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## The Influence of Hepatic Function on Prostate Cancer Outcomes Following Radical Prostatectomy

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### Abstract

Prostate growth is dependent on circulating androgens which can be influenced by hepatic function. Liver disease has been suggested to influence prostate cancer (CaP) incidence. However, the effect of hepatic function on CaP outcomes has not been investigated. A total of 1,181 patients who underwent radical prostatectomy (RP) between 1988 and 2008 at four Veterans Affairs hospitals that comprise the Shared Equal Access Regional Cancer Hospital (SEARCH) database and had available liver function test (LFT) data were included in the study. Independent associations of LFTs with unfavorable pathological features and biochemical recurrence were determined using logistic and Cox regression analyses. Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels were elevated in 8.2% and 4.4% of patients, respectively. After controlling for CaP features, logistic regression revealed a significant association between SGOT levels and pathological Gleason sum 7(4+3) cancer (odds ratio=2.12; 95% confidence interval=1.11-4.05; p=0.02). Mild hepatic dysfunction was significantly associated with adverse CaP grade but was *not* significantly associated with other adverse pathological features or biochemical recurrence in a cohort of men undergoing R. The

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### CONFLICTS OF INTEREST

Authors report no conflicts of interest.

effect of moderate to severe liver disease on disease outcomes in CaP patients managed non-surgically remains to be investigated.

### Keywords

Prostate neoplasm; Prognosis; Staging; Pathology; PSA Recurrence; Radical Prostatectomy; Liver function tests; Logistic regression; Kaplan-Meier analysis; Cox Proportional Hazards models

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## INTRODUCTION

Prostate adenocarcinoma proliferation is highly dependent on circulating sex steroids, specifically testosterone and dihydrotestosterone, and the binding of these hormones to receptors on prostate cancer cells.<sup>1-2</sup> Poorly-differentiated, rapidly proliferating prostate cancers commonly lose much of their dependence on these hormones. Conditions that result in changes in sex steroid production, particularly decreased androgens and/or increased estrogens, can inhibit the growth and development of well-differentiated prostate cancers but may have little influence or even an undesirable effect on poorly-differentiated prostate tumors. This phenomenon has been demonstrated with finasteride, which decreases the conversion of testosterone to dihydrotestosterone by inhibition of 5-alpha reductase enzyme. In the Prostate Cancer Prevention Trial, finasteride was found to significantly prevent or delay prostate cancer by almost 25% overall, however, the risk for having high-grade disease, specifically Gleason grade 7 to 10 tumors, was significantly increased.<sup>3</sup> Though, the exact underlying mechanism by which finasteride reduces risk for prostate cancer while simultaneously promote aggressive disease requires further study, investigators could speculate that reduction of circulating androgens may be, in part, responsible.

Obesity is another condition which may exert a similar paradoxical effect on prostate cancer incidence. Obese men have increased estradiol levels resulting from increased peripheral conversion of steroids in adipose tissues by the enzyme aromatase. This phenomenon results in an anti-androgenic effect driving down testosterone levels similar to administration of finasteride. Though more recent studies point to other causes for increased risk of advanced prostate cancer in obese men (such as detection bias secondary to prostate specific antigen (PSA) hemodilution)<sup>4</sup> some investigators have suggested that obesity decreases the overall rate of prostate cancer development and increases the incidence of more aggressive prostatic tumors through decreased testosterone production,<sup>5-6</sup> though confirmatory studies are clearly needed.

Hepatic dysfunction, most commonly from excess alcohol consumption, can also result in diminished androgen and increased estrogen effects.<sup>7-10</sup> Several authors have investigated the effect of alcohol intake on the incidence of prostate cancer and, similar to finasteride administration and obesity, there seems to be a diminished incidence of prostate cancer in alcoholic beverage drinkers implying a protective effect.<sup>11-17</sup> Hypogonadal effects of alcohol-induced liver disease are similarly ascribed to reduced androgen production and are, thus, suggested to influence development of prostate cancer. However, studies have not investigated the effect of impaired hepatic function on pathological or biochemical outcomes in men being treated surgically for prostate cancer. In the current study, we sought to determine whether impaired liver function, pre-operatively, as exemplified by abnormal liver function tests (LFTs) influences the risk for adverse pathological features of prostate cancer or biochemical recurrence, post-operatively, in a multi-ethnic cohort of men undergoing radical prostatectomy in the equal-access setting of Veterans Affairs hospitals.

