Relationship between vegetable and carotene intake and risk of prostate cancer: the JACC study

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Background: We examined the associations of intakes of vegetables and carotenes with risk of prostate cancer in Japanese.

Methods: A total of 15471 Japanese men participating in the Japan Collaborative Cohort study completed a questionnaire including food intake. Of them, 143 incident prostate cancers were documented. We examined the associations stated above by using Cox proportional hazard model.

Results: Vegetable intake was not associated with the risk of prostate cancer, but so was dietary alpha-carotene intake. The multivariable hazard ratio (95%CI) in the secondary highest and highest quintiles of alpha-carotene intake was 0.50 (0.26–0.98) (P = 0.043) and 0.46 (0.22–0.97) (P = 0.041) (P for trend = 0.224), respectively. Beta-carotene intake was not associated with the risk of prostate cancer.

Conclusion: Alpha-carotene intake was associated with lower risk of prostate cancer among Japanese.

Prostate cancer is one of the most common cancers among men. Several epidemiological studies have identified age, family history (Kiciński et al, 2011) and obesity (MacInnis and English, 2006) as risk factors for prostate cancer. The intakes of tomato and lycopene, a type of carotene, was reported to associate inversely with the risk of prostate cancer (Chen et al, 2001; Giovannucci et al, 2002); however, the reported associations between the intake of other vegetables or other carotenes and the risk of prostate cancer have been inconsistent (Kirsh et al, 2007; Takachi et al, 2010).

The aim of the present study was to determine the association between the intake of vegetables and carotene and the risk of prostate cancer in Japanese whose consumption of vegetables seems higher than those in Westerners (Blanck et al, 2008; Ministry of Health, Labour and Welfare, 2011). Our a priori hypothesis is that the intake of vegetables or carotenes is inversely associated with the risk of prostate cancer.

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MATERIALS AND METHODS

The Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risks, sponsored by the Ministry of Education, Sport, and Science, was conducted from 1988 to 1990. The sampling methods and protocols of the JACC Study have been described elsewhere (Tamakoshi et al, 2013). A total of 46 395 men, 40–79 years of age, completed self-administered questionnaires about their lifestyles and medical histories. Of them, we used the data of 26 429 men who lived in 24 communities that underwent follow-up research of cancer incidence. We additionally excluded 10 023 men owing to the lack of valid responses to dietary intake-related questions, and 935 men owing to the presence of past history of cancer and cardiovascular disease at baseline. Finally, we used the data of 15 471 men for analysis.

The incidence of prostate cancer was based on the records of population-based cancer registries. The incidence data were coded by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems. We used the first diagnosis for incidence. We defined prostate cancer as C61. The incidence of prostate cancer in the present study was similar to that estimated from the Japan cancer registry (Matsuda et al, 2013).

Each participant recorded the frequency of the intake of 35 foods which included five items for vegetable intake as cabbage/head lettuce, Chinese cabbage, tomato, carrot/pumpkin and:

| Table 1. Characteristics of the subjects according to quintiles of frequency of vegetable intake and quintiles of amount of carotene intake |
|---------------------------------------------------------------|
| **Quintiles** | 1 (low) | 2 | 3 | 4 | 5 (high) | P for ANOVA |
|---------------------------------------------------------------|
| **Total vegetable intake** | | | | | | |
| Frequency of total vegetable intake (serves per week) | 1.0–8.0 | 8.3–11.9 | 12.0–15.5 | 15.8–20.5 | 20.9–33.0 | | |
| N | 3113 | 3086 | 3103 | 3113 | 3056 | | |
| Age (years) | 54.4 | 55.0 | 55.9 | 56.5 | 57.7 | <0.001 | |
| Body mass index (kg m⁻²)* | 22.7 | 22.6 | 22.7 | 22.6 | 22.7 | 0.457 | |
| Current drinker (%)* | 75 | 77 | 77 | 76 | 74 | 0.025 | |
| Current smoker (%)* | 58 | 53 | 52 | 52 | 50 | <0.001 | |
| Family history of prostate cancer (%)* | 0.3 | 0.3 | 0.4 | 0.2 | 0.5 | 0.272 | |
| **Green and yellow vegetable intake** | | | | | | |
| Frequency of green and yellow vegetable intake (serves per week) | 1.0–4.9 | 5.0–6.9 | 7.0–9.5 | 10.0–12.5 | 13.5–19.0 | | |
| N | 2989 | 2928 | 3268 | 3423 | 2863 | | |
| Age (years) | 54.0 | 54.9 | 55.7 | 56.9 | 57.9 | <0.001 | |
| Body mass index (kg m⁻²)* | 22.6 | 22.7 | 22.7 | 22.7 | 22.6 | 0.211 | |
| Current drinker (%)* | 75 | 77 | 77 | 77 | 73 | <0.001 | |
| Current smoker (%)* | 60 | 54 | 50 | 53 | 48 | <0.001 | |
| Family history of prostate cancer (%)* | 0.3 | 0.3 | 0.3 | 0.4 | 0.5 | 0.623 | |
| **Other vegetable intake** | | | | | | |
| Frequency of other vegetable intake (serves per week) | 0–1.9 | 3.0–3.5 | 3.9–5.0 | 7.0–8.5 | 10.5–14.0 | | |
| N | 2762 | 3367 | 2798 | 3892 | 2652 | | |
| Age (years) | 55.7 | 55.4 | 55.8 | 56.0 | 56.8 | <0.001 | |
| Body mass index (kg m⁻²)* | 22.6 | 22.7 | 22.7 | 22.7 | 22.8 | 0.077 | |
| Current drinker (%)* | 75 | 76 | 76 | 75 | 76 | 0.530 | |
| Current smoker (%)* | 56 | 53 | 52 | 52 | 53 | 0.022 | |
| Family history of prostate cancer (%)* | 0.2 | 0.3 | 0.3 | 0.4 | 0.5 | 0.368 | |
| **Alpha-carotene intake** | | | | | | |
| Median alpha-carotene intake (µg day⁻¹) | 105 | 175 | 236 | 317 | 497 | | |
| N | 3094 | 3094 | 3095 | 3094 | 3094 | | |
| Age (years) | 53.7 | 54.8 | 55.9 | 56.9 | 58.2 | <0.001 | |
| Body mass index (kg m⁻²)* | 22.6 | 22.6 | 22.7 | 22.7 | 22.7 | 0.189 | |
| Current drinker (%)* | 82 | 77 | 75 | 74 | 70 | <0.001 | |
| Current smoker (%)* | 60 | 55 | 52 | 50 | 49 | <0.001 | |
| Family history of prostate cancer (%)* | 0.2 | 0.3 | 0.3 | 0.4 | 0.5 | 0.347 | |
| **Beta-carotene intake** | | | | | | |
| Median beta-carotene intake (µg day⁻¹) | 986 | 1569 | 2107 | 2739 | 3718 | | |
| N | 3094 | 3094 | 3095 | 3094 | 3094 | | |
| Age (years) | 53.1 | 54.4 | 56.0 | 57.2 | 58.8 | <0.001 | |
| Body mass index (kg m⁻²)* | 22.6 | 22.7 | 22.7 | 22.7 | 22.7 | 0.527 | |
| Current drinker (%)* | 81 | 76 | 77 | 74 | 70 | <0.001 | |
| Current smoker (%)* | 60 | 54 | 51 | 51 | 48 | <0.001 | |
| Family history of prostate cancer (%)* | 0.2 | 0.4 | 0.3 | 0.3 | 0.5 | 0.304 | |

*Adjusted for age.
spins/chard chrysanthemum. Five responses were possible for 33 food items including vegetables: ‘rarely’, ‘1–2 days per month’, ‘1–2 days per week’, ‘3–4 days per week’ and ‘almost every day’; the consumption of each food was calculated by multiplying the frequency score of consumption of each food 0, 0.38, 1.5, 3.5 and 7, respectively. As for soybean paste soup and rice intake, the frequency and number of cups/bowls per day were recorded. We determined the non-valid data as follows: the missing for rice frequency and number of cups/bowls per day were recorded. We respectively. As for soybean paste soup and rice intake, the consumption of each food was calculated by multiplying the frequency of cabbage/head lettuce and Chinese cabbage.

