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Liver fibrosis scores and prostate cancer risk and mortality in the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Subclinical liver impairment due to fibrosis could influence the development and detectability of prostate cancer. To investigate the association between liver fibrosis and prostate cancer incidence and mortality, we included 5,284 men (mean age: 57.6 years, 20.1% Black) without cancer or liver disease at Visit 2 in Atherosclerosis Risk in Communities study. Liver fibrosis was assessed using the aspartate aminotransferase to platelet ratio index (APRI), fibrosis 4 index (FIB-4), and non-alcoholic fatty liver disease fibrosis score (NFS). Over 25 years, 215 Black and 511 White men were diagnosed prostate cancer, and 26 Black and 51 White men died from the disease. We estimated hazard ratios (HRs) for total and fatal prostate cancer using Cox regression. FIB-4 (quintile 5 versus 1: HR=0.47, 95%CI:0.29–0.77, p-trend=0.004) and NFS (HR=0.56, 95%CI:0.33–0.97, p-trend=0.03) were inversely associated with prostate cancer risk in Black men.

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Compared with no abnormal score, men with ≥1 abnormal score had a lower prostate cancer risk if they were Black (HR=0.46, 95%CI:0.24–0.89), but not White (HR=1.04, 95% CI:0.69–1.58). Liver fibrosis scores did not appear to be associated with fatal prostate cancer in Black or White men. Among men without a clinical diagnosis of liver disease, higher liver fibrosis scores were associated with lower incidence of prostate cancer in Black men, but not in White men, and not with fatal prostate cancer in either race. Further research is needed to understand the influence of subclinical liver disease on prostate cancer development versus detectability and the racial differences observed.

Keywords

liver fibrosis; prostate cancer; risk; cohort study

Introduction

Lower serum prostate-specific antigen (PSA) concentration in men with liver disease, as shown in our previous research and others, may adversely impact the accuracy for early detection of prostate cancer. (1–4) PSA screening has been the primary tool for the early detection of prostate cancer in the US for 30 years(5), and the burden of liver disease has been increasing over the same period(6). Further, the higher burden of liver diseases in certain subgroups, e.g., the higher prevalence of viral hepatitis in Black men,(7) might help partially explain, the racial disparity observed in prostate cancer mortality. Given that early detection may be beneficial for prostate cancer treatment and survival, a delayed diagnosis of a potentially aggressive prostate cancer could contribute to the higher prostate cancer mortality in US Black men.(8) We are not suggesting that men with a substantially reduced life expectancy due to chronic liver disease should be screened for prostate cancer. However, men with early liver fibrosis, well before clinically apparent cirrhosis, may not have markedly shortened life expectancy, and thus, may have prostate cancer as a competing risk of death. These latter men, especially in populations with a higher prostate cancer mortality, might benefit from the early detection of prostate cancer.

Besides affecting the accuracy of PSA screening, liver impairment resulting from fibrosis may play a complex role in prostate cancer development and progression (biology), and may additionally affect prostate cancer detection through effects on prostate size. The liver is involved in regulating androgen levels and produces sex hormone binding globulin (which carries androgen in circulation); and prostate cancer(9) and prostate(10) size are both, in part, dependent on androgens, albeit in complex ways.(11,12) Any influence of androgens on prostate volume is important for prostate cancer diagnosis following a positive screen, as biopsy is more sensitive in detecting prostate cancer in men with smaller prostate volumes. (13) Liver conditions also affect the regulation of other pathways that in turn may influence prostate cancer risk. For example, NAFLD is considered to be a hepatic manifestation of insulin resistance(14) and studies have observed that men with insulin resistance (but not frank diabetes) have increased prostate cancer risk.(15,16)

No firm link has been established between liver disease and prostate cancer incidence or mortality. With respect to risk, the prevalence of prostate cancer was higher in men who were hepatitis C antibody positive compared with negative in a retrospective cohort of US men who underwent prostate biopsy.(17) A prospective cohort study using the UK Biobank found that men with higher serum aspartate aminotransferase (AST, a biomarker for liver function) had a lower prostate cancer risk.(18) With respect to outcomes, NAFLD status was inversely associated with biochemical recurrence (BCR) in Korean men surgically treated for prostate cancer.(19) In contrast, AST (also called serum glutamic-oxaloacetic transaminase, SGOT) and alanine aminotransferase (ALT; also called serum glutamate pyruvate transaminase, SGPT; another liver function biomarker) were not associated with BCR among surgically treated patients in Shared Equal Access Regional Cancer Hospital (SEARCH) database.(12) Whether these observed associations may be explained by the influence of liver impairment on the development of prostate cancer, detection bias, another non-causal explanation, or a combination of these effects is unclear.

Thus, we aimed to evaluate the association between liver fibrosis, as measured by three non-invasive scores, and total and fatal prostate cancer risk in Black and White men without a clinical diagnosis of liver disease at the start of follow-up in the Atherosclerosis Risk in Communities (ARIC) study. We hypothesized that if subclinical liver fibrosis only reduces the sensitivity of PSA-based prostate cancer screening, we would observe an inverse association with prostate cancer risk and a positive association with fatal prostate cancer due to delayed detection and treatment.

