Comparison of plasma levels of nutrient-related biomarkers among Japanese populations in Tokyo, Japan, São Paulo, Brazil, and Hawaii, USA

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Previous studies of Japanese migrants have suggested that the increase in colorectal cancer rates occurring after migration is slower among Japanese Brazilians than among Japanese Americans. We hypothesized that this difference may partly reflect differences in vegetable and fruit intake between the populations. Using data from validation studies of food frequency questionnaires being used in comparative case–control studies of colorectal adenoma in Tokyo, São Paulo, and Hawaii, plasma carotenoid, retinol, tocopherol, and coenzyme Q10 levels were measured by high-performance liquid chromatography, and 25-hydroxy vitamin D levels were estimated by enzyme-linked immunosorbent assay. Plasma levels were compared by analysis of covariance between 142 Japanese in Tokyo, 79 Japanese Brazilians in São Paulo, and 78 Japanese Americans in Hawaii. Overall, we found significantly lower plasma carotenoid levels, except for lycopene levels, and retinol levels in Japanese Americans compared with Japanese in Tokyo and Japanese Brazilians. The plasma total carotenoid level was highest in Japanese Brazilians. Compared with the mean level among Japanese Brazilians (1741.2 ng/ml), *P* for difference was 0.03 among Japanese in Tokyo (1514.4 ng/ml) and less than 0.01 for Japanese Americans (1257.7 ng/ml). Plasma lycopene and tocopherol levels did not substantially differ between the three populations. We also found significantly lower plasma levels of 25-hydroxy vitamin D and total coenzyme Q10 in Japanese in Tokyo than in Japanese Americans and Japanese Brazilians. Higher levels of plasma carotenoids among Japanese Brazilians than among Japanese in Tokyo and Hawaii may have contributed to the slower pace of the increase in colorectal cancer rates observed in that population after migration. ***European Journal of Cancer Prevention*** **24:155–161**

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Introduction

Migrant studies have provided several lines of evidence that lifestyle and environmental factors are major contributors to cancer causation and have helped generate hypotheses on the etiology of cancer. For example, the marked increase in colorectal cancer incidence among Japanese who migrated to the USA was observed as early as in the first generation of migrants. This pattern is particularly of interest because the change occurred more gradually, over several generations, for the other main cancers (Shimizu *et al.*, 1987, 1991). Between 1983 and 1987, Japanese American men in Hawaii and Los Angeles had the highest incidence rates of colorectal cancer among the more than 175 populations followed for cancer incidence worldwide (Parkin *et al.*, 1992). In contrast, between 1969 and 1978 colorectal cancer rates had not increased among first-generation Japanese migrants to São Paulo, despite a high red meat intake and a higher BMI compared with Japanese in Japan (Tsugane *et al.*, 1990, 1994, 1996). However, more recent data, from 2000, showed that mortality from colorectal cancer among first-generation Japanese migrants to São Paulo had approximated that among Japanese in Japan (Iwasaki *et al.*, 2004, 2008).

These descriptive epidemiologic features might reflect differences in risk factors between populations or in screening practices. The slower pace of increase in colorectal cancer among Japanese Brazilians than among Japanese Americans implies the existence of either or both preventive factors in São Paulo and risk factors in

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Hawaii. Given that the frequency of consuming green and yellow vegetables was much higher among Japanese Brazilians than among Japanese in the cross-sectional studies (Tsugane *et al.*, 1996), it was hypothesized that the frequent intake of vegetables and fruits among Japanese Brazilians might have lowered their risk (Iwasaki *et al.*, 2004). Indeed, accumulating epidemiological evidence has suggested that intake of vegetables and fruits is associated with a decreased risk of colorectal cancer, likely owing to the effect of antioxidants or other phytochemicals (World Cancer Research Fund and American Institute for Cancer Research, 2007). However, no study has compared the consumption of vegetables and fruits among these three populations, namely, Japanese in Japan, Japanese Brazilians in Brazil, and Japanese Americans in the USA.

