

Original Article

Serum adiponectin concentration in 2,939 Japanese men undergoing screening for prostate cancer

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ABSTRACT

Background: Recent investigations suggest that serum adiponectin levels are negatively associated with the development of aggressive prostate cancer, however, not all epigenetic studies support the inverse association.

Methods: We analyzed serum adiponectin levels, prostate-specific antigen (PSA) levels, and outcomes of prostate cancer screening of 2,939 participants of a PSA-based screening program conducted by a single institute in Japan.

Results: The median body mass index (BMI) of the participants was 23.9 kg/m², and 31% had a BMI \geq 25 kg/m². The adiponectin levels were significantly and negatively correlated with BMI ($r = -0.260$, $P < 0.0001$). However, a significant and positive correlation was observed between adiponectin levels and PSA levels ($r = 0.054$, $P = 0.0061$). After screening, 24 (0.82%) patients were diagnosed with prostate cancer. Interestingly, the adiponectin levels of the 24 prostate cancer patients (average 9.86 μ g/mL) were significantly higher than those of the 2,817 participants with PSA levels $<$ 4 ng/mL (average 7.63 μ g/mL) ($P = 0.0049$). However, when restricted to the eight high-risk prostate cancer patients, the adiponectin levels did not differ from those of the participants with PSA levels $<$ 4 ng/mL. The age-adjusted cancer detection rate of the participants was calculated by stratifying the BMI (cut-off level 25 kg/m²) and adiponectin levels (cut-off level 6.7 μ g/mL). The cancer detection rate in the high-BMI and high-adiponectin group was 1.67%, which was the highest among all groups.

Conclusions: There was a significant positive correlation between adiponectin levels and PSA levels. The present findings also suggest that the incidence of low- or intermediate-risk prostate cancer might be increased in overweight men with high serum adiponectin levels.

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1. Introduction

Prostate cancer (PCA) is the most commonly diagnosed cancer among men in many regions of the world.¹ In Asian countries,

including Japan, the incidence of PCA continues to increase.^{2,3} Risk factors for PCA include age, familial history, high-fat food ingestion, and obesity. Obesity has become more prevalent in most developed countries, including Japan, and is increasingly recognized as a major risk factor for several common types of cancer.⁴ Unfortunately, obesity is becoming a common problem in most Asian countries.⁵

Regarding the molecular pathways of obesity-associated cancer, recent investigations revealed that several physiologically active substances including adiponectin (APN), leptin, tumor necrosis factor-alpha, and interleukin-6 are closely associated with the

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development of various types of cancer.⁴ APN is an anti-inflammatory cytokine produced by adipose tissue (a so-called adipokine), but unlike other adipokines, APN production decreases in obesity. APN presents in plasma as a trimer, hexamer, and high-molecular-weight multimer (HMW); among them, the HMW-APN is known to be the most bioactive form.⁶

Epidemiologically, hypoadiponectinemia is not restricted to a variety of obesity-associated benign diseases, but has been reported to be a risk factor for various types of cancer, including breast cancer, endometrial cancer, colorectal cancer, and gastric cancers.^{6,7} Indeed, APN receptors are known to be expressed by different types of cancer,⁸ and APN *in vitro* can inhibit cancer cell proliferation.⁶ The precise molecular mechanism underlying the association between hypoadiponectinemia and the development of cancer has not been established.

A considerable number of case control studies^{9–16} and cross-sectional studies^{17,18} testing the association of PCA with APN have been published. In accordance with other types of cancer, most of these investigations showed an inverse association of APN levels and high-stage or high-grade PCA.^{9–13} However, some authors reported that the inverse relationships were observed only in overweight or obese men.^{13,14} Moreover, some case control studies suggested a positive correlation between APN levels and PCA after adjustment for body mass index (BMI).^{14–16} In addition, unfortunately, little is known about the association between APN levels and the development of increased risk or early-stage disease, which includes the majority of PCA cases detected by prostatic-specific antigen (PSA)-based screening. In PSA-based screening studies, findings regarding the association between APN levels and PSA levels also conflict, finding no correlation,¹⁷ or a negative correlation.¹⁸

To address these clinical questions, we conducted the present large-scale cross-sectional study. We analyzed serum APN levels, PSA levels, and outcomes of PCA screening of approximately 3,000 participants who attended the PSA-based screening program conducted by a single institute. To the best of our knowledge, this is the largest cross-sectional study for investigating the relationship between serum APN and outcomes of PCA screening.