Materials and Methods

Study population

The ARIC study is a US prospective cohort with 15,792 participants aged 45–66 years old when recruited in 1987–1989 from four communities: Forsyth County, NC; Jackson, MS; Minneapolis, MN; and Washington County, MD. Details are described elsewhere.(20,21) Participants were interviewed and examined at baseline, and then returned for follow-up study visits (2–5: 1990–1992, 1993–1995, 1996–1998, 2011–2013; and with additional visits after the end of follow up for cancer). Local institutional review boards approved the ARIC protocol and written informed consent was obtained from all ARIC participants. The research was conducted under the U.S. Common Rule. The majority (99.7%) of participants gave approval for follow-up for non-cardiovascular diseases.

We used Visit 2, when liver enzymes were first measured, as the start of follow up, and included men without a cancer diagnosis by Visit 2 who had complete data to calculate liver fibrosis scores and key covariates. We excluded men with a clinical diagnosis of liver disease based on response to the question “Has a doctor ever told you that you have cirrhosis or another chronic liver disease” at Visit 3. For men who missed Visit 3, routinely collected hospital discharge summaries for liver reasons (ICD-9: 571 or ICD-10: K74) was used to determine chronic liver disease status if they had a history of hospitalization. Since most ARIC participants were Black (27.0%) or White (72.7%), we also excluded men with a self-reported race other than Black or White, and Black men from the Minneapolis and Washington County field centers, which had very few Black participants.

Exposures

Serum liver enzymes – AST, ALT – platelet count and albumin were measured at Visit 2 as part of the ARIC study protocol. To assess the presence and extent of liver fibrosis, we calculated three non-invasive fibrosis scores for each man as we did previously(4): AST/platelet ratio index (APRI), fibrosis 4 index (FIB-4) and NAFLD fibrosis score (NFS). Specifically, we used Visit 2 liver enzyme concentrations and Visit 1 platelet counts (were not measured for all field centers at Visit 2). We used 33 U/L as upper-limit of normal of AST as we did previously.(22) Visit 2 body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Men were classified as having impaired fasting glucose or diabetes if they had fasting glucose >100 mg/dL (if not fasting: >140 mg/dL), self-reported a physician's diagnosis of diabetes, or used a diabetes medication. We defined abnormal fibrosis score as APRI>1, FIB-4>2.67 or NFS>0.676.(23,24)

Outcomes

Outcomes were first primary incident, lethal (metastasis to any organ or death from prostate cancer as the underlying cause), and fatal prostate cancer (death from prostate cancer as the underlying cause) that occurred after Visit 2 through 12/31/2015. Prostate cancer status, including stage at diagnosis, was ascertained through linkage with the MN, NC, MD, and MS state cancer registries. Additional cases were identified by the review of medical records following a cancer-specific telephone call, archived hospital discharge codes, and death certificates.(21) The median follow-up time in the study was 20.1 years, with a range of 0.01 to 25.9 years. Through 2015, 726 (511 White and 215 Black) men were diagnosed with prostate cancer, and of these, 83 (55 White and 28 Black) had lethal prostate cancer, and 77 (51 White and 26 Black) died of prostate cancer in the analytic cohort.

Covariates

Other variables considered were (Visit 2 unless otherwise specified): age, race and field center (Visit 1), diabetes, BMI, waist-hip ratio, cigarette smoking status (never, quit<10 years, current/quit within 10 years), alcohol consumption (never, former, current), family history of prostate cancer (Visit 3), and statin and aspirin use; these are known or purported risk or protective factors for total or lethal prostate cancer.(25)

Socioeconomic status (SES) and its correlates, such as access to and uptake of healthcare, may confound the association between liver fibrosis and prostate cancer. Generally, persons with poorer liver function tend to have lower SES, which is in turn linked with reduced access to care, and may limit opportunities for cancer screening.(26) We generated a propensity score (see Statistical analysis) that included childhood, early adulthood, and later adulthood SES each calculated using Visit 4 data as previously done in ARIC(27); US Census tract data on neighborhood income for the year 1990(28); typical frequency of routine medical examinations at Visits 1–3; health insurance status at Visit 1; type of health insurance at Visit 2; usual type of medical care at Visit 2.

Statistical analysis

Cox proportional hazards regression was used to estimate adjusted hazard ratios (HR) for the association between liver fibrosis scores and (1) prostate cancer incidence, (2) lethal prostate

cancer incidence, and (3) prostate cancer mortality. Person-years at risk were calculated from the date of Visit 2 until the date of prostate cancer diagnosis, diagnosis of a different cancer, death from another cause, or administrative censoring, whichever occurred first. For fatal prostate cancer, follow-up was through date of prostate cancer death, death from another cause, or administrative censoring, whichever occurred first. We expressed the liver fibrosis scores as continuous (per standard deviation) or in quintiles. We tested the linear trend for each score by modeling the median of each quintile as a continuous term. We ran three models: Model 1 adjusted for age and the combination of race and field center; Model 2 further adjusted for BMI, waist circumference, diabetes/impaired fasting glucose status, alcohol drinking, cigarette smoking status, family history of prostate cancer, and statin or aspirin use; and Model 3 further adjusted for a propensity score for SES and correlated variables (fully-adjusted model). To generate the propensity score, we modeled the association between liver fibrosis scores (normal vs. abnormal) and SES at each of the 3 points in life and the correlated variables using logistic regression and predicted the propensity score for each participant.

