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Original Article

Validity of a Self-Administered Food Frequency Questionnaire for Middle-Aged Urban Cancer Screenees: Comparison With 4-Day Weighed Dietary Records

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ABSTRACT

Background: The validity of estimates of dietary intake calculated using a food frequency questionnaire (FFQ) depends on the specific population. The 138-item FFQ used in the 5-year follow-up survey for the Japan Public Health Center-based Prospective Study was initially developed for and validated in rural residents. However, the validity of estimates based on this FFQ for urban residents, whose diet and lifestyle differ from those of rural residents, has not been clarified. We examined the validity of ranking individuals according to level of dietary consumption, as estimated by this FFQ, among an urban population in Japan.

Methods: Among 896 candidates randomly selected from examinees of cancer screening provided by the National Cancer Center, Japan, 144 participated in the study. In 2007–2008, at an average 2.7 years after cancer screening, participants were asked to respond to the questionnaire and to provide 4-day weighed diet records (4d-DRs) for use as the reference intake. Spearman correlation coefficients (CCs) between the FFQ and 4d-DR estimates were calculated, after correction for intraindividual variation of 4d-DRs.

Results: The median (range) deattenuated CC for men and women was 0.57 (0.23 to 0.89) and 0.47 (0.08 to 0.94), respectively, across 45 nutrients and 0.51 (0.10 to 0.98) and 0.51 (−0.36 to 0.88) for 43 food groups.

Conclusions: Although the FFQ was developed for a rural population, it provided reasonably valid measures of consumption for many nutrients and food groups in middle-aged screenees living in urban areas in Japan.

Key words: dietary assessment; food frequency questionnaire; validity

INTRODUCTION

Accuracy in measuring individual dietary intake is an important issue in the analysis and evaluation of results from epidemiologic studies of the association between diet and disease. Food frequency questionnaires (FFQs) provide a view of usual food or nutrient intake over time and have been developed and validated in target populations of epidemiologic studies.[1] Because the foods listed in an FFQ are selected according to their percentage contribution to the total consumption of nutrients among representatives of the target population for whom the FFQ is to be used, they might not necessarily reflect the foods eaten by a different population. Further, accuracy in remembering foods consumed appears to differ by education level and the degree of interest in diet.[1] The validity of FFQ estimates of dietary intake therefore appears to depend on the specific population.

The FFQ used for the Japan Public Health Center-based Prospective Study 5-year follow-up survey was developed for use with residents of rural cohort areas.[2] Of these resident, 27% worked in management, clerical, sales, or services, and 21% were employed in the agriculture, forestry, and fisheries sector.[3] Further, the FFQ was validated among subsamples of these rural residents.[4–6] It is therefore unclear whether this FFQ is accurate in estimating dietary intake among Japanese with an urbanized lifestyle. In addition, to our knowledge no such validation study has been restricted to an examination of subjects living in urban and adjacent areas.[7]

To confirm the suitability of this FFQ for use in epidemiologic studies of cancer screenees at the National Cancer

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Center, such as the participants in the Colorectal Adenoma Study in Tokyo, we evaluated the validity and reproducibility of ranking individuals by levels of dietary consumption—as estimated by this FFQ after minor modification—as a means of assessing dietary intake among middle-aged urban cancer screenees.[8]

METHODS

Study setting and participants

The study participants were selected from adults who underwent cancer screening at the Research Center for Cancer Prevention and Screening, National Cancer Center, "Japan from January 2004 through July 2006. Eligibility criteria were age between 40 and 69 years, residence in metropolitan Tokyo, and no previous or present diagnosis of cancer, cardiovascular disease, or diabetes mellitus. Eligible subjects were stratified by sex and age (40–49, 50–59, and 60–69 years) and randomly numbered for recruiting priority.

Among the 896 invited candidates, 187 (response rate: 20.9%) agreed to participate in the study. After excluding those who could not attend the study orientation, 144 participated in the study. As an incentive to participate, participants received a report of their results regarding the consumption of energy and nutrients based on 4-day dietary records, a small gift (an instrument for measuring the salt concentration of soup), and a free invitation to attend a class on healthful cooking. The study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan. All participants provided their written informed consent for participation, at the study orientation.

Data collection

The reference intake was 4-day weighed diet records (4d-DRs), which were obtained over 4 consecutive days during the period from May 2007 through April 2008. Before the start of data collection, all participants were invited to attend the study orientation, where the 4d-DR procedure was explained by trained dietitians. The self-administered FFQ was first administered during 2004–2006 at the time of cancer screening (FFQ0) and then during 2007–2008 at the orientation session (FFQ1).

Dietary assessment

The 4d-DR included 3 weekdays and 1 weekend day and was used as the reference method. Food portions were measured by each participant during meal preparation using supplied digital scales and measuring spoons and cups. For foods purchased or consumed outside the home, the participants were instructed to record the approximate quantity of all foods in the meal and/or the names of the product and company. Daily weighed records were faxed to the study office at the Research Center for Cancer Prevention and Screening, National Cancer Center on the morning after completion of that day's record. Trained dietitians checked the record with the examinee by telephone and coded the foods and weights. Stores and restaurants were asked about the recipes of certain meals eaten outside the home.

The FFQ consisted of 138 food and beverage items and 9 frequency categories, which ranged from almost never to 7 or more times per day (or to 9 glasses per day, for beverages), and asked about the usual consumption of listed foods during the previous year. The food list, which was initially developed for the Japan Public Health Center-based Prospective Study,[2] was modified for a middle-aged urban population as follows: 11 foods mainly consumed in specific areas (Okinawa and Nagano) or at specific times were excluded (luncheon meats, vivipara, *qing-geng-cai* [bok choy], leaf mustard, bitter gourd, chard, loofah, mugwort, *yushi-tofu* [soft, boiled tofu], calcium beverages, and beta carotene beverages), and 11 foods consumed throughout the year in urban areas were added (beef, stir-fried; chicken, stir-fried; chicken, stew; low-fat milk; Japanese amberjack; Welsh onion; eggplant; edible burdock; *konnyaku* foods [devil's tongue]; and jam, strawberry or marmalade). Portion size was specified for each food item, using 3 standard sizes: medium (the standard amount), small (50% smaller), and large (50% larger).

Intakes of energy, 45 nutrients, and 43 food groups were calculated using the Standardized Tables of Food Composition, Fifth revised edition[9,10] and a specially developed food composition table for isoflavones and lycopene in Japanese foods.[11,12] We collapsed the individual food items into 18 predefined food groups according, to the Food Composition Tables, and 25 stream-specific subgroups. The grouping scheme for subgroups, eg, cruciferous vegetables and red meat, was based on the similarity of nutrient profiles or culinary usage among the foods and was somewhat similar to that used in other studies.

Statistical analysis

The mean intake of each nutrient and food group estimated using the FFQ1 was compared to that estimated using the 4d-DR among the 143 participants who completed both. Percentage differences were calculated for each nutrient and food group by dividing the difference in intake on the FFQ1 from that on the 4d-DR by those using the 4d-DR. To determine the validity of the FFQ, Spearman rank correlation coefficients (CCs) between intake estimates of the FFQ1 and 4d-DR were calculated for crude and energy-adjusted values. Regression coefficients between nutrient intakes according to the FFQ1 and 4d-DR were calculated for energy-adjusted values to examine the degree of attenuation in a diet–disease association in a hypothetical study using the FFQ.[1] A residual model was used for energy adjustment.[1] We corrected the observed CCs for the attenuating effect of random intraindividual error from the usual intake of each energy and nutrient and each food group. The deattenuated value was corrected using the ratios of the within- to between-individual

variances based on the 4-day DRs according to the following formula:

$$\text{deattenuated } CC_x = \text{en-}CC_x * \text{SQRT}(1 + \lambda_x/n),$$

where the observed en-CC_x is the correlation in energy-adjusted value for nutrient x, λ_x is the ratio of within- to between-individual variance, and n is the number of dietary records (4 days).[1] To measure the validity of categorization, we computed the number of participants classified into the same, adjacent, and extreme categories by joint classification according to both quintiles using the FFQ1 and the 4d-DR. For reproducibility, CCs between the FFQ1 and FFQ0 were calculated for crude and energy-adjusted values for the 144 participants who completed both FFQs. We confirmed the cumulative percentage among the top 20 foods for energy, because food variety was important in confirming the extent to which the list of FFQ items could be covered. Percentages of the sum of energy by individual foods eaten to total energy during the 4 days were also calculated. All analyses were performed using SAS Version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Participants in the validation study

Age distribution (40s, 50s, 60s) at recruitment (2004–2006) was $n = 11$, 29, and 29, respectively, for men and $n = 16$, 30, and 29 for women. Mean body mass index (standard deviation) for men and women was 23.5 (2.5) and 21.5 (2.5), respectively. Overall, 51% of the participants were employed in management, clerical, sales, or services, and 2% worked in agriculture, forestry, or fisheries.

Mean intakes and FFQ validity

Table 1 shows daily intakes of energy and 45 nutrients, as assessed by 4d-DR and FFQ1, percentage differences between FFQ1 and the 4d-DR, and their correlations among men and women. Although estimated intake levels for energy were very similar between the 2 methods (difference: −6% for men, 2% for women), the percentage difference in nutrient intake between the 4d-DR and FFQ1 varied from −35% and −20% for beta-carotene to +99% and +198% for cryptoxanthin in men and women, respectively. The CCs of the crude values varied from 0.12 for retinol equivalents to 0.71 for daidzein in men and from 0.10 for polyunsaturated fatty acid to 0.57 for vitamin K in women. The median across the 45 nutrients was 0.43 for both men and women. After energy adjustment and deattenuation, the median CC improved to 0.57 in men and 0.47 in women. The regression coefficient for nutrient intake varied from 0.16 for retinol equivalents to 0.61 for copper in men and from 0.05 for cryptoxanthin to 0.63 for pantothenic acid in women (data not shown).

