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Prospective study showing that dietary vitamin C reduced the risk of age-related cataracts in a middle-aged Japanese population

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Abstract *Background* In Western countries, many epidemiological studies have demonstrated that specific dietary nutrients are associated with the risk of developing age-related cataracts. These reports have suggested that dietary antioxidant vitamins, in particular vitamin C, can play a role in preventing the onset or progression of age-related visual impairment. However, few prospective studies have examined this relationship in a general Asian population. Therefore, in this study, we investigated whether dietary vitamin C was associated with a lower incidence of age-related cataracts by performing a 5-year prospective population-based analysis using data from a cohort of over 30,000 Japanese residents recruited to the Japan Public Health Center-based Prospective Study (JPHC Study) cohort I. *Aim of the study* We carried out a prospective analysis of the association between vitamin C intake and age-related cataracts among middle-aged Japanese, to study the effects of dietary antioxidants in an Asian population. *Methods* This 5-year population-based study included 16,415 men and 18,771 women (aged 45–64 years), who were recruited onto the JPHC Study and

had not reported cataracts in baseline surveys. Vitamin C was calculated from the nutrient intake assessed by self-administered food-frequency questionnaires (FFQ). Self-reported questionnaires were used to assess two endpoints: diagnosis or extraction of cataracts. **Results** At follow-up, 216 men and 551 women reported new diagnoses, and 110 men and 187 women reported extractions of

cataracts. For both endpoints, a higher vitamin C intake was associated with a reduced incidence of cataracts in both sexes. After adjusting for potential confounding factors, the multivariate odds ratios (ORs) for men and women in the highest quintiles of energy-adjusted vitamin C intake, relative to the lowest quintiles, were 0.65 (95% CI, 0.42–0.97) and 0.59 (95% CI, 0.43–0.89) for cataract diag-

noses, and 0.70 (95% CI, 0.44–1.20) and 0.64 (95% CI, 0.41–0.94) for cataract extractions, respectively. **Conclusions** Dietary vitamin C intake might lower the risk of age-related cataracts among middle-aged Japanese.

■ **Key words** cataract – cataract extraction – antioxidants – vitamin C – prospective studies

Introduction

Age-related cataracts are an important public-health problem globally and remain a leading cause of blindness worldwide, with surgical extractions increasing the medical care costs in many developed countries [1]. The oxidation of proteins or lipids within the lens is known to be associated with the formation of age-related cataracts [2–4]. Recent experimental studies have shown that antioxidants can protect against the effects of oxidative stress in animal models [5, 6]. Clarifying the protective role of antioxidants in age-related cataracts in humans will be important for establishing preventive approaches for this disease.

In Western countries, many epidemiological studies [7–16] have demonstrated that specific dietary nutrients are associated with the risk of developing age-related cataracts. These reports [7–14] have suggested that dietary antioxidant vitamins, in particular vitamin C, can play a role in preventing the onset or progression of age-related visual impairment because dietary vitamin C intake is related to eye-tissue ascorbate levels and because there are available epidemiologic data indicating a protective role for vitamin C on age-related cataracts [17]. However, few prospective studies have examined this relationship in a general Asian population. Therefore, in this study, we investigated whether dietary vitamin C was associated with a lower incidence of age-related cataracts by performing a 5-year prospective population-based analysis using data from a cohort of over 30,000 Japanese residents recruited to the Japan Public Health Center-based Prospective Study (JPHC Study) cohort I [18].