All analyses were conducted in the overall population, and stratified by race given the racial difference in prostate cancer risk. In addition, since NFS calculation includes BMI and diabetes, we ran a Model 4 for NFS in which we adjusted the variables in Model 3 but without these two factors to avoid potential over-adjustment. We also cross-categorized the men with respect to all three cores (APRI, FIB-4, NFS) to improve the accuracy of the classification of the absence of liver fibrosis (0 abnormal scores), and examined the association between the cross-categorized score and prostate cancer incidence; the number of lethal and fatal prostate cancers was too sparse to conduct this analysis.

Statistical tests were two-sided and $P<0.05$ was considered as statistically significant. All analyses were performed using STATA 14.2.

Data availability

The data analyzed in this study are available from the Atherosclerosis Risk in Communities (ARIC) study. Detailed information about data access and sharing is available online (https://sites.cscc.unc.edu/aric/sites/default/files/public/listings/ARIC%20data%20sharing.pdf).

Results

The analysis included 5,284 men with a mean age of 57.6 years. Table 1 shows age-adjusted characteristics by liver fibrosis status. Abnormal liver fibrosis scores were present in 0.68% (APRI), 3.20% (FIB-4), and 4.83% (NFS) of men. These percentages were higher in Black (APRI, FIB-4, NFS: 1.12%, 5.42%, 8.31%) than White (0.57%, 2.63%, 3.94%) men. Men with abnormal liver fibrosis scores were more likely to be diabetic, obese (BMI ≥30 kg/m^2), current smokers, less likely to have health insurance, and have a family history of prostate cancer. Alcohol drinking status was similar between those with and without abnormal liver fibrosis scores in these participants without diagnosed liver disease.

As shown in Table 2, in each model, including the fully-adjusted model (Model 3, and Model 4 for NFS), men with a higher APRI, FIB-4, and NFS score had a lower risk of

prostate cancer, although neither the associations nor the linear trends were statistically significant (all *P*>0.05). After stratifying by race, these associations appeared to be null in White men (Table 3). However, in Black men, prostate cancer risk was significantly lower comparing the highest to lowest quintile of FIB-4 (HR=0.47, 95%CI: 0.29–0.77; *P*-trend=0.004) and NFS (HR=0.56, 95%CI: 0.33–0.97; *P*-trend=0.03; Table 4). In Black men, the HR for APRI was modestly below the null, but was not statistically significant (HR= 0.91, 95%CI: 0.54–1.55). A one-standard deviation increase in the APRI, FIB-4, and NFS scores was associated with an 11%, 23%, and 28%, respectively, decrease in the HR of prostate cancer incidence in Black men.

Quintiles of the liver fibrosis scores were not clearly associated with lethal or fatal prostate cancer (all *P*>0.05), and most of the HRs for per standard deviation increase in fibrosis scores were close to 1 overall and in both Black and in White men (fully-adjusted model; Table 5).

In the cross-categorized fibrosis scores analysis, compared with men with zero abnormal scores, men with any abnormal score had a lower risk of prostate cancer if they were Black (HR=0.46, 95%CI: 0.24–0.89), but not if they were White (HR=1.04, 95%CI: 0.69–1.58, *P*-interaction=0.04).

Discussion

In middle-aged and older community dwelling men without a diagnosis of chronic liver disease, we observed an inverse association between higher liver fibrosis scores and prostate cancer incidence in Black men but not in White men. Liver fibrosis scores did not appear to be associated with lethal or fatal prostate cancer in either Black or White men.

We were motivated to conduct this study following our prior work suggesting that men with higher liver fibrosis scores had lower serum PSA.(4) We had two hypotheses about how liver fibrosis might affect the apparent risk of total and fatal prostate cancer: 1) biological influences on the development and progression of prostate cancer and 2) related to the influence of liver disease on PSA levels (decreasing the accuracy). If among those with liver fibrosis, reduced PSA concentration delays prostate cancer detection, then we would expect a lower prostate cancer risk in men with liver fibrosis than in men without liver fibrosis. We would also expect a higher risk of lethal prostate cancer and prostate cancer mortality in men with liver fibrosis, given that a delay in detection leading to later treatment could increase the likelihood of lethal disease progression. Regarding biological influences, if liver fibrosis results in a lower probability of prostate cancer development, we would expect that the risk of total, lethal, and fatal prostate cancer would be lower in men with liver fibrosis than those without. Overall, our findings did not support one of these hypotheses over the other. In Black men, we observed higher liver fibrosis scores were associated with a lower risk of prostate cancer, but not with lethal or fatal prostate cancer. Thus, in Black men, the patterns together suggest that liver fibrosis may influence the observed risk of prostate cancer through the combination of biology and detection bias, if other non-causal explanations can be ruled out. Conversely, in White men, associations appeared to be null for liver fibrosis scores with total prostate cancer, and with lethal or fatal disease. In White

men, both detection bias and biology could be acting, but their balance differs from that in Black men. Alternatively, we cannot rule out the roles of chance and other sources of bias.