Table 2 shows daily intakes of 43 food groups assessed by the 4d-DR and FFQ1, the percentage difference between

Table 1. Energy and nutrient intakes according to food frequency questionnaire 1 (FFQ1), percentage difference between FFQ1 and 4-day diet record (DR), and their correlations in men and women

	Men ($n = 69$)						Women ($n = 74$)					
	4-day DR	FFQ1[a]	%[b]	Correlation coefficient[c]			4-day DR	FFQ1[a]	%[b]	Correlation coefficient[c]		
	Mean ± SD	Mean ± SD		Crude	Energy-adjusted	Deattenuated[d]	Mean ± SD	Mean ± SD		Crude	Energy-adjusted	Deattenuated[d]
Energy (kcal)	2271 ± 426	2141 ± 737	−6	0.48	—	0.53	1842 ± 298	1875 ± 733	2	0.29	—	0.34
Protein (g)	89.2 ± 15.6	76.2 ± 32.3	−15	0.31	0.55	0.67	75.0 ± 13.6	70.5 ± 32	−6	0.56	0.39	0.47
Total fat (g)	64.6 ± 14.3	64.6 ± 33.2	0	0.27	0.30	0.42	57.8 ± 16.3	63.0 ± 32.9	9	0.22	0.28	0.35
SFA (g)	18.12 ± 4.85	20.21 ± 11.23	12	0.27	0.29	0.44	16.82 ± 5.84	20.04 ± 12.21	19	0.37	0.34	0.41
MUFA (g)	22.63 ± 6.56	22.79 ± 13.15	1	0.31	0.28	0.38	20.34 ± 7.06	22.59 ± 12.41	11	0.26	0.39	0.49
PUFA (g)	14.62 ± 3.21	13.38 ± 6.73	−8	0.53	0.53	0.72	12.33 ± 2.99	12.4 ± 6.01	1	0.10	0.24	0.38
n-3 PUFA (g)	3.10 ± 1.05	2.58 ± 1.59	−17	0.26	0.34	0.56	2.48 ± 0.91	2.35 ± 1.28	−5	0.34	0.28	0.68
n-6 PUFA (g)	11.45 ± 2.74	10.73 ± 5.43	−6	0.58	0.53	0.76	9.79 ± 2.51	9.97 ± 4.81	2	0.11	0.31	0.47
Cholesterol (mg)	367 ± 132	303 ± 278	−18	0.31	0.39	0.51	333 ± 117	271 ± 168	−19	0.35	0.28	0.38
Carbohydrate (g)	301 ± 72.9	270.8 ± 99.2	−10	0.58	0.52	0.56	245.2 ± 46.9	245.7 ± 84.4	0	0.25	0.39	0.43
Total dietary fiber (g)	20.3 ± 6.3	14.1 ± 6.6	−31	0.55	0.61	0.67	18.0 ± 4.6	15.3 ± 7.4	−15	0.44	0.46	0.53
Water soluble (g)	4.7 ± 1.7	3.6 ± 1.9	−23	0.53	0.59	0.65	4.1 ± 1.2	3.8 ± 1.9	−9	0.44	0.48	0.56
Water insoluble (g)	14.3 ± 4.6	9.9 ± 4.6	−31	0.55	0.64	0.71	13.0 ± 3.4	10.9 ± 5.3	−16	0.43	0.38	0.44

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	Men (n = 69)						Women (n = 74)					
	4-day DR	FFQ1[a]	%[b]	Correlation coefficient[c]			4-day DR	FFQ1[a]	%[b]	Correlation coefficient[c]		
	Mean ± SD	Mean ± SD		Crude	Energy-adjusted	Deattenuated[d]	Mean ± SD	Mean ± SD		Crude	Energy-adjusted	Deattenuated[d]
Sodium (mg)	4728 ± 1745	4269 ± 2312	−10	0.44	0.42	0.45	3943 ± 944	3920 ± 1953	−1	0.33	0.39	0.47
Salt equivalent (g)	11.9 ± 4.4	10.8 ± 5.9	−9	0.44	0.39	0.42	9.9 ± 2.4	9.9 ± 4.9	0	0.33	0.38	0.46
Potassium (mg)	3695 ± 983	3072 ± 1208	−17	0.37	0.60	0.65	3204 ± 708	2992 ± 1318	−7	0.48	0.62	0.70
Calcium (mg)	707 ± 234	665 ± 423	−6	0.48	0.58	0.64	637 ± 204	657 ± 469	3	0.55	0.55	0.61
Magnesium (mg)	393 ± 112	317 ± 117	−19	0.43	0.53	0.58	323 ± 64	293 ± 125	−9	0.43	0.45	0.54
Phosphorus (mg)	1395 ± 296	1221 ± 512	−12	0.38	0.57	0.65	1183 ± 227	1144 ± 569	−3	0.55	0.40	0.47
Iron (mg)	11.2 ± 3.2	9.6 ± 3.8	−15	0.45	0.62	0.68	9.3 ± 2	8.8 ± 3.5	−6	0.46	0.44	0.55
Zinc (mg)	10.0 ± 2.2	8.8 ± 3.5	−12	0.40	0.53	0.65	8.7 ± 1.8	7.8 ± 3.2	−10	0.49	0.26	0.34
Copper (mg)	1.59 ± 0.41	1.35 ± 0.54	−15	0.59	0.67	0.74	1.31 ± 0.26	1.23 ± 0.47	−6	0.35	0.40	0.49
Manganese (mg)	5.03 ± 2.7	4.22 ± 1.75	−16	0.54	0.41	0.44	3.93 ± 1.31	4.35 ± 2.13	11	0.41	0.37	0.41
Retinol (μg)	318 ± 379	364 ± 308	14	0.21	0.32	0.56	348 ± 528	361 ± 274	4	0.13	0.11	0.16
Retinol Eq (μg)	749 ± 433	678 ± 383	−10	0.12	0.15	0.23	782 ± 560	754 ± 412	−4	0.35	0.24	0.33
α-carotene (μg)	542 ± 381	474 ± 387	−13	0.38	0.37	0.50	667 ± 534	632 ± 736	−5	0.51	0.53	0.78
β-carotene (μg)	4580 ± 2697	2960 ± 1854	−35	0.34	0.36	0.49	4588 ± 2281	3658 ± 2751	−20	0.54	0.53	0.70
Cryptoxanthin (μg)	539 ± 1148	1071 ± 1262	99	0.50	0.52	0.55	482 ± 668	1439 ± 1656	198	0.15	0.07	0.08
Lycopene (mg)	6583 ± 7892	4888 ± 7441	−26	0.48	0.45	0.52	4456 ± 5151	4319 ± 5617	−3	0.23	0.33	0.40
β-carotene Eq (μg)	5152 ± 2860	3731 ± 2289	−28	0.40	0.39	0.52	5194 ± 2625	4693 ± 3391	−10	0.54	0.49	0.62
Vitamin D (μg)	11.3 ± 6.5	7.9 ± 5.8	−30	0.47	0.52	0.88	9.9 ± 6.1	8.1 ± 6.2	−18	0.34	0.22	0.37
α-tocopherol (mg)	9.8 ± 3.0	8.1 ± 4.2	−17	0.26	0.41	0.48	8.6 ± 2.5	8.1 ± 4.3	−6	0.27	0.42	0.51
β-tocopherol (mg)	0.4 ± 0.1	0.4 ± 0.2	0	0.34	0.30	0.48	0.3 ± 0.1	0.4 ± 0.2	17	0.14	0.21	0.33
γ-tocopherol (mg)	13 ± 4	12 ± 6.8	−8	0.53	0.47	0.69	11.1 ± 3.5	10.9 ± 5.3	−1	0.10	0.22	0.33
δ-tocopherol (mg)	3.4 ± 1.4	3 ± 2.1	−10	0.69	0.68	0.89	2.7 ± 0.9	2.6 ± 1.2	−4	0.18	0.25	0.51
Vitamin K (μg)	345 ± 194	303 ± 306	−12	0.64	0.67	0.79	290 ± 108	270 ± 133	−7	0.57	0.61	0.94
Vitamin B_1 (mg)	1.21 ± 0.38	1.01 ± 0.43	−17	0.23	0.47	0.54	1.05 ± 0.28	0.99 ± 0.45	−5	0.44	0.35	0.42
Vitamin B_2 (mg)	1.71 ± 0.55	1.66 ± 0.79	−3	0.27	0.38	0.42	1.47 ± 0.37	1.58 ± 0.8	8	0.47	0.46	0.53
Niacin (mg)	24.2 ± 7.3	20.3 ± 8.6	−16	0.38	0.36	0.44	19.8 ± 5.2	19.0 ± 8.4	−4	0.44	0.26	0.32
Vitamin B_6 (mg)	1.91 ± 0.55	1.57 ± 0.6	−18	0.38	0.39	0.44	1.53 ± 0.4	1.45 ± 0.63	−5	0.46	0.49	0.57
Vitamin B_{12} (μg)	10.8 ± 5.6	7.9 ± 5.1	−27	0.13	0.30	0.57	8.6 ± 4.6	7.2 ± 5.1	−16	0.46	0.36	0.67
Folate (μg)	512 ± 188	418 ± 176	−18	0.48	0.60	0.66	449 ± 124	433 ± 194	−3	0.48	0.35	0.41
Pantothenic acid (mg)	8.02 ± 1.9	7.66 ± 3.5	−4	0.41	0.58	0.67	6.83 ± 1.5	7.09 ± 3.15	4	0.53	0.57	0.66
Vitamin C (mg)	178 ± 82	136 ± 83	−24	0.62	0.67	0.73	156 ± 62	163 ± 96	4	0.45	0.45	0.51
Daidzein (mg)	17.14 ± 9.78	20.39 ± 20.45	19	0.71	0.66	0.84	12.81 ± 7.28	14.98 ± 8.08	17	0.49	0.49	0.79
Genistein (mg)	28.6 ± 16.27	34.13 ± 35.71	19	0.69	0.64	0.81	21.87 ± 12.3	24.84 ± 13.7	14	0.46	0.47	0.75
MEDIAN				**0.43**	**0.52**	**0.57**				**0.43**	**0.39**	**0.47**

Abbreviations: SD, standard deviation; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; Eq, equivalent.

[a]Intakes based on second FFQ, conducted in 2007–2008. [b]Percentage differences: (FFQ1 − DR)/DR * 100 (%). [c]Spearman's rank correlation coefficients based on crude and energy-adjusted values. For men, $r \geq 0.24 = P < 0.05$, $r \geq 0.31 = P < 0.01$, $r \geq 0.39 = P < 0.001$. For women, $r \geq 0.23 = P < 0.05$, $r \geq 0.30 = P < 0.01$, $r \geq 0.38 = P \leq 0.001$. [d]Deattenuated CC_x = observed CC_x * SQRT(1 + λ_x/n), where λ_x is the ratio of within- to between-individual variance for nutrient x, and n is number of dietary records; observed CCs were based on energy-adjusted values other than energy intake.