## METHODS

After obtaining institutional review board approval for data abstraction from each institution, demographic and clinicopathological data from 2,374 patients who underwent radical prostatectomy from 1988–2008 at the Veterans Affairs Medical Centers of Augusta, Georgia, Durham, North Carolina, West Los Angeles, California and Palo Alto, California were retrospectively collected. These databases comprise the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Because the distribution of all clinicopathological variables was similar between the four SEARCH sites, data from all four sources were combined for analysis. To be included in the study, patients must have the results of at least 1 pre-operative liver function test (LFT) available, specifically, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) or serum gamma glutamyl transferase (GGT). Men who did not have any available LFT data (n=1,158) were excluded. We also excluded men treated with neoadjuvant radiation/hormonal therapy (n=35). This resulted in a final study population of 1,181. Radical prostatectomy specimens were sectioned and evaluated per standard protocol of each institution by pathologists blinded to the status of hepatic function.

LFT data were analyzed as continuous terms after logarithmic transformation, and normal versus elevated LFT categories according to the following upper limits in normal reference ranges: SGOT= 40 IU/L; SPGT= 56 IU/L; SGGT= 65 IU/L. As continuous terms, associations between LFT and clinicopathological variables were assessed using Spearman rank test. The distribution of clinicopathological characteristics across LFT categories were compared using chi-squared test for categorical variables and Mann-Whitney test for continuous variables. Logistic regression was used to determine the association of LFTs to the following binary outcome variables: pathological Gleason sum 7(3+4), 7(4+3), 8, extracapsular extension, positive surgical margins and seminal vesicle invasion; only a few men had lymph node metastasis. We adjusted for preoperative PSA level (continuous after logarithmic transformation), biopsy Gleason score grouping (2–6, 3+4, and 4+3), age at surgery (continuous), race (Caucasian, African-American, or other), body mass index (BMI: categorical; <25, 25–29.9, 30–34.0, and ≥35 kg/m<sup>2</sup>), surgery year (continuous), clinical stage (cT1c versus cT2/T3), and surgical center (categorical).

Kaplan-Meier test was used to assess the association of LFTs with biochemical recurrence-free survival. Biochemical progression was defined as one PSA level of >0.2 ng/mL, two of 0.2 ng/mL, or secondary treatment for a high PSA level after radical prostatectomy. LFTs were also entered as continuous terms after logarithmic transformation into a Cox proportional hazards regression model adjusting for preoperative characteristics, as described above, as well as pathological features of prostate cancer including pathological Gleason sum (2–6, 3+4, and 4+3), margin status, extracapsular extension, seminal vesicle invasion, lymph node metastasis, and prostate weight (continuous after logarithmic transformation). To estimate the risk of biochemical progression associated with LFTs, indicator variables for normal versus elevated categories for LFTs were entered into separate Cox models controlling for pre-operative and pathological confounders as described above. Associations with p-values <0.05 were considered statistically significant. All analyses were performed with STATA 10 (Statacorp., College Station, TX).

## RESULTS

Demographic and clinicopathological characteristics of the study population are shown in Table 1. Median follow-up time was 9.5 months (interquartile range 14–70 months). Overall, 8.2% of patients (95/1156) had elevated SGOT levels, 4.4% (51/1156) had elevated SGPT levels, and 107 men (3.4%) had both elevated SGOT and SGPT levels. Of the 421

men with SGGT results, 60 (14%) had abnormally elevated results. Men with elevated SGOT and SGPT tended to be younger ( $p^{\text{SGOT}}=0.002$ ;  $p^{\text{SGPT}}<0.001$ ) and treated with radical prostatectomy in later years ( $p^{\text{SGOT}}=0.002$ ;  $p^{\text{SGPT}}=0.02$ ). Spearman rank tests showed significant inverse relationships between LFTs and PSA ( $\rho^{\text{SGOT}}=-0.06$ ;  $p^{\text{SGOT}}=0.05$ ;  $\rho^{\text{SGPT}}=-0.14$ ;  $p^{\text{SGPT}}<0.001$ ) and LFTs and prostate weight ( $\rho^{\text{SGOT}}=-0.07$ ;  $p^{\text{SGOT}}=0.02$ ;  $\rho^{\text{SGPT}}=-0.07$ ;  $p^{\text{SGPT}}=0.02$ ). Elevated SGPT, SGOT, SGGT, singularly or in all combinations, were *not* found to be associated with pathological Gleason sum 7(3+4), 7(4+3), 8, extracapsular extension, positive surgical margins and seminal vesicle invasion on univariate analysis.