Given the difficulty of accurately assessing dietary intake of vegetables and fruits among different populations, we instead measured and compared plasma nutrient levels in the present study. Carotenoids might be one component of vegetables and fruits responsible for a lower risk, and plasma levels of carotenoids can more generally be used as biomarkers of vegetable and fruit intake over the preceding weeks or months (Record *et al.*, 2001; Al-Delaimy *et al.*, 2005). In addition, retinol, tocopherols, 25-hydroxy vitamin D, and coenzyme Q10 are of particular interest in relation to colorectal cancer risk (Wakai *et al.*, 2005; Chai *et al.*, 2010; Gandini *et al.*, 2011; Lee *et al.*, 2011; Kabat *et al.*, 2012). Characterization of differences in the levels of these nutrient-related biomarkers between the three populations above might further help our understanding of colorectal cancer etiology and its potential prevention.

Here, we conducted a cross-sectional study to compare plasma levels of carotenoids, retinol, tocopherols, 25-hydroxy vitamin D, and coenzyme Q10 between Japanese in Tokyo, Japanese Brazilians in São Paulo, and Japanese Americans in Hawaii.

Materials and methods

Study population

Japanese in Tokyo

Study participants were participants in the validation study of a semi-quantitative food frequency questionnaire (FFQ) used in a case–control study of colorectal adenoma in Tokyo (Yamaji *et al.*, 2009, 2010). They were selected from among examinees of the cancer screening program at the Research Center for Cancer Prevention and Screening, National Cancer Center, Japan, who met the following criteria: (i) age between 40 and 69 years, (ii) residence in Tokyo and suburban prefectures, and (iii) no previous or present diagnosis of cancer, cardiovascular disease, or diabetes mellitus. Between May 2007 and April 2008, 144 men and women provided weighed dietary records over four consecutive days, self-administered an FFQ, provided a fasting blood sample, from which serum and EDTA-2Na plasma samples were prepared and stored frozen at −80°C, and provided a 24-h urine sample. The study design and data collection for the validation study have been described in detail elsewhere (Takachi *et al.*, 2011). The study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan.

Japanese Brazilians in São Paulo

Study participants were participants in a validation study of the quantitative FFQ used in a case–control study of colorectal adenoma in São Paulo (Sharma *et al.*, 2009). They were selected from among participants in a case–control study of colorectal adenoma in São Paulo who met the following criteria: (i) age between 40 and 79 years, (ii) residence in the state of São Paulo for at least 6 months before recruitment, (iii) at least three grandparents of pure Japanese ancestry, and (iv) no history of colorectal cancer or other invasive cancers over the past 10 years. A total of 96 men and women provided food diaries over four consecutive days, as well as a fasting blood sample, from which heparinized plasma was stored frozen at −80°C, between August 2008 and November 2009. In this study, 79 participants whose samples were available for analysis were included. Details of the validation study have been described elsewhere (Pakseresht *et al.*, 2012). The study was approved by the University of Hawaii, Committee on Human Studies, as well as by the Brazilian Ministries of Health, Science, and Technology, and Foreign Affairs, and the Brazilian National Ethics Commission.

Japanese Americans in Hawaii

Study participants were selected from among Japanese American participants in an endoscopy-based case–control study of adenoma in Hawaii (Le Marchand *et al.*, 2010; Ognjanovic *et al.*, 2010). Seventy-eight participants aged between 40 and 79 years, who did not have a history of cancer, completed a 4-day food record and provided a fasting blood sample between April 2002 and May 2007. Heparinized plasma was stored at −80°C until analysis. The study was approved by the Committee on Human Studies, University of Hawaii.