Table 2. Food-group intakes according to food frequency questionnaire 1 (FFQ1), percentage difference between FFQ1 and 4-day diet record (DR), and their correlations in men and women

	Men (n = 69)						Women (n = 74)					
	4-day DR	FFQ1[a]		Correlation coefficient[c]			4-day DR	FFQ1[a]		Correlation coefficient[c]		
	Mean ± SD (g)	Mean ± SD (g)	%[b]	Crude	Energy-adjusted	Deatte-nuated[d]	Mean ± SD (g)	Mean ± SD (g)	%[b]	Crude	Energy-adjusted	Deatte-nuated[d]
Cereals	447 ± 173	510 ± 215	14	0.67	0.45	0.51	332 ± 78	425 ± 153	28	0.29	0.33	0.41
Rice	306 ± 169	351 ± 173	15	0.72	0.42	0.51	210 ± 85	259 ± 110	24	0.49	0.43	0.59
Bread	47 ± 38	40 ± 57	−13	0.66	0.67	0.80	42 ± 27	53 ± 77	26	0.60	0.68	0.87
Noodles	85 ± 71	97 ± 88	15	0.53	0.52	0.98	72 ± 49	95 ± 72	33	0.39	0.42	—
Other cereals	10 ± 11	21 ± 34	111	0.15	0.15	0.19	8 ± 11	17 ± 24	103	0.26	0.26	0.33
Potatoes and starches	46 ± 33	27 ± 21	−41	0.29	0.32	0.49	44 ± 32	38 ± 29	−13	0.09	0.25	0.39
Sugar	9 ± 8	2 ± 4	−80	0.36	0.25	0.30	8 ± 8	1 ± 4	−82	0.07	0.06	0.07
Pulses	102 ± 106	97 ± 144	−6	0.59	0.53	0.66	72 ± 44	67 ± 44	−6	0.27	0.30	0.45
Nuts and seeds	7 ± 11	3 ± 4	−61	0.31	0.30	0.40	5 ± 7	3 ± 9	−33	0.01	−0.06	−0.09
Vegetables	403 ± 180	218 ± 145	−46	0.48	0.48	0.55	354 ± 125	245 ± 175	−31	0.39	0.45	0.52
Green and yellow vegetables	194 ± 134	110 ± 90	−43	0.43	0.47	0.59	170 ± 86	114 ± 87	−33	0.38	0.41	0.57
White vegetables	209 ± 102	108 ± 96	−48	0.53	0.50	0.68	184 ± 75	131 ± 128	−29	0.39	0.41	0.57
Pickled vegetables	21 ± 51	15 ± 21	−32	0.43	0.37	0.42	18 ± 21	21 ± 50	21	0.32	0.34	0.45
Cruciferous vegetables	91 ± 59	54 ± 68	−41	0.63	0.64	0.82	87 ± 64	55 ± 41	−37	0.46	0.45	0.54
Green, leafy vegetable	43 ± 43	20 ± 20	−54	0.33	0.28	0.37	38 ± 23	21 ± 14	−43	0.26	0.29	0.41
Yellow vegetables	128 ± 113	78 ± 83	−39	0.49	0.52	0.63	105 ± 73	79 ± 76	−25	0.36	0.42	0.51
Other vegetables	121 ± 73	54 ± 38	−56	0.31	0.36	0.51	109 ± 55	71 ± 73	−35	0.34	0.37	0.56
Fruits	193 ± 160	209 ± 184	8	0.60	0.64	0.69	184 ± 113	255 ± 196	38	0.40	0.55	0.63
Citrus fruit	49 ± 75	81 ± 88	67	0.46	0.46	0.51	43 ± 49	109 ± 139	153	0.23	0.18	0.20
Other fruit	143 ± 126	126 ± 108	−12	0.54	0.57	0.75	140 ± 104	144 ± 103	3	0.31	0.49	0.85
Fungi	18 ± 17	11 ± 11	−36	0.48	0.48	0.57	23 ± 22	14 ± 12	−38	0.42	0.38	0.46
Algae	15 ± 22	8 ± 7	−43	0.18	0.17	0.22	10 ± 10	9 ± 8	−9	0.35	0.32	0.47
Fish and shellfish	115 ± 53	78 ± 66	−32	0.40	0.47	0.69	89 ± 40	73 ± 60	−18	0.44	0.35	0.57
Meats	72 ± 43	62 ± 57	−15	0.43	0.48	0.70	65 ± 38	55 ± 35	−17	0.35	0.26	0.36
Processed meat	13 ± 16	6 ± 8	−52	0.46	0.45	0.63	13 ± 15	7 ± 7	−48	0.30	0.33	0.47
Red meat	40 ± 30	42 ± 43	5	0.36	0.41	0.74	36 ± 29	32 ± 23	−11	0.45	0.36	0.53
Poultry	19 ± 26	13 ± 18	−30	0.25	0.25	0.38	16 ± 19	15 ± 13	−5	0.27	0.22	0.36
Eggs	36 ± 23	32 ± 55	−11	0.50	0.46	0.67	33 ± 19	25 ± 30	−24	0.35	0.35	0.53
Milk and dairy products	176 ± 147	275 ± 305	56	0.62	0.58	0.66	174 ± 110	257 ± 337	48	0.70	0.62	0.76
High-fat milk	87 ± 96	99 ± 157	13	0.47	0.44	0.50	95 ± 91	120 ± 201	26	0.64	0.59	0.69
Low-fat milk	89 ± 137	177 ± 286	98	0.62	0.56	0.60	79 ± 83	137 ± 207	74	0.68	0.61	0.70
Fats and oils	11 ± 6	12 ± 8	12	0.40	0.35	0.45	10 ± 6	12 ± 8	24	0.38	0.52	0.73
Butter	2 ± 2	1 ± 2	−49	0.32	0.34	0.50	2 ± 2	1 ± 4	−12	0.35	0.35	0.56
Margarine and oils	9 ± 5	11 ± 8	25	0.31	0.26	0.35	9 ± 6	11 ± 6	31	0.29	0.42	0.57
Confectionaries	29 ± 28	23 ± 32	−19	0.28	0.37	0.45	37 ± 30	37 ± 46	1	0.34	0.32	0.43
Japanese confectionery	11 ± 15	8 ± 15	−29	0.21	0.24	0.33	15 ± 23	15 ± 20	−1	0.09	0.04	0.05
Western confectionery	18 ± 24	15 ± 21	−13	0.34	0.41	0.50	21 ± 21	22 ± 32	2	0.26	0.24	0.32

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	Men (n = 69)					Women (n = 74)				
	4-day DR	FFQ1[a]		Correlation coefficient[c]		4-day DR	FFQ1[a]		Correlation coefficient[c]	
	Mean ± SD (g)	Mean ± SD (g)	%[b]	Crude	Energy-adjusted	Mean ± SD (g)	Mean ± SD (g)	%[b]	Crude	Energy-adjusted
Alcoholic beverages	219 ± 276	263 ± 281	20	0.80	0.80	76 ± 151	90 ± 187	19	0.65	0.57
Nonalcoholic beverages	749 ± 772	863 ± 699	15	0.45	0.37	617 ± 434	888 ± 621	44	0.33	0.33
Green tea	386 ± 738	519 ± 427	35	0.68	0.67	246 ± 220	603 ± 560	145	0.46	0.42
Coffee	176 ± 204	199 ± 281	13	0.81	0.80	167 ± 175	157 ± 155	−6	0.82	0.82
Other beverage	210 ± 260	144 ± 358	−31	0.43	0.45	268 ± 359	128 ± 190	−52	0.31	0.32
Seasonings and spices	138 ± 100	23 ± 15	−83	0.04	0.08	142 ± 111	20 ± 14	−86	−0.28	−0.31
MEDIAN				**0.45**	**0.45**				**0.35**	**0.35**

	Men (n = 69)					Women (n = 74)				
	4-day DR	FFQ1[a]		Correlation coefficient[c]		4-day DR	FFQ1[a]		Correlation coefficient[c]	
	Mean ± SD (g)	Mean ± SD (g)	%[b]	Crude	Deattenuated[d]	Mean ± SD (g)	Mean ± SD (g)	%[b]	Crude	Deattenuated[d]
Alcoholic beverages	219 ± 276	263 ± 281	20	0.80	0.88	76 ± 151	90 ± 187	19	0.65	0.60
Nonalcoholic beverages	749 ± 772	863 ± 699	15	0.45	0.40	617 ± 434	888 ± 621	44	0.33	0.35
Green tea	386 ± 738	519 ± 427	35	0.68	0.72	246 ± 220	603 ± 560	145	0.46	0.45
Coffee	176 ± 204	199 ± 281	13	0.81	0.84	167 ± 175	157 ± 155	−6	0.82	0.88
Other beverage	210 ± 260	144 ± 358	−31	0.43	0.49	268 ± 359	128 ± 190	−52	0.31	0.35
Seasonings and spices	138 ± 100	23 ± 15	−83	0.04	0.10	142 ± 111	20 ± 14	−86	−0.28	−0.36
MEDIAN				**0.45**	**0.51**				**0.35**	**0.51**

Abbreviation: SD, standard deviation.
[a]Intakes based on second FFQ, conducted in 2007–2008. [b]Percentage differences: (FFQ1 − DR)/DR * 100 (%). [c]Spearman's rank correlation coefficients based on crude and energy-adjusted values. For men, $r \geq 0.24 = P < 0.05$, $r \geq 0.31 = P < 0.01$, $r \geq 0.39 = P < 0.001$. For women, $r \geq 0.23 = P < 0.05$, $r \geq 0.30 = P < 0.01$, $r \geq 0.38 = P \leq 0.001$. [d]Deattenuated CC_x = observed CC_x * SQRT(1 + λ_x/n), where λ_x is the ratio of within- to between-individual variance for nutrient x, and n is number of dietary records; observed CCs were based on energy-adjusted values other than energy intake.
—: not applicable for calculation.

FFQ1 and 4d-DR, and their correlations among men and women. The percent difference in intakes between the 4d-DR and FFQ1 varied from −83% and −86% for seasonings and spices in men and women, respectively, to +111% for other cereals in men and +153% for citrus fruit in women. The CCs of the crude values varied from 0.04 and −0.28 for seasonings to 0.81 and 0.82 for coffee in men and women, respectively. The medians across 43 food groups for men and women were 0.45 and 0.35, respectively. After energy adjustment and deattenuation, the median CC slightly improved to 0.51 (varying from 0.10 for seasonings to 0.98 for noodles) in men and 0.51 (varying from −0.36 for seasonings to 0.88 for coffee) in women.

Joint classification by quintile

We conducted further analysis to compare FFQ1 with the 4d-DR based on joint classification by quintile. Most nutrients and food groups were classified into the opposite extreme categories by 5% or less of men or women, with a corresponding median value for men and women of 1% and 3%, respectively, for nutrients, and of 3% and 3%, respectively, for food groups (Supplemental Tables 1 and 2). In contrast, retinol for men and women showed a relatively high percentage of extreme categories by joint classification (6% and 12%, respectively) and a relatively low CC (0.32 and 0.11, respectively) and regression coefficient (0.18 and 0.15, respectively). Further, cryptoxanthin for women showed a relatively low percentage of the same and adjacent categories (53%) and a relatively low CC (0.07) and regression coefficient (0.05).