Table 2. Associations between quintiles of frequency of vegetable intake and risk of prostate cancer

| Quintiles of frequency of vegetable intake | P for trend |
|-----------------------------------------|------------|
| **Total vegetable intake**              |            |
| Total vegetable intake (serves per week) |            |
| 1 (low) 2 3 4 5 (high)                  |            |
| Number of subjects                      |            |
| Number of events                        |            |
| Age-adjusted                            |            |
| Multivariable-adjusted*                 |            |
| Multivariable-adjustedb                 |            |
| **Green and yellow vegetable intake**   |            |
| Green and yellow vegetable intake (serves per week) |            |
| Number of subjects                      |            |
| Number of events                        |            |
| Age-adjusted                            |            |
| Multivariable-adjusted*                 |            |
| Multivariable-adjustedb                 |            |
| **Other vegetable intake**              |            |
| Other vegetable intake (serves per week) |            |
| Number of subjects                      |            |
| Number of events                        |            |
| Age-adjusted                            |            |
| Multivariable-adjusted*                 |            |
| Multivariable-adjustedb                 |            |

*Adjusted for age, body mass index (kg m\(^{-2}\)), ethanol intake (current drinker or not), smoking status (three categories), daily green tea intake (yes or no) and work schedule (rotating-shift or not).

**Adjusted further for frequency of dairy products intake (quintiles), soy products intake (quintiles), fish products intake (quintiles) and beef intake (five categories).**
The present study was approved by the ethics committees of Nagoya University School of Medicine and Kyoto Prefectural University of Medicine Graduate School of Medical Science. We used SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA) in all analyses.

RESULTS

The characteristics of subjects according to vegetable intake and carotene intake are summarised in Table 1. Intakes of total, green and yellow and other vegetables, and alpha- and beta-carotenes were correlated positively with age, but negatively with the proportion of current smokers. Intakes of total, green and yellow vegetables, and alpha- and beta-carotenes were correlated inversely with the proportion of current drinkers.

During the follow-up, 143 incident cases of prostate cancer were documented. Table 2 presents the age-adjusted and multivariate-adjusted hazard ratios (95% CI) according to the quintiles of frequency of vegetable intake. With regard to total vegetable intake, compared with the lowest quintile, other quintiles showed lower risk of prostate cancer. The relationship between total vegetable intake and risk of prostate cancer showed a threshold pattern with lower risk in the secondary lowest and higher quintiles of total vegetable intake. The multivariate hazard ratio (95% CI) in the secondary highest versus the lowest quintiles was 0.55 (0.31–0.96) ($P = 0.035$) and in the highest versus lowest quintiles was 0.65 (0.37–1.12) ($P = 0.116$) ($P$ for trend $= 0.294$). Green and yellow vegetable intake and other vegetable intake were not associated with the risk of prostate cancer.

Table 3 shows the hazard ratios (95% CI) according to quintiles of carotene intake. As for alpha-carotene intake, compared with the lowest quintile, the highest and the secondary lowest quintile showed lower risk of prostate cancer. The relationship between alpha-carotene intake and risk of prostate cancer showed a threshold pattern with lower risk in the secondary lowest and higher quintiles of alpha-carotene intake. The multivariate hazard ratio (95% CI) in the secondary highest and highest versus lowest quintile of alpha-carotene intake was 0.50 (0.26–0.98) ($P = 0.043$) and 0.46 (0.22–0.97) ($P = 0.041$) ($P$ for trend $= 0.224$). Beta-carotene intake was not associated with risk of prostate cancer.

DISCUSSION

The main finding of this large prospective study of Japanese men was that vegetable intake was not associated with the risk of prostate cancer; however, a possible threshold effect was suggested. Moderate to high alpha-carotene intake was associated with lower risk of prostate cancer.

A previous prospective study of Japanese showed no significant association between total vegetable intake and risk of prostate cancer (Takachi et al, 2010). Other prospective studies also reported no association between vegetable intake and risk of prostate cancer (Hsing et al, 1990; Schuurman et al, 1998). However, two prospective studies of US men indicated inverse association between vegetable or vegetable fat intake and risk of prostate cancer progression (Kirsh et al, 2007; Richman et al, 2013). As for the association between alpha-carotene intake and risk of prostate cancer, no other prospective study has examined it.

