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Long-chain n-3 polyunsaturated fatty acids and incidence rate of coronary artery calcification in Japanese in Japan and United States whites – population-based prospective cohort study

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Abstract

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Contributorship

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Sekikawa A, Lee S, and Bertolet M analyzed data or performed statistical analysis.

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All authors read and approved the final manuscript.

Competing interests

None to be declared

Statements

Objective—To determine whether serum levels of long-chain n-3 polyunsaturated fatty acids (LCn3PUFAs) contribute to the difference in incidence rate of coronary artery calcification (CAC) between Japanese in Japan and U.S. whites.

Methods—In a population-based prospective-cohort study, 214 Japanese and 152 white men aged 40–49 years at baseline (2002–2006) with coronary calcium score (CCS) = 0 were reexamined for CAC in 2007–2010. Among these, 175 Japanese and 113 whites participated in the follow-up exam. Incident cases were defined as participants with CCS ≥ 10 at follow-up. A relative risk regression analysis was used to model incidence rate ratio between Japanese and whites. The incidence rate ratio was first adjusted for potential confounders at baseline and then further adjusted for serum LCn3PUFAs at baseline.

Results—Mean (standard deviation) serum percentage of LCn3PUFA was > 100% higher in Japanese than in whites (9.08 (2.49) versus 3.84 (1.79), respectively, p<0.01). Japanese had a significantly lower incidence rate of CAC compared to whites (0.9 versus 2.9/100 person-years, respectively, p < 0.01). Incidence rate ratio of CAC taking follow-up time into account between Japanese and white men was 0.321 (95% confidence interval (CI) 0.150, 0.690: p<0.01). After adjusting for age, systolic-blood pressure, low-density-lipoprotein cholesterol, diabetes, and other potential confounders, the ratio remained significant: 0.262 (95% CI: 0.094, 0.731, p=0.01). After further adjusting for LCn3PUFAs, however, the ratio was attenuated and became non-significant (0.376 (95% CI: 0.090, 1.572, p=0.18).

Conclusions—LCn3PUFAs significantly contributed to the difference in CAC incidence between Japanese and white men.

Keywords

long-chain n-3 fatty acids; coronary artery calcification; prospective cohort study; incidence; risk factors

Introduction

Coronary heart disease (CHD) is a major public health problem not only in developed but also developing countries. [1] CHD rates in Japan is uniquely low compared to the U.S. and other developed countries. [2] Even among men born after World War II in Japan who are exposed to Westernized lifestyle since childhood, CHD mortality in Japan is much lower than in the U.S. despite a less favorable or similar profile of many cardiovascular risk factors in Japanese, including blood pressure (BP), low-density lipoprotein cholesterol (LDL-C), smoking, and type 2 diabetes (T2DM). [3] The low CHD mortality in Japan is not due to misclassification of the cause of death[4] or a cohort effect. [3]

Coronary artery calcification (CAC) is highly correlated to atherosclerotic burden of the coronary arteries. [5] Studies in the general population, [6, 7, 8] e.g., the Coronary Artery Risk Development in Young Adult (CARDIA), [6] the Multi-Ethnic Study of Atherosclerosis (MESA)[7] and ours[8] reported that CAC is associated with traditional risk factors. Moreover, CAC is a strong independent predictor of CHD. [9] We have previously reported that prevalence of CAC in Japanese was lower than that in U.S. whites whereas that in Japanese Americans was higher as compared to U.S. whites, [10] indicating that low CHD mortality in Japanese in Japan is unlikely to be primarily due to genetic factors.

Long-chain n-3 polyunsaturated fatty acids (LCn3PUFAs) are major regulators of multiple molecular pathways among other fatty acids, causing various biological effects, including anti-arrhythmic and anti-atherogenic effects. [11] The anti-arrhythmic effect is well documented and the results of some, but not all, randomized clinical trials (RCTs) support this effect. [12] Although several RCTs in patients with CHD or T2DM reported the effect

of LCn3PUFAs on the progression of atherosclerosis, [13, 14] no previous studies have reported the association of LCn3PUFAs with the progression of atherosclerosis in the general population.

