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

Motoki Iwasaki^a, Adrian A. Franke^b, Gerson Shigeaki Hamada^c, Nelson Tomio Miyajima^d, Sangita Sharma^e, Junko Ishihara^{a,f}, Ribeka Takachi^{a,g}, Shoichiro Tsugane^a, and Loïc Le Marchand^b

^aEpidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

^bEpidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii, USA

^cNikkei Disease Prevention Center, São Paulo, Brazil

^dSociedade Beneficente de Cotia Hospital, São Paulo, Brazil

^eDepartment of Medicine, University of Alberta, Edmonton, Canada

^fDepartment of Nutrition Management, Sagami Women's University, Kanagawa, Japan

^gDepartment of Community Preventive Medicine, Division of Social and Environmental Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Abstract

Objectives—Previous studies of Japanese migrants have suggested that the increase in colorectal cancer rates occurring after migration is slower among Japanese Brazilians than Japanese Americans. We hypothesized that this difference may partly reflect differences in vegetable and fruit intake between populations.

Methods—Using data from validation studies of food frequency questionnaires being used in a comparative case-control study of colorectal adenoma in Tokyo, São Paulo, and Hawaii, plasma carotenoids, retinol, tocopherols, and coenzyme Q10 levels were measured by high-performance liquid chromatography, and 25-hydroxy vitamin D levels 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.

Results—Overall, we found significantly lower plasma carotenoid levels, except for lycopene, and retinol levels in Japanese Americans than in Japanese in Tokyo and Japanese Brazilians. Plasma total carotenoids level was highest in Japanese Brazilians. Compared to mean level among Japanese Brazilians (1741.2 ng/mL), *p* for difference was 0.03 for Japanese in Tokyo (1514.4

Address for correspondence: Motoki Iwasaki, MD, PhD, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan. Phone: +81-3-3542-2511 (ext 3391), Fax: +81-3-3547-8578, moiwasak@ncc.go.jp.

Statement of conflict of interest

The authors have no conflict of interest.

ng/mL) and <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-hydroxyvitamin D and total coenzyme Q10 levels in Japanese in Tokyo than in Japanese Americans and Japanese Brazilians.

Conclusion—Higher levels of plasma carotenoids among Japanese Brazilians than Japanese in Tokyo and Hawaii may contribute to the slower pace of increase in colorectal cancer rates observed in that population following migration.

Keywords

carotenoids; tocopherols; Japanese Americans; Japanese Brazilians

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 observed among Japanese who migrated to the United States (US) occurred 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 [1,2]. In 1983–1987, Japanese American men in Hawaii and Los Angeles had the highest incidence rates for colorectal cancer among the more than 175 populations followed for cancer incidence worldwide [3]. In contrast, colorectal cancer rates in 1969–78 had not increased among first-generation Japanese migrants to São Paulo, despite a high red meat intake and a higher body mass index (BMI) compared to Japanese in Japan [4–6]. However, more recent data from 2000 showed that mortality from colorectal cancer among first-generation Japanese migrants to São Paulo had approximated that of Japanese in Japan [7,8].

These descriptive epidemiologic features might reflect differences in risk factors between populations, or screening practices. The slower pace of increase in colorectal cancer among Japanese Brazilians than Japanese Americans implies the existence of either or both preventive factors in São Paulo or risk factors in 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 [6], it was hypothesized that the frequent intake of vegetables and fruits among Japanese Brazilians might lower their risk [7]. 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 [9]. 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 US.

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 lower risk, and plasma levels of these agents can more generally be used as biomarkers of vegetable and fruit intake over the preceding weeks or months [10,11]. In addition, retinol,

tocopherols, 25-hydroxy vitamin D and coenzyme Q10 are of particular interest in relation to colorectal cancer risk [12–16]. The characterization of differences in 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 subjects 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 [17,18]. They were selected from examinees of the cancer screening program at the Research Center for Cancer Prevention and Screening, National Cancer Center, Japan, who met the following criteria: 1) age between 40 and 69 years; 2) residence in Tokyo and suburban prefectures; and 3) 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 FFQ; a fasting blood sample, from which serum and EDTA-2Na plasma was prepared and stored frozen at -80°C ; and a 24-hour urine sample. The study design and data collection for the validation study have been described in detail elsewhere [19]. The study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan.