Several aspects of this study warrant discussion. First, while the number of prostate cancer cases is relatively large, the number of prostate cancer deaths was small (77 cases in 5,284 men), resulting in limited statistical power to detect modest to moderate associations. Second, the non-invasive indicators might result in misclassification of liver fibrosis compared with imaging and the gold standard liver biopsy. However, cross-categorizing the men with all three scores supported the main findings. We expected that men “truly” without liver fibrosis would tend to score low on all three scores and thus increase the sensitivity. Third, NFS includes factors known to be associated with prostate cancer (abnormal fasting glucose, diabetes) or with lethal/fatal disease (BMI). Results for NFS, with or without further adjustment for BMI and diabetes status, showed similar results for APRI, suggesting the BMI and diabetes do not fully underlie the findings. Fourth, while we excluded men with a known clinical diagnosis of liver disease, men with and without unrecognized severe liver fibrosis might be different on many demographic, health, and lifestyle characteristics. We accounted for these by multivariable adjustment, including propensity scores for SES and associated access to care variables . Fifth, PSA-based prostate cancer screening and prostate biopsy histories are not available in ARIC. Whether any differences by race in the patterns of the recommendation and uptake of PSA screening contributed to the differences in findings between Black and White men cannot be directly determined. Finally, we were not able to conclusively distinguish between detection bias versus biology as explanations for the observed pattern. If detection bias, which stems from lower PSA in those with liver fibrosis, were the sole explanation for the inverse association between liver fibrosis scores and prostate cancer risk, we would have expected a positive association for lethal/fatal prostate cancer as result of delayed detection and treatment. While we did not observe a positive association with lethal/fatal prostate cancer, including in Black men, the number of events was small. Even longer follow up, and time-varying measures of both PSA and liver fibrosis scores, would be needed to fully capture the long-term impact of delayed detection on prostate cancer death. Thus, additional studies to determine whether liver impairment affects prostate cancer detection in Black men, is of particular importance because Black men have more than twice the risk of dying from prostate cancer than non-Hispanic White men.(29)

Despite possible limitations, ARIC has several strengths for addressing the present research question. First, to our knowledge, this study is the first and largest to examine the association between mild to moderate liver disease and prostate cancer risk. Second, ARIC is a prospective study with clinical and biomarker measures relevant to liver impairment and cancer follow-up. Liver enzymes were measured in the cohort without indication/suspicion of liver fibrosis, and when included in the scores calculations, provide a non-invasive assessment of the likelihood and severity of liver fibrosis. We were able to exclude participants with a diagnosis of liver disease, who may not be eligible for prostate cancer screening, and have a higher risk of death from liver disease, reducing the competing risk of death. Additionally, the participants were from four distinct US geographic sites and included a large proportion of Black participants, making our findings generalizable to similar groups in the US.(21)

In conclusion, in men without a clinical diagnosis of liver disease, having a higher liver fibrosis score was associated with a lower risk of prostate cancer, but only in Black men. Whether the findings for Black men reflect the influence of subclinical liver disease on the development versus the detectability of prostate cancer, including by PSA, or whether there is another explanation requires further study, as does the difference in findings by race.

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Prevention Relevance Statement

Investigating the link between liver fibrosis and prostate cancer risk and mortality, our study reveals the potential influence of liver health on prostate cancer detection using prostate-specific antigen (PSA) test, urging further research to optimize prevention and intervention strategies.

Table 1.

Age-adjusted Characteristics of Participants by Liver Fibrosis Scores at Visit 2, Men in the Atherosclerosis Risk in Communities Study, 1990–1992