Japanese have markedly higher dietary intake of LCn3PUFAs compared to other populations, e.g., 1,000 mg/day in Japan versus <100 mg/day in typical Western diet including the U.S. [15] We have previously reported in our cross-sectional study that high serum levels of LCn3PUFAs in Japanese significantly contributed to the difference in CAC prevalence between Japanese and U.S. whites. [10] In the current study, we hypothesized that CAC incidence rate was significantly lower in Japanese than U.S. whites and that higher levels of LCn3PUFAs contributed to the difference in CAC incidence rate. We tested these hypotheses in the electron-beam tomography, risk factor assessment among Japanese and U.S. men in the post-World-War-II birth cohort (ERA JUMP Study), a population-based study of 868 men aged 40–49 in the Japanese in Japan, U.S. whites, and Japanese Americans.

Methods

Study sample

The ERA JUMP Study is an international population-based study of atherosclerosis in men aged 40–49 at baseline. A detailed description of study design and methods has been published previously. [10] Briefly, 313 Japanese from Kusatsu, Shiga, Japan, 310 whites from Allegheny County, Pennsylvania, and 303 Japanese Americans in Honolulu, Hawaii, U.S. from a representative sample of offspring of fathers who participated in the Honolulu Heart Program were examined at baseline between 2002 and 2006. All participants were without clinical cardiovascular disease. The recruitment of the follow-up study in Japanese and whites started in 2007 and completed in 2010 whereas that in Japanese Americans started in 2009 and is ongoing. Thus, the current study presents data excluding Japanese Americans.

All participants from the baseline examination were invited to the follow-up. The rates of participation were 83.7% in Japanese (262/313) and 79.0% in whites (245/310). Among them, we excluded individuals with missing CAC (n=9) resulting in a total of 498 participants (255 Japanese and 243 white men). Characteristics of participants and non-participants were not statistically significantly different (online Table 1).

The current study analyzed incidence rather than progression of CAC because prevalence of CAC defined as a CCS ≥10 was low (9.3 %) in Japanese at baseline. [10] Incident cases were defined as individuals with a CCS = 0 at baseline (214 Japanese and 152 whites) and a CCS≥ 10 at follow-up. We used CCS ≥10 because 54% in Japanese (27/50) and 43% in whites (19/67) with CCS > 0 and <10 at baseline reverted to CCS = 0 at follow-up whereas only three Japanese and two whites with CCS ≥10 reverted to CCS = 0 at follow-up (online Table 2). Thus, the final sample consisted of individuals with CCS = 0 at baseline: 175 Japanese and 113 whites. Informed consent was obtained from all participants. The study was approved by the Institutional Review Boards of Shiga University of Medical Science, Otsu, Japan and University of Pittsburgh, Pittsburgh, U.S.

Coronary artery calcification (CAC)

CAC was measured using electron-beam computed tomography (EBT) (Imatron C150, GE Medical Systems, South San Francisco, US) at baseline both in Japan and the U.S. and follow-up in the U.S. [10] At follow-up in Japan, CAC was measured using a 16 multi-detector computed tomography (MDCT) (Toshiba Medical System Corporation, Tochigi, Japan). Scanners were calibrated regularly by technicians following a standardized protocol.

A total of 30 to 40 contiguous 3-mm-thick transverse images were obtained from the level of the aortic root to the apex of the heart. Images were recorded during a maximal breath hold using ECG-guided triggering. CAC was considered to be present with three contiguous pixels (area=1 mm^2) ≥130 Hounsfield Unit. One trained reader at the Cardiovascular Institute, University of Pittsburgh, read the images using a Digital-Imaging-and-Communications-in-Medicine workstation and software by the AccuImage Diagnostic Corporation, San Francisco, which calculates a coronary calcium score (CCS) with the Agatston scoring method. [10] The reader was blinded to participant's characteristics and the study centers. The intra-reader reproducibility of non-zero CCSs had an intra-class correlation of 0.98.