Subjects and methods

■ Study cohort

The JPHC Study began in 1990 and is still ongoing. It is a multi-purpose longitudinal cohort study, which

aims to investigate cancer, cardiovascular disease, and other lifestyle-related disorders. The cohort has been divided into two groups: Cohort I, which started recruitment in 1990; and Cohort II, which started recruitment in 1993. The current analysis was conducted in the population recruited to Cohort I, which was composed of 54,498 residents (27,063 men and 27,435 women aged 40–59 years in 1990) with registered addresses in 14 administrative districts, who were supervised by four public health center (PHC) areas on January 1, 1990: 6,022 men and 6,269 women were from the city of Ninohe and the town of Karumai in the Ninohe PHC area in Iwate Prefecture; 7,559 men and 8,223 women were from the city of Yokote and the town of Omonogawa in the Yokote PHC area in Akita Prefecture; 6,173 men and 6,046 women were from eight locations (the towns of Usuda, Saku, and Koumi, and the villages of Kawakami, Minamimaki, Minami-aiki, Kita-aiki, and Yachiho) in the Minami-Saku District in the Saku PHC area in Nagano Prefecture; and 7,309 men and 6,897 women were from the city of Gushikawa and the village of Onna in the Ishikawa PHC area in Okinawa Prefecture. The enrolled residents were born between January 1, 1930 and December 31, 1949. Other criteria for selecting the areas and the subjects, along with the methods of data collection and the geographic profiles of the four PHC areas, have been reported previously [18]. This study was approved by the human ethics review committees of the National Cancer Center of Japan.

■ Surveys and measurements

In 1990, a self-administered questionnaire concerning demographic characteristics, medical history, lifestyle, and diet was distributed to everyone in Cohort I and, in addition, blood samples and anthropological data were collected. In total, 43,149 individuals completed and returned the questionnaires, giving a response rate of 79%.

Second and third follow-up questionnaires were sent to each participant in 1995 and 2000, respec-

tively. Blood samples and anthropological data were also collected in 1995. The second follow-up questionnaires were completed and returned by 42,174 individuals, a response rate of 79%, of which 37,086 also completed and returned the third follow-up questionnaires.

In the present study, vitamin C was calculated from the nutrient intake assessed by self-administered food-frequency questionnaires (FFQ). In 1995, the FFQ were distributed with the follow-up questionnaires and the usual nutrient intake for each individual was calculated as the average intake using the Standard Tables of Food Composition in Japan [19]. The FFQ asked about the usual consumption of 138 food items, which were mainly single items but included some grouped items, and 14 supplements during the previous year. Nine frequency categories were used for the majority of foods (almost never, 1–3 times per month, 1–2 times per week, 3–4 times per week, 5–6 times per week, daily, 2–3 times per day, 4–6 times per day, or 7 or more times per day). The portion sizes were specified and respondents were asked to answer in three categories relative to this (less than half, the same, or more than one and a half times). Data on the use of vitamin supplements was requested in terms of frequency (1–2 pills per week, 3–4 pills per week, 5–6 pills per week, 1 pill per day, 2–3 pills per day, 4–6 pills per day, or 7 or more pills per day) and duration of use (less than 1 year, 1–2 years, 3–4 years, 5–9 years, 10–19 years, or 20 or more years). This study was restricted to looking at vitamin C obtained from food, and so individuals using vitamin supplements were excluded. We have previously reported data showing the validity of estimating dietary vitamin C intake levels using the FFQ: correlation coefficients between the energy-adjusted vitamin C intakes estimated from FFQs and from 28-day weighted dietary records (DRs) were 0.42 in men and 0.22 in women [20].

We ascertained whether participants had been diagnosed with age-related cataracts using the following questions in the second and third follow-up questionnaires: “Has a doctor ever told you that you had cataracts?” and “Have you ever had a lens extracted?” The validity of self-reported data on cataracts has been confirmed by medical records review. From the 1,072 individuals who had reported age-related cataracts in the second follow-up survey, we randomly selected 97 subjects from the 14 administrative districts of the Ninohe, Yokote, Saku, and Ishikawa PHC areas. Of the 70 subjects who gave permission for us to review their medical records, we were able to review 56 and compare them with their self-reported questionnaires. As a result, the diagnoses of age-related cataracts were confirmed in a total of 49 of the 53 self-reporters (92.5%), and cataract

extractions were confirmed in 25 out of 25 self-reporters (100%) [21].

