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

M Umesawa[1,2], H Iso*[,3], K Mikami[4], T Kubo[5], K Suzuki[6], Y Watanabe[7], M Mori[8], T Miki[4], A Tamakoshi[9] and JACC Study Group

[1]Department of Public Health, Dokkyo Medical University School of Medicine, Mibu, Tochigi 321-0293, Japan; [2]Department of Public Health Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba 305-8577, Japan; [3]Public Health, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Osaka 565-0871, Japan; [4]Department of Urology, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto 602-8566, Japan; [5]Department of Preventive Medicine and Community Health, School of Medicine, University of Occupational and Environmental Health, Kitakyusyu 807-8555, Japan; [6]Department of Public Health, Fujita Health University School of Health Sciences, Toyoake 470-1192, Japan; [7]Department of Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto 602-8566, Japan; [8]Department of Public Health, Sapporo Medical University School of Medicine, Sapporo 060-8556, Japan and [9]Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo 060-8638, Japan

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

Methods: A total of 15 471 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.

*Correspondence: Professor H Iso; E-mail: iso@pbhel.med.osaka-u.ac.jp

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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})[a]	22.7	22.6	22.7	22.6	22.7	0.457
Current drinker (%)[a]	75	77	77	76	74	0.025
Current smoker (%)[a]	58	53	52	52	50	<0.001
Family history of prostate cancer (%)[a]	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})[a]	22.6	22.7	22.7	22.7	22.6	0.211
Current drinker (%)[a]	75	77	77	77	73	<0.001
Current smoker (%)[a]	60	54	50	53	48	<0.001
Family history of prostate cancer (%)[a]	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})[a]	22.6	22.7	22.7	22.7	22.8	0.077
Current drinker (%)[a]	75	76	76	75	76	0.530
Current smoker (%)[a]	56	53	52	52	53	0.022
Family history of prostate cancer (%)[a]	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})[a]	22.6	22.6	22.7	22.7	22.7	0.189
Current drinker (%)[a]	82	77	75	74	70	<0.001
Current smoker (%)[a]	60	55	52	50	49	<0.001
Family history of prostate cancer (%)[a]	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})[a]	22.6	22.7	22.7	22.7	22.7	0.527
Current drinker (%)[a]	81	76	77	74	70	<0.001
Current smoker (%)[a]	60	54	51	51	48	<0.001
Family history of prostate cancer (%)[a]	0.2	0.4	0.3	0.3	0.5	0.304

[a]Adjusted for age.

spinach/garland 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 intake, miso soup intake, alcohol intake, $\geqslant 5$ items out of 33 food items; and/or extremely low or high total energy intakes (<800 kcal day^{-1} or >4000 kcal day^{-1}). The reproducibility and validity of this dietary questionnaire were reported elsewhere (Date *et al*, 2005). The energy-adjusted nutrient intake was calculated by the residual method. The frequency of total vegetable intake was calculated by totalling the frequency of cabbage/head lettuce, Chinese cabbage, tomato, carrot/pumpkin and spinach/garland chrysanthemum intakes. The frequency of green and yellow vegetable intakes was calculated by totalling the frequency of tomato, carrot/pumpkin and spinach/garland chrysanthemum intakes. The frequency of other vegetable was calculated by totalling the frequency of cabbage/head lettuce and Chinese cabbage.

Statistical analysis was based on incident rates of prostate cancer during the follow-up period from 1989 to 2009. For each participant, the person-years of follow-up were calculated from the date of filling out the baseline questionnaire to death, moving out of the community, or the end of follow up, whichever was first. The median follow-up period was 16.0 years. The number of moving out was 821.