Serum LCn3PUFAs and other covariates

All participants underwent a physical examination, lifestyle questionnaire, and laboratory assessment as described previously. [10] BP was measured in the right arm of the seated participant after the participant emptied his bladder and sat quietly for five minutes, using an appropriate-sized cuff, with an automated sphygmomanometer (BP-8800, Colin Medical Technology, Komaki, Japan). The average of two measurements was used. T2DM was defined as an individual with fasting glucose ≥ 7.0 mmol/L or under diabetic medication. Alcohol drinkers were defined as those who drank alcohol ≥two days per week.

Venipuncture was performed early in the clinic visit after a 12-hour fast. Serum and plasma samples were stored at −80°C, shipped on dry ice to University of Pittsburgh to determine levels of LDL-C, HDL-C, triglycerides, glucose, and CRP. Gas chromatography was used to determine serum n-3 and other fatty acid content which is expressed as a percentage of serum total fatty acids. The coefficients of variation between runs for major marine-derived n-3 fatty acids, eicosapentaenoic acid (20:5n-3) (EPA) and docosahexaenoic acid (22:6n-3) (DHA) were 4.5% and 7.2%, respectively as previously reported. [10]

Statistical Methods

An incidence rate was calculated as the number of incident cases divided by the number of population exposed to risk between baseline and follow-up scans (per 100 person year). To compare baseline characteristics between Japanese and whites as well as between incident and non-incident cases in each of Japanese and whites, t-test or Mann-Whitney-U test for continuous variables and Chi-square test for categorical variables were used.

A relative risk regression analysis was used to model incidence rate ratio between Japanese and whites after adjusting for potential confounders, using a generalized linear model with log link and binomial error distribution. First, we showed a relative risk in unadjusted model which took follow-up time into account. Then, in model I, we adjusted for age, systolic BP, LCL-C, HDL-C, triglycerides, diabetes, BMI, pack-years of smoking, and medication for hypertension based on previous literature. [16, 17] Finally in model II, we further adjusted for total LCn3PUFAs, which were defined as the sum of EPA, DHA and docosapentaenoic acid. P values of < 0.05 were considered to indicate statistical significance. All these statistical analyses were performed with Stata version 11.2 (StataCorp LP, College Station, TX, U.S.).

Results

Baseline characteristics show that age, systolic BP, LDL-C, triglycerides and rates of T2DM were not significantly different between the two groups ($p > 0.10$). Japanese compared to whites had significantly higher rates of both current and former smokers and higher levels of glucose (p values <0.05), although Japanese had significantly lower levels of BMI and CRP

and significantly higher levels of HDL-C (p values <0.05). Mean percentages of total LCn3PUFAs, EPA, and DHA were more than 100% higher in Japanese than in whites (p values <0.01). Among these individuals, 10 Japanese and 15 whites had a CCS ≥10 at follow-up and the incidence rate of CAC was significantly lower in Japanese than in whites (p <0.01) (Table 1).

Table 2 shows risk factors and other covariates between incident and non-incident cases in each group. These factors were not significantly different in either Japanese or whites (p > 0.10). The only exception was systolic BP in Japanese, which was significantly higher in incident cases than non-incident cases (p <0.01).

The incidence rate ratio of CAC between Japanese and white men was 0.321 (p < 0.01) in an unadjusted model (Table 3). After adjusting for systolic BP, LCL-C, HDL-C, triglycerides, diabetes, BMI, pack-years of smoking, and medication for hypertension, the incidence rate ratio remained significant (Model I in Table 3). After further adjusting for total LCn3PUFAs, the statistical significant difference in incidence rate ratio was attenuated and became non-significant (Model II in Table 3).