2. Participants and methods

2.1. Participants

Between April 2008 and March 2009, 3,716 men attended the PCA screening program as part of the annual periodic health checkup at the Hitachi Health Care Center (HHCC). All of them were employees of the same company (Hitachi Ltd., Ibaraki, Japan). During the same period, the HHCC undertook an epidemiological study to examine the association between APN and general health. This study was approved by the Ethics Committee (approval number 2012-52) of Hitachi General Hospital and Japan's National Center for Global Health and Medicine (approval number 514).

As part of the PCA screening program, the serum APN levels of 2,939 men were measured. Written informed consent was obtained from all participants. Therefore, both serum APN levels and PSA levels were available for all of the participants. In the present study, we analyzed the serum APN levels, PSA levels, and outcomes of PCA screening of 2,939 men.

2.2. PCA screening program at HHCC

In the PCA screening, further examinations to detect PCA were recommended to participants with PSA levels > 4.0 ng/mL. The indication of prostate biopsy was generally based on PSA levels, the findings of a digital rectal examination, transrectal

ultrasonography, and/or magnetic resonance imaging. The final decision of prostate biopsy was decided depending on each participant's physician and physician–participant communication. For recheck of PSA, participants who did not have a biopsy had follow-up examinations and were strongly recommended to have a prostate biopsy if their PSA level was increasing. Because 106 of the 122 participants with high levels of PSA received further examinations at the same institute, the decision-making process might not have differed largely among these participants.

Basically, a repeat biopsy is recommended if the PSA level has increased after a negative first biopsy. The information available from the screening program included participant age, height and weight, and the results of a prostate biopsy, if performed. BMI was calculated by height and weight at the PCA screening. Underweight, normal, overweight, and obese BMIs were defined as < 20 kg/m², 20–25 kg/m², 25–30 kg/m², and > 30 kg/m², respectively. The screening data were aggregated until August 2013.

2.3. PSA and APN measurements

Serum PSA levels were assayed using an Abbott AxSYM immunoanalyzer (Abbott Laboratories, Abbot Park, IL, USA). Total serum APN levels were measured using a latex particle-enhanced turbidimetric immunoassay (human adiponectin latex kit; Otsuka Pharmaceutical Co., Tokyo, Japan) as described.¹⁹ The results were highly correlated with enzyme-linked immunosorbent assay-based methods ($r = 0.99$).

2.4. Statistical analysis

The Pearson correlation test was used to evaluate the associations between serum APN levels and BMI and between APN levels and PSA levels in each participant. Differences in the factors related to cancer detection proportions at the further examination (age, BMI, serum PSA level, serum adiponectin level, Gleason score, and clinical stage) were tested using simple logistic regression and chi-square tests. The cancer detection rate (CDR: the rate of the number of prostate cancers detected by screening to the number of men screened) was calculated for each subgroup divided by APN level and BMI. In addition, the age-specific CDR was calculated for four age groups (aged < 50 years, 50–59 years, 60–69 years, and > 69 years). The age-adjusted CDR was calculated based on the observed age-specific CDR by applying serum APN measurement and PCA screening to the age-specific populations in 2,931 participants in 2008. A P -value < 0.05 was considered significant. All statistical analyses were performed using the software package JMP version 10.0.2 (SAS Institute, Cary, NC).

3. Results

The profiles of the participants are shown in Table 1. The median age was 58 years (range 28–74 years). The median BMI was 23.9 kg/m² (range 15.1–38 kg/m²). The proportions of underweight, normal, overweight, and obese men were 5.5%, 60.1%, 28.5%, and 2.3%, respectively. The median PSA level was 0.9 ng/mL (range 0.1–38.8 ng/mL). When the cut-off values of BMI and PSA were set at 25 kg/m² and 4 ng/mL, 907 men (32.0%) and 122 men (4.15%) were classified to the higher BMI group and higher PSA group, respectively. The median APN level was 6.7 µg/mL, however, it varied from 1.0 µg/mL to 38.8 µg/mL.

All 122 men with PSA levels > 4 ng/mL attended the further examination. Prostate biopsy was performed on 65 of the 122 men (53%), and 24 participants were diagnosed with PCA. Twenty of these 24 participants were diagnosed with clinical T1c disease and the other four were diagnosed with clinical T2 disease. According to

Table 1
Profile of the prostate-specific antigen screening participants.

