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ORIGINAL ARTICLE

Plasma 25-hydroxy vitamin D and subsequent prostate cancer risk in a nested Case-Control study in Japan: The JPHC study

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BACKGROUND/OBJECTIVES: Although vitamin D has been experimentally reported to inhibit tumorigenesis, cell growth and prostate cancer invasion, epidemiologic data regarding prostate cancer risk are inconsistent, and some studies have suggested positive but nonsignificant associations. Further, the impact of vitamin D on prostate cancer between Western and Japanese populations may differ due to different plasma vitamin D levels.

SUBJECTS/METHODS: We performed a nested case–control study within the Japan Public Health Center–based Prospective (JPHC) Study in 14,203 men (40–69 years) who answered a self-administered questionnaire at baseline (1990–1994) and gave blood samples, and were followed until 2005. We identified 201 prostate cancers which are newly diagnosed during follow-up (mean 12.8 years). We selected two matched controls for each case from the cohort. We used a conditional logistic regression model to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for prostate cancer with respect to levels of 25-hydroxy vitamin D (25(OH)D) in plasma.

RESULTS: We did not observe statistically significant association between 25(OH)D level and total prostate cancer (multivariate OR = 1.13 (95%CI = 0.66–1.94, $P_{trend} = 0.94$) for the highest versus lowest tertile) However, 25(OH) levels were slightly positively associated with advanced cancer. The results remained substantially unchanged after stratification by intake of fish or calcium intake.

CONCLUSIONS: 25(OH)D level showed no association with overall prostate cancer among Japanese men in this large cohort.

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INTRODUCTION

The estimated age-standardized rates (ASR, world standard) of prostate cancer incidence in Asia (ASR 9.4 per 100 000) is much lower in Northern America and Europe (ASR 97.2 and 64.0 per 100 000, respectively).[1] Findings that the incidence of prostate cancer increases after men migrate to higher incidence[2,3] suggest that the causes of prostate cancer might relate to environmental factors including lifestyle and diet.

Most experimental reports of the relation between vitamin D and prostate cancer have shown that it exerts protective effects via the inhibition of tumorigenesis, cell growth and prostate cancer invasion.[4,5] In contrast, a recent meta-analysis of 25-hydroxy vitamin D (25(OH)D) in serum and prostate cancer risk showed a statistically significant increase in the risk of prostate cancer for the higher group, with an OR of 1.17 (95%CI = 1.05–1.30).[6] To date, however, the association between 25(OH)D in blood and prostate cancer in Asian populations has not been reported.

UV-B radiation is effectively blocked by melanin in the skin. The degree of skin pigmentation influences circulating 25(OH)D levels and obviously differ according to race.[7,8] In addition, vitamin D is also procured from the diet, and Western and Asian diets differ: common dietary sources are supplements and fortified milk in Western countries[9–11] versus fish in Japan.[12] Furthermore, Japanese consume less calcium than Western populations, and dietary intake of calcium could help increase levels of 25(OH) D. Thus, the impact of vitamin D on prostate cancer in Asian men might differ from those in Western men.

Here, we conducted a nested case-control study within a prospective cohort study in a large Japanese population to clarify the association of 25(OH)D level in plasma with prostate cancer.

MATERIALS AND METHODS

Study population

The Japan Public Health Center-based Prospective Study (JPHC Study) was conducted in two cohorts, with Cohort I started in 1990 and Cohort II started in 1993. Details of the study design have been reported previously.[13] Briefly, the target study population was all residents living in 11 PHC-based areas throughout Japan, aged 40 to 59 years in Cohort I and 40 to 69 years in Cohort II at the respective baseline survey. The study included 68 721 middle-aged males. The Tokyo subjects (2,919 men) were not included in data analyses in the present study due to a lack of data for cancer incidence. Further, after the exclusion of 144 patients with non-Japanese nationality (n = 31), late report of moving from Japan before the study ($n = 107$), incorrect date of birth ($n = 1$), duplicated registration ($n = 2$) and a self-reported history of prostate cancer ($n = 3$), we established a population-based cohort of 65 658 men. The study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan. Informed consent was considered to have been provided by each participant implicitly at the time they filled in the baseline questionnaire, which described the aim of the study as well as its follow-up.