To estimate the incidence of age-related cataracts for the 5-year period from 1995 to 2000, and to investigate the relationship between dietary vitamin C intake from food and the risk of age-related cataracts, we excluded 1,747 individuals who reported a history of cataract diagnosis or cataract surgery in the second follow-up questionnaire survey, or who took dietary supplements containing vitamin C. Individuals for whom data were missing for any of the possible confounding factors described below were also excluded. After these exclusions, a total of 35,186 individuals (16,415 men and 18,771 women) were enrolled in the study.

■ Statistical analysis

All analyses were performed separately for men and women. Multiple logistic-regression analyses were used to obtain the odds ratios (ORs). These were adjusted for age and the following potential confounding factors: body-mass index (BMI), which was calculated as weight (kg)/height squared (m^2) and grouped into four categories (<21.0 , 21.0 – 22.9 , 23.0 – 24.9 , and ≥ 25.0); a history of hypertension (yes or no) and diabetes (yes or no); weekly alcohol intake (g/week) using four levels of consumption in men (ALC_0 = non-drinkers and infrequent or occasional drinkers; ALC_1 = 1–299 g/week; ALC_2 = ≥ 300 g/week) and in women (ALC_0, non-drinkers and infrequent or occasional drinkers; ALC_1 = 1–59 g/week; ALC_2 = ≥ 60 g/week); cigarette smoking, using three levels (non-smokers who had never smoked, current smokers, and ex-smokers); and the PHC area. The 95% confidence interval (CI) for each OR was calculated. The trend across increasing levels of energy-adjusted dietary vitamin C intake was analyzed using the extended Mantel-Haenszel method. Energy-adjusted value of dietary vitamin C intake according to a residual model was used for analyses [22]. All statistical analyses were carried out using the SAS statistical software package, version 8.2 [23].

Results

Table 1 shows the incidence of age-related cataracts in the JPHC cohort by gender. In the 5-year follow-up, there were 216 new diagnoses of cataracts amongst the men (1.32%) and 551 (2.94%) amongst the women, and there were 110 surgical removals of cataracts (0.67%) amongst the men and 187 (1.00%) amongst the women.

Table 1 Five-year incidence of diagnoses and extractions of cataracts in the JPHC study according to gender and PHC area

		Cataract cases		Total
		Diagnosis	Extraction	
Men				
	Ninohe PHC	62 (1.62)	22 (0.57)	3,830
	Yokote PHC	68 (1.36)	26 (0.52)	5,011
	Saku PHC	50 (1.09)	34 (0.74)	4,586
	Ishikawa PHC	36 (1.20)	28 (0.94)	2,988
	Total	216 (1.32)	110 (0.67)	16,415
Women				
	Ninohe PHC	192 (4.09)	64 (1.36)	4,692
	Yokote PHC	206 (3.49)	38 (0.64)	5,910
	Saku PHC	109 (2.25)	66 (1.36)	4,849
	Ishikawa PHC	44 (1.33)	19 (0.57)	3,320
	Total	551 (2.94)	187 (1.00)	18,771

Data are cataract cases/total participants with the percentages in parentheses

When the baseline characteristics of the cohort were categorized according to energy-adjusted vitamin C intake levels by quintile (Table 2), a higher intake of energy-adjusted vitamin C was found to be associated with a greater age. The percentages of male non-smokers and ex-smokers, and female non-smokers were also positively associated with a higher intake of energy-adjusted vitamin C. By contrast, the percentage of current smokers was inversely associated with a higher intake of energy-adjusted vitamin C in both sexes. Amongst the groups of men and women with the highest alcohol consumption (ALC_2), the percentages of consumers were inversely associated with the intake of energy-adjusted vitamin C in both sexes.