Japanese Brazilians in São Paulo—Study subjects were participants in a validation study of the quantitative FFQ used in a case-control study of colorectal adenoma in São Paulo [20]. They were selected from participants in a case-control study of colorectal adenoma in São Paulo who met the following criteria: 1) age between 40 and 79 years; 2) residence in the state of São Paulo for at least six months prior to recruitment; 3) at least three grandparents of pure Japanese ancestry; and 4) no history of colorectal cancer or history of other invasive cancer in the past ten years. A total of 96 men and women provided food diaries over four consecutive days and a fasting blood sample, from which heparinized plasma was stored frozen at -80°C , between August 2008 and November 2009. In this study, 79 subjects whose samples were available for analysis were included. Details of the validation study have been described elsewhere [21]. The study was approved by the University of Hawaii, Committee on Human Studies, as well as the Brazilian Ministries of Health, Science and Technology, and of Foreign Affairs, and the Brazilian National Ethics Commission.

Japanese Americans in Hawaii—Study subjects from Hawaii were selected from among the Japanese American participants in an endoscopy-based case-control study of adenoma in Hawaii [22,23]. Seventy-eight subjects aged 40–79 years old who did not have history of cancer completed a four-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 photo diode array detection after extraction with hexane [24,25]. Plasma total coenzyme Q10 was measured by a recently established HPLC method with precolumn electrochemical oxidation and photo diode array detection [26]. Plasma levels of 25-hydroxy vitamin D were measured using a commercial enzyme immunoassay kit (Immunodiagnostic Systems Inc., enzymatic kit AA-35F1) 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. In order to calibrate values from EDTA-2Na plasma samples, we measured all biomarkers in both EDTA-2Na and heparinized plasma samples prepared from the same subjects ($n=15$). In addition, blind triplicate heparinized plasma samples from 15 subjects were included in each assay as quality control. Lower detection limits (LODs) and intra-assay coefficients of variation (CV) for each biomarker are presented in Table S1. The CVs for 9 of 16 biomarkers were 5% or lower and those for 6 biomarkers were between 5% and 10%. In contrast, the CV for total coenzyme Q10 was highest among the 16 biomarkers, at 17.4%.

Statistical analysis

We excluded subjects 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 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 subjects. The intercepts and slopes of these regressions were then used to estimate calibrated values for Japanese in Tokyo based on 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 (CIs) 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 hours or less, more than 10 hours), smoking status (never, past, current smoker), BMI (continuous), alcohol intake (g per day), and plasma levels of high-density lipoprotein (HDL) cholesterol (continuous), non-HDL cholesterol (continuous), and triglyceride (continuous). 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 significance level was set at $p<0.05$. All statistical analyses were performed with SAS software version 9.1 (SAS Institute, Inc., Cary, NC).

Results

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

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

Table 2 compares plasma carotenoids and retinol levels between Japanese in Tokyo, Japanese Brazilians in São Paulo, and Japanese Americans in Hawaii. Overall, plasma carotenoids and retinol levels were significantly lower for Japanese Americans than for the other two populations, except for lycopene. Plasma levels of alpha-carotene, total beta-carotene, trans-beta-carotene, cis-beta-carotene, and alpha-cryptoxanthin were significantly lower in Japanese Americans than in the other two populations. Plasma total carotenoids and trans-beta-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 also significantly different between 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. Plasma 5-cis-lycopene level was lower in Japanese in Tokyo than in the other two populations but significant difference was observed between Japanese in Tokyo and Japanese Brazilians only.

Plasma levels of tocopherols, vitamin D, and coenzyme Q10 in the three populations are compared in Table 3. No significant difference in plasma level of alpha-tocopherol and beta+gamma-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. Plasma total carotenoids level was 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 since 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 subjects (n =15) and calibrated 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 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 subjects were recruited. Since 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 subjects were generally symptomatic patients who had undergone colonoscopy in the respective participating hospitals. We therefore cannot deny the possibility that this difference 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 preceding weeks or months [10,11]. 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 Japan 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 carotenoids levels were highest in Japanese Brazilians, followed by Japanese in Tokyo, and Japanese Americans. These findings suggest that consumption of green and yellow vegetables was 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 to Japanese Americans, might partially result from higher plasma carotenoids levels among Japanese Brazilians. We note that although plasma beta-carotene levels were the lowest in Japanese Americans, their mean level (249.8 ng/mL) was nevertheless not particularly low compared to that in a study which showed an inverse association between serum beta-carotene and the risk of colorectal cancer [12]. Indeed, compared to the lowest tertile (less than 173.5 ng/mL), hazard ratio (95% confidence interval) for the middle (between 173.5 and 334.5 ng/mL) and highest tertiles (more than 334.5 ng/mL) was 0.57 (0.32–1.00) and 0.47 (0.25–0.88), respectively.