Reproducibility

We also examined the reproducibility of dietary intake estimated by 2 identical FFQs (FFQ0 and FFQ1) administered at an average interval of 2.7 years (range 1.3–4.0 years). CCs for nutrient intakes in the crude values varied from 0.54 for retinol to 0.80 for phosphorus (median $r = 0.70$) in men and from 0.48 for cholesterol and 0.72 for vitamin C (median $r = 0.61$) in women. With regard to the food groups, CC in the crude values varied from 0.35 for other cereals to 0.75 for coffee (median $r = 0.64$) in men and from 0.48 for red meat and 0.80 for coffee (median $r = 0.63$) in women (Supplemental Tables 3 and 4).

Percentage contributions of the top 20 foods to total energy

Finally, we conducted an additional analysis of the cumulative percentage contributions of the top 20 foods for energy, based on the 4d-DRs, to assess the foods listed in the FFQ. The cumulative percentage of the top 20 foods for energy was 44.0% and 41.0% for men and women, respectively (Supplemental Table 5).

Supplementary Table 1. Comparison of food frequency questionnaire 1 (FFQ1) with 4-day diet record for energy-adjusted nutrients, based on joint classification by quintile (%)

	Men (n = 69)			Women (n = 74)		
	Same category	Same and adjacent category	Extreme category	Same category	Same and adjacent category	Extreme category
Energy	35	71	1[a]	28	64	5[a]
Protein	35	77	1	23	60	1
Total fat	28	61	1	31	70	4
SFA	35	65	6	26	65	5
MUFA	22	59	4	31	68	0
PUFA	30	67	0	28	62	4
n-3 PUFA	26	59	3	27	58	3
n-6 PUFA	38	73	0	26	66	5
Cholesterol	25	67	1	28	62	4
Carbohydrate	44	70	1	30	73	4
Total dietary fiber	39	78	1	26	69	1
Water soluble	35	80	1	31	70	1
Water insoluble	33	84	0	24	64	1
Sodium	36	68	3	32	57	1
Salt equivalent	36	68	3	27	61	1
Potassium	38	75	0	39	78	1
Calcium	28	73	0	30	68	0
Magnesium	39	73	0	37	65	1
Phosphorus	35	77	0	35	70	1
Iron	36	80	1	31	72	3
Zinc	38	74	1	23	61	3
Copper	36	80	0	24	65	1
Manganese	28	67	3	31	69	4
Retinol	33	62	6	23	62	12
Retinol Eq	28	62	9	26	62	4
α-carotene	38	68	3	37	70	0
β-carotene	33	65	6	35	70	0
Cryptoxanthin	33	78	3	18	53	4
Lycopene	38	75	4	31	70	5
β-carotene Eq	33	67	4	28	72	1
Vitamin D	36	75	1	22	58	3
α-tocopherol	29	61	1	22	69	3
β-tocopherol	20	67	4	19	57	4
γ-tocopherol	28	68	3	20	68	8
δ-tocopherol	42	80	0	18	68	4
Vitamin K	32	83	0	27	73	0
Vitamin B_1	29	74	1	32	64	3
Vitamin B_2	30	65	4	26	70	0
Niacin	30	65	3	27	64	5
Vitamin B_6	33	67	1	41	69	0
Vitamin B_{12}	22	65	4	30	65	3
Folate	32	70	0	26	66	4
Pantothenic acid	45	78	1	42	73	0
Vitamin C	39	87	0	26	68	0
Daidzein	30	81	0	27	76	1
Genistein	32	80	0	31	70	1
MEDIAN	**33**	**70**	**1**	**28**	**68**	**3**

Abbreviations: SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; Eq, equivalent.
[a]Joint classification for energy intake was calculated by using crude values.

DISCUSSION

We examined the validity of ranking middle-aged urban-dwelling cancer screenees in Japan by level of dietary intake using an FFQ, with 4-day DR data as the reference method. The FFQ was initially developed and validated in rural populations. As compared with reference intakes, differences in mean absolute consumption based on the FFQ varied and tended to be underestimated. However, using the FFQ, dietary assessment of many nutrients and food groups showed

Supplementary Table 2. Comparison of food frequency questionnaire 1 (FFQ1) with 4-day diet record for energy-adjusted food groups based on joint classification by quintile (%)

	Men (n = 69)			Women (n = 74)		
	Same category	Same and adjacent category	Extreme category	Same category	Same and adjacent category	Extreme category
Cereals	26	70	0	32	68	4
Rice	30	71	3	42	72	3
Bread	30	80	0	41	76	0
Noodles	29	68	0	37	72	5
Other cereals	19	52	4	24	55	5
Potatoes and starches	30	67	1	20	64	3
Sugar	26	57	3	16	55	7
Pulses	38	74	3	30	62	3
Nuts and seeds	26	58	0	15	54	10
Vegetables	26	70	1	27	73	3
Green and yellow vegetables	45	68	4	27	70	0
White vegetables	25	77	1	27	68	1
Pickled vegetables	30	68	4	30	68	5
Cruciferous vegetables	42	80	1	31	64	1
Green, leafy vegetable	28	67	6	27	61	1
Yellow vegetables	30	77	3	27	73	1
Other vegetables	19	64	1	28	65	4
Fruits	49	81	1	38	73	0
Citrus fruit	36	77	3	23	60	5
Other fruit	36	77	1	30	69	1
Fungi	33	71	3	24	62	3
Algae	33	58	6	22	64	3
Fish and shellfish	28	71	1	23	61	3
Meats	38	78	6	28	66	7
Processed meat	28	67	1	32	72	3
Red meat	29	71	6	32	62	1
Poultry	25	61	3	28	54	5
Eggs	36	74	1	26	61	3
Milk and dairy products	41	78	3	35	78	0
High-fat milk	41	67	4	42	87	3
Low-fat milk	36	78	3	42	82	3
Fats and oils	30	61	4	39	72	0
Butter	32	64	6	34	70	5
Margarine and oils	29	61	4	34	66	1
Confectionaries	20	67	1	28	62	3
Japanese confectionery	22	64	4	14	55	5
Western confectionery	32	65	0	24	60	5
Alcoholic beverages	46	91	0	42	72	0
Nonalcoholic beverages	26	64	1	22	65	3
Green tea	48	80	0	27	65	0
Coffee	45	93	0	50	91	0
Other beverage	29	68	0	26	65	4
Seasonings and spices	16	49	4	16	42	12
MEDIAN	**30**	**68**	**3**	**28**	**65**	**3**

moderate validity and reproducibility in ranking urban residents, whose diet and lifestyle might differ from those of rural residents.

In comparison with 4d-DRs corrected for intraindividual variance, for most nutrients, the validity of the FFQ was similar to or better than that observed in a comparison with 28-day weighed diet records among the rural residents for which the FFQ was developed.[6] In that initial validation study, median CCs for energy and 45 nutrients were 0.43 and 0.39 for men and women, respectively, and 0.38 and 0.32 for 19 main food groups. Evaluation of diet might be complicated by the apparently wider variety of foods eaten by urban as compared with rural residents in Japan (percent energy from cereal areas among the former was less than that among the latter[13]), as has been seen in China[14] and Morocco,[15] although we saw no large difference in the validity of intakes, as estimated by the FFQ, between urban and rural populations in the present study.

Supplementary Table 3. Spearman rank correlation coefficients between 2 food frequency questionnaires, administered at an average interval 2.7 years, for estimated nutrient intakes

	Men (n = 69)		Women (n = 75)	
	Crude	Energy-adjusted	Crude	Energy-adjusted
Energy	0.72	—	0.59	—
Protein	0.76	0.65	0.59	0.55
Total fat	0.73	0.51	0.62	0.40
SFA	0.75	0.54	0.66	0.55
MUFA	0.71	0.47	0.62	0.41
PUFA	0.68	0.62	0.54	0.44
n-3 PUFA	0.64	0.52	0.63	0.59
n-6 PUFA	0.68	0.59	0.52	0.42
Cholesterol	0.76	0.50	0.48	0.46
Carbohydrate	0.65	0.77	0.57	0.43
Total dietary fiber	0.70	0.74	0.62	0.66
Water soluble	0.65	0.65	0.62	0.62
Water insoluble	0.70	0.75	0.64	0.64
Sodium	0.71	0.52	0.66	0.58
Salt equivalent	0.71	0.52	0.66	0.59
Potassium	0.73	0.74	0.65	0.76
Calcium	0.77	0.72	0.62	0.56
Magnesium	0.73	0.75	0.61	0.74
Phosphorus	0.80	0.74	0.61	0.51
Iron	0.70	0.66	0.61	0.69
Zinc	0.71	0.65	0.58	0.67
Copper	0.65	0.69	0.59	0.70
Manganese	0.72	0.75	0.69	0.70
Retinol	0.54	0.39	0.49	0.48
Retinol Eq	0.61	0.45	0.53	0.44
α-carotene	0.65	0.60	0.68	0.63
β-carotene	0.68	0.64	0.68	0.67
Cryptoxanthin	0.68	0.64	0.64	0.72
Lycopene	0.59	0.52	0.49	0.37
β-carotene Eq	0.68	0.64	0.69	0.67
Vitamin D	0.63	0.43	0.67	0.54
α-tocopherol	0.63	0.53	0.58	0.58
β-tocopherol	0.67	0.54	0.52	0.41
γ-tocopherol	0.64	0.51	0.51	0.46
δ-tocopherol	0.68	0.64	0.59	0.58
Vitamin K	0.65	0.67	0.55	0.58
Vitamin B_1	0.74	0.61	0.59	0.51
Vitamin B_2	0.74	0.62	0.67	0.67
Niacin	0.71	0.50	0.67	0.55
Vitamin B_6	0.72	0.54	0.65	0.66
Vitamin B_{12}	0.69	0.57	0.66	0.56
Folate	0.70	0.69	0.67	0.77
Pantothenic acid	0.71	0.76	0.61	0.69
Vitamin C	0.78	0.76	0.72	0.77
Daidzein	0.61	0.63	0.60	0.58
Genistein	0.61	0.63	0.60	0.58
MEDIAN	**0.70**	**0.63**	**0.61**	**0.58**

Abbreviations: SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; Eq, equivalent.
For men, $r \geq 0.24 = P < 0.05$, $r \geq 0.31 = P < 0.01$, $r \geq 0.39 = P < 0.001$. For women, $r \geq 0.23 = P < 0.05$, $r \geq 0.30 = P < 0.01$, $r \geq 0.38 = P \leq 0.001$.