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Questionnaire survey

The self-administered questionnaire was distributed to eligible registered residents in 1990–1994. This questionnaire included alcohol consumption, smoking habits, and personal and household medical history, as well as diet and other lifestyle factors. Responses were received from 50 435 men, giving a response rate of 77%. Diet was assessed using baseline data from the validated food frequency questionnaires, which incorporated 44[ref. 14] and 52[ref. 15] food items for Cohorts I and II, respectively. The two questionnaires slightly differed with regard to items of food, method of expression and frequency category.

Blood collection

During health checkups conducted from 1990 to 1995, subjects provided 10 ml of blood, with consent. The plasma and buffy layer were separated and stored at − 80 °C until analyzed. 14 203 men (28%) provided blood among baseline questionnaire respondents.

Plasma 25(OH)D levels were analysed by radioimmunoassay, with all samples assayed by a single commercial lab (Mitsubishi Kagaku Bio-Clinical Laboratories Inc., Tokyo, Japan). Matched samples were assayed together by analysts who were blinded to the case or control status of the samples. Intra-assay coefficient of variation was 8.9% from quality control samples. The limit of detection for this assay is 2.1 pg/ml.

Follow-up

We followed subjects from the date of the baseline survey until 31st December 2005. Information regarding change of address and survival was obtained annually by reporting from the residential registry in each subject's residential area. A total of 749 subjects (5.3%) moved away from the study area and a further 28 (0.2%) could not be followed during the period of this study.

Selection of cases and controls

We obtained incidence information for cancer from two data sources, namely the records of major area hospitals and population-based cancer registries, with permission from the local government responsible for the specific registry. We also used death certificates as supplementary information for cancer incidence. Case coding was done with the International Classification of Diseases for Oncology, Third Edition. After blood collection, 201 newly diagnosed cases of prostate cancer were identified during the study period among the 14 203 men who responded to the baseline questionnaire, provided blood samples and who had no reported history of prostate cancer. The proportion of pathologically confirmed cases was 97%, whereas 0.5% were death certificate only. Of these 201 cases, we defined advanced cases as having extraprostatic or metastatic cancer which involves the lymph nodes or other organs at the time of the prostate cancer was first diagnosed. If no information was

Table 1. Baseline characteristics of case and matched control subjects at baseline

	Case (n = *201)*	*Control* (n = *402)*	p^a
Age (years) (s.d.)	58.6 (6.4)	58.4 (6.6)	–
Body mass index ($\geqslant$ 25kg/m^2), (%)	24.9	24.4	0.89
Current smoker (%)	33.8	40.6	0.13
Alcohol intake ($\geqslant$1-2 times/week), (%)	69.2	72.4	0.42
Living with spouse, yes (%)	93.5	90.6	0.26
Green tea, daily (%)	81.1	80.4	0.97
Miso soup, daily (%)	82.6	78.9	0.18
fish intake ($\geqslant$3 times/week), (%)	55.0	55.2	0.95
25-hydroxy vitamin D (ng/ml) (median, interquartile range)	33.0 (28.0–39.0)	33.0 (28.0–38.0)	0.60

[a]P for Mantel-Haenszel test with matched-pair strata.

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of prostate cancer according to plasma 25-hydroxyvitamin D (25(OH)VitD) level