With regard to Japanese in Tokyo and Japanese Brazilians, plasma levels of total carotenoids and trans-beta-cryptoxanthin were significantly higher in the latter, while plasma total trans-lutein/zeaxanthin levels were significantly higher in the former. This difference in carotenoid profile might reflect different intake composition and intake amounts of vegetables and fruits between these populations. For example, higher beta-cryptoxanthin levels may reflect a higher intake of citrus fruits among Japanese Brazilians compared to 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 [27]. 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 [12,13]. 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 [28], 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 significant difference was observed between Japanese Americans and Japanese Brazilians, for which we used heparinized plasma samples. Unlike retinol, vitamin E has no known principal storage compartment and plasma levels are moderately responsive to alpha-tocopherol intake [29,30]. Surprisingly, however, we found no substantial difference in plasma tocopherol level 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 vitamin D in the body is derived from the diet but is mainly (90%) synthesized in the 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 approximately 35 degrees north - versus approximately - 23 degrees south for São Paulo and 21 degrees north for Hawaii. Since recent meta-analyses of circulating 25-hydroxy vitamin D levels have fairly consistently shown a significant inverse association for colorectal cancer [14,15], 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 an important cellular antioxidant [31]. Although several epidemiological studies have investigated an association between plasma coenzyme Q10 level and the risk of several sites of cancer [16,32], 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 [33]. The observed difference might be explained by the difference in foods which contribute to the dietary intake of coenzyme Q10 or prevalence of supplement users between the populations (or both) [34].

In 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 levels 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

BMI	body mass index
CV	coefficient(s) of variation
CI	confidence interval
FFQ	food frequency questionnaire
HDL	high-density lipoprotein
HPLC	high-performance liquid chromatography
LOD	lower detection limit

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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, number (%)	68 (48.0)	28 (35.0)	37 (47.0)	0.17
Smoking status				
Never smokers, number (%)	79 (55.6)	54 (68.4)	43 (55.1)	
Past smokers, number (%)	46 (32.4)	19 (24.1)	29 (37.2)	
Current smokers, number (%)	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
Body mass index (kg/m ²)				
Mean (SD)	22.4 (2.7)	24.5 (4.0)	26.7 (4.3)	<0.01
Plasma level of high-density lipoprotein (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

SD, standard deviation; HDL, high-density lipoprotein.

^aNon-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 (CI) in the three populations.

	Tokyo	São Paulo	Hawaii	P for difference		
				p ^a	p ^b	p ^c
Total carotenoids (ng/mL)						
Number of subjects	142	79	76			
Multivariate ^d (95% CI)	1514.4 (1408.1–1628.7)	1741.2 (1555.3–1949.2)	1257.7 (1114.6–1419.1)	0.03	0.01	<0.01
alpha-Carotene (ng/mL)						
Number of subjects	142	79	76			
Multivariate ^d (95% CI)	91.4 (82.1–101.7)	89.4 (75.7–105.6)	61.6 (51.5–73.6)	0.82	<0.01	<0.01
Total beta-carotene (ng/mL)						
Number of subjects	142	79	76			
Multivariate ^d (95% CI)	434.6 (383.3–492.8)	372.5 (306.5–452.6)	249.8 (202.8–307.8)	0.17	<0.01	<0.01
trans-beta-Carotene (ng/mL)						
Number of subjects	142	79	76			
Multivariate ^d (95% CI)	402.2 (354.6–456.3)	341.5 (280.8–415.2)	230.0 (186.6–283.6)	0.15	<0.01	<0.01
cis-beta-Carotene (ng/mL)						
Number of subjects	142	79	76			
Multivariate ^d (95% CI)	31.0 (27.2–35.3)	29.3 (23.9–35.8)	19.4 (15.6–24.1)	0.62	<0.01	<0.01
Total lycopene (ng/mL)						
Number of subjects	142	78	76			
Multivariate ^d (95% CI)	388.5 (364.8–413.8)	406.0 (368.1–447.9)	398.5 (358.9–442.6)	0.44	0.68	0.75
trans-Lycopene (ng/mL)						
Number of subjects	141	77	76			
Multivariate ^d (95% CI)	122.0 (113.9–130.6)	115.8 (104.0–128.9)	130.1 (116.1–145.8)	0.40	0.34	0.07
5-cis-Lycopene (ng/mL)						
Number of subjects	142	77	76			
Multivariate ^d (95% CI)	158.0 (148.5–168.0)	181.6 (164.8–200.1)	169.1 (152.6–187.4)	0.01	0.27	0.21
alpha-Cryptoxanthin (ng/mL)						
Number of subjects	142	78	74			