Laboratory analysis

All assays were performed at the University of Hawaii Cancer Center. Plasma levels of carotenoids, tocopherols, and retinol were determined by high-performance liquid chromatography (HPLC), with photodiode array detection after extraction with hexane (Franke *et al.*, 1993; Cooney *et al.*, 1995). Plasma total coenzyme Q10 levels were measured by a recently established HPLC method with precolumn electrochemical oxidation and photodiode array detection (Franke *et al.*, 2010). Plasma levels of 25-hydroxy vitamin D were measured using a commercial enzyme immunoassay kit (enzymatic kit

AA-35F1; Immunodiagnostic Systems Inc.) in accordance with the manufacturer's instructions.

We used EDTA-2Na plasma samples from Japanese in Tokyo and heparinized plasma samples from Japanese Brazilians and Japanese Americans for the present study. To calibrate values from EDTA-2Na plasma samples, we measured all biomarkers in both EDTA-2Na and heparinized plasma samples prepared from the same participants ($n = 15$). In addition, blind triplicate heparinized plasma samples from 15 participants were included in each assay as a quality control. Lower detection limits (LODs) and intra-assay coefficients of variation (CVs) for each biomarker are presented in Table S1. The CVs for nine of 16 biomarkers were 5% or lower and for six biomarkers were between 5 and 10%. In contrast, the CV for total coenzyme Q10 was the highest among the 16 biomarkers, at 17.4%.

Statistical analysis

We excluded participants whose plasma samples were not available, leaving 142 Japanese in Tokyo, 79 Japanese Brazilians in São Paulo, and 78 Japanese Americans in Hawaii for inclusion in the present analyses.

Measurement values below the LOD were assigned half the value of the LOD if measurable values below the LOD were not available. For each biomarker, measurement values from heparinized plasma samples were linearly regressed on those from EDTA-2Na plasma samples among 15 participants. The intercepts and slopes of these regressions were then used to estimate calibrated values for Japanese in Tokyo on the basis of measurement values from the EDTA-2Na plasma samples. All values were natural log-transformed to produce approximately normal distributions. We excluded outliers, which were defined as below or above the value equal to three times the interquartile range based on the overall study population (Table S1). Geometric mean levels and their 95% confidence intervals were calculated for each of the three populations using multivariate regression analysis with adjustment for age (continuous), sex, season (spring, summer, autumn, winter), fasting status (≤ 10 h, > 10 h), smoking status (never, past, current smoker), BMI (continuous), alcohol intake (g/day), and plasma levels of high-density lipoprotein (HDL) cholesterol (continuous), non-HDL cholesterol (continuous), and triglycerides (continuous). The non-HDL cholesterol level was calculated by subtracting the level of HDL cholesterol from that of total cholesterol. Analysis of covariance was used to test for differences in mean levels between the three populations. For comparisons between populations, each population was successively used as the reference group. All reported P-values are two-sided, and the significance level was set at P less than 0.05. All statistical analyses were carried out with SAS software version 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Table S1 shows the number of participants with values below the LOD and with an insufficient amount of plasma for each assay. Except for values of *cis*-β-carotene, there were only a few participants whose values were below the LOD. Nine participants for 25-hydroxy vitamin D and two for other biomarkers were excluded because of an insufficient amount of plasma. The number of eligible participants in the present analyses varied between 288 and 297.

Characteristics of the three study populations are presented in Table 1. The proportions of men and current smokers did not significantly differ. A significant difference was observed for mean age, alcohol intake, BMI, and plasma levels of HDL cholesterol, non-HDL cholesterol, and triglycerides.

Table 2 compares plasma carotenoids and retinol levels between Japanese in Tokyo, Japanese Brazilians in São Paulo, and Japanese Americans in Hawaii. Overall, plasma carotenoid and retinol levels were significantly lower for Japanese Americans than for the other two populations, except for lycopene. Plasma levels of α-carotene, total β-carotene, *trans*-β-carotene, *cis*-β-carotene, and α-cryptoxanthin were significantly lower in Japanese Americans than in the other two populations. Plasma total carotenoid and trans-β-cryptoxanthin levels significantly differed between populations, with the highest levels in Japanese Brazilians, followed by Japanese in Tokyo and Japanese Americans. Plasma levels of total *trans*-lutein/zeaxanthin and retinol were