	Tertile category				
	Low	*Middle*	*High*	P *for trend*	*Per 10 ng/ml increment*
Total					
25(OH)VitD, median (ng/ml)	25.0	32.0	49.0		
Cases/controls	59/118	63/136	79/148		
OR (95%CI)	1.00	0.93 (0.59–1.48)	1.11 (0.67–1.81)	0.68	1.03 (0.91–1.17)
OR[a] (95%CI)	1.00	0.94 (0.57–1.55)	1.17 (0.69–2.01)	0.53	1.06 (0.93–1.22)
OR[b] (95%CI)	1.00	0.98 (0.59–1.62)	1.13 (0.66–1.94)	0.58	1.01 (0.99–1.02)
Localized					
25(OH)VitD, median (ng/ml)	24.0	32.0	49.5		
Cases/controls	37/89	53/95	54/104		
OR (95%CI)	1.00	1.43 (0.82–2.49)	1.37 (0.75–2.50)	0.34	1.06 (0.92–1.22)
OR[a] (95%CI)	1.00	1.30 (0.72–2.36)	1.25 (0.66–2.37)	0.55	1.07 (0.92–1.25)
OR[b] (95%CI)	1.00	1.37 (0.76–2.48)	0.99 (0.52–1.89)	0.94	1.01 (0.99–1.02)
Advanced					
25(OH)VitD, median (ng/ml)	25.0	32.0	38.0		
Cases/controls	18/31	10/29	20/36		
OR (95%CI)	1.00	0.57 (0.22–1.52)	0.99 (0.39–2.51)	0.94	1.07 (0.81–1.42)
OR[a] (95%CI)	1.00	0.74 (0.20–2.73)	1.26 (0.30–5.27)	0.73	1.12 (0.73–1.70)
OR[b] (95%CI)	1.00	0.72 (0.11–4.58)	2.74 (0.44–16.85)	0.24	1.06 (1.00–1.12)

[a]Adjusted for smoking status, alcohol intake, marital status, body mass index, and intake of green tea and miso soup. [b]Meta-analysis of the results of cohort I and II. Adjusted for smoking status, alcohol intake, marital status, body mass index, and intake of green tea, miso soup and calcium.

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) of prostate cancer according to plasma 25-Hydroxyvitamin D level by fish intake and calcium intake at baseline

	Low	*Middle*	*High*	P-*value*
Fish intake				
⩾3 times/week				
25(OH)VitD, median (ng/ml)	26.0	34.0	56.0	
Cases/controls	36/70	31/74	41/73	
Total[a]	1.00	0.78 (0.42–1.43)	1.10 (0.61–2.00)	0.86
25(OH)VitD, median (ng/ml)	26.0	34.0	55.0	
Cases/controls	26/47	25/56	28/54	
Localized[a]	1.00	0.73 (0.35–1.50)	0.79 (0.38–1.66)	0.53
25(OH)VitD, median (ng/ml)	25.5	34.0	55.0	
Cases/controls	8/14	3/18	14/17	
Advanced[a]	1.00	0.18 (0.03–1.05)	1.04 (0.22–4.98)	0.87
<3 times/week				
25(OH)VitD, median (ng/ml)	24.0	31.0	39.0	
Cases/controls	25/54	28/62	29/57	
Total[a]	1.00	1.06 (0.52–2.17)	1.20 (0.58–2.51)	0.62
25(OH)VitD, median (ng/ml)	23.0	29.5	38.0	
Cases/controls	14/35	18/40	27/45	
Localized[a]	1.00	1.29 (0.51–3.25)	1.40 (0.57–3.41)	0.51
25(OH)VitD, median (ng/ml)	25.0	32.0	38.0	
Cases/controls	9/14	6/16	4/16	
Advanced[a]	1.00	1.36 (0.19–9.60)	0.75 (0.10–5.47)	0.79
Calcium intake				
High				
Cases/controls	60/36	65/21	68/42	
Total[b]	1.00	0.81 (0.40–1.65)	0.81 (0.41–1.62)	0.51
Cases/controls	41/24	44/23	53/29	
Localized[b]	1.00	0.77 (0.32–1.89)	0.47 (0.18–1.21)	0.11
Cases/controls	11/9	17/3	16/12	
Advanced[b]	1.00	0.01 (0.0002–1.08)	0.49 (0.015–15.77)	0.95
Low				
Cases/controls	61/22	72/35	76/35	
Total[b]	1.00	1.17 (0.57–2.43)	1.41 (0.66–3.00)	0.22
Cases/controls	45/14	51/29	47/21	
Localized[b]	1.00	1.17 (0.56–2.45)	1.41 (0.66–3.00)	0.37
Cases/controls	13/7	17/6	21/7	
Advanced[b]	1.00	147.2 (0.26–84093.8)	8.17 (0.10–657.2)	0.03

[a]Odds ratios were adjusted for matching variables, smoking status, alcohol intake, marital status, body mass index, and intake of green tea and miso soup.
[b]Meta-analysis in results of cohort I and II. Adjusted for smoking status, alcohol intake, marital status, body mass index, and intake of green tea and miso soup.

available, these were defined as cases with a high Gleason score (8 to 10) or alternatively having poor differentiation. The other cases were all organ-localized. Finally, we analysed 48 advanced and 144 localized cases. Stage could not be determined in a further nine cases (4% of total).