Wakai[7] reviewed 21 validation studies of FFQs developed in Japan and reported a median CC for energy intake of 0.46 (range 0.20 to 0.87) and a median CC among the 21 studies ranging from 0.22 (n-6 PUFA) to 0.58 (calcium) for energy and 24 nutrients. As compared with the median CCs among the 21 studies for energy and 24 nutrients and 17 food groups, the CCs for the many nutrients and food groups evaluated in the present study were not substantially different or higher.[7] Attenuation caused by measurement error may be unavoidable in studies that use FFQs to investigate diet–disease associations. For example, based on a true relative risk of 2.0, if the regression coefficient of intakes according to an

Supplementary Table 4. Spearman rank correlation coefficients between 2 food frequency questionnaires, administered at an average interval 2.7 years, for estimated food-group intakes

	Men (n = 69)		Women (n = 75)	
	Crude	Energy-adjusted	Crude	Energy-adjusted
Cereals	0.63	0.69	0.49	0.55
Rice	0.64	0.62	0.65	0.63
Bread	0.73	0.70	0.55	0.60
Noodles	0.64	0.60	0.49	0.51
Other cereals	0.35	0.38	0.65	0.64
Potatoes and starches	0.60	0.60	0.65	0.60
Sugar	0.74	0.68	0.65	0.50
Pulses	0.45	0.51	0.65	0.56
Nuts and seeds	0.42	0.32	0.63	0.60
Vegetables	0.63	0.63	0.70	0.64
Green and yellow vegetables	0.64	0.58	0.61	0.51
White vegetables	0.69	0.62	0.69	0.62
Pickled vegetables	0.74	0.70	0.76	0.67
Cruciferous vegetables	0.65	0.60	0.50	0.46
Green, leafy vegetables	0.57	0.53	0.57	0.61
Yellow vegetables	0.60	0.55	0.60	0.46
Other vegetables	0.71	0.65	0.70	0.58
Fruits	0.70	0.67	0.63	0.69
Citrus fruit	0.67	0.61	0.62	0.66
Other fruit	0.66	0.64	0.61	0.55
Fungi	0.73	0.75	0.60	0.60
Algae	0.65	0.65	0.57	0.56
Fish and shellfish	0.62	0.39	0.70	0.62
Meats	0.69	0.57	0.54	0.52
Processed meat	0.67	0.62	0.71	0.70
Red meat	0.63	0.53	0.48	0.47
Poultry	0.54	0.36	0.50	0.49
Eggs	0.66	0.53	0.50	0.51
Milk and dairy products	0.73	0.69	0.61	0.52
High-fat milk	0.49	0.45	0.71	0.66
Low-fat milk	0.68	0.65	0.50	0.52
Fats and oils	0.63	0.53	0.63	0.51
Butter	0.57	0.45	0.63	0.55
Margarine and Oils	0.61	0.54	0.64	0.51
Confectionaries	0.63	0.60	0.63	0.64
Japanese	0.56	0.57	0.60	0.62
Western	0.66	0.62	0.60	0.55
Alcoholic beverages	0.86	0.86	0.76	0.68
Non-alcoholic beverages	0.61	0.61	0.68	0.63
Green tea	0.68	0.66	0.75	0.67
Coffee	0.75	0.69	0.80	0.76
Other beverage	0.45	0.48	0.56	0.52
Seasonings and spices	0.69	0.70	0.53	0.48
MEDIAN	**0.64**	**0.61**	**0.63**	**0.58**

For men, $r \geq 0.24 = P < 0.05$, $r \geq 0.31 = P < 0.01$, $r \geq 0.39 = P < 0.001$. For women, $r \geq 0.23 = P < 0.05$, $r \geq 0.30 = P < 0.01$, $r \geq 0.38 = P \leq 0.001$.

FFQ and DR varies from 0.6 to 0.2, the corresponding relative risk is further attenuated from 1.52 to 1.15.[1] A similar attenuation might be unavoidable in any examination that uses the present FFQ to assess diet–disease associations. Further investigation will be needed to examine the effects of measurement error on diet–disease associations in an actual dataset.

The CC for energy intake among women in this study (deattenuated CC: $r = 0.34$) was lower than the median of 21 previous studies. Further, the CCs of intakes based on the FFQ appeared to be lower in women than in men for most of the energy and nutrients examined (median deattenuated CC: 0.57 and 0.47 for men and women, respectively). This lower correlation in women than men has been previously observed in Japanese and Western populations.[7,16] Sex differences in validity might be partly due to disparities in the ease of response to the structured questionnaire that result from differences between men and women in their interest in dietary habits.[4] Moreover, we also found that the cumulative percentage among the top 20 foods for energy was lower for women than for men and that it was also lower than among subjects during the development of the initial FFQ (men: 63.9%, women: 56.3%).[17] These results suggest that the lower validity for energy intake among women is partly attributable

Supplementary Table 5. Cumulative percentage contribution of the top 20 foods to energy intake, as assessed by 4-day diet record

Code	Food	kcal/day	Cumulative percent
Men (n = 69)			
1088	Rice, Paddy rice grain, Well-milled rice	422.9	18.6
1026	Breads, White table bread	61.1	21.3
16006	Fermented alcoholic beverages, Beer, pale	52.8	23.6
12004	Hen's eggs, whole, raw	51.0	25.9
13003	Liquid milks, Ordinary liquid milk	49.5	28.0
1085	Rice, Paddy rice grain, Brown rice	45.8	30.1
14006	Fats and oils, Vegetable oil, blend	44.7	32.0
4046	*Natto* (Fermented soybean), *Itohiki-natto*	31.7	33.4
1048	Chinese noodles, Wet form, boiled	28.8	34.7
16015	Distilled alcoholic beverages, *Shochu*, 25% alcohol	25.2	35.8
13025	Yogurt, Whole milk, unsweetened	24.0	36.9
1087	Rice, Paddy rice grain, Under-milled rice	22.8	37.9
1039	*Udon*, Wet form, boiled	20.8	38.8
7107	Bananas, Raw fruit	19.2	39.6
11221	Chicken, Broiler meats, Thigh, with skin, raw	18.2	40.4
3003	Sugars, Soft sugars, White	17.6	41.2
1064	Macaroni, spaghetti, Dry form, boiled	16.2	41.9
2017	Potatoes, Tuber, raw	16.1	42.6
11123	Pork, large breeds, Loin, lean and fat, raw	16.1	43.3
4032	*Tofu* (soybean curd), *Momen-tofu*	15.7	44.0
Women (n = 74)			
1088	Rice, Paddy rice grain, Well-milled rice	286.0	15.5
1026	Breads, White table bread	67.9	19.2
13003	Liquid milks, Ordinary liquid milk	54.3	22.2
12004	Hen's eggs, whole, raw	46.8	24.7
14006	Fats and oils, Vegetable oil, blend	36.4	26.7
1048	Chinese noodles, Wet form, boiled	28.6	28.2
1085	Rice, Paddy rice grain, Brown rice	21.1	29.4
4046	*Natto* (Fermented soybean), *Itohiki-natto*	20.9	30.5
1089	Rice, Paddy rice grain, Well-milled rice with germ	19.1	31.6
2017	Potatoes, Tuber, raw	17.9	32.5
4040	*Abura-age* (Fried thin slices of pressed *tofu*, soybean curd)	17.3	33.5
1039	*Udon*, Wet form, boiled	17.2	34.4
13025	Yogurt, Whole milk, unsweetened	16.6	35.3
7148	Apples, Raw fruit	15.8	36.2
16006	Fermented alcoholic beverages, Beer, pale	15.7	37.0
15098	Biscuits, soft, Western-style confectioneries	15.3	37.8
11221	Chicken, Broiler meats, Thigh, with skin, raw	14.8	38.6
14001	Fats and oils, Olive oil	14.4	39.4
1117	Glutinous rice products, Rice cake	14.1	40.2
7107	Bananas, Raw fruit	14.1	41.0

to a lower contribution to energy by individual foods in women than in men, as was seen among subjects during the development of the initial FFQ.

Our study has several potential limitations. First, the response rate was not necessarily high, although the participants were randomly chosen and recruited from among cancer screenees. Selection bias, eg, a higher proportion of health-conscious subjects than in the actual population, was likely present, and thus the possibility of overestimating the validity of the FFQ cannot be ruled out. This response rate is nevertheless reasonable considering the burden posed by studies such as this. Second, reference intakes were based on 4-day values, versus the 28-day values used for the initial validation study of the FFQ.[4–6] A simple comparison of CCs might have been difficult, even though the present CCs were corrected for intraindividual variance. Moreover, although the dietary records were completed on consecutive days (ie, in the same season), the FFQ inquired about the previous year. In addition, responses to the FFQ might have depended on the season,[18] and FFQ1 was conducted in the season during which the dietary record was done. Thus, the possibility that validity might have been overestimated cannot be ruled out, especially for seasonal foods such as fruit and vegetables. Third, in the examination of reproducibility, we were unable to consider the "true" change in diet. Although we would have liked to examine the effects of random variation in response to the FFQ, the effects of such variation and the "true" change of diet could not be readily separated, and both might have attenuated the reproducibility of the FFQ.[1] Therefore, the reproducibility of this FFQ (in random variation in response) might have been underestimated.

In general, the advantages of FFQ-based dietary assessment are that the burden on participants is not heavy, an interviewer is unnecessary, costs are relatively low,[19] and the long-term diet can be ranked. In the present study, too, the median percentages of extreme categories based on joint classification by quintile between FFQ and DR for nutrients and food groups were 1% and 3%, indicating that this FFQ is suitable for the ranking of individuals with regard to intakes of many nutrients and food groups in large-scale studies of urban populations. However, some nutrient and food group intakes estimated by this FFQ showed relatively low CCs and regression coefficients; thus, any application of this FFQ to the examination of diet–disease associations, such as investigations of retinol and cryptoxanthin, must carefully address the problem of classification.

In conclusion, these results indicate that the present FFQ, which was initially developed for rural populations, provides reasonably valid measures in ranking middle-aged cancer screenees in urban areas in Japan according to level of consumption of many nutrients and food groups.