Table 1 Characteristics of Japanese populations in Tokyo, Japan, São Paulo, Brazil, and Hawaii, USA

	Tokyo	São Paulo	Hawaii	*P* for difference
Number of participants	142	79	78	
Age				
Mean (SD)	58.6 (7.4)	62.0 (10.2)	61.9 (10.8)	< 0.01
Sex				
Men [*n* (%)]	68 (48.0)	28 (35.0)	37 (47.0)	0.17
Smoking status				
Never smokers [*n* (%)]	79 (55.6)	54 (68.4)	43 (55.1)	
Past smokers [*n* (%)]	46 (32.4)	19 (24.1)	29 (37.2)	
Current smokers [*n* (%)]	17 (12.0)	6 (7.6)	6 (7.7)	0.26
Alcohol intake (g/day)				
Mean (SD)	14.9 (21.4)	2.1 (8.3)	4.2 (9.8)	< 0.01
BMI (kg/m^2)				
Mean (SD)	22.4 (2.7)	24.5 (4.0)	26.7 (4.3)	< 0.01
Plasma level of HDL cholesterol (mg/dl)				
Mean (SD)	57.1 (16.4)	47.6 (17.7)	41.6 (13.0)	< 0.01
Plasma level of non-HDL cholesterol (mg/dl)[a]				
Mean (SD)	143.8 (27.0)	149.5 (34.6)	121.9 (30.5)	< 0.01
Plasma level of triglyceride (mg/dl)				
Mean (SD)	79.2 (47.8)	122.3 (67.8)	123.5 (85.8)	< 0.01

HDL, high-density lipoprotein.
[a]Non-HDL cholesterol level was calculated by subtracting the level of HDL cholesterol from that of total cholesterol.

Table 2 Adjusted geometric means and 95% confidence intervals in the three populations

	Tokyo	São Paulo	Hawaii	*P* for difference		
				P^a	P^b	P^c
Total carotenoids (ng/ml)						
Number of participants	142	79	76			
Multivariate[d]	1514.4	1741.2	1257.7	0.03	0.01	< 0.01
95% CI	1408.1–1628.7	1555.3–1949.2	1114.6–1419.1			
α-Carotene (ng/ml)						
Number of participants	142	79	76			
Multivariate[d]	91.4	89.4	61.6	0.82	< 0.01	< 0.01
95% CI	82.1–101.7	75.7–105.6	51.5–73.6			
Total β-carotene (ng/ml)						
Number of participants	142	79	76			
Multivariate[d]	434.6	372.5	249.8	0.17	< 0.01	< 0.01
95% CI	383.3–492.8	306.5–452.6	202.8–307.8			
Trans-β-carotene (ng/ml)						
Number of participants	142	79	76			
Multivariate[d]	402.2	341.5	230.0	0.15	< 0.01	< 0.01
95% CI	354.6–456.3	280.8–415.2	186.6–283.6			
Cis-β-carotene (ng/ml)						
Number of subjects	142	79	76			
Multivariate[d]	31.0	29.3	19.4	0.62	< 0.01	< 0.01
95% CI	27.2–35.3	23.9–35.8	15.6–24.1			
Total lycopene (ng/ml)						
Number of participants	142	78	76			
Multivariate[d]	388.5	406.0	398.5	0.44	0.68	0.75
95% CI	364.8–413.8	368.1–447.9	358.9–442.6			
Trans-lycopene (ng/ml)						
Number of participants	141	77	76			
Multivariate[d]	122.0	115.8	130.1	0.40	0.34	0.07
95% CI	113.9–130.6	104.0–128.9	116.1–145.8			
5-*cis*-lycopene (ng/ml)						
Number of participants	142	77	76			
Multivariate[d]	158.0	181.6	169.1	0.01	0.27	0.21
95% CI	148.5–168.0	164.8–200.1	152.6–187.4			
α-Cryptoxanthin (ng/ml)						
Number of participants	142	78	74			
Multivariate[d]	33.8	31.6	26.6	0.17	< 0.01	< 0.01
95% CI	32.0–35.7	28.9–34.4	24.2–29.2			
Trans-β-cryptoxanthin (ng/ml)						
Number of participants	142	79	76			
Multivariate[d]	188.7	289.1	126.5	< 0.01	0.01	< 0.01
95% CI	162.9–218.5	230.2–363.0	99.1–161.4			
Total *trans*-lutein/zeaxanthin (ng/ml)						
Number of participants	142	79	76			
Multivariate[d]	194.1	152.7	114.1	< 0.01	< 0.01	< 0.01
95% CI	179.6–209.7	135.4–172.2	100.4–129.8			
Retinol (ng/ml)						
Number of participants	142	79	75			
Multivariate[d]	639.7	589.0	520.6	0.04	< 0.01	< 0.01
95% CI	611.4–669.3	549.0–631.9	482.6–561.5			