For each newly diagnosed case of prostate cancer, two controls were selected at random from those participants without a history of prostate cancer at the time the diagnosis was made. Matching conditions were age (3 years), area (town or city, and village), PHC area, the date and time of day of blood collection (within 60 days and within 3 hours, respectively) and length of fasting time at blood sampling (within 3 h).

Statistical analysis

Statistical analysis was done using SAS software (version 9.3, SAS Institute, Inc., Cary, NC). *P*-values are two-sided, and a value less than 0.05 was used to indicate statistical significance.

Baseline characteristics and plasma 25(OH)D levels between cases and controls were compared using the Mantel-Haenszel test with matched pair strata. Odds ratios (ORs) and 95% confidence intervals (CIs) for plasma 25(OH)D in tertiles using the control distribution were calculated using a conditional logistic regression model. We adjusted ORs and 95%CIs for the a number of variables, namely alcohol consumption (almost never, 1–3 times per month, ⩾1 times per week), smoking status (never, former, and current), body mass index (BMI, continuous), living with a spouse (yes/no), and consumption of green tea (<1 cup/day, 1-2 cups/day, 3-4 cups/day, ⩾5 cups/day) and miso soup (<3 bowls/week, 1 bowl/day, 2 bowls/day, ⩾3 bowls/day). These variables are known or suspected risk factors for cancer, or alternatively were previously associated with prostate cancer risk.[16–19] Owing to the slight difference in the questionnaires used in Cohorts I and II regarding food products, manner of expression and frequency categories, we estimated adjusted ORs for calcium intake for Cohorts I and II separately, and then analyzed the combined result with a fixed-effects model. The linear trend for OR was evaluated by assigning ordinal variables for each category. ORs were also presented using 10 ng/ml increments of 25(OH)D level. In additional, we also estimated the ORs of prostate cancer after stratification by stage and for all cases.

RESULTS

Table 1 shows the baseline characteristics of case and matched controls. Cases tended to be nonsmokers while controls tended to have higher miso soup consumption. The percentage of subjects did not materially differ with regard to a BMI of 25 or more; consumption of alcohol, green tea and fish; or median concentration of 25(OH)D. Vitamin D deficiency was not seen in these subjects (<10 ng/ml). We also shows the characteristics of men according to tertile of 25(OH)D in supplementary Table 1.

ORs and 95%CIs of prostate cancer risk according to plasma 25(OH)D level by stage of disease are shown in Table 2.

We observed no association between level of 25(OH)D in plasma and total or localized prostate cancer, although adjusted ORs per 10 ng/ml increment was elevated to 1.06 (1.00–1.12) in advanced prostate cancer.

Additionally, we stratified subjects by the frequency of fresh fish intake (⩾3days/wk or < 3days/wk) and calcium intake (⩾middle point (Cohort I: 558.1mg/day, Cohort II: 332.0 mg/day) or < middle point), because fish intake is the principal source of vitamin D in Japanese and calcium consumption may change vitamin D activity. No association between 25(OH)D level in plasma and prostate cancer was observed. We observed a nonsignificantly increased risk in subjects with low calcium intake, but these results were not statistically significant and the 95%CI was substantially broad because of the small sample (Table 3).

Furthermore, we analyzed the relationship between 25(OH)D and prostate cancer by using cut points of referred values (20–30 ng/ml). ORs with low and high 25(OH)D levels showed a slightly increased risk of total prostate cancer, but without statistically significance (ORs (95%CI), at 1.45 (0.45–4.57) for low and 1.12 (0.75–1.70) for high levels).