Discussion

This international study has shown that CAC incidence rate was significantly lower in Japanese than in U.S. whites and that the significant difference in CAC incidence rate, which remained after adjusting for risk factors and potential confounders, became non-significant after further adjusting for serum LCn3PUFAs. The results of the longitudinal study extended our previous findings from our cross-sectional study, [10] suggesting that high dietary intake of LCn3PUFAs contributed to the low levels of atherosclerosis in Japanese.

Results from two recent large studies in Japan support the anti-atherogenic effect of LCn3PUFAs. [18, 19] The Japan EPA Lipid Intervention Study (JELIS) tested a hypothesis that long-term supplementation with 1,800 mg/day EPA prevented major coronary events in 18,645 hypercholesterolemic individuals. [18] After a mean follow-up of 4.6 years, a 19% significant relative reduction in primary endpoint occurred in the EPA group. Similarly, a 10-year-longitudinal population-based study of 41,578 individuals aged 40–59 in Japan reported that dietary intake of LCn3PUFAs had a significant inverse association with non-fatal coronary events. [19]

In contrast, several recent RCTs of LCn3PUFAs on cardiovascular disease, i.e., SU.FOL.OM3, [20] Alpha Omega Trail, [21] ORIGIN, [22] and the Risk and Prevention Study[23] failed to show their beneficial effect. However, doses of LCn3PUFAs used in these RCTs were much lower than the dose in JELIS: 376 to 900 mg/day vs. 1,800 mg/day, respectively. Moreover, background dietary intake of LCn3PUFAs in these populations is substantially lower than that in Japan. Therefore, these results from recent RCTs do not address the question whether LCn3PUFAs at levels observed in Japanese have the anti-atherogenic effect.

We defined incident cases of CAC as those with CCS = 0 at baseline and CCS ≥10 at follow-up. This is because we cannot deny the possibility that CCSs of 1 to 9 is a noise. Indeed a substantial proportion of individuals with CCSs > 0 and <10 at baseline reverted to CCS = 0 at follow-up (39% (46/117)). Inter-scan variability of CCS is much higher when CCSs are >0 and <10 as compared to CCSs ≥10. [24] For this reason, the Dallas Heart Study used CCS ≥10 as the presence of CAC. [24] Although CARDIA and MESA defined incident cases of CAC as individuals with CCA = 0 at baseline and CCS >0 at follow-up, a noise caused by inter-scan variability in these studies is expected to be lower than our study

because these studies scanned twice at both baseline and follow-up[25] whereas our study scanned once both at baseline and follow-up.

The effect of LCn3PUFAs on cardiovascular risk factors has been documented in RCTs and experimental studies showing that LCn3PUFAs significantly lower triglycerides and BP, non-significantly raise HDL-C, and have inconsistent effects on LDL-C, glucose, and CRP. [11, 26, 27] The anti-atherogenic effect of LCn3PUFAs is, however, unlikely to be mediated through these factors in the current study because the difference in the incidence rate ratio of CAC remained significant after adjusting for these factors but became non-significant after further adjusting for LCn3PUFAs. Experimental studies show that LCn3PUFAs have various anti-atherogenic properties including suppressing the production of inflammatory cytokines, and the expression of cell-adhesion molecules as well as improving endothelial function, platelet function, and plaque stability. [11, 27] Additionally, long-term exposure to high dose of LCn3PUFAs observed in Japanese is likely to have effects on immune cell and gene expressions such as inhibiting the activation of nuclear factor kappa-B, which in turn results in reduced expression of genes encoding proteins involved in inflammation. [11, 27] In fact, it is speculated that many of these anti-atherogenic actions of LCn3PUFAs most likely require their intakes ≥ 1 g/day. [11]