After controlling for the various demographic and clinicopathological variables of prostate cancer, logistic regression analysis revealed a significant association between SGOT levels (treated as a logarithmically-transformed continuous variable) and pathological Gleason sum 7(4+3) cancer (odds ratio (OR)=2.12; 95% confidence interval (CI)=1.11–4.05;  $p=0.02$ ; Table 2) and a marginally significant association between SGOT levels and pathological Gleason sum 8 cancer (OR=2.03; 95% CI=0.91–4.52;  $p=0.08$ ). Taken as logarithmically transformed continuous terms or categorical terms (normal versus elevated), SGPT and SGGT were not associated with pathological Gleason sum 7(3+4), 7(4+3) or 8 prostate cancer. Furthermore, there was no association between LFTs and extracapsular extension, positive surgical margin and seminal vesicle invasion (Table 2).

Kaplan-Meier test did not reveal any association between elevated LFTs and biochemical recurrence after radical prostatectomy. Likewise, Cox proportional hazards models did not reveal any association between LFTs (continuous or categorical) and recurrence-free survival independent of the various demographic and clinicopathological variables (Table 3).

## DISCUSSION

There is some evidence that hepatic dysfunction may decrease the risk for being diagnosed with prostate cancer though the mechanism for this association is unclear. In the current analysis, we hypothesized that liver dysfunction as measured by increased LFTs could possibly decrease the risk for advanced stage disease or decrease the risk of biochemical relapse following surgical extirpation of the prostate. We, however, found that LFTs were *not* associated with favorable pathological or biochemical outcomes in prostate cancer patients treated surgically. On the contrary, we found a modest association between SGOT levels and high-grade prostate cancer. Thus, at least in radical prostatectomy patients, liver function does not seem to be of value in terms of predicting or affecting cancer-specific outcomes.

Based on the study population of 1,181 patients and an alpha of 0.05, our analysis was adequately powered (0.89) to detect a 40% difference in survival. Cox regression models for elevated SGOT, elevated SGPT, and both elevated LFTs did not show any increase in recurrence-free survival estimates when compared to individuals with normal liver function tests. No such correlation was seen with increased SGGT levels as well, however, only 36% of the participants had SGGT data. In this study, survival end-point was defined by the occurrence of biochemical recurrence as measured by post operative PSA. Though previous studies show a possible protective effect of hepatic dysfunction for being diagnosed with prostate cancer, liver disease appears to only affect outcomes modestly, if at all, once prostate cancer is diagnosed and treated surgically. Furthermore, despite the high positive margin rates among VA patients (44%), which is characteristic of high-risk multi-racial populations with predominantly low socioeconomic status, we did *not* find any association between LFTs and surgical margin status.

The growth of well-differentiated prostate cancers is thought to be dependent on testosterone. Conversely, resistance to androgens is associated with poorly-differentiated and rapidly proliferating tumors. Poorly-differentiated cancers would behave aggressively with a larger percentage being high grade, when compared to those that are well-differentiated, and therefore have a higher recurrence rate post radical prostatectomy. This was seen in a study by Schatzl *et al.* which found that higher Gleason sum cancers were associated with decreased circulating testosterone levels.<sup>18</sup> Hepatic dysfunction is associated with decreased peripheral circulating testosterone secondary to its conversion to estrogens. Theoretically, greater conversion to estrogens would then favor the growth of poorly-differentiated prostate cancer, while providing inadequate stimulation for proliferation of well-differentiated tumors. This process was described in a paper by Lucia *et al.* in association with finasteride administration.<sup>19</sup> In that study, an increase in the percentage of incident high grade prostate cancers were found in the group of men receiving finasteride.<sup>19</sup> Thus, it is reasonable to hypothesize that a similar biological mechanism may explain how liver dysfunction may be protective for incident well-differentiated tumors but may be associated with high-grade tumors.