DISCUSSION

Our results do not support the experimental reports that prostate cancer may be prevented by vitamin D. However, they support the results of a previous meta-analysis (21 relevant publications including 11 941 cases and 13 870 controls), which reported that higher levels of 25(OH)D were positively associated with the risk of prostate cancer.[6] As far as we know, this is the first study to show that plasma level of 25(OH)D is not related clearly with risk for prostate cancer in an Asian men.

Our results show 25(OH)D has a 6% increased risk of advanced prostate cancer. This is consistent with preciding investigations, which reported significant or nonsignificant positive associations between 25(OH)D and advanced prostate cancer.[20–23] Some experimental studies have suggested that the ability to convert from 25(OH)D to 1,25 dihydroxy vitamin D ($1,25(OH)_2D$) in plasma tends to be lost in prostate cancer cells because of lack of 1-a hydroxylase activity.[24,25] An increase in 25(OH)D may reflect the inability of prostate cancer to efficiently change from 25(OH) D to $1,25(OH)_2D$, which might suggest that 25(OH)D is a predictive marker for advanced prostate cancer.

The plasma level of 25(OH)D in our study ranged higher and narrower (interquartile range 28.0–39.0 ng/ml) than in other studies. Two studies from Europe which showed an inverse association reported lower and narrower ranges, with an interquartile range in Finland of 12.4–22 ng/ml[26] and a range in the middle tertile of 15–25 ng/ml in the Czech Republic.[27] Additionally, some studies which showed a positive association with both high and low levels of 25(OH)D reported wider ranges.[23,28–30] The reason our study did not show clear association between 25(OH)level and prostate cancer is likely because of the range and level of 25(OH)D.

Vitamin D helps the absorption of calcium, for which high serum levels are positively related with an elevated risk of prostate cancer.[31,32] Albanes *et al.* reported a synergistic effect in subjects with high intake of calcium and high 25(OH)D,[22] but our study showed that 25(OH)D was not associated with prostate cancer after stratification according to calcium intake. In western countries, a principal source of vitamin D is milk, which contains calcium,[9] and high plasma 25(OH)D might reflect a diet high which is high in calcium sources, such as milk. In contrast, we observed a nonsignificantly increased risk in subjects with low calcium intake. However, the interpretation of this result requires caution due to the small sample size.

Chiang *et al.* reported that fish oils increase the anti-proliferative activity of $1,25(OH)_2D$.[33] Additionally, Ordonez-Mena *et al.*[30] reported that the risk of total cancer was significantly increased in men having low 25(OH)D and subjects reporting low fish consumption. Given that fish is a principal source of vitamin D in Japan,[12] we expected that our study would show synergistic preventive effects of fish intake and 25(OH)D on prostate cancer, but were surprised to find null association between 25(OH)D and prostate cancer by fish intake. Only a few studies have researched the effects of fish intake on the association between 25 (OH)D and prostate cancer, however, and further studies might be needed.

Low selection bias is a major strength of our study. Blood sampling was done prior to the diagnosis of prostate cancer in a longitudinal population-based design (nested case-control design) and cases and controls were selected from the same cohort. In contrast, the interpretation of our findings also warrants mention due to several limitations. First, we measured plasma 25(OH)D levels only one time. Although misclassification would weaken true association, we matched the date of donated blood samples within two months. Furthermore, although subjects were chosen from a large general population, they were limited to those engaged in health checkup survey at baseline. A universalization of our results should therefore be made with caution.

In conclusion, 25(OH)D was not associated with total prostate cancer in Japanese men, although 25(OH)D was slightly associated with an increased the risk of advanced cancer.

CONFLICT OF INTEREST

The authors have nothing to declare. Manami Inoue is the beneficiary of a financial contribution from the AXA Research fund as a chair holder on the AXA Department of Health and Human Security, Graduate School of Medicine, The University of Tokyo. The AXA Research Fund had no role in the design, data collection, analysis, interpretation or manuscript drafting, or in the decision to submit the manuscript for publication.

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MEMBERS OF THE JAPAN PUBLIC HEALTH CENTER-BASED PROSPECTIVE STUDY (JPHC STUDY, PRINCIPAL INVESTIGATOR: S. TSUGANE) GROUP

JPHC members are listed at the following site (as of April 2016): http://epi.ncc.go.jp/en/jphc/781/3838.html.

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