	Overall	APRI		FIB-4		NFS	
Factor		**Normal**	**Abnormal[a]**	**Normal**	**Abnormal[a]**	**Normal**	**Abnormal[a]**
N	5284 (100%)	5248 (99.32%)	36 (0.68%)	5115 (96.80%)	169 (3.20%)	5029 (95.17%)	255 (4.83%)
Age in year, mean (SD)	57.6 (5.7)	57.6 (5.7)	58.1 (5.8)	57.5 (5.7)	60.8 (5.3)	57.5 (5.7)	60.4 (5.5)
Race, % (95% CI) [b]							
White	79.9 (78.8–81.0)	80.0 (78.9–81.1)	66.5 (50.9–82.0)	80.5 (79.4–81.6)	63.0 (55.5–70.5)	80.8 (79.7–81.9)	62.7 (56.6–68.8)
Black	20.1 (19.0–21.2)	20.0 (18.9–21.1)	33.5 (18.0–49.1)	19.5 (18.4–20.6)	37.0 (29.5–44.5)	19.2 (18.1–20.3)	37.3 (31.2–43.4)
Field center, % (95% CI)							
Forsyth, North Carolina	26.2 (25.0–27.4)	26.3 (25.1–27.5)	13.9 (2.6–25.2)	26.2 (25.0–27.4)	25.7 (19.1–32.4)	26.2 (25.0–27.4)	27.0 (21.5–32.4)
Jackson, Mississippi	17.6 (16.6–18.7)	17.5 (16.5–18.6)	30.7 (15.6–45.9)	17.1 (16.1–18.2)	32.8 (25.5–40.2)	16.9 (15.8–17.9)	32.5 (26.6–38.5)
Minneapolis, Minnesota	29.0 (27.8–30.3)	29.2 (27.9–30.4)	11.1 (0.8–21.3)	29.5 (28.3–30.8)	14.3 (9.1–19.6)	29.8 (28.5–31.0)	14.5 (10.2–18.8)
Washington County, Maryland	26.8 (25.6–28.0)	26.7 (25.5–27.9)	44.1 (27.9–60.4)	26.7 (25.5–28.0)	28.0 (21.3–34.7)	26.8 (25.6–28.0)	26.8 (21.4–32.2)
Diabetes status, % (95% CI)	11.1 (10.2–11.9)	11.0 (10.1–11.8)	27.2 (12.7–41.7)	10.9 (10.1–11.8)	15.4 (10.1–20.6)	9.2 (8.4–10.0)	50.5 (44.3–56.8)
BMI (BMI>=30), % (95% CI)	25.3 (24.1–26.5)	25.3 (24.1–26.5)	27.9 (13.2–42.6)	25.3 (24.1–26.5)	26.6 (19.8–33.4)	23.8 (22.7–25.0)	53.6 (47.4–59.8)
Smoking status, % (95% CI)							
Never smoker	29.1 (27.8–30.3)	29.1 (27.9–30.4)	16.7 (4.5–29.0)	29.0 (27.8–30.3)	30.5 (23.4–37.6)	28.9 (27.6–30.1)	32.4 (26.5–38.2)
Current smoker or former smoker that quit <10 years ago	39.5 (38.2–40.8)	39.4 (38.0–40.7)	64.2 (48.5–79.9)	39.3 (38.0–40.6)	46.3 (38.7–53.9)	39.6 (38.3–41.0)	37.1 (31.1–43.2)
Former smoker that quit >=10 years ago	31.0 (29.7–32.2)	31.0 (29.8–32.3)	18.7 (6.1–31.3)	31.2 (29.9–32.5)	23.3 (17.1–29.4)	31.0 (29.7–32.3)	30.0 (24.5–35.6)
Drinking status, % (95% CI)							
Never drinker	11.1 (10.3–12.0)	11.1 (10.3–12.0)	8.2 (−0.7–17.1)	11.1 (10.3–12.0)	9.9 (5.5–14.3)	11.1 (10.2–12.0)	11.1 (7.3–14.9)

Factor	Overall	APRI		FIB-4		NFS	
		Normal	Abnormal[a]	Normal	Abnormal[a]	Normal	Abnormal[a]
Current drinker	64.5 (63.2–65.8)	64.4 (63.1–65.7)	72.6 (58.1–87.1)	64.4 (63.0–65.7)	67.8 (60.8–74.8)	64.9 (63.6–66.2)	56.0 (49.9–62.1)
Former drinker	24.4 (23.2–25.5)	24.4 (23.2–25.6)	19.2 (6.4–32.0)	24.4 (23.3–25.6)	22.3 (16.1–28.4)	23.9 (22.8–25.1)	32.7 (27.0–38.5)
Statin and aspirin use, % (95% CI)	48.6 (47.2–49.9)	48.6 (47.3–50.0)	47.0 (30.7–63.3)	48.7 (47.3–50.0)	46.9 (39.3–54.4)	48.6 (47.3–50.0)	47.6 (41.4–53.7)
Family history of prostate cancer, % (95% CI)	6.0 (5.4–6.6)	6.0 (5.3–6.6)	11.0 (0.8–21.2)	5.9 (5.3–6.6)	7.9 (3.9–11.9)	5.9 (5.2–6.5)	8.7 (5.2–12.1)
Frequency of routine medical examinations, % (95% CI)							
Do not have routine physical examinations	33.8 (32.5–35.1)	33.7 (32.4–35.0)	44.8 (28.4–61.1)	33.8 (32.5–35.1)	33.5 (26.2–40.8)	33.7 (32.4–35.0)	35.7 (29.7–41.7)
At least once a year	30.6 (29.4–31.9)	30.6 (29.4–31.9)	32.5 (17.1–47.8)	30.5 (29.2–31.8)	35.0 (27.9–42.1)	30.2 (28.9–31.5)	38.8 (32.8–44.8)
At least once every five years	29.8 (28.6–31.1)	30.0 (28.7–31.2)	11.2 (0.8–21.5)	30.0 (28.7–31.2)	25.2 (18.5–31.8)	30.3 (29.0–31.5)	21.0 (16.0–26.1)
Less than once every five years	5.2 (4.6–5.8)	5.2 (4.6–5.8)	11.1 (0.8–21.4)	5.2 (4.6–5.8)	5.5 (2.0–9.0)	5.3 (4.7–5.9)	3.6 (1.3–5.9)
Health insurance status, % (95% CI)	92.2 (91.5–92.9)	92.3 (91.5–93.0)	80.6 (67.6–93.5)	92.4 (91.6–93.1)	86.9 (81.8–92.1)	92.4 (91.7–93.2)	87.0 (82.8–91.2)
Type of medical care, % (95% CI)							
Private physician	72.8 (71.6–74.0)	72.8 (71.6–74.0)	74.9 (60.8–89.1)	72.8 (71.6–74.0)	72.9 (66.1–79.7)	72.7 (71.5–73.9)	74.5 (69.1–79.9)
HMO	5.8 (5.2–6.5)	5.9 (5.2–6.5)	2.8 (−2.6–8.2)	5.9 (5.2–6.5)	4.2 (1.2–7.3)	6.0 (5.3–6.6)	3.6 (1.3–5.9)
Walk-in clinic	1.6 (1.2–1.9)	1.6 (1.2–1.9)	2.7 (−2.5–7.9)	1.6 (1.2–1.9)	2.7 (0.1–5.4)	1.6 (1.2–1.9)	2.2 (0.3–4.1)
Regular clinic	12.7 (11.8–13.6)	12.7 (11.8–13.6)	13.8 (2.6–25.0)	12.8 (11.8–13.7)	12.5 (7.5–17.4)	12.7 (11.8–13.6)	13.2 (9.1–17.3)
Hospital ER	3.5 (3.0–4.0)	3.5 (3.0–4.0)	2.7 (−2.6–8.0)	3.5 (3.0–4.0)	3.4 (0.5–6.2)	3.6 (3.0–4.1)	2.6 (0.5–4.7)
Other	3.2 (2.8–3.7)	3.2 (2.8–3.7)	2.8 (−2.6–8.1)	3.2 (2.7–3.7)	4.1 (1.1–7.1)	3.2 (2.7–3.7)	3.5 (1.2–5.7)