CI, confidence interval.
[a]*P*-values for testing differences in the mean levels between Japanese in Tokyo and Japanese Brazilians in São Paulo.
[b]*P*-values for testing differences in mean levels between Japanese in Tokyo and Japanese Americans in Hawaii.
[c]*P*-values for testing differences in mean levels between Japanese Brazilians in São Paulo and Japanese Americans in Hawaii.
[d]Adjusted for sex, age, season, fasting status, smoking status, BMI, alcohol intake, and plasma levels of high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and triglyceride.

also significantly different between the populations, with the highest levels for Japanese in Tokyo, followed by Japanese Brazilians and Japanese Americans. Plasma total lycopene and *trans*-lycopene levels did not significantly differ between the three populations. The plasma 5-*cis*-lycopene level was lower in Japanese in Tokyo than in the other two populations, but a significant difference was observed between Japanese in Tokyo and Japanese Brazilians only.

Plasma levels of tocopherol, vitamin D, and coenzyme Q10 in the three populations are compared in Table 3. No significant difference in plasma levels of α-tocopherol and β + γ-tocopherol was found. Plasma levels of 25-hydroxy vitamin D and total coenzyme Q10 were significantly lower in Japanese in Tokyo than in the other two populations.

Discussion

Overall, we found significantly lower levels of plasma carotenoids (except for lycopene) and retinol in Japanese Americans in Hawaii than in Japanese in Tokyo and Japanese Brazilians in São Paulo. The plasma total

Table 3 Adjusted geometric means and 95% confidence intervals in the three populations

	Tokyo	São Paulo	Hawaii	*P* for difference		
				P[a]	*P*[b]	*P*[c]
α-Tocopherol (ng/ml)						
Number of participants	142	79	70			
Multivariate[d]	11869.5	11316.9	12244.8	0.26	0.52	0.08
95% CI	11 320.79–12 444.7	10 511.7–12 183.9	11 300.22–13 268.3			
β + γ-Tocopherol (ng/ml)						
Number of participants	142	78	75			
Multivariate[d]	1527.6	1377.4	1412.0	0.18	0.35	0.75
95% CI	1402.4–1664.0	1205.0–1574.4	1224.3–1628.4			
25-hydroxy vitamin D (nmol/l)						
Number of subjects	142	78	68			
Multivariate[e]	52.8	62.2	61.4	< 0.01	< 0.01	0.78
95% CI	50.0–55.7	57.1–67.7	56.4–66.8			
Total coenzyme Q10 (ng/ml)						
Number of participants	141	79	76			
Multivariate[e]	1018.5	1249.8	1221.8	0.01	0.02	0.76
95% CI	934.1–1110.6	1093.6–1428.3	1071.7–1392.8			

