence can be detected by immunohistochemical staining.[8] P53 plays an important role in the regulation of cell proliferation, so that the occurrence of p53 mutations may become one marker of abnormal cell proliferation. Some studies show that expression of p53 are found in patients with metastatic and hormone refractory prostate cancer.[9]

In prostate cancer, PSA has been used as a progression marker because of elevated PSA is sensitive enough as an indicator of relapse and the incidence of metastases after treatment, so it is interesting to find the correlation between elevated PSA with prostate cancer proliferation activity. One of this effort is by measuring the expression of mutant p53.[10]

This study found significant correlation (p = 0,006) between increased expression of p53 mutants and increased PSA serum levels. This is consistent with the research conducted by Gurova et al (2002). PSA levels increased because among mutant p53 genes there are gene pieces that play a role as PSA promoter. However, this is found primarily in prostate cancer metastases and hormone refractory.[7] In early stages, the increase of PSA in prostate cancer occurs due to the damage to the normal architecture of the prostate gland, but when p53 mutations occur, PSA will rise 6-8 fold due to abnormal production of the PSA.[7]

The results of this study contradict those found by Papadopoulos et al (1996) who disclosed that there was no relationship between PSA serum levels with the expression of p53,[5] but the explanation of this finding was that because the study samples were taken from localized patients and locally advanced prostate cancer without metastases. Whereas, p53 expression is associated with elevated levels of PSA serum occurs in prostate cancer metastasis or hormone refractory.[7]

CONCLUSION

There is a significant relationship between p53 expression and increased PSA levels. This relationship is primarily seen in prostate cancer metastasis.

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