[a] Cut point for abnormal liver fibrosis score equates to advanced fibrosis (APRI >1, FIB-4 >2.67 and NFS >0.676);

[b] Results were centered by mean age (57.6 years).

Table 2.

Hazard Ratios and 95% CIs for the Association between Fibrosis Scores and Total Prostate Cancer Incidence, Atherosclerosis Risk in Communities Study, 1990–1992

	Quintile of Fibrosis Scores						Per SD increase in fibrosis score[f]	
	1	2	3	4	5	*P* value for Trend[e]	HR (95%CI)	*P* value
APRI								
Events, No.	138	154	144	150	140		726	
Person-years	17689	18811	18888	18624	18325		92338	
Model 1 HR (95%CI)[a]	1 [Reference]	1.05 (0.83,1.32)	0.97 (0.77,1.23)	1.00 (0.79,1.26)	0.91 (0.72,1.16)	0.33	0.98 (0.90,1.06)	0.57
Model 2 HR (95%CI)[b]	1 [Reference]	1.01 (0.80,1.27)	0.95 (0.75,1.21)	0.95 (0.75,1.20)	0.85 (0.67,1.07)	0.11	0.96 (0.87,1.05)	0.34
Model 3 HR (95%CI)[c]	1 [Reference]	1.03 (0.81,1.31)	0.96 (0.75,1.22)	0.95 (0.75,1.21)	0.84 (0.65,1.07)	0.08	0.91 (0.82,1.01)	0.09
FIB-4								
Events, No.	134	147	149	140	156		726	
Person-years	19526	19291	18542	18462	16516		92338	
Model 1 HR (95%CI)[a]	1 [Reference]	1.01 (0.80,1.28)	0.99 (0.78,1.26)	0.87 (0.68,1.11)	0.97 (0.76,1.25)	0.69	0.99 (0.91,1.07)	0.81
Model 2 HR (95%CI)[b]	1 [Reference]	0.99 (0.78,1.26)	0.94 (0.74,1.19)	0.83 (0.64,1.06)	0.91 (0.71,1.17)	0.40	0.97 (0.89,1.06)	0.54
Model 3 HR (95%CI)[c]	1 [Reference]	0.99 (0.78,1.26)	0.89 (0.70,1.15)	0.81 (0.63,1.04)	0.86 (0.66,1.11)	0.19	0.92 (0.83,1.02)	0.12
NFS								
Events, No.	144	143	155	151	133		726	
Person-years	19709	19771	18990	17927	15941		92338	
Model 1 HR (95%CI)[a]	1 [Reference]	0.92 (0.73,1.16)	0.96 (0.76,1.21)	0.93 (0.73,1.17)	0.82 (0.64,1.06)	0.15	0.95 (0.89,1.01)	0.13
Model 2 HR (95%CI)[b]	1 [Reference]	0.92 (0.73,1.17)	0.94 (0.74,1.18)	0.93 (0.73,1.18)	0.88 (0.67,1.15)	0.39	0.96 (0.88,1.04)	0.28
Model 3 HR (95%CI)[c]	1 [Reference]	0.92 (0.73,1.17)	0.87 (0.69,1.11)	0.92 (0.71,1.17)	0.83 (0.63,1.10)	0.22	0.91 (0.81,1.01)	0.08
Model 4 HR (95%CI)[d]	1 [Reference]	0.92 (0.73,1.17)	0.87 (0.68,1.11)	0.90 (0.71,1.15)	0.77 (0.59,1.00)	0.06	0.88 (0.80,0.98)	0.02

[a]Model 1 adjusted for age and race*field center;

[b]Model 2 adjusted for the age, race*field center, obesity, waist-hip ratio, diabetes status, alcohol drinking status, smoking status and family history of prostate cancer;

[c]Model 3 adjusted for the variables in model 2 and the propensity score of socio-economic status and access to and uptake of medical care;

[d]Model 4 adjusted for the variables in model 3 but without BMI or diabetes status;

[e] *P* value for trend was calculated by modeling the median of each quintile as a continuous term;

[f] The standard deviations (SD) for APRI, FIB-4, and NFS are 0.19, 0.68, and 1.41, respectively.