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Original Contribution

Association Between Plasma 25-Hydroxyvitamin D and Colorectal Adenoma According to Dietary Calcium Intake and Vitamin D Receptor Polymorphism

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The anticarcinogenic potential of vitamin D might be mediated by not only calcium metabolism but also other mechanisms initiated by vitamin D receptor (VDR). The authors measured plasma 25-hydroxyvitamin D in healthy volunteer examinees who underwent total colonoscopy in Tokyo, Japan, 2004–2005, and evaluated its influence on colorectal adenoma, both alone and in interaction with *VDR* polymorphisms, which correspond to the *Fok*I and *Taq*I restriction sites. The main analysis of plasma 25-hydroxyvitamin D included 737 cases and 703 controls. Compared with the lowest quintile of plasma 25-hydroxyvitamin D, only the highest was related to a significantly decreased odds ratio of colorectal adenoma (odds ratio = 0.64, 95% confidence interval: 0.45, 0.92). In contrast, all but the lowest quintile of dietary calcium intake presented similarly reduced odds ratios (odds ratio for the highest = 0.67, 95% confidence interval: 0.47, 0.95). Of note, the association between plasma 25-hydroxyvitamin D levels and colorectal adenoma was modified by the *Taq*I polymorphism of the *VDR* gene ($P_{interaction} = 0.03$) but not by dietary calcium intake ($P_{interaction} = 0.93$). These observations highlight the importance of vitamin D in colorectal tumorigenesis. Vitamin D might protect against colorectal neoplasia, mainly through mechanisms other than the indirect mechanism via calcium metabolism.

adenoma; calcium; case-control studies; intestine, large; Japan; polymorphism, single nucleotide; vitamin D

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism; VDR, vitamin D receptor.

Accumulating evidence has indicated that adequate levels of vitamin D may confer protection against the risk of colorectal cancer and adenoma, a well-established precursor lesion of colorectal cancer (1, 2). Recent meta-analyses of vitamin D intake and colorectal neoplasia have generally shown a weak inverse association (2, 3), while those of serum/plasma 25-hydroxyvitamin D, the predominant form of vitamin D in the circulation, have fairly consistently demonstrated a significant inverse association (3–5). This discrepancy in the magnitude of the association may reflect the fact that vitamin D in the body is derived from not only the diet but also the skin, where a substantial amount of pre-vitamin D can be synthesized from 7-dehydrocholesterol through stimulation by solar ultraviolet B radiation (6).

The primary role of vitamin D is the maintenance of calcium homeostasis, the disruption of which is also related to colorectal carcinogenesis (2, 7). Vitamin D exerts its effects on calcium metabolism through binding to vitamin D receptor (VDR), a member of the nuclear receptor superfamily, which regulates the transcription of genes involved in calcium absorption from the small intestine. The VDR gene (*VDR*) has a number of single nucleotide polymorphisms (SNPs), including rs2228570 (previously rs10735810) and rs731236. These 2 polymorphisms, which correspond to the *Fok*I and *Taq*I restriction sites, respectively, have been intensively explored over the last decade for their possible association with colorectal tumorigenesis (8, 9). The *Fok*I polymorphism exists at exon 2 of the *VDR* gene, and the *Taq*I polymorphism exists at exon 9. Given their distinctly separate locations, it is likely that the *Fok*I and *Taq*I polymorphisms are differently related to the development of colorectal neoplasia, if indeed they are related (9).

Although several epidemiologic studies have investigated the association between circulating vitamin D levels and colorectal neoplasia in conjunction with total/dietary calcium intake (10–15), few have done so in consideration of *VDR* polymorphisms (13, 14), despite the fact that the anticarcinogenic potential of vitamin D might be mediated by not only calcium metabolism but also other mechanisms initiated by VDR. Here, we measured plasma concentrations of 25-hydroxyvitamin D in 1,520 middle-aged and elderly Japanese and evaluated its influence on colorectal adenoma, both alone and in interaction with dietary calcium intake and the *Fok*I and *Taq*I polymorphisms of the *VDR* gene.

MATERIALS AND METHODS

Study population

The Colorectal Adenoma Study in Tokyo (16, 17), a case-control study conducted by the Research Center for Cancer Prevention and Screening, a branch of the National Cancer Center of Japan, was specifically designed to investigate environmental and genetic factors related to the early stage of colorectal carcinogenesis among healthy volunteer examinees of a colorectal cancer screening program. The Research Center conducts its cancer screening programs on a research basis and accordingly requires all examinees to provide written informed consent prior to admission to the use of data and materials collected through the screening programs to be used for medical research. This means that virtually no examinee refuses to participate in medical research initiated by the Research Center. Examinees who attend the Research Center are primarily self-referred, and more than 90% reside in Tokyo and its 6 neighboring prefectures, collectively called the Kanto region. The study protocol was approved by the institutional review board of the National Cancer Center.

Eligible subjects were defined in advance as men aged 50–79 years and women aged 40–79 years who underwent total colonoscopy from the anus to the cecum and who were without a history of colorectal adenoma, any malignant neoplasia, ulcerative colitis, Crohn's disease, familial adenomatous polyposis, carcinoid tumor, or colectomy. Of a consecutive series of 3,212 examinees undergoing magnifying colonoscopy with indigo carmine dye spraying between February 2004 and February 2005, 2,234 met these conditions. On the basis of the pit pattern of colorectal lesions, namely, the characteristics of mucosal crypts, 526 men and 256 women were determined to have at least 1 adenoma and were thus included as adenoma cases. Pit-pattern classification based on magnifying chromoendoscopy has been detailed elsewhere (18). Of the remaining 1,452 examinees, we identified 482 men and 721 women as potential controls who were also free from other benign lesions (e.g., hyperplastic polyps, inflammatory polyps, and diverticula). Because there were fewer potential controls than cases in men, all potential male controls were included in the study, whereas female controls were randomly selected from potential controls and frequency matched to the female cases in 5 age categories (40–49, 50–54, 55–59, 60–64, and ≥65 years of age) and 2 screening periods (first and second halves). The screening period was matched because standard operating procedures were improved during the first half period after the establishment of the Research Center, which might have influenced, for example, the accuracy of diagnosis. Finally, the study enrolled 526 cases and 482 controls in men and 256 cases and 256 controls in women. A total of 242 male and 104 female cases had adenomas of ≥5 mm in diameter and were referred to clinical hospitals for definitive diagnosis and treatment. Of 1,362 adenomatous lesions referred to the National Cancer Center in 2004–2008, 1,221 (90%), 53 (4%), and 88 (6%) were histologically confirmed as adenoma, early cancer, and nonneoplastic lesions, respectively (unpublished data).

Blood collection and laboratory procedures

Blood is collected from all examinees of the Research Center for research purposes almost without exception. Examinees were scheduled for blood collection prior to any cancer screening procedures on the first day of screening. Fasting venous blood was drawn into a vacutainer tube with ethylenediaminetetraacetic acid (EDTA). The vacutainer tubes were centrifuged to obtain the plasma and buffy coat layer, and the blood samples were preserved at −80°C until analysis. Plasma and buffy coat samples were available for all subjects of this study.

Plasma 25-hydroxyvitamin D concentrations were measured by a radioimmunoassay method by using a commercially available reagent (Kyowa Medex, Tokyo, Japan) with a minimum detection level of 6 ng/mL at an external laboratory (SRL, Tokyo, Japan). The laboratory reported intra- and interassay coefficients of variation of 5.96% and 5.31% for plasma 25-hydroxyvitamin D concentrations of 25.0 and 20.1 ng/mL, respectively. All laboratory personnel were blinded with respect to case and control status.

Genomic DNA was extracted from white blood cells in the buffy coat layer by using a FlexiGene DNA kit (Qiagen, Hilden, Germany) in our laboratory. More than 90% of buffy coat samples provided a sufficient amount of genomic DNA to perform genotyping. The *Fok*I and *Taq*I polymorphisms of the *VDR* gene were analyzed by using the TaqMan SNP genotyping assays (Applied Biosystems, Foster City, California). These analyses were carried out with blinding to case and control status.

Self-administered questionnaire

Prior to cancer screening, all examinees were encouraged to complete a self-administered questionnaire concerning lifestyle and socioeconomic characteristics, as well as personal and family medical history. Details of the questionnaire have been described elsewhere (16, 17). Although some examinees left individual items blank, no examinee refused to answer any substantial portion of the questionnaire.

The questionnaire also included a food frequency questionnaire of 145 food and beverage items with standard portions/units and 9 frequency categories. The amount of each food consumed per day in the past year was first calculated from the responses, and then total energy and nutrient intakes, including calcium, were estimated by reference to the *Standard Tables of Food Composition in Japan*, Fifth Revised Edition (19). The food frequency questionnaire of the present study was

essentially the same as that used in a large prospective cohort study among a Japanese population (20, 21). A validation study conducted among subsamples of cancer screening examinees revealed that the dietary calcium intake estimated from this food frequency questionnaire was relatively well correlated with that from 4-day dietary records, with deattenuated Spearman's correlation coefficients for energy-adjusted calcium intake of 0.64 and 0.61 for men and women, respectively (unpublished data).

Statistical analysis

Odds ratios and 95% confidence intervals of colorectal adenoma for plasma 25-hydroxyvitamin D, dietary calcium intake, and the *Fok*I and *Taq*I polymorphisms of the *VDR* gene were estimated by using an unconditional logistic regression model. Dietary calcium intake was energy adjusted for each sex by using a linear regression model with natural logarithm-transformed intakes of total energy and calcium as independent and dependent variables, respectively (22). Plasma 25-hydroxyvitamin D concentrations and dietary calcium intake were divided into sex-specific quintiles by cutoff points derived from the distribution among controls. Statistical adjustment was made in a manner similar to that in our previous studies of colorectal adenoma (16, 17). Model 1 controlled for sex, matching variables (i.e., age categories and screening periods), and season of blood collection (spring, summer, fall, and winter). Model 2 adjusted for the same variables as model 1 and additionally for cigarette smoking (never, ≤20, 21–40, and >40 pack-years), alcohol drinking (never, past, <150, 150–299, and ≥300 g/week), body mass index (<21.0, 21.0–22.9, 23.0–24.9, and ≥25.0 kg/m^2), family history of colorectal cancer (yes or no), and nonsteroidal anti-inflammatory drug use (yes or no). Model 2 also adjusted for attained adult height, an indicator of gross energy intake in childhood and adolescence, and average daily energy intake in the past year. These variables were divided into quintiles, the cutoff points of which were based on the sex-specific distribution among controls. Linear trends in the odds ratios of colorectal adenoma were examined by assigning ordinal values to quintiles of plasma 25-hydroxyvitamin D and dietary calcium intake.

We then investigated the influence of plasma 25-hydroxyvitamin D on colorectal adenoma in interaction with dietary calcium intake and the *Fok*I and *Taq*I polymorphisms of the *VDR* gene. Three genotypes of each *VDR* polymorphism were dichotomized on the basis of the dominant model, with the first homozygous for the major allele and the second heterozygous and homozygous for the minor allele combined. Similarly, quintiles of plasma 25-hydroxyvitamin D and dietary calcium intake were reduced to 2 levels, namely, lower and higher, on the basis of their association with colorectal adenoma. The likelihood ratio test with 1 df was used to evaluate whether dietary calcium intake and the *VDR* polymorphisms modified the association between plasma 25-hydroxyvitamin D and colorectal adenoma.

