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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/m^2, and 31% had a BMI $\geq$ 25 kg/m^2. 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 μg/mL) were significantly higher than those of the 2,817 participants with PSA levels < 4 ng/mL (average 7.63 μg/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/m^2) and adiponectin levels (cut-off level 6.7 μg/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.

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/m^2, 20–25 kg/m^2, 25–30 kg/m^2, and > 30 kg/m^2, 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/m^2 (range 15.1–38 kg/m^2). 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/m^2 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