Table 3 shows the age-adjusted and multivariate ORs, with 95% CIs, for cataracts according to the energy-adjusted vitamin C intake, by quintile. For cases of both the diagnosis and extraction of cataracts, a higher intake of vitamin C was associated with a reduced incidence of cataracts in both sexes. Age-adjusted ORs for those in the highest quintile of energy-adjusted vitamin C intake, compared with those in the lowest quintile, were 0.69 (95% CI, 0.45–1.02) in men and 0.55 (95% CI, 0.35–0.86) in women for cataract diagnoses, and 0.75 (95% CI, 0.47–1.26) in men and 0.61 (95% CI, 0.46–0.90) in women for cataract extractions. These associations remained after adjustment for age, BMI, history of hypertension and diabetes, weekly alcohol intake, cigarette smoking, and PHC area. The multivariate ORs for those in the highest quintile of energy-adjusted vitamin C intake, compared with those in the lowest quintile, were 0.65 (95% CI, 0.42–0.97) in men and 0.59 (95% CI, 0.43–0.89) in women for cataract diagnoses, and 0.70 (95% CI, 0.44–1.20) in men and 0.64 (95% CI, 0.41–0.94) in women for cataract extractions.

Table 2 Baseline characteristics according to energy-adjusted vitamin C small intake by quintile in middle-aged Japanese men and women

	Quintiles of energy-adjusted vitamin C [†]				
	1 (Low)	2	3	4	5 (High)
Men					
No. of participants	3,312	3,202	3,320	3,289	3,292
Age, year	53.9	54.0	54.3	55.0	55.5
Mean BMI, kg/m ²	23.8	23.6	23.6	23.5	23.4
Median vitamin C intake, mg/day	52.3	83.1	112.2	147.6	211.9
Smoking status, %					
Non-smokers	34.4	35.1	34.3	36.1	40.6
Current smokers	50.7	48.8	48.1	45.8	41.0
Ex-smokers	14.9	16.1	17.6	18.1	18.4
Alcohol intake [*] , %					
ALC_0	25.4	22.3	22.4	22.4	26.7
ALC_1	39.2	43.4	43.9	45.2	44.0
ALC_2	35.4	34.3	33.7	32.4	29.3
History of hypertension, %	16.1	16.0	17.5	16.4	15.8
History of diabetes, %	4.8	5.1	5.8	5.0	5.2
Women					
No. of participants	3,788	3,724	3,705	3,750	3,804
Age, year	54.4	54.4	54.5	54.9	55.0
Mean BMI, kg/m ²	23.8	23.7	23.6	23.5	23.5
Median vitamin C intake, mg/day	75.5	112.8	147.8	188.0	258.8
Smoking status, %					
Non-smokers	92.7	94.3	95.8	95.8	96.3
Current smokers	6.2	4.8	3.6	3.7	3.2
Ex-smokers	1.1	0.9	0.6	0.5	0.5
Alcohol intake [*] , %					
ALC_0	83.0	83.1	82.0	82.9	82.5
ALC_1	8.5	10.9	11.8	11.8	12.6
ALC_2	6.8	6.0	6.2	5.3	4.9
History of hypertension, %	17.6	17.2	17.0	16.0	16.8
History of diabetes, %	3.0	2.5	2.0	2.5	2.0

[†]Energy was adjusted by residual model for intake

^{*}Alcohol intake (g/week ethanol):

ALC_0: non-drinkers and infrequent occasional drinkers for men and women,

ALC_1: 1–299 for men and 1–59 for women,

ALC_2: ≥300 for men and ≥60 for women

Discussion

In this large prospective population study, we confirmed the inverse association between dietary vitamin C intake and the risk of age-related cataracts for both men and women, which have been reported in other cohort and case-control studies investigating this relationship. Previous cohort studies, the Beaver Dam Eye Study [9, 10], the Blue Mountains Eye Study [11] and the Nurses' Health Study [12, 13], have observed a lower risk of developing cataracts in people with a higher intake of dietary vitamin C. Several case-control studies [7, 8, 14] have also reported preventive effects for dietary vitamin C intake on the occurrence of cataracts. However, our findings are not in agreement with all previous studies. No significant association between vitamin C intake from food, and the risk of cortical [8, 15] and nuclear [15] cataracts

Table 3 Age-adjusted and multivariate Odds Ratios (ORs) with 95% CIs for cataract diagnosis and extraction according to energy-adjusted vitamin C intake by quintile in middle-aged Japanese men and women