CI, confidence interval.
[a]*P*-values for testing differences in the mean levels between Japanese in Tokyo and Japanese Brazilians in São Paulo.
[b]*P*-values for testing differences in the mean levels between Japanese in Tokyo and Japanese Americans in Hawaii.
[c]*P*-values for testing differences in the mean levels between Japanese Brazilians in São Paulo and Japanese Americans in Hawaii.
[d]Adjusted for sex, age, season, fasting status, smoking status, BMI, alcohol intake, and plasma levels of high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and triglycerides.
[e]Adjusted for sex, age, season, fasting status, smoking status, BMI, and alcohol intake.

carotenoid level was the highest in Japanese Brazilians among the three populations, whereas plasma lycopene and tocopherol levels did not substantially differ. We also found significantly lower levels of plasma 25-hydroxy vitamin D and total coenzyme Q10 in Japanese in Tokyo than in Japanese Americans and Japanese Brazilians.

As an initial comment, differences in study protocols should be considered, as we cannot exclude the possibility that these explain the differences observed in the present study. One major difference is the method of blood collection. We used EDTA-2Na plasma samples from Japanese in Tokyo and heparinized plasma samples from Japanese Brazilians and Japanese Americans. Although both were plasma samples, the difference in anticoagulants may have affected the analytical values. To minimize this possibility, we measured all biomarkers in both EDTA-2Na and heparinized plasma samples in a subset of participants ($n = 15$) and calibrated the values in the study using EDTA-2Na plasma samples. The difference in anticoagulants is therefore unlikely to have caused the observed differences in analytes across the three populations. Moreover, although the blood collection methods were somewhat different, we measured each biomarker in the same laboratory and in batched samples, so that the same numbers of samples from the three populations were analyzed in each analytical batch, minimizing the effect of laboratory variation.

Another source of variation may have been the way the participants were recruited. As the Japanese in Tokyo were examinees of a cancer screening program, they were asymptomatic, and possibly particularly health conscious. In contrast, the Japanese Brazilian and Japanese American participants were generally symptomatic patients who had undergone colonoscopy in the respective participating hospitals. We therefore cannot deny the possibility that this difference could have affected the study findings, although several biomarkers significantly differed between Japanese Americans and Japanese Brazilians but not between Japanese in Tokyo and Japanese Brazilians.

Plasma carotenoid levels can be used as biomarkers of intake of vegetables and fruits over the preceding weeks or months (Record *et al.*, 2001; Al-Delaimy *et al.*, 2005). Supplement use is also an important determinant of plasma nutrient levels; here, however, a lack of composition data for supplements meant that we were unable to calculate intake from this source, and plasma carotenoid levels accordingly reflect intake from both diet and supplements. Given the low prevalence of supplement users for carotenoids, at 3.5 and 0% by Japanese in Tokyo and Japanese Brazilians, respectively, the major determinant in the present study appears likely to be dietary intake, particularly considering that these two populations had the highest plasma carotenoid levels.

We found significantly lower plasma carotenoid levels in Japanese Americans in Hawaii than in Japanese in Tokyo and Japanese Brazilians in São Paulo, whereas plasma lycopene levels did not substantially differ between the three populations. In particular, plasma carotenoid levels were the highest in Japanese Brazilians, followed by Japanese in Tokyo and Japanese Americans. These findings suggest that consumption of green and yellow vegetables is the lowest in Japanese Americans and highest in Japanese Brazilians and support our hypothesis that the slower pace of increase in colorectal cancer upon migration in Japanese Brazilians, compared with Japanese

Americans, might partially result from higher plasma carotenoid levels among Japanese Brazilians. We note that, although plasma β-carotene levels were the lowest in Japanese Americans, the mean level (249.8 ng/ml) was nevertheless not particularly low compared with that in a study that showed an inverse association between serum β-carotene levels and the risk of colorectal cancer (Kabat *et al.*, 2012). Indeed, compared with the lowest tertile (< 173.5 ng/ml), the hazard ratio (95% confidence interval) for the middle (between 173.5 and 334.5 ng/ml) and highest (>334.5 ng/ml) tertiles was 0.57 (0.32–1.00) and 0.47 (0.25–0.88), respectively.