The degree of hepatic dysfunction must also be taken into close consideration when interpreting the results of our study. Severity of liver dysfunction is usually assessed for using the Child-Pugh score, which employs serum total bilirubin, serum albumin, international normalized ratio (INR), presence and severity of ascites and hepatic encephalopathy to classify patients with chronic liver disease into three categories (Child-Pugh Class A to C) based on worsening survival.<sup>20</sup> Participants that consented to a surgical treatment who had liver disease would only have relatively mild disease (Child-Pugh Class A) because moderate to severe hepatic dysfunction (Child-Pugh Class B and C) would exclude the patient from undergoing surgical resection of the tumor. In our study cohort of military veterans, we suspect the most likely cause for liver dysfunction is alcoholic beverage intake. Indeed, cirrhosis is known to decrease circulating testosterone and the degree of reduced testosterone levels has been shown to correlate with the severity of patient's cirrhosis.<sup>10</sup> The majority of study participants had relatively low grade, well-differentiated prostate cancer. In this population, where cancer growth is testosterone-dependent, decrease in circulating testosterone found in liver cirrhosis may lead to a slower rate of tumor growth; however, men from our study had only mild dysfunction. Thus, the participants in this study are hypothesized to have a decrease in the circulating testosterone levels to a point that suppresses, but does not prevent the growth of well-differentiated, organ-confined prostate cancer, while not selecting for more aggressive poorly-differentiated cancer.

We found a significant inverse association between LFTs and pre-operative serum PSA in our study. This is in agreement with previous studies which found that cirrhotic patients have significantly lower PSA levels than men with normal liver function.<sup>21–22</sup> Furthermore, liver dysfunction, which has been shown to influence the development of BPH, is associated with smaller prostate size.<sup>23</sup> This association between liver function and prostate size may further contribute to lower PSA levels in men with hepatic dysfunction. Thus, given that that biochemical relapse is defined by post-operative PSA levels, detection of recurrent disease among men with hepatic dysfunction may have been confounded by the hepatic dysfunction-related lowering of PSA. However, the potential effect of liver disease-related lowering of PSA on detection of PSA recurrence requires further study.

Unfortunately, we did not have data on the lifetime cumulative exposure to ingested alcohol among the study participants which could potentially shed more light on the modest association between LFTs and prostate cancer pathology. Indeed, several studies have found an increased risk for incident prostate cancer in alcoholic beverage drinkers.<sup>13, 24</sup> In fact,

distinct types of alcoholic beverages may have differing effects on prostate cancer outcomes which could have further confounded our study. 17 Moreover, continued use of alcohol intake post-surgery could also affect key dietary nutrients from being absorbed and therefore could confound the surgical outcomes observed. Lastly, serum testosterone levels were not taken pre-operatively among the study participants preventing us from examining possible correlation between LFTs, alcohol intake and circulating androgens and the effect of these associations with prostate cancer outcomes.

Only patients who underwent radical prostatectomy were included in this study. This may exert a selection bias as poor liver function would impart increased risk for post-operative complications, such as bleeding and poor wound healing, excluding such patients from being a candidate for prostatectomy. Thus, the effect of hepatic dysfunction on patients undergoing other treatment modalities, particularly external beam radiation, brachytherapy and androgen deprivation therapy, deserves further investigation. Subsequently, the effect of liver function on circulating sex hormones and the findings in this study of its effect on prostate cancer have led to a follow-up study currently underway to examine the effects of liver function on those patients undergoing hormone therapy for treatment of prostate cancer.

## CONCLUSION

In a cohort of men with mild to absent liver disease, all undergoing radical prostatectomy in an equal-access setting, mild hepatic dysfunction was associated with increased risk for high-grade prostate cancer but did *not* appear to influence biochemical recurrence post-operatively. Results may differ for patients with significant liver dysfunction who are not typically candidates for radical prostatectomy and would not have been included in this study.

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**Table 1**

## Baseline demographic and clinicopathological features of men undergoing radical prostatectomy

Number of patients	1,181
Age at surgery	
Mean $\pm$ SD, years	61.0 $\pm$ 6.6
Year of surgery	
Median (IQR)	2001 (1997-2004)
Race	
Caucasian	569 (59%)
African American	524 (45%)
Others	70 (6%)
BMI (kg/m <sup>2</sup> )	
<25	286 (27%)
25–29.9	482 (45%)
30–34.9	197 (19%)
35	97 (9%)
PSA	
Median (IQR)	6.9 (4.8-10.6)
SGOT	
Median (IQR), IU/L	22 (19-29)
SGPT	
Median (IQR), IU/L	23 (17-31)
SGGT	
Median (IQR), IU/L	30 (22-46)
Biopsy Gleason Sum	
2–6	687 (62%)
7	322 (29%)
8–10	101 (9%)
Clinical Stage	
cT1	609 (55%)
cT2/T3	495 (45%)
Pathologic Gleason Sum	
2–6	477 (42%)
7	532 (47%)
8–10	122 (10%)
Prostate Weight	
Median (IQR), grams	38 (30-50)