Of 1,443 subjects without extreme energy intakes (<800 or >4,200 kcal/day) or calcium supplement use, 3 subjects had missing information, 1 with regard to height and 2 for cigarette smoking. These were then excluded, and the analyses of plasma 25-hydroxyvitamin D and dietary calcium intake were conducted in the remaining 737 cases and 703 controls. Of note, we excluded calcium supplement users, who accounted for <4% of study subjects, and focused our analysis on dietary calcium intake. In the analyses of the *Fok*I and *Taq*I polymorphisms of the *VDR* gene, 7 and 8 subjects with an undetermined genotype were excluded, respectively, from 1,332 subjects with a sufficient amount of genomic DNA to perform genotyping, leaving 1,325 (684 cases, 641 controls) and 1,324 (684 cases, 640 controls), respectively, for inclusion. Two-sided P values less than 0.05 were regarded as statistically significant. All statistical analyses were carried out using SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 1 shows selected characteristics of controls according to plasma 25-hydroxyvitamin D level. Increasing levels of plasma 25-hydroxyvitamin D were associated with older age and a higher intake of dietary vitamin D, while other selected characteristics were not related to plasma 25-hydroxyvitamin D levels.

Plasma 25-hydroxyvitamin D levels were inversely associated with the prevalence of colorectal adenoma (Table 2), albeit in a nonlinear manner. Compared with the lowest quintile of plasma 25-hydroxyvitamin D, only the highest showed a statistically significant decrease in the adjusted odds ratio of colorectal adenoma (odds ratio (OR) = 0.64, 95% confidence interval (CI): 0.45, 0.92). A similar pattern was noted when the analysis was replicated in men and women separately ($P_{\text{interaction}} = 0.30$) (Web Table 1, the first of 3 Web tables posted on the *Journal*'s Web site (http://aje.oupjournals.org/)). Given the well-known seasonal variation in circulating levels of 25-hydroxyvitamin D, we also conducted a stratified analysis by season of blood collection, which revealed that the association between plasma 25-hydroxyvitamin D levels and colorectal adenoma was not modified by season of blood collection ($P_{\text{interaction}} = 0.55$) (Web Table 2). A nonlinear inverse association was also observed for dietary calcium intake, although this differed from that for plasma 25-hydroxyvitamin D: Using the first quintile of dietary calcium intake as reference, we found that the second showed a significant decrease in the adjusted odds ratio of colorectal adenoma (OR = 0.64, 95% CI: 0.45, 0.90), while the third to fifth showed no further decline. Again, we saw no apparent difference in the association by sex ($P_{\text{interaction}} = 0.70$) (Web Table 1). When mutually adjusted for plasma 25-hydroxyvitamin D and dietary calcium intake, the odds ratio for the highest quintile of plasma 25-hydroxyvitamin D was 0.66 (95% CI: 0.46, 0.95), whereas those for the second and fifth quintiles of dietary calcium intake were 0.65 (95% CI: 0.46, 0.92) and 0.69 (95% CI: 0.48, 0.99), respectively. The *Fok*I and *Taq*I polymorphisms of the *VDR* gene were not associated with the prevalence of colorectal adenoma (Table 2). Genotype frequencies among controls were in agreement with Hardy-Weinberg equilibrium for both *VDR* polymorphisms ($P = 0.79$ and 0.82 for *Fok*I and *Taq*I, respectively).

Table 1. Selected Characteristics of Controls According to Plasma 25-Hydroxyvitamin D Level, the Colorectal Adenoma Study in Tokyo, Japan, 2004–2005[a]

Characteristic	Plasma 25-Hydroxyvitamin D Level[b]									$P_{difference}$[c]
	Quintile 1 (Lowest)			Quintile 3 (Middle)			Quintile 5 (Highest)			
	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)	
Continuous variables										
Plasma 25-hydroxyvitamin D, ng/mL			16 (14–19)			24 (24–26)			32 (31–34)	<0.001
Age, years			57 (54–63)			60 (56–65)			61 (57–65)	0.005
Height, cm			165 (158–169)			163 (156–169)			162 (155–168)	0.60
Energy intake, kcal/day			1,855 (1,540–2,212)			1,829 (1,594–2,182)			1,894 (1,599–2,227)	0.96
Dietary vitamin D intake, μg/day			6.0 (4.3–7.7)			6.6 (4.7–8.4)			7.2 (4.9–10.0)	0.02
Dietary calcium intake, mg/day			542 (383–685)			565 (422–784)			590 (459–781)	0.15
Categorical variables										
Men	86	66.6		95	65.5		100	63.6		0.73
Ever smoker	64	49.6		74	51.0		70	44.5		0.79
Ever drinker	93	72.0		111	76.5		121	77.0		0.89
Overweight or obesity	33	25.5		32	22.0		30	19.1		0.71
NSAID user	12	9.3		13	8.9		8	5.1		0.53
Family history of colorectal cancer[d]	19	14.7		17	11.7		20	12.7		0.91

Abbreviations: IQR, interquartile range; NSAID, nonsteroidal antiinflammatory drug.

[a] Presenting characteristics of controls in quintiles 1, 3, and 5.

[b] Respective median (range) of each plasma 25-hydroxyvitamin D quintile by sex—for men, quintile 1: 18 ng/mL (1–20); quintile 3: 25 ng/mL (24–26); quintile 5: 33 ng/mL (≥31); for women, quintile 1: 15 ng/mL (1–17); quintile 3: 23 ng/mL (22–24); quintile 5: 30 ng/mL (≥28).

[c] Based on the Wilcoxon rank-sum test for median difference and the Fisher exact test for percentage difference.

[d] History of colorectal cancer in parents and siblings.

Among 737 cases, 325 had a largest adenoma of ≥5 mm in diameter (44.1%). Excluding 12 cases with missing information, 388 had the largest adenoma at the proximal colon (53.5%), 259 at the distal colon (35.7%), and 78 at the rectum (10.8%). We then investigated the association of plasma 25-hydroxyvitamin D and dietary calcium intake with the size and location of the largest adenoma using a multinomial logistic regression model (Table 3). The inverse association of plasma 25-hydroxyvitamin D and dietary calcium intake was even more striking in cases with a largest adenoma of ≥5 mm in diameter. By location of the largest adenoma, the inverse association of plasma 25-hydroxyvitamin D was most pronounced in cases of proximal colon adenoma, whereas that of dietary calcium intake was most prominent in rectal adenoma cases.

We further evaluated the association of plasma 25-hydroxyvitamin D and dietary calcium intake with colorectal adenoma stratified by major risk factors of colorectal adenoma, namely, smoking and drinking habits and body fatness. Although no interaction of dietary calcium intake with body fatness was seen, such an interaction was suggested for plasma 25-hydroxyvitamin D ($P_{interaction} = 0.05$), in which the odds ratio of colorectal adenoma for the highest compared with lowest quintile was statistically significant in subjects with a body mass index of <23 kg/m^2 but not in those of ≥23 kg/m^2 (Web Table 3). With respect to smoking and drinking habits, we did not see any effect modification for either plasma 25-hydroxyvitamin D or dietary calcium intake (data not shown).

Table 4 shows the association of plasma 25-hydroxyvitamin D with colorectal adenoma according to dietary calcium intake and *VDR* polymorphism. Although we saw no multiplicative interaction, higher levels of plasma 25-hydroxyvitamin D and dietary calcium intake combined were related to the greatest decrease in odds ratio of colorectal adenoma (OR = 0.49, 95% CI: 0.33, 0.72). With regard to the *VDR* polymorphisms examined, we observed a significant interaction with the *Taq*I polymorphism ($P_{interaction} = 0.03$), for which an inverse association of plasma 25-hydroxyvitamin D was more evident in heterozygotes and homozygotes for the minor allele combined ($P_{trend} = 0.001$) than in homozygotes for the major allele ($P_{trend} = 0.25$). When examined in heterozygotes or homozygotes for the minor allele of *Taq*I, the adjusted odds ratio of colorectal adenoma for higher compared with lower levels of plasma 25-hydroxyvitamin D was 0.32 (95% CI: 0.16, 0.65).

DISCUSSION

In this study, we found a nonlinear inverse association of plasma 25-hydroxyvitamin D and dietary calcium intake with colorectal adenoma. Moreover, we noted a significant

Table 2. Association of Plasma 25-Hydroxyvitamin D, Dietary Calcium Intake, and Vitamin D Receptor Polymorphisms With Colorectal Adenoma, the Colorectal Adenoma Study in Tokyo, Japan, 2004–2005

Variable	No. of Subjects		Model 1[a]		Model 2[b]	
	Cases	Controls	OR	95% CI	OR	95% CI
Plasma 25-hydroxyvitamin D[c]						
Quintile 1 (lowest)	145	129	1	Referent	1	Referent
Quintile 2	132	128	0.89	0.63, 1.26	0.86	0.60, 1.24
Quintile 3 (middle)	157	145	0.90	0.64, 1.26	0.91	0.64, 1.29
Quintile 4	175	144	1.01	0.72, 1.41	1.03	0.73, 1.46
Quintile 5 (highest)	128	157	0.66	0.47, 0.94	0.64	0.45, 0.92
P_{trend}				0.08		0.09
Dietary calcium intake[d]						
Quintile 1 (lowest)	201	140	1	Referent	1	Referent
Quintile 2	124	140	0.58	0.42, 0.81	0.64	0.45, 0.90
Quintile 3 (middle)	141	141	0.64	0.46, 0.88	0.78	0.55, 1.10
Quintile 4	142	140	0.63	0.45, 0.87	0.80	0.56, 1.13
Quintile 5 (highest)	129	142	0.55	0.39, 0.77	0.67	0.47, 0.95
P_{trend}				0.002		0.13
FokI genotype[e,f]						
FF	274	260	1	Referent	1	Referent
Ff	324	294	1.06	0.83, 1.34	1.01	0.79, 1.29
ff	86	87	0.93	0.66, 1.32	0.91	0.63, 1.31
Ff/ff	410	381	1.03	0.82, 1.29	0.99	0.78, 1.25
TaqI genotype[e,f]						
TT	523	492	1	Referent	1	Referent
Tt	156	139	1.06	0.82, 1.39	1.06	0.81, 1.40
tt	5	9	0.56	0.18, 1.70	0.47	0.15, 1.51
Tt/tt	161	148	1.03	0.80, 1.34	1.03	0.79, 1.34

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Model 1 was adjusted for sex, age, screening period, and season of blood collection.

[b] Model 2 was adjusted for the same variables as model 1 and additionally for cigarette smoking, alcohol drinking, body mass index, family history of colorectal cancer, nonsteroidal antiinflammatory drug use, daily energy intake, and height.