	Median (range)
Age (yr)	58 (28–74)
BMI	23.9 kg/m ² (15.1–38)
Adiponectin level	6.7 mg/mL (1.0–38.8)
PSA level	0.9 mg/mL (0.1–38.8)
	No. (%)
First screening attender	2,939
BMI group	
Underweight	161 (5.5)
Normal	1,766 (60.1)
Overweight	838 (28.5)
Obese	69 (2.3)
Unknown	105 (3.6)
Second screening attender	122 (4.2)
Men underwent prostate biopsy	65 (2.2)
Men diagnosed with PCA	24 (0.8)
Clinical T stage	
cT1c	20
cT2a	1
cT2b	1
cT2c	2
D'Amico classification	
Low	6
Intermediate	10
High	8

BMI, body mass index; PCA, prostate cancer; PSA, prostate-specific antigen.

the D'Amico classification, 16 of these 24 participants were classified as the low- or intermediate-risk group, and the other eight were classified as the high-risk group.

Fig. 1 represents the correlations between APN levels and BMI and between APN levels and PSA levels among all participants. The APN level was significantly and negatively correlated with BMI ($r = -0.260$, $P < 0.0001$; Fig. 1A). However, a significant and positive correlation was observed between APN levels and PSA levels ($r = 0.054$, $P = 0.0061$), as shown in Fig. 1B. When the participants were divided by the PSA cut-off level, the difference was significant ($P = 0.0031$): the mean APN levels of the participants with PSA levels ≥ 4 ng/mL and of those with PSA levels < 4 ng/mL were 8.70 $\mu\text{g/mL}$ and 7.61 $\mu\text{g/mL}$, respectively. The significantly higher APN levels were observed even when participants were stratified by BMI with the cut-off level of 25 kg/m².

As shown in Fig. 2A and 2B the, APN levels of the participants with PSA levels ≥ 4 ng/mL were significantly higher than those of the participants with lower PSA levels in both groups. As expected, when limited to the participants with PSA levels < 4 ng/mL, the

average APN level of the participants with a BMI ≥ 25 kg/m² was significantly lower than that of participants with a BMI < 25 kg/m² (8.06 kg/m² and 6.66 kg/m², respectively, $P < 0.001$) and the average PSA level of the participants with a BMI > 25 kg/m² (average 1.05 ng/mL) was significantly lower than that of the participants with BMI < 25 kg/m² (average 1.11 ng/mL; $P = 0.0497$).

The APN levels of PCA patients (average 9.96 ng/mL) were significantly higher than nonprostate cancer participants (average 7.64 ng/mL; $P < 0.001$). Fig. 3 shows the distribution of APN levels according to outcomes of the PCA screening program. We compared the APN levels of the PCA patients with those of the participants with PSA levels < 4 ng/mL and the participants who had PSA levels ≥ 4 ng/mL but were not diagnosed with PCA. As shown in Fig. 3, the APN levels in PCA patients (average 9.86 $\mu\text{g/mL}$) were significantly higher than those of the participants with PSA levels < 4 ng/mL (average 7.63 $\mu\text{g/mL}$; $P = 0.0049$).

Interestingly, the APN levels of the participants who had PSA levels ≥ 4 ng/mL but were not diagnosed with PCA after the further examination were not significantly different from those of the participants with PSA levels < 4 ng/mL. When the PCA patients were divided into low/intermediate-risk ($n = 16$) and high-risk ($n = 8$) groups, the APN levels in the high-risk group (average 8.12 $\mu\text{g/mL}$) were lower than those in the low/intermediate-risk group (average 10.73 $\mu\text{g/mL}$), however, the difference was not significant. Thus, when restricted to high-risk PCA patients, the APN levels did not differ from those of the participants with PSA levels < 4 ng/mL.

Finally, we analyzed the impact of APN level on the age-adjusted CDR in the present PCA screening program. In the analysis, the APN cut-off level of 6.7 $\mu\text{g/mL}$ was used as the median level. As shown in Table 2, the CDR of the low/intermediate-risk PCA participants among the high APN group was higher than that of the low APN group (0.717% and 0.294%, respectively), however, the difference was not significant. As expected, there was no significant difference in the CDRs of high-risk PCA between both APN groups. When the participants were stratified by both BMI and APN level, the age-adjusted CDR in the high BMI + high APN group was 1.67%, which was the highest among all groups (Table 2).