Extracapsular Extension	262 (23%)
Positive Surgical Margins	491 (44%)
Seminal Vesicle Invasion	104 (9%)
Lymph Node Involvement	14 (1%)

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(SD= standard deviation; IQR= inter-quartile range; PSA= prostate specific antigen; SGOT= serum glutamic oxaloacetic transaminase; IU/L= international units per liter; SPGT= serum glutamic pyruvic transaminase; SGGT= serum gammaglutamyl transferase; BMI= body mass index)

**Table 2**

Risk of Adverse Pathology Associated With Liver Function Test Results

		SGOT			SGPT		
		OR	95% CI	p-value	OR	95% CI	p-value
Pathological Gleason Sum	7 (3+4)						
Crude		1.06	0.79 – 1.43	0.68	1.26	0.99 – 1.59	0.06
Adjusted		1.31	0.76 – 2.24	0.33 <sup>†</sup>	0.87	0.54 – 1.40	0.57 <sup>‡</sup>
Pathological Gleason Sum	7 (4+3)						
Crude		1.33	0.95 – 1.86	0.10	1.10	0.84 – 1.45	0.48
Adjusted		2.12	1.11 – 4.05	0.02 <sup>†</sup>	0.66	0.37 – 1.16	0.15 <sup>‡</sup>
Pathological Gleason Sum	8						
Crude		1.21	0.77 – 1.89	0.41	1.10	0.76 – 1.58	0.62
Adjusted		2.03	0.91 – 4.52	0.08 <sup>†</sup>	0.59	0.29 – 1.21	0.15 <sup>‡</sup>
Extracapsular Extension							
Crude		1.24	0.89 – 1.73	0.21	1.27	0.97 – 1.67	0.08
Adjusted		1.53	0.83 – 2.79	0.17 <sup>†</sup>	0.86	0.51 – 1.47	0.59 <sup>‡</sup>
Positive Surgical Margins							
Crude		1.00	0.75 – 1.34	0.98	1.15	0.92 – 1.46	0.22
Adjusted		1.02	0.62 – 1.67	0.94 <sup>†</sup>	1.14	0.75 – 1.75	0.54 <sup>‡</sup>
Seminal Vesicle Invasion							
Crude		0.85	0.51 – 1.42	0.54	0.84	0.56 – 1.23	0.38
Adjusted		1.04	0.39 – 2.72	0.94 <sup>†</sup>	1.00	0.45 – 2.20	0.99 <sup>‡</sup>

<sup>†</sup>Using logistic regression adjusting for age at surgery, race, year of surgery, BMI, log-transformed PSA, biopsy Gleason score, clinical stage, surgical center and log-transformed SGPT levels

<sup>‡</sup>Using logistic regression adjusting for age at surgery, race, year of surgery, BMI, log-transformed PSA, biopsy Gleason score, clinical stage, surgical center and log-transformed SGOT levels

(PSA = prostate specific antigen; BMI = body mass index; SGOT= serum glutamic oxaloacetic transaminase; SGPT= serum glutamic pyruvic transaminase)

**Table 3**

Risk of Biochemical Recurrence Associated With Serum Liver Function Test Results

	SGOT			SGPT		
	HR	95% CI	p-value	HR	95% CI	p-value
Crude	1.01	0.77 – 1.31	0.95	0.98	0.80 – 1.19	0.82
Adjusted <sup>†</sup>	1.34	0.82 – 2.18	0.24	0.72	0.47 – 1.08	0.11

<sup>†</sup>Adjusted for pre-operative and post-operative factors: age at surgery, race, year of surgery, BMI, log-transformed PSA, biopsy Gleason sum, clinical stage, surgical center and log-transformed SGOT and SGPT levels, pathological Gleason sum, extracapsular extension, surgical margin status, seminal vesicle invasion, lymph node status and prostate specimen weight

(PSA = prostate specific antigen; BMI = body mass index; SGOT= serum glutamic oxaloacetic transaminase; SGPT= serum glutamic pyruvic transaminase)