Study Limitations

The current study has several limitations. The number of CAC incident cases was small and our univariate analyses were unable to identify factors significantly associated with incident cases except for systolic BP in Japanese. The current study examined men aged 40–49 at baseline and the results may not be generalized to older age groups or women. However, we chose this age group specifically because unlike older age groups, levels of serum total cholesterol and BP have been similar between Japanese and U.S. whites throughout their lifetime in men in this birth cohort. [8] Although EBT was used at baseline both in the U.S. and Japan, and at follow-up in the U.S., MDCT was used at follow-up in Japan. Moreover the current study did not use an external standard to calibrate CCS between EBT and MDCT in Japan. Since MDCT as compared to EBT may be less sensitive in detecting low CCSs, [28] our analysis defining incident cases as those with CCSs ≥10 at follow-up should be more robust than analysis defining incidence cases as those with CCSs >0 at follow-up. Although individuals with CCSs ≥10 are reported to have a significant association with all-cause mortality as compared to individuals with CCS=0, [29] incidence cases of CAC are not a clinical outcome. Because the study is observational, our finding might be due to unmeasured confounders. Serum LCn3PUFAs reflect short-term dietary fat intake and may not reflect long-term dietary intake. [30] However, because the variation in serum LCn3PUFAs occurs randomly, the actual association of LCn3PUFAs with CAC incidence is likely to be stronger than was observed in the current study.

Conclusions

In summary, the present study has shown that CAC incidence rate was significantly lower in Japanese than in U.S. whites and that this difference cannot be explained by differences in known risk factors. It did, however, became non-significant after further adjusting for serum LCn3PUFAs. These results may suggest the anti-atherogenic effect of LCn3PUFAs at levels observed in Japanese.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known about this subject?

Much higher serum levels of long-chain n-3 polyunsaturated fatty acids (LCn3PUFAs) in Japanese in Japan than in the U.S. significantly contributed to the cross-sectional difference in atherosclerosis evaluated by coronary artery calcification (CAC) and intima-media thickness of the carotid artery, both are independent predictors of future cardiovascular events, between men in Japan and the U.S.

What does this study add

Serum levels of LCn3PUFAs in Japanese in Japan significantly contributed to the longitudinal difference in CAC, i.e., incidence of CAC, in men between Japan and the U.S., independent of other cardiovascular risk factors.

How might this impact on clinical practice?

Higher dose of LCn3PUFAs than that used in recent randomized clinical trials of LCn3PUFAs on cardiovascular disease may potentially have beneficial effects on cardiovascular disease.

Table 1

Characteristics of participants with zero coronary calcium score at baseline, number of incidence cases and incidence rates in Japanese and whites

	Japanese (n=175)	Whites (n=113)
Age (years)	44.9 (2.8)	44.7 (2.9)
Body-mass index (kg/m^2)	23.2 (2.8)	26.3 (3.0)
Systolic blood pressure (mmHg)	124.0 (15.3)	121.6 (11.0)
Medication for hypertension (%)	4.0	5.3
LDL-C (mmol/L)	3.33 (0.95)	3.45 (0.81)
HDL-C (mmol/L)	1.41 (0.36)	1.25 (0.30)
Triglycerides (mmol/L)	1.48 (1.08, 1.97)	1.36 (1.02, 1.87)
Medication for hyperlipidemia (%)	1.7	8.0
Glucose (mmol/L)	5.81 (0.69)	5.52 (0.47)
Diabetes (%)	4.6	1.8
C-reactive protein (mg/L)	0.30 (0.15, 0.65)	0.83 (0.44, 1.65)
Smoking		
Current (%)	48.6	8.0
Former (%)	32.0	18.6
Pack years	18.0 (3.0, 29.0)	0.0 (0.0, 1.6)
Alcohol		
Drinker (≥2 day/week)	68.0	54.9
Ethanol consumption (g/day)	14.0 (2.9, 38.0)	8.2 (1.6, 18.7)
Total LCn3PUFAs (%)	9.08 (2.49)	3.84 (1.79)
Eicosapentaenoic acids (EPA) (%)	2.36 (1.12)	0.79 (0.63)
Docosahexaenoic acids (DHA) (%)	5.88 (1.51)	2.38 (1.24)
Number of incident cases	10	15
Follow-up time (years)	6.2 (0.4)	4.6 (0.2)
Incidence rate (/100 person years)	0.9	2.9

Values are expressed as mean (standard deviation) or median (25th and 75th percentile) for continuous variables and % for categorical variables.