Table 3.

Hazard Ratios and 95% CIs for the Association between Fibrosis Scores and Total Prostate Cancer Incidence Among White Men, Atherosclerosis Risk in Communities Study, 1990–1992

	Quintile of Fibrosis Scores						Per SD increase in fibrosis score[f]	
	1	2	3	4	5	*P* value for Trend[e]	HR (95%CI)	*P* value
APRI								
Events, No.	105	104	108	102	92		511	
Person-years	14929	15826	15487	15087	13747		75076	
Model 1 HR (95%CI)[a]	1 [Reference]	0.93 (0.71,1.22)	1.00 (0.76,1.31)	0.94 (0.72,1.24)	0.95 (0.72,1.26)	0.82	1.00 (0.90,1.10)	0.94
Model 2 HR (95%CI)[b]	1 [Reference]	0.90 (0.69,1.19)	0.98 (0.74,1.28)	0.90 (0.69,1.19)	0.90 (0.68,1.20)	0.58	0.99 (0.89,1.09)	0.81
Model 3 HR (95%CI)[c]	1 [Reference]	0.93 (0.71,1.24)	0.98 (0.74,1.30)	0.93 (0.70,1.23)	0.90 (0.67,1.21)	0.51	0.97 (0.86,1.09)	0.59
FIB-4								
Events, No.	95	107	109	91	109		511	
Person-years	16892	15946	15407	14629	12201		75076	
Model 1 HR (95%CI)[a]	1 [Reference]	1.10 (0.83,1.45)	1.08 (0.81,1.43)	0.89 (0.66,1.21)	1.18 (0.88,1.60)	0.42	1.02 (0.94,1.11)	0.62
Model 2 HR (95%CI)[b]	1 [Reference]	1.07 (0.81,1.42)	1.02 (0.76,1.35)	0.85 (0.63,1.15)	1.13 (0.83,1.52)	0.58	1.01 (0.92,1.10)	0.84
Model 3 HR (95%CI)[c]	1 [Reference]	1.06 (0.80,1.42)	0.96 (0.71,1.28)	0.87 (0.64,1.19)	1.09 (0.80,1.49)	0.65	1.00 (0.90,1.10)	0.93
NFS								
Events, No.	109	108	108	101	85		511	
Person-years	17142	16871	15499	14133	11432		75076	
Model 1 HR (95%CI)[a]	1 [Reference]	0.94 (0.72,1.22)	0.95 (0.72,1.25)	0.93 (0.70,1.23)	0.91 (0.67,1.23)	0.54	0.99 (0.89,1.09)	0.78
Model 2 HR (95%CI)[b]	1 [Reference]	0.94 (0.72,1.23)	0.93 (0.71,1.23)	0.96 (0.72,1.28)	1.02 (0.74,1.40)	0.92	1.02 (0.90,1.15)	0.77
Model 3 HR (95%CI)[c]	1 [Reference]	0.94 (0.71,1.23)	0.88 (0.66,1.17)	0.96 (0.72,1.29)	0.99 (0.72,1.38)	0.97	1.01 (0.88,1.15)	0.94
Model 4 HR (95%CI)[d]	1 [Reference]	0.93 (0.71,1.22)	0.87 (0.65,1.15)	0.93 (0.69,1.23)	0.87 (0.64,1.19)	0.43	0.95 (0.85,1.08)	0.45

[a]Model 1 adjusted for age and race*field center;

[b]Model 2 adjusted for the age, race*field center, obesity, waist-hip ratio, diabetes status, alcohol drinking status, smoking status and family history of prostate cancer;

[c]Model 3 adjusted for the variables in model 2 and the propensity score of socio-economic status and access to and uptake of medical care;

[d]Model 4 adjusted for the variables in model 3 but without BMI or diabetes status;

[e] *P* value for trend was calculated by modeling the median of each quintile as a continuous term;

[f] The standard deviations (SD) for APRI, FIB-4, and NFS are 0.19, 0.68, and 1.41, respectively.

Table 4.