Several mechanisms may account for the inverse association of vegetable and carotene intake and risk of prostate cancer. First, prostate cancer cells carry numerous genome defects which allow malignant cell growth and survival (Nelson et al, 2009). Vegetable components such as glucosinolates and isothiocyanates stimulate cancer cell apoptosis and activate phase 2 enzyme that detoxificates carcinogen (Hayes et al, 2008, Ho et al, 2009). For example, sulforaphane, one of isothiocyanates, acts as a histone deacetylase inhibitor which allows DNA to open their chromatin and proceed RNA transcription (Richon et al, 2000). That effect activates tumour suppressor genes such as P21 which induces cell cycle arrest of damaged DNA and Bax which induces apoptosis through the stimulation of anion channel (Ho et al, 2009). Second, carotene intake reduces cancer cell generation through the inhibition of

Table 3. Associations between carotene intake and risk of prostate cancer

| Quintiles of each nutrition intake | 1 (low) | 2 | 3 | 4 | 5 (high) | $P$ for trend |
|-----------------------------------|--------|---|---|---|---------|-------------|
| **Alpha-carotene**                |        |   |   |   |         |             |
| Median alpha-carotene intake (µg/d) | 105   | 175 | 236 | 317 | 496   |             |
| Number of subjects                | 3094  | 3094 | 3095 | 3094 | 3094 |             |
| Person-years                      | 37 902 | 40 786 | 41 688 | 42 456 | 41 783 |             |
| Number of events                  | 22     | 18   | 25   | 45   | 33    |             |
| Number of events (per 1000 person-years) | 0.58 | 0.44 | 0.60 | 1.06 | 0.79 |             |
| Age-adjusted                      | 1.00   | 0.61 (0.33–1.15) | 0.74 (0.42–1.32) | 1.16 (0.69–1.95) | 0.81 (0.47–1.40) | 0.173 |
| Multivariable-adjusted*           | 1.00   | 0.60 (0.32–1.13) | 0.71 (0.40–1.27) | 1.10 (0.65–1.86) | 0.74 (0.42–1.29) | 0.333 |
| Multivariable-adjusted*           | 1.00   | 0.50 (0.26–0.98) | 0.55 (0.28–1.08) | 0.77 (0.39–1.51) | 0.46 (0.22–0.97) | 0.224 |

**Beta-carotene**

| Median beta-carotene intake (µg/d) | 986 | 1569 | 2107 | 2739 | 3718 |
| Number of subjects                | 3094  | 3094 | 3095  | 3094  | 3094 |
| Person-years                      | 39 331 | 41 197 | 41 397 | 41 638 | 41 052 |
| Number of events                  | 22     | 22   | 29   | 30   | 40   |
| Number of events (per 1000 person-years) | 0.56 | 0.53 | 0.70 | 72.00 | 0.97 |
| Age-adjusted                      | 1.00   | 0.77 (0.42–1.39) | 0.90 (0.51–1.57) | 0.83 (0.48–1.45) | 0.97 (0.57–1.65) | 0.218 |
| Multivariable-adjusted*           | 1.00   | 0.74 (0.41–1.34) | 0.85 (0.49–1.50) | 0.79 (0.45–1.39) | 0.90 (0.52–1.54) | 0.351 |
| Multivariable-adjusted*           | 1.00   | 0.65 (0.33–1.26) | 0.67 (0.33–1.37) | 0.52 (0.24–1.14) | 0.51 (0.22–1.19) | 0.200 |

*Adjusted for age, body mass index (kg m$^{-2}$), ethanol intake (current drinker or not), smoking status (three categories), daily green tea intake (yes or no) and work schedule (rotating-shift or not).

bAdjusted further for saturated fat intake (quintiles), isoflavone intake (quintiles) and alpha-tocopherol intake (quintiles).
systemic inflammation which is a known risk factor of prostate cancer (Sfanos and De Marzo, 2012). A randomized controlled trial showed that a high intake of carotenoid-rich vegetables and fruits lowered plasma C-reactive protein concentrations, a biomarker of systemic inflammation (Watzl et al. 2005). Third, alpha-carotene has a stronger inhibitory effect on carcinogenesis than beta-carotene according to an animal study (Murakoshi et al., 1992). It accorded with our finding that alpha-carotene intake, but not beta-carotene, was inversely associated with the risk of prostate cancer.

The strengths of the present study include the study design and subjects. We used a large prospective cohort enrolled from the Japanese general populations, and we first showed inverse association between alpha-carotene intake and risk of prostate cancer in Asian populations.

As for a limitation of the present study, we did not obtain the information about TNM stage, Gleason score and pathological information about TNM stage, Gleason score and pathological stage. Therefore, we could not evaluate the effect of vegetable and carotene intake on the advancement of prostate cancer. However, a previous cohort study of Japanese showed that vegetable intake was not associated with risk of localised or advanced prostate cancer (Takachi et al., 2010).

In conclusion, our large prospective study of Japanese men indicated that moderate to high alpha-carotene intakes may contribute to reduced risk of prostate cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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