LDL-C: low-density-lipoprotein cholesterol, HDL-C: high-density-lipoprotein cholesterol, CAC: coronary artery calcification

Total LCn3PUFAs were defined as the sum of eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids. Fatty acids were expressed as a percentage of total serum fatty acids.

Table 2

Description of risk factors between incident and non-incident subjects in Japanese and Whites

	Japanese (n=175)		Whites (n=113)	
	Incident (n=10)	**Non-incident (n=165)**	**Incident (n=15)**	**Non-incident (n=98)**
Age (years)	45.4 (3.6)	44.9 (2.8)	44.2 (2.9)	44.7 (2.9)
Body-mass index (kg/m^2)	22.8 (1.7)	23.2 (2.9)	27.7 (3.1)	26.2 (3.0)
Systolic blood pressure (mmHg)	140.6 (24.0)	123.0 (14.0)	122.7 (9.6)	121.4 (11.2)
Hypertension medication (%)	10.0	3.6	6.7	5.1
LDL-C (mmol/L)	3.13 (1.13)	3.34 (0.95)	3.26 (0.77)	3.48 (0.82)
HDL-C (mmol/L)	1.42 (0.35)	1.41 (0.36)	1.13 (0.20)	1.27 (0.31)
Triglycerides (mg/dL)	1.46 (1.31, 1.64)	1.48 (1.08, 1.98)	1.27 (1.08, 1.91)	1.36 (0.99, 1.87)
Medication for hyperlipidemia (%)	0	1.8	0	9.2
Glucose (mmol/L)	5.83 (0.64)	5.81 (0.70)	5.47 (0.40)	5.53 (0.48)
Diabetes (%)	10.0	4.2	2.0	0
C-reactive protein (mg/L)	0.3 (0.2, 07)	0.3 (0.2, 0.7)	1.0 (0.7, 1.8)	0.8 (0.4, 1.6)
Smoking				
Current smokers (%)	60.0	47.9	0	9.2
Former smokers (%)	30.0	32.1	20.0	18.4
Pack years of smoking	21.3 (4.6, 44.1)	18.0 (2.9, 28.3)	0 (0, 0)	0 (0, 2.1)
Alcohol				
Alcohol drinker (%)	80.0	67.3	53.3	55.1
Ethanol consumption (g/day)	36.0 (17.0, 51.4)	14.0 (2.3, 37.0)	6.2 (0.8, 27.8)	8.7 (1.6, 18.6)
Marine n-3fatty acids (%)	8.5 (2.6)	9.1 (2.5)	3.47 (1.76)	3.90 (1.80)
Eicosapentaenoic acids (%)	1.9 (0.8)	2.4 (1.1)	0.81 (0.65)	0.72 (0.53)
Docosahexaenoic acids (%)	5.7 (1.8)	5.9 (1.5)	2.11 (1.27)	2.42 (1.24)
Follow-up (years)	6.3 (0.3)	6.2 (0.4)	4.7 (0.1)	4.6 (0.2)

Values are expressed as mean (standard deviation) or median (25th and 75th percentile) for continuous variables and % for categorical variables.

For abbreviations and definitions of variables, refer to table 1.

Table 3

Incidence rate ratio of coronary artery calcification between Japanese and whites

	Incidence rate ratio (95% confidence interval)	p
Unadjusted model	0.321 (0.150, 0.690)	<0.01
Model I	0.262 (0.094, 0.731)	0.01
Model II	0.376 (0.090, 1.572)	0.18

Unadjusted model took the follow-up time into account.

Model I: Adjusted for age, systolic blood pressure, low-density lipoprotein cholesterol, high-density-lipoprotein cholesterol, triglycerides, body-mass index, diabetes, pack-years of smoking, and medication for hypertension.

Model II: Further adjusted for total LCn3PUFAs in addition to model I.