Hazard Ratios and 95% CIs for the Association between Fibrosis Scores and Total Prostate Cancer Incidence Among Black Men, Atherosclerosis Risk in Communities Study, 1990–1992

	Quintile of Fibrosis Scores						Per SD increase in fibrosis score[f]	
	1	2	3	4	5	*P* value for Trend[e]	HR (95%CI)	*P* value
APRI								
Events, No.	33	50	36	48	48		215	
Person-years	2761	2985	3402	3537	4578		17262	
Model 1 HR (95%CI)[a]	1 [Reference]	1.41 (0.91,2.18)	0.89 (0.55,1.42)	1.12 (0.72,1.75)	0.87 (0.56,1.35)	0.16	0.94 (0.81,1.09)	0.41
Model 2 HR (95%CI)[b]	1 [Reference]	1.36 (0.87,2.12)	0.89 (0.55,1.44)	1.09 (0.70,1.71)	0.79 (0.50,1.23)	0.06	0.91 (0.78,1.07)	0.26
Model 3 HR (95%CI)[c]	1 [Reference]	1.26 (0.74,2.15)	0.69 (0.37,1.28)	1.02 (0.59,1.76)	0.91 (0.54,1.55)	0.57	0.89 (0.73,1.09)	0.26
FIB-4								
Events, No.	39	40	40	49	47		215	
Person-years	2633	3345	3135	3834	4316		17262	
Model 1 HR (95%CI)[a]	1 [Reference]	0.78 (0.50,1.21)	0.77 (0.49,1.20)	0.75 (0.49,1.15)	0.62 (0.40,0.96)	0.05	0.92 (0.79,1.07)	0.28
Model 2 HR (95%CI)[b]	1 [Reference]	0.79 (0.51,1.23)	0.75 (0.48,1.17)	0.74 (0.48,1.14)	0.58 (0.37,0.91)	0.03	0.90 (0.77,1.06)	0.21
Model 3 HR (95%CI)[c]	1 [Reference]	0.81 (0.51,1.30)	0.64 (0.39,1.04)	0.67 (0.42,1.07)	0.47 (0.29,0.77)	0.004	0.77 (0.63,0.93)	0.01
NFS								
Events, No.	35	35	47	50	48		215	
Person-years	2568	2900	3491	3794	4509		17262	
Model 1 HR (95%CI)[a]	1 [Reference]	0.85 (0.53,1.36)	0.91 (0.59,1.42)	0.86 (0.56,1.34)	0.67 (0.43,1.05)	0.09	0.82 (0.70,0.97)	0.02
Model 2 HR (95%CI)[b]	1 [Reference]	0.87 (0.54,1.39)	0.90 (0.58,1.41)	0.83 (0.53,1.30)	0.64 (0.39,1.05)	0.08	0.79 (0.66,0.96)	0.01
Model 3 HR (95%CI)[c]	1 [Reference]	0.91 (0.55,1.52)	0.84 (0.52,1.36)	0.80 (0.49,1.30)	0.56 (0.33,0.97)	0.03	0.72 (0.59,0.88)	0.00
Model 4 HR (95%CI)[d]	1 [Reference]	0.92 (0.55,1.52)	0.88 (0.55,1.42)	0.84 (0.52,1.36)	0.60 (0.36,0.99)	0.03	0.75 (0.62,0.90)	0.00

[a]Model 1 adjusted for age and race*field center;

[b]Model 2 adjusted for the age, race*field center, obesity, waist-hip ratio, diabetes status, alcohol drinking status, smoking status and family history of prostate cancer;

[c]Model 3 adjusted for the variables in model 2 and the propensity score of socio-economic status and access to and uptake of medical care;

[d]Model 4 adjusted for the variables in model 3 but without BMI or diabetes status;

[e] *P* value for trend was calculated by modeling the median of each quintile as a continuous term;

[f] The standard deviations (SD) for APRI, FIB-4, and NFS are 0.19, 0.68, and 1.41, respectively.

Table 5.

Hazard Ratios and P for Trend for Per Standard Deviation Increase in Liver Fibrosis Scores of Lethal and Fatal Prostate Cancer, Atherosclerosis Risk in Communities Study, 1990–1992

	Total[a]		White		Black	
	HR per SD increase in fibrosis score (95%CI)[c]	*P* value for Trend[d]	HR per SD increase in fibrosis score (95%CI)[c]	*P* value for Trend[d]	HR per SD increase in fibrosis score (95%CI)[c]	*P* value for Trend[d]
Lethal Prostate Cancer [b]						
Events, No.	83		55		28	
Person-years	92532		75263		17270	
APR	1.02 (0.84,1.24)	0.80	0.91 (0.61,1.35)	0.09	1.08 (0.83,1.41)	0.13
FIB-4	1.03 (0.86,1.24)	0.67	1.00 (0.76,1.32)	0.77	1.06 (0.75,1.51)	0.84
NFS	1.04 (0.76,1.43)	0.61	1.22 (0.83,1.80)	0.44	0.74 (0.42,1.29)	0.79
Fatal Prostate Cancer						
Events, No.	77		51		26	
Person-years	105682		85453		20228	
APR	0.89 (0.64,1.25)	0.79	0.83 (0.50,1.37)	0.17	0.89 (0.55,1.44)	0.36
FIB-4	0.95 (0.71,1.26)	0.70	0.98 (0.67,1.43)	0.62	0.90 (0.58,1.40)	0.95
NFS	1.06 (0.76,1.49)	0.50	1.31 (0.87,1.97)	0.24	0.71 (0.39,1.29)	0.64

[a] All results were adjusted for the variables in model 3;

[b] The associations for incidence among total, White, and Black are shown in Tables 2, 3, and 4, respectively;

[c] The standard deviations (SD) for APRI, FIB-4, and NFS are 0.19, 0.68, and 1.41, respectively;

[d] *P* value for trend was calculated by modeling the median of each quintile as a continuous term.