With regard to Japanese in Tokyo and Japanese Brazilians, the plasma levels of total carotenoids and *trans*-β-cryptoxanthin were significantly higher in the latter, whereas plasma total *trans*-lutein/zeaxanthin levels were significantly higher in the former. This difference in carotenoid profile might reflect different intake compositions and intake amounts of vegetables and fruits between these populations. For example, higher β-cryptoxanthin levels may reflect a higher intake of citrus fruits among Japanese Brazilians compared with Japanese in Tokyo. We previously compared serum total carotene levels between six populations, namely male Japanese Brazilians in São Paulo and Japanese men living in five different prefectures (Iwate, Akita, Tokyo, Nagano, and Okinawa), and observed the highest values in Japanese Brazilians (Tsugane, 1996). This is in general agreement with the present findings, albeit that this investigation was conducted in 1989.

It has been speculated that higher plasma retinol and/or tocopherol levels might be associated with a decreased risk of colorectal cancer, owing to their antioxidant and other biological properties. Findings from previous epidemiological studies, however, have been inconsistent (Wakai *et al.*, 2005; Kabat *et al.*, 2012). Here, we found a significantly lower level of plasma retinol in Japanese Americans in Hawaii than in Japanese in Tokyo and Japanese Brazilians in São Paulo. Given that the circulating level of retinol is highly regulated and essentially homeostatically controlled when liver stores are adequate (Olson, 1984), the reason for the lower level in Japanese Americans is unclear. In addition, this difference cannot be explained by the difference in blood collection anticoagulants, because a significant difference was observed between Japanese Americans and Japanese Brazilians, for whom we used heparinized plasma samples. Unlike retinol, vitamin E has no known principal storage compartment and plasma levels are moderately responsive to α-tocopherol intake (Jacques *et al.*, 1993; Willett *et al.*, 1983). Surprisingly, however, we found no substantial difference in plasma tocopherol levels between the three populations.

We found significantly lower levels of plasma 25-hydroxy vitamin D in Japanese in Tokyo than in Japanese Americans and Japanese Brazilians. Given that some of the vitamin D in the body is derived from diet but it is mainly (≥90%) synthesized in sun-exposed skin, the lower plasma 25-hydroxy vitamin D levels in Japanese in Tokyo may be the result of geographical differences, with the latitude of Tokyo at ∼35° North versus ∼23° South for São Paulo and 21° North for Hawaii. As recent meta-analyses of circulating 25-hydroxy vitamin D levels have fairly consistently shown a significant inverse association with colorectal cancer (Gandini *et al.*, 2011; Lee *et al.*, 2011), our findings suggest that plasma 25-hydroxy vitamin D levels may be a more important risk factor for Japanese in Tokyo than for the other two populations.

Coenzyme Q10 is a component of the mitochondrial respiratory chain and is considered to be an important cellular antioxidant (Crane, 2001). Although several epidemiological studies have investigated associations between plasma coenzyme Q10 levels and the risk of several types of cancer (Chai *et al.*, 2010, 2011), to our knowledge no study has reported on colorectal cancer. The present study observed a significantly lower total coenzyme Q10 level in Japanese in Tokyo than in the other two populations. Coenzyme Q10 is synthesized by human cells and is derived from dietary intake (Bentinger *et al.*, 2010). The observed difference might be explained by differences in foods that contribute to the dietary intake of coenzyme Q10 or in the prevalence of supplement users in the populations (or both) (Weber *et al.*, 1997).

Conclusion

This cross-sectional study found lower levels of plasma carotenoids and retinol in Japanese Americans in Hawaii than in Japanese in Tokyo and Japanese Brazilians in São Paulo, and lower levels of plasma 25-hydroxy vitamin D and total coenzyme Q10 in Japanese in Tokyo than in the other two populations. These differences may contribute to the previously observed differences in colorectal cancer incidence and mortality between the three populations and provide leads with regard to the primary prevention of this cancer in each population.

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Conflicts of interest

There are no conflicts of interest.

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