		Quintiles of energy-adjusted vitamin C [†]					P for trend
		1 (Low)	2	3	4	5 (High)	
Men							
Cataract diagnosis							
No. of cases		54	46	47	40	29	
Age-adjusted OR (95% CI)		1.00	0.93 (0.63–1.35)	0.96 (0.68–1.37)	0.87 (0.61–1.22)	0.69 (0.45–1.02)	0.109
Multivariate OR* (95% CI)		1.00	0.91 (0.64–1.30)	0.94 (0.68–1.35)	0.83 (0.58–1.18)	0.65 (0.42–0.97)	0.094
Cataract extraction							
No. of cases		27	24	23	21	15	
Age-adjusted OR (95% CI)		1.00	1.05 (0.72–1.69)	0.96 (0.65–1.49)	0.92 (0.60–1.47)	0.75 (0.47–1.26)	0.186
Multivariate OR* (95% CI)		1.00	1.00 (0.70–1.63)	0.94 (0.64–1.46)	0.88 (0.58–1.42)	0.70 (0.44–1.20)	0.177
Women							
Cataract diagnosis							
No. of cases		132	120	112	110	77	
Age-adjusted OR (95% CI)		1.00	0.94 (0.65–1.33)	0.84 (0.66–1.09)	0.82 (0.64–1.06)	0.55 (0.35–0.86)	0.028
Multivariate OR* (95% CI)		1.00	0.97 (0.67–1.38)	0.87 (0.68–1.13)	0.84 (0.67–1.11)	0.59 (0.43–0.89)	0.047
Cataract extraction							
No. of cases		47	44	34	35	27	
Age-adjusted OR (95% CI)		1.00	0.98 (0.73–1.38)	0.74 (0.50–1.09)	0.79 (0.53–1.16)	0.61 (0.46–0.90)	0.055
Multivariate OR* (95% CI)		1.00	0.97 (0.71–1.39)	0.80 (0.52–1.21)	0.80 (0.51–1.24)	0.64 (0.41–0.94)	0.042

[†]Energy was adjusted by residual model for intake

*Multivariate model adjusted for age, BMI (<21.0, 21.0–22.9, 23.0–24.9, and ≥25.0), history of hypertension and diabetes (yes or no), alcohol intake (g/week ethanol: non-drinkers and infrequent occasional drinkers for men and women, 1–299 for men and 1–59 for women, and ≥300 for men and ≥60 for women), cigarette smoking (non-smokers, current smokers, and ex-smokers), and PHC area

or cataract extraction [16], was observed in the Lens Opacities Case-Control Study [8], the Baltimore Longitudinal Study [15], and the study carried out by Tavani et al. [16].

There have been many studies investigating the relationship between the use of vitamin C supplements and the risk of developing cataracts. These studies also observed a lower prevalence of cataracts [9, 12, 13, 24–26] or cataract extractions [27] amongst users of vitamin C supplements compared with those who did not use vitamin C supplements. However, the US Physicians Health Study [28] found no benefit for vitamin C supplement use on the prevalence of cataracts or cataract extraction, and the Beaver Dam Eye Study [29] observed an increase in the prevalence of cataracts among users of vitamin C supplements compared with non-users. A few nutritional intervention trials with vitamin C have been carried out to look at cataract prevention. A clinical trial of nutritional supplements carried out by the Italian-American Cataract Study Group [30] found higher plasma levels of vitamin C to be associated with reduced prevalence of age-related cataracts. The Linxian Cataract Study [31] showed no association between the administration of vitamin C in combination with molybdenum and the prevalence of cataracts. No beneficial effect on the prevention of cataracts was also detected in the Age-Related Eye Disease Study Research Group [32]. The Antioxidants in Prevention of Cataracts Study in South India [33] demonstrated

no significant difference between placebo and active treatment groups with beta-carotene, vitamin C and E for cataract progression. However, the objective of our current study was to examine the association of vitamin C intake from food with the incidence of cataracts, and individuals who took vitamin C supplements were not included in our analysis.