4. Discussion

Accumulating evidence suggests that obesity is associated with a greater risk of death from PCA.²⁰ Several investigations showed that the serum level of APN, a multifunctional adipokine, was negatively associated with the development of aggressive PCA.^{9–13} However, not all epidemiologic studies support this inverse association of APN and PCA.^{14–16} In the present study, our extensive

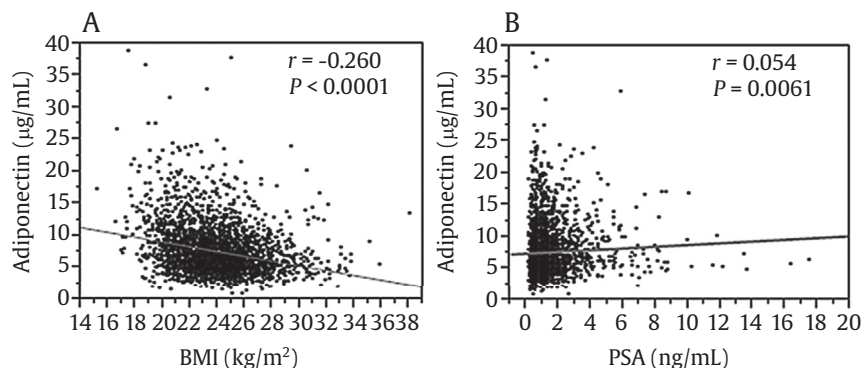


Fig. 1. Graphs showing the adiponectin (APN) level was negatively correlated with body mass index (BMI) but positively correlated with prostate-specific antigen (PSA) levels. (A) Correlations between APN level and BMI. (B) Correlations between APN levels and PSA levels among all participants ($n = 2,939$).

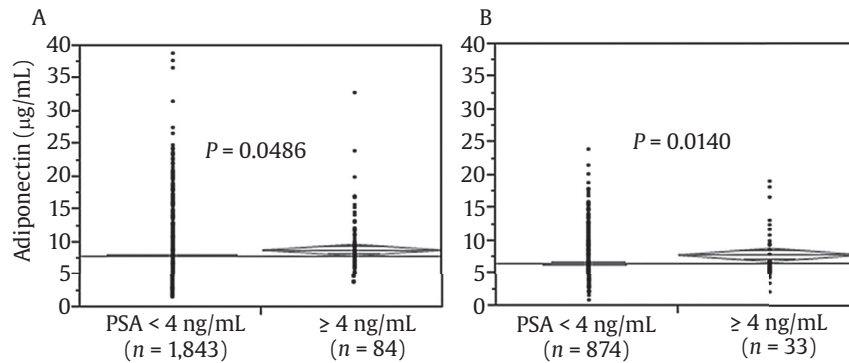


Fig. 2. Adiponectin levels of participants stratified by prostate-specific antigen (PSA) levels and body mass index (BMI). The APN levels of the participants with PSA ≥ 4 ng/mL ($n = 117$) were significantly higher than those of the participants with PSA levels < 4 ng/mL ($n = 2717$) in both BMI groups: (A) BMI < 25 kg/m 2 ; and (B) BMI ≥ 25 kg/m 2 . APN, adiponectin.