[c] Respective median (range) of each plasma 25-hydroxyvitamin D quintile by sex—for men, quintile 1: 18 ng/mL (1–20); quintile 3: 25 ng/mL (24–26); quintile 5: 33 ng/mL (≥31); for women, quintile 1: 15 ng/mL (1–17); quintile 3: 23 ng/mL (22–24); quintile 5: 30 ng/mL (≥28).

[d] Respective median (range) of each dietary calcium intake quintile by sex—for men, quintile 1: 288 mg/day (1–366); quintile 3: 514 mg/day (463–567); quintile 5: 867 mg/day (≥717); for women, quintile 1: 419 mg/day (1–498); quintile 3: 676 mg/day (613–742); quintile 5: 1,069 mg/day (≥881).

[e] The number of subjects providing sufficient genomic DNA to perform genotyping was 1,332.

[f] For *FokI* and *TaqI*, 7 and 8 subjects with undetermined genotype were excluded, respectively.

interaction between plasma 25-hydroxyvitamin D and the *TaqI* polymorphism of the *VDR* gene. These findings underline the importance of vitamin D in colorectal carcinogenesis, at least in its early stage.

Circulating levels of 25-hydroxyvitamin D have been evaluated in at least 7 prospective studies of colorectal cancer and 6 observational studies of colorectal adenoma (best summarized by Gandini et al. (23)). However, only 2 of these were conducted in an Asian or, more specifically, Japanese population (6, 24). Although neither reported a straightforward overall association, the investigation of colorectal adenoma showed a nonlinear inverse association, similar to ours, but only in subjects who provided blood during the winter season (24). With respect to total/dietary calcium intake, we are aware of at least 4 observational studies of colorectal cancer in Asian populations (21, 25–27) but no study of colorectal adenoma in a similar population. Even when the lower consumption levels in Asian than Western populations were considered, all studies consistently reported an inverse association (21, 25–27).

A recent comprehensive review that estimated optimal concentrations of 25-hydroxyvitamin D for multiple health

Table 3. Association of Plasma 25-Hydroxyvitamin D and Dietary Calcium Intake With the Size and Location of the Largest Adenoma, the Colorectal Adenoma Study in Tokyo, Japan, 2004–2005

Variable	Size of Largest Adenoma						Location of Largest Adenoma[a]								
	≥5 mm in Diameter			<5 mm in Diameter			Proximal Colon			Distal Colon			Rectum		
	No. of Cases	OR[b]	95% CI	No. of Cases	OR[b]	95% CI	No. of Cases	OR[b]	95% CI	No. of Cases	OR[b]	95% CI	No. of Cases	OR[b]	95% CI
Plasma 25-hydroxyvitamin D[c]															
Quintile 1 (lowest)	70	1	Referent	75	1	Referent	75	1	Referent	53	1	Referent	17	1	Referent
Quintile 2	56	0.75	0.48, 1.17	76	0.97	0.64, 1.47	80	1.00	0.66, 1.51	40	0.74	0.45, 1.21	9	0.49	0.20, 1.16
Quintile 3 (middle)	67	0.81	0.52, 1.25	90	1.03	0.69, 1.55	74	0.82	0.54, 1.24	65	1.10	0.70, 1.74	18	0.87	0.41, 1.82
Quintile 4	79	0.94	0.61, 1.43	96	1.12	0.74, 1.67	93	1.03	0.68, 1.55	58	0.96	0.60, 1.54	18	0.88	0.42, 1.85
Quintile 5 (highest)	53	0.54	0.34, 0.86	75	0.74	0.49, 1.13	66	0.63	0.41, 0.96	43	0.62	0.38, 1.02	16	0.68	0.31, 1.46
P_{trend}			0.06			0.35			0.07			0.21			0.72
Dietary calcium intake[d]															
Quintile 1 (lowest)	101	1	Referent	100	1	Referent	96	1	Referent	75	1	Referent	29	1	Referent
Quintile 2	53	0.55	0.36, 0.84	71	0.76	0.51, 1.14	60	0.63	0.41, 0.95	48	0.72	0.46, 1.13	16	0.59	0.29, 1.17
Quintile 3 (middle)	67	0.74	0.49, 1.13	74	0.84	0.56, 1.26	73	0.78	0.51, 1.17	52	0.87	0.55, 1.37	12	0.47	0.22, 1.00
Quintile 4	54	0.60	0.39, 0.94	88	1.04	0.70, 1.56	83	0.90	0.60, 1.36	44	0.76	0.47, 1.22	13	0.55	0.26, 1.16
Quintile 5 (highest)	50	0.50	0.32, 0.79	79	0.88	0.58, 1.33	76	0.74	0.49, 1.13	40	0.66	0.41, 1.09	8	0.29	0.12, 0.70
P_{trend}			0.009			0.91			0.57			0.17			0.007

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Twelve cases had missing information on the location of the largest adenoma.

[b] Adjusted for sex, age, screening period, season of blood collection, cigarette smoking, alcohol drinking, body mass index, family history of colorectal cancer, nonsteroidal antiinflammatory drug use, daily energy intake, and height.

[c] Respective median (range) of each plasma 25-hydroxyvitamin D quintile by sex—for men, quintile 1: 18 ng/mL (1–20); quintile 3: 25 ng/mL (24–26); quintile 5: 33 ng/mL (≥31); for women, quintile 1: 15 ng/mL (1–17); quintile 3: 23 ng/mL (22–24); quintile 5: 30 ng/mL (≥28).

[d] Respective median (range) of each dietary calcium intake quintile by sex—for men, quintile 1: 288 mg/day (1–366); quintile 3: 514 mg/day (463–567); quintile 5: 867 mg/day (≥717); for women, quintile 1: 419 mg/day (1–498); quintile 3: 676 mg/day (613–742); quintile 5: 1,069 mg/day (≥881).

Table 4. Association of Plasma 25-Hydroxyvitamin D With Colorectal Adenoma According to Dietary Calcium Intake and Vitamin D Receptor Polymorphism, the Colorectal Adenoma Study in Tokyo, Japan, 2004–2005

Variable	Plasma 25-Hydroxyvitamin D								$P_{interaction}$
	Quintiles 1–4 (Lower)				Quintile 5 (Higher)				
	No. of Cases	No. of Controls	OR[a]	95% CI	No. of Cases	No. of Controls	OR[a]	95% CI	
Dietary calcium intake									0.93
Quintile 1 (lower)	169	113	1	Referent	32	27	0.69	0.38, 1.26	
Quintiles 2–5 (higher)	440	433	0.73	0.54, 0.98	96	130	0.49	0.33, 0.72	
*Fok*I genotype[b,c]									0.27
FF	228	212	1	Referent	46	48	0.85	0.53, 1.36	
Ff/ff	338	291	1.06	0.82, 1.38	72	90	0.65	0.44, 0.96	
*Taq*I genotype[b,c]									0.03
TT	423	388	1	Referent	100	104	0.80	0.57, 1.11	
Tt/tt	143	113	1.17	0.87, 1.57	18	35	0.43	0.23, 0.79	

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Adjusted for sex, age, screening period, season of blood collection, cigarette smoking, alcohol drinking, body mass index, family history of colorectal cancer, nonsteroidal antiinflammatory drug use, daily energy intake, and height.

[b] The number of subjects providing sufficient genomic DNA to perform genotyping was 1,332.

[c] For *Fok*I and *Taq*I, 7 and 8 subjects with undetermined genotype were excluded, respectively.

outcomes, including colorectal cancer, concluded that the most advantageous concentrations of 25-hydroxyvitamin D began at around 30 ng/mL for all endpoints assessed (28), with which our observations essentially agree. With regard to dietary calcium intake, a pooled analysis of 10 cohort studies reported a threshold effect of dietary calcium intake in which all quintiles above the lowest showed a similar decrease in the risk of colorectal cancer (7), which strongly supports our present results.

We saw no multiplicative interaction between plasma 25-hydroxyvitamin D and dietary calcium intake. Previous observational studies of primary colorectal cancer and adenoma have also failed to identify such interaction (10–15). Although these findings do not rule out the existence of biologic interaction, they may suggest that vitamin D exerts an anticarcinogenic effect on the large intestine itself, and that its influence on calcium homeostasis plays only a minor role in colorectal tumorigenesis.

Although not nonsynonymous, the *Taq*I polymorphism of the *VDR* gene appears to be in linkage disequilibrium with a series of polymorphisms in the 3′ end of the *VDR* gene (29), for example, the polyadenylated microsatellite in the 3′ untranslated region, the length of which likely determines messenger RNA stability and hence likely affects intracellular levels of VDR (30). To date, the 2 studies of colorectal neoplasia that have examined the *Taq*I polymorphism in conjunction with vitamin D, as measured by dietary intake (31) or circulating levels ((14); the results were shown in the text only), indicated the absence of any obvious interaction.

We investigated effect modification by the *VDR* gene using 2 traditional SNPs, although the gene spans approximately 100 kilobases and has numerous genetic polymorphisms. In fact, sequencing of the *VDR* gene in a Japanese population identified >20 SNPs with a minor allele frequency of >0.05, including *Fok*I and *Taq*I polymorphisms, at least some of which would serve as tag SNPs to capture the common variation in the gene (32). Further, recent genome-wide scans revealed several genes associated with circulating 25-hydroxyvitamin D concentrations (33, 34). Our findings, based on a limited number of SNPs in a single gene, provide at most an intriguing insight into the gene-environmental interaction in the vitamin D pathway.

The strengths of the present study include its measurement of plasma 25-hydroxyvitamin D concentrations, which may provide a relatively accurate classification of study subjects by vitamin D status. In addition, the provision of total colonoscopy to all study subjects likely decreased the possibility of misclassification between cases and controls. Conversely, a major limitation is its cross-sectional nature, and the observed associations might have been due to reverse causality. In contrast to colorectal cancer, however, colorectal adenoma likely does not affect circulating levels of vitamin D, because colorectal adenoma is an asymptomatic benign tumor. A second limitation is that adenoma cases were not histologically confirmed and necessarily included those with an early cancer or nonneoplastic lesion. However, our preliminary survey reported an accuracy of diagnosis based on magnifying chromoendoscopy of 90%, a result similar to those previously reported (35, 36), and the influence of any misclassification caused by the technique is therefore likely to have been minimal. Third, we were unable to analyze groups of cases and their frequency-matched controls in single batches, because single groups contained too many subjects to allow placement in the same batch. Although the impact of variability in assay performance was not reduced by simultaneously analyzing all subjects in a matching category, blood samples were at least analyzed irrespective of case and control status, reducing differential misclassification between cases and controls. Fourth, blinded control samples from the study population were not available and were therefore not