International Journal of Cardiology 266 (2018) 245–249

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Comparison of carotid plaque burden among healthy middle-aged men living in the US, Japan, and South Korea

Abhishek Vishnu [a,b,c,*], Jina Choo [d], Aya Kadota [e], Emma J.M. Barinas-Mitchell [a], Akira Fujiyoshi [f], Dorothy Leann Long [g], Takashi Hisamatsu [f,k], Vasudha Ahuja [a], Yasuyuki Nakamura [h], Rhobert W. Evans [a], Katsuyuki Miura [f], Kamal H. Masaki [i], Chol Shin [j], Hirotsugu Ueshima [f], Akira Sekikawa [a]

[a] Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, United States
[b] The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[c] Department of Biostatistics, School of Public Health, West Virginia University, Morgantown, WV, United States
[d] College of Nursing, Korea University, Seoul, South Korea
[e] Department of School Nursing and Health Education, Osaka Kyoiku University, Kashiwara, Osaka, Japan
[f] Department of Health Science, Shiga University of Medical Science, Otsu, Shiga, Japan
[g] Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, United States
[h] The First Department of Internal Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan
[i] Department of Geriatric Medicine, University of Hawaii, Honolulu, HI, United States
[j] Division of Pulmonary Critical Care Medicine, Department of Internal Medicine, Korea University Ansan Hospital, Ansan, South Korea
[k] Department of Environmental Medicine and Public Health, Faculty of Medicine, Shimane University, Izumo, Japan

ARTICLE INFO

Article history:
Received 30 September 2017
Received in revised form 22 December 2017
Accepted 3 March 2018

Keywords:
Atherosclerotic plaque
Carotid stenosis
Carotid intima-media thickness
Risk factors
Epidemiology
Global health

ABSTRACT

Background: Carotid plaque has emerged as a marker of coronary heart disease (CHD) risk. Comparison of carotid plaque burden between different race/ethnic groups may provide a relative estimate of their future CHD risk.
Methods: We conducted a population-based study among apparently healthy middle-aged men aged 40–49 years (ERA JUMP study (n = 924)) and recruited 310 Whites in Pittsburgh, US, 313 Japanese in Otsu, Japan, and 301 Koreans in Ansan, South Korea. The number of carotid plaque and CHD risk factors was assessed using a standardized protocol across all centers. The burden of carotid plaque was compared between race/ethnic groups after adjustment for age and BMI, and after multivariable adjustment for other CHD risk factors using marginalized zero-inflated Poisson regression models. Cross-sectional associations of risk factors with plaque were examined.
Results: Whites (22.8%) had more than four-fold higher prevalence ($p < 0.01$) of carotid plaque than Japanese men (4.8%) while the prevalence among Koreans was 10.6%. These differences remained significant after adjustment for age, BMI as well as other risk factors – incidence density ratio (95% confidence interval) for plaque was 0.13 (0.07, 0.24) for Japanese and 0.32 (0.18, 0.58) for Koreans as compared to Whites. Age, hypertension and diabetes were the only risk factors significantly associated with presence of carotid plaque in the overall population.
Conclusion: Whites have significantly higher carotid plaque burden than men in Japan and Korea. Lower carotid plaque burden among Japanese and Koreans is independent of traditional CVD risk factors.

1. Introduction

Presence of plaque in the carotid artery has emerged as a strong predictor of coronary heart disease (CHD) [1]. Carotid plaque is recently reported to be a stronger predictor of CHD than carotid intima-media thickness (IMT) [1,2] which is commonly used as a surrogate measure of subclinical atherosclerosis in epidemiological studies. Thus, comparison of carotid plaque burden between different race/ethnic groups may provide a relative estimate of their future risk of CHD.

CHD remains the leading cause of mortality in the United States (US), with more than three-fold higher CHD mortality rates in the US than in Japan [3]. Although being industrialized for several decades with westernization of diet and lifestyle, Japan continues to have extremely low CHD rates. Similar to Japan, South Korea has extremely low CHD rates in spite of rapid westernization [3]. While several studies have examined racial/ethnic differences in CHD as well as markers of subclinical disease such as carotid IMT [4,5], only a few studies have compared prevalence of carotid plaque across different race/ethnic groups [6]. Further, previous studies have used varying methodology to examine and define carotid plaque [1], thus limiting the validity of any post-hoc comparison of plaque prevalence between different studies. With the emergence of carotid plaque as a predictor of CHD, it

* Corresponding author at: 1468 Madison Avenue, A18-80, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States.
E-mail address: abhishek.vishnu@mssm.edu (A. Vishnu).

https://doi.org/10.1016/j.ijcard.2018.03.010
0167-5273/

is now important to systematically examine the differences in carotid plaque burden between populations in the US and Japan.