	Tokyo	São Paulo	Hawaii	P for difference		
				p ^a	p ^b	p ^c
Multivariate ^d (95% CI)	33.8 (32.0–35.7)	31.6 (28.9–34.4)	26.6 (24.2–29.2)	0.17	<0.01	<0.01
trans-beta-Cryptoxanthin (ng/mL)						
Number of subjects	142	79	76			
Multivariate ^d (95% CI)	188.7 (162.9–218.5)	289.1 (230.2–363.0)	126.5 (99.1–161.4)	<0.01	0.01	<0.01
Total trans-lutein/zeaxanthin (ng/mL)						
Number of subjects	142	79	76			
Multivariate ^d (95% CI)	194.1 (179.6–209.7)	152.7 (135.4–172.2)	114.1 (100.4–129.8)	<0.01	<0.01	<0.01
Retinol (ng/mL)						
Number of subjects	142	79	75			
Multivariate ^d (95% CI)	639.7 (611.4–669.3)	589.0 (549.0–631.9)	520.6 (482.6–561.5)	0.04	<0.01	<0.01

CI, confidence interval.

^aP values for testing differences in mean levels between Japanese in Tokyo and Japanese Brazilians in São Paulo.

^bP values for testing differences in mean levels between Japanese in Tokyo and Japanese Americans in Hawaii.

^cP values for testing differences in mean levels between Japanese Brazilians in São Paulo and Japanese Americans in Hawaii.

^dAdjusted for sex, age, season, fasting status, smoking status, body mass index, alcohol intake, and plasma levels of high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and triglyceride.

Table 3

Adjusted geometric means and 95% confidence intervals (CI) in the three populations.

	Tokyo	São Paulo	Hawaii	P for difference		
				p ^a	p ^b	p ^c
alpha-Tocopherol (ng/mL)						
Number of subjects	142	79	70			
Multivariate ^d (95% CI)	11869.5 (11320.8–12444.7)	11316.9 (10511.7–12183.9)	12244.8 (11300.2–13268.3)	0.26	0.52	0.08
beta++ gamma-Tocopherol (ng/mL)						
Number of subjects	142	78	75			
Multivariate ^d (95% CI)	1527.6 (1402.4–1664.0)	1377.4 (1205.0–1574.4)	1412.0 (1224.3–1628.4)	0.18	0.35	0.75
25-hydroxy vitamin D (nM)						
Number of subjects	142	78	68			
Multivariate ^e (95% CI)	52.8 (50.0–55.7)	62.2 (57.1–67.7)	61.4 (56.4–66.8)	<0.01	<0.01	0.78
Total coenzyme Q10 (ng/mL)						
Number of subjects	141	79	76			
Multivariate ^e (95% CI)	1018.5 (934.1–1110.6)	1249.8 (1093.6–1428.3)	1221.8 (1071.7–1392.8)	0.01	0.02	0.76

CI, confidence interval.

^aP values for testing differences in mean levels between Japanese in Tokyo and Japanese Brazilians in São Paulo.

^bP values for testing differences in mean levels between Japanese in Tokyo and Japanese Americans in Hawaii.

^cP values for testing differences in mean levels between Japanese Brazilians in São Paulo and Japanese Americans in Hawaii.

^dAdjusted for sex, age, season, fasting status, smoking status, body mass index, alcohol intake, and plasma levels of high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and triglyceride.

^eAdjusted for sex, age, season, fasting status, smoking status, body mass index, and alcohol intake.