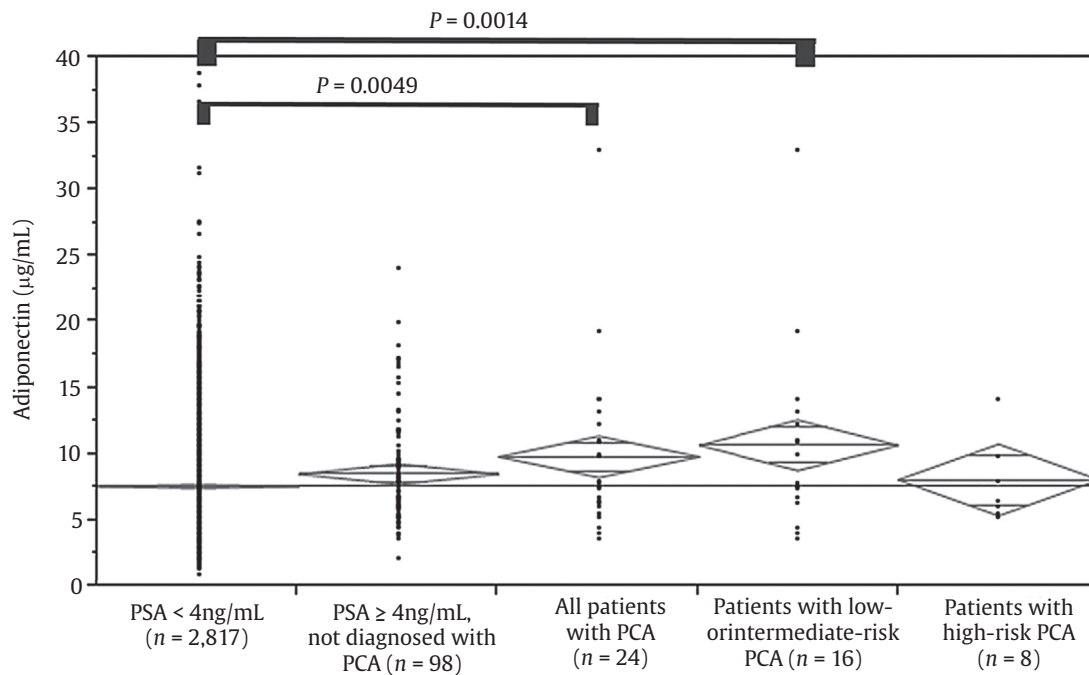


Fig. 3. Distribution of adiponectin (APN) levels according to the outcomes of the prostate cancer (PCA) screening. The APN levels in the PCA patients were significantly higher than those of the participants with prostate-specific antigen levels < 4 ng/mL, however, when restricted to the high-risk PCA patients, the APN levels did not differ from those of the participants with prostate-specific antigen levels < 4 ng/mL. PSA, prostate-specific antigen.

Table 2

Age-adjusted cancer detection rate (CDR) among the screening participants.

CDR of low- to intermediate- and high-risk PCA according to APN level (%)	CDR of low- to intermediate- and high-risk PCA according to APN level (%)	
	Low or intermediate-risk PCA	High-risk PCA.
APN level ≥ 6.7 mg/mL	0.717	0.254
APN level < 6.7 mg/mL	0.294	0.323
CDR of PCA according to APN level and BMI (%)	CDR of PCA according to APN level and BMI (%)	
	BMI ≥ 25 kg/m 2	BMI < 25 kg/m 2
APN level ≥ 6.7 mg/mL	1.670	0.725
APN level < 6.7 mg/mL	0.577	0.633

APN, adiponectin; BMI, body mass index; PCA, prostate cancer.

analysis of the association between serum APN, PSA, and CDR among 2,939 men who attended a PCA screening revealed several interesting findings.

Firstly, there was a significant positive correlation between APN levels and PSA levels. By contrast, APN levels were inversely correlated with BMI, which is consistent with a number of previous

studies.²¹ It is also well known that BMI is inversely associated with PSA levels.^{22,23} The latter association is partly explained with a hemodilution effect due to the higher blood volume of obese men.^{22,23} Indeed, in the present study, when limited to participants with PSA < 4 ng/mL, the average PSA level of the participants with BMI ≥ 25 kg/m 2 was significantly lower than that of the participants with BMI < 25 kg/m 2 . When considering the association of the three parameters of APN levels, BMI, and PSA levels, the observed positive correlation between APN levels and PSA levels is entirely comprehensible. However, to our knowledge, this is the first report to show a positive association between both parameters.

In relevant literature, there are two cross-sectional studies that analyzed the association between APN levels and PSA levels. Fowke et al¹⁷ investigated 242 African-American and Caucasian men and found no association between APN levels and PSA levels. Alokail et al¹⁸ examined 219 Arab men and reported that there was an inverse association between the two parameters.¹⁸ At present, we cannot explain why our results are different from those studies,

however, it is notable that the sample size of the present study is considerably larger than those of the previous studies. As another explanation, the lower frequency of obese men in the present study might have affected the results, but it may have limited impact. Even when restricted to men with BMI ≥ 25 kg/m², the APN levels of the present participants with PSA levels ≥ 4 ng/mL were significantly higher than those of the participants with PSA < 4 ng/mL (Fig. 2B). This finding also suggests that mechanisms unrelated to obesity might be involved in the positive correlation between APN levels and PSA levels.

Secondly, the APN levels of our participants who were diagnosed with PCA were significantly higher than that of the participants with PSA < 4 ng/mL. Among the PCA patients, although the difference was not significant, the APN levels of the low- or intermediate-risk PCA patients tended to be higher compared with those of the high-risk PCA patients. Consequently, when restricted to high-risk PCA patients, the APN levels were not significantly different from those of the participants with PSA < 4 ng/mL.