Although many population-based studies have assessed the prevalence of carotid plaque [6,7], no study has compared the burden of carotid plaque between the US and Japan or South Korea. We used a standardized protocol to compare the number of carotid plaques among Whites in the US, Japanese in Japan, and Koreans in South Korea in the ERA JUMP study, an international population-based study for assessing subclinical atherosclerosis in 40–49 year-old men. We have previously reported lower coronary atherosclerosis and lower IMT among Japanese men than US whites [8]. Therefore, we hypothesized that the burden of carotid plaque is highest among Whites. We further examined which CHD risk factors were associated with the presence of carotid plaque in this sample population.

2. Methods and materials

2.1. Participants

During 2002–2006, a population-based sample of 925 men aged 40–49 years, with no clinical cardiovascular disease (CVD) or other severe diseases was recruited from 3 centers: 310 Whites from Pittsburgh, Pennsylvania; 313 Japanese from Kusatsu city, Shiga, Japan; and 302 Koreans from Ansan, Gyeonggi-do, South Korea as previously described [8]. The final sample for this study consisted of 924 men (310 Whites, 313 Japanese men in Japan, and 301 Koreans) with complete data. Written informed consent was obtained from all participants. The study was approved by the Institutional Review Boards of the following institutions: the University of Pittsburgh, Pittsburgh, Pennsylvania, US; Shiga University of Medical Science, Otsu, Japan; and Korea University, Seoul, South Korea.

2.2. B-mode carotid ultrasound scanning

Presence and extent of plaque were evaluated in each of 4 segments of the left and right carotid arteries i.e., distal and proximal common carotid artery (CCA), carotid bulb, and the proximal internal carotid artery (ICA). Plaque was defined as a distinct area of the vessel wall protruding into the vessel lumen that was at least 50% thicker than the adjacent IMT. The number of distinct plaques was counted in the abovementioned carotid segments on both sides and used as a measure of the carotid plaque burden [9].

Before the start of the study, sonographers at all centers received training for carotid scanning provided by the Ultrasound Research Laboratory at the University of Pittsburgh. Continuous-quality assessment programs developed by the Ultrasound Research Laboratory to assure scanning quality were applied across all study sites throughout the study [9]. Pittsburgh and Kusatsu sites used a Toshiba 140A scanner (Tokyo, Japan) equipped with a 7.5-MHz-linear-array imaging probe while the Ansan site used a Titan high-resolution ultrasound system with a 10.5 MHz linear array. Readers were blinded to participants' characteristics and the study centers. Under continuous-quality assessment programs, there was excellent agreement between sonographers for carotid plaque assessment (kappa statistic, $\kappa = 0.78$). For IMT measurement, digitized carotid artery images were sent to the University of Pittsburgh from other centers, and were read by a trained reader using a standardized protocol and a semi-automated edge detection software. The sonographer measured the average IMT across 1-cm segments of near and far walls of the common carotid arteries and the far wall of the carotid bulb and internal carotid arteries on both sides. Average IMT was calculated by taking a mean of the IMT measurements [8].

2.3. Risk factor assessment

All participants underwent a physical examination, completed a lifestyle questionnaire and a laboratory assessment as described previously [8,10,11]. Body weight and height were measured while the participant was wearing light clothing without shoes. Body-mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Blood pressure was measured—after the participants emptied their bladder and sat quietly for 5 min—twice on the right arm with an automated sphygmomanometer (BP-8800, Colin Medical Technology, Komaki, Japan) using an appropriate sized cuff width; the average of the two measurements was used. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg or use of anti-hypertensive medications [12]. Venipuncture was performed early in the clinic visit after a 12-hour fast. Blood samples were stored at −80 °C and shipped on dry ice to the University of Pittsburgh. Serum lipids were determined using the protocol standardized by the Centers for Disease Control and Prevention [13]. Dyslipidemia was defined as LDL-c ≥160 mg/dl or use of lipid-lowering medications [14]. Serum glucose was determined by using hexokinase–glucose-6-phosphate-dehydrogenase enzymatic assay. Diabetes was defined as individuals with fasting glucose ≥126 mg/dl or use of medications for diabetes [15]. Alcohol drinking was defined as intake ≥twice/week. Ever smoking was defined as current or past cigarette smoking. Use of blood pressure-lowering, diabetes, and lipid-lowering medication was ascertained through questionnaire. Data collection procedures were standardized across all centers.