The endpoints of this study, self-reported diagnosis or extraction of age-related cataract ascertained from the questionnaires, were consecutively decreasing with increasing levels of energy-adjusted vitamin C in both sexes. It is suggested that younger persons usually don't expect to have cataract, while this expectation is growing with age. After adjustment for age and multiple potential confounding factors, age-adjusted ORs as well as multivariate ORs are also inversely associated with a higher intake of vitamin C in both sexes. We were confident that ascertaining the occurrence of age-related cataracts in this study from self-reporting questionnaires was reliable, for both new diagnoses and extractions, as we had previously carried out a study to validate this method in 1998 and 1999 [21]. The positive-predictive values confirmed by medical records review were 92.5% for the diagnoses of age-related cataracts and 100% for cataract extractions. These high positive-predictive values suggested case definitions from self-reporting questionnaires were reliable for both the diagnosis and extraction of cataracts. However, there was at least one major limitation in this validation study: we

were unable to evaluate the negative-predictive value of individuals who had not reported a past history of a diagnosis or extraction of cataracts.

We have also assessed the validity of the measures of dietary vitamin C intake used in this study [20]. The levels of vitamin C intake estimated by FFQs were compared with those assessed in DRs. In total, 120 couples (that is, 120 men and 120 women) were selected for this validation study from a subgroup of the study cohort. Of these, a total of 215 subjects (102 men and 113 women), from four different PHC areas (51 from Karumai town in the Ninohe PHC area, 58 from Omonogawa town in the Yokote PHC area, 51 from Usuda and Saku town in the Saku PHC area, and 55 from Gushikawa city in the Ishikawa PHC area) volunteered to participate and were registered for the validation study. Correlation coefficients between the energy-adjusted vitamin C intakes estimated from FFQs and from DRs were 0.42 in men and 0.22 in women, indicating a moderate association between these two methods.

Our study showed that the incidence of age-related cataracts was higher in women than in men. This finding is in agreement with other epidemiological studies [1]; however, we should point out the important limitations that our study might have had. As the definition of cases of cataracts in this study relied on self-reporting questionnaires rather than the assessment of lens opacity with a slit lamp, there might have been a detection bias. Simon [34] suggested that women might be more likely to visit their doctors than men and, consequently, be more frequently diagnosed with early lens opacities. This implies that the incidence of age-related cataracts in men in this study could have been underestimated compared with that in women. In addition, as the early development of cataracts can progress without symptoms or obvious visual impairment for a long time, individuals who had early lens opacities but retained a relatively high quality of vision might have been less likely to visit their doctors or have not been

informed about a beginning cataracts even if they had visited their doctors, and would be excluded from the cases reported. These sources of detection bias might have led to an underestimation of the overall incidence of age-related cataracts. Further analyses from longer follow-up studies will be required to obtain reliable evidence of the effect of dietary vitamin C intake on the incidence of age-related cataracts.

Although we did not measure plasma ascorbate levels in our study participants, there is much interest in a possible causal relationship between ascorbate levels in lens and dietary vitamin C intake. Experimental reports have shown that dietary vitamin C intake is related to eye-tissue ascorbate levels [35] and that increasing ascorbate concentration in lens protect against cataractlike damage [36]. In addition, Jacques [7] and Knekt [37] observed that cataracts were less likely in persons with high plasma ascorbate levels than in persons with low plasma ascorbate levels. Oxidative damage to lens protein is believed to play a crucial role in the development of age-related lens opacities. Thus, the effects of dietary vitamin C intake on ascorbate levels in lens might account for a protective role for dietary vitamin C intake on cataracts.

In conclusion, the present large-cohort study showed that dietary vitamin C intake was associated with a reduced incidence of age-related cataracts in Japanese men and women; this association was found using both cataract diagnosis and extraction as endpoints. A protective role for vitamin C on aging processes in the lens, which has been suggested previously for Caucasian populations, was reported here for a Japanese cohort.

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