The relatively low APN levels of poor risk PCA patients presented here are in accordance with most of the previous case control studies of PCA patients who underwent radical prostatectomy. There have been at least six studies showing an inverse association of APN levels and high-stage or high-grade PCA.^{9–14} It is notable that the significant association was observed only among overweight and obese men in two of the six studies. In the present study, we observed significantly higher APN levels in the PCA patients compared with the participants with PSA < 4 ng/mL, however, this was limited to the low/intermediate-risk PCA patients. Moreover, it should be emphasized that 69% of the participants were normal or underweight men.

From this point of view, the results of a case control study conducted by Nishimura et al¹⁵ are noteworthy in that the participants had a BMI distribution similar to that of the present study. By comparing Japanese PCA patients and benign prostatic hypertrophy patients, Nishimura et al¹⁵ showed that patients with APN levels higher than the median APN level had a significantly elevated risk of PCA after adjustment for body weight.¹⁵

Finally, we calculated the age-adjusted CDR of our participants with stratified BMI (cut-off level of 25 kg/m²) and APN levels (cut-off level of 6.7 μ g/mL). Interestingly, the highest age-adjusted CDR was observed in the men with higher BMIs and higher APN levels. As expected, the CDR of the low/intermediate-risk PCA patients was higher in the participants with APN ≥ 6.7 μ g/mL compared with the participants with lower APN. The difference in CDR by APN levels was not observed in our high-risk PCA patients. Although the sample size is relatively small for analyzing CDR, to our knowledge, this is the first report showing an increase in the CDR of PCA among men with higher APN levels.

Recently, Medina et al¹⁶ reported notable results of a nested case control study based on a prospective cohort including $>4,000$ men who annually underwent PSA testing. A total of 228 cases (PCA patients) and 239 controls were analyzed. Those authors showed that the percentage of HMW-APN but not total APN levels had a significant relationship with PCA. More importantly, overweight men (with a BMI between 25 kg/m² and 30 kg/m²) had a higher probability of PCA as the percentage of HMW-APN increased. Interestingly, just the opposite association was observed in obese men. It is notable that in the present study, 93% of the men with a BMI ≥ 25 kg/m² were overweight but not obese.

Several investigations have demonstrated the antitumor effect of APN through antiproliferative and antiangiogenic effects in various types of cancer.⁶ APN inhibited cell growth in both androgen-dependent and -independent PCA cell lines.²⁴ Therefore, based on those *in vitro* data, it is difficult to explain the positive association of APN levels and PCA. Some authors speculated that

the increased APN levels in cancer patients might be a protective response against tumor progression,²⁵ however, most of the patients in the present study were diagnosed with PCA at an early stage. Although the exact mechanisms cannot be specified, the positive correlation between APN levels and PSA levels might be a clue to further understanding. It is possible that the positive correlation of both parameters resulted in a detection bias in the present PSA-based PCA screening, however, the proportion of participants who underwent a biopsy did not differ between the participants with APN ≥ 6.7 μ g/mL and those with APN < 6.7 μ g/mL (2.07% and 2.24%, respectively, $P = 0.77$). Although the difference was not significant, the positive biopsy rates tended to be higher in the participants with APN ≥ 6.7 μ g/mL compared with those with APN < 6.7 μ g/mL (47.1% and 25.8%, respectively). Therefore, detection bias, if present, cannot explain the positive correlation between the APN levels and PSA levels presented here. It is of great interest to investigate the regulatory role of APN in PSA secretion and the interaction of APN with androgen-responsive elements.

Our study had several limitations. Because it was a cross-sectional study, it was not possible to predict the causal relation between APN levels and development of PCA. Prostate biopsy was performed on 65 men. The reasons why only 65 persons received a prostate biopsy were that we comprehensively determined the indication, and also that some participants hesitated to undergo biopsy. As expected in the PCA screening database, almost all patients were diagnosed in the early stage. In contrast with studies in Western countries, the proportion of obese men with a BMI > 30 kg/m² was extremely low. This makes it difficult to simply extrapolate our results to a population with a different proportion of obese men. Finally, we did not evaluate APN multimers, especially HMW-APN, the most biologically active isoform of APN.

In conclusion, using a large-scale cross-sectional study, we demonstrated that there was a significant positive correlation between APN levels and PSA levels. To the best of our knowledge, this is the largest database that simultaneously analyzes both parameters. The results of our study also suggest that the incidence of low- or intermediate-risk PCA might be increased in overweight men with high serum APN levels.

Conflicts of interest

The authors have no conflicts of interest directly relevant to the content of this article.

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