2.4. Statistical methods

Descriptive characteristics and segment-wise presence of carotid plaque were assessed after stratification by race/ethnicity. The overall population was also described in terms of carotid plaque presence. To compare the burden of carotid plaque between these population groups, crude, age-BMI adjusted, and multivariable-adjusted incidence density ratios were calculated using a marginalized zero-inflated Poisson regression model with NLMIXED procedure in SAS [16,17]. This approach allowed us to account for the large fraction of sample population with no plaque (inflated zeroes), and provided incidence density ratio as the measure to compare plaque between the three racial groups.

To examine which CVD risk factors were associated with the presence of carotid plaque, we performed forward-selection logistic regression analyses in a combined sample of the three race/ethnic groups. We kept carotid plaque presence as the outcome variable and the following variables as independent variables in the regression model—age, race/ethnicity, BMI, SBP, glucose, ever smoking, alcohol drinking status, TC/HDL-c, LDL-c, and triglycerides (log-transformed). Alpha (two-sided) was set at 0.05 for determining statistical significance. As a confirmatory analysis, we performed the above analyses using a traditional logistic regression model forcing all the above variables into the regression equation. All analyses were performed using SAS/STAT software v 9.4 of the SAS System, Cary, NC, USA.

Table 1
Descriptive characteristics of the study population.

	Whites (W, n = 310)	Japanese (J, n = 313)	Koreans (K, n = 301)	Differences ($p < 0.05$)[‖]
Age (years)	45.0 ± 2.8	45.1 ± 2.8	44.8 ± 2.8	J = W = K
BMI (kg/m^2)	28.0 ± 4.4	23.7 ± 3.1	24.7 ± 2.7	W > K = J
Systolic BP (mm Hg)	122.6 ± 11.2	125.0 ± 16.1	121.6 ± 14.1	J > W = K
Hypertension (%)[a]	15.2	26.5	15.6	J > K = W
Glucose (mmol/l)	5.65 ± 0.86	5.93 ± 1.04	5.71 ± 1.0	J > K = W
Diabetes (%)[b]	3.6	6.1	9.6	K = J = W
Ever smoking (%)	27.1	82.8	74.1	J > K > W
Alcohol drinker (%)[c]	44.3	67.3	44.0	J > W = K
LDL-cholesterol (mmol/l)	3.48 ± 0.86	3.42 ± 0.93	3.00 ± 0.82	W = J > K
HDL-cholesterol (mmol/l)	1.23 ± 0.33	1.40 ± 0.35	1.18 ± 0.30	J > W > K
Triglycerides, mmol/l[d]	1.46 (1.04, 2.08)	1.55 (1.16, 2.05)	1.51 (1.08, 2.27)	J = K = W
TC:HDL ratio	4.69 ± 1.29	4.27 ± 1.29	4.43 ± 1.16	W > J > K
Medications (%)				
Hypertension	8.7	5.4	4.6	W = J = K
Diabetes	1.0	1.9	0.3	J = W = K
Lipids	12.3	3.5	1.3	W > J = K

Values are mean ± SD unless otherwise mentioned.
TC:HDL = total cholesterol: high-density lipoprotein cholesterol ratio; BP = blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein.
[a] Hypertension was defined as presence of one or more of following—i) Systolic blood pressure (BP) ≥140 mm Hg, ii) Diastolic BP ≥90 mm Hg, or iii) use of antihypertensive medication.
[b] Diabetes was defined as either fasting glucose ≥7 mmol/L or use of diabetic medication, or both.
[c] Alcohol drinking was defined as 2 or more drinks per week.
[d] Median (interquartile range).
[‖] Inter-group differences for continuous variables were calculated using *t*-tests except for triglycerides (non-parametric tests), and categorical variables (chi-square tests). "=" represents no statistical significance for the difference while ">" represents $p < 0.05$.