Age-adjusted and multivariable-adjusted hazard ratios of prostate cancer were defined as the incidence rate among participants according to quintiles of frequency of vegetable intake and quintiles of amount of carotene intake. The hazard ratios of prostate cancer and their 95% confidence intervals (95% CI) were calculated after adjustment for age and potential confounding factors by using the Cox proportional hazard model. These confounding variables included body mass index (kg m^{-2}), smoking status (never, ex-smoker and current smoke), ethanol intake (current drinker or not), daily green tea intake (yes or no) and work schedule (rotating-shift or not). We also used the quintiles of frequency of dairy products, bean products, fish products and beef intake as confounding variables with analyses of vegetable intake. We used quintiles of saturated fatty acid, isoflavone and alpha-tocopherol intake as confounding variables with analyses of carotene intake. Test for a linear trend across the vegetable and carotene intake quintiles were conducted by linear regression using the median variable of vegetable and carotene intake in each quintile. We tested the interaction of alcohol intake and smoking for each analysis, and found no significant interactions. As for family history of prostate cancer, we found no cases with it. Thus, we did not include it as a confounding variable.

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

	Quintiles of frequency of vegetable intake					
	1 (low)	2	3	4	5 (high)	*P* for trend
Total vegetable intake						
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	
Number of subjects	3113	3086	3103	3113	3056	
Person-years	40 293	40 827	41 118	41 506	40 870	
Number of events	28	22	31	26	36	
Number of events (per 1000 person-years)	0.69	0.54	0.75	0.63	0.88	
Age-adjusted	1.00	0.74 (0.42–1.29)	0.95 (0.57–1.58)	0.74 (0.44–1.27)	0.94 (0.57–1.55)	0.602
Multivariable-adjusted[a]	1.00	0.72 (0.41–1.26)	0.93 (0.56–1.56)	0.72 (0.42–1.24)	0.90 (0.54–1.48)	0.767
Multivariable-adjusted[b]	1.00	0.63 (0.36–1.10)	0.77 (0.45–1.30)	0.55 (0.31–0.96)	0.65 (0.37–1.12)	0.294
Green and yellow vegetable intake						
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	
Number of subjects	2989	2928	3268	3423	2863	
Person-years	39 213	38 865	43 386	45 730	37 420	
Number of events	24	23	29	37	30	
Number of events (per 1000 person-years)	0.61	0.59	0.67	0.81	0.80	
Age-adjusted	1.00	0.88 (0.50–1.56)	0.95 (0.55–1.64)	1.01 (0.60–1.69)	0.92 (0.54–1.58)	0.740
Multivariable-adjusted[a]	1.00	0.86 (0.48–1.53)	0.92 (0.54–1.59)	0.98 (0.59–1.65)	0.87 (0.50–1.50)	0.913
Multivariable-adjusted[b]	1.00	0.76 (0.43–1.37)	0.76 (0.43–1.32)	0.76 (0.44–1.32)	0.61 (0.34–1.10)	0.200
Other vegetable intake						
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	
Number of subjects	2762	3367	2798	3892	2652	
Person-years	34 927	44 974	36 002	52 144	36 567	
Number of events	23	26	28	39	27	
Number of events (per 1000 person-years)	0.66	0.58	0.78	0.75	0.74	
Age-adjusted	1.00	0.84 (0.48–1.48)	1.16 (0.67–2.01)	1.04 (0.62–1.74)	0.95 (0.55–1.66)	0.513
Multivariable-adjusted[a]	1.00	0.85 (0.49–1.50)	1.15 (0.66–2.00)	1.04 (0.62–1.75)	0.92 (0.53–1.62)	0.627
Multivariable-adjusted[b]	1.00	0.80 (0.45–1.41)	1.01 (0.58–1.78)	0.89 (0.52–1.52)	0.75 (0.42–1.36)	0.657

[a]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).
[b]Adjusted further for frequency of dairy products intake (quintiles), soy products intake (quintiles), fish products intake (quintiles) and beef intake (five categories).

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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 day^{-1})	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[a]	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[b]	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 day^{-1})	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[a]	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[b]	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

[a]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).
[b]Adjusted 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 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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