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BASELINE DATA OF SHIZUOKA AREA IN THE JAPAN MULTI-INSTITUTIONAL COLLABORATIVE COHORT STUDY (J-MICC STUDY)

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ABSTRACT

The Japan Multi-Institutional Collaborative Cohort (J-MICC) Study launched in 2005 by ten research groups throughout Japan aimed to examine gene-environment interactions in lifestyle-related diseases, especially cancers. This paper describes one component of the J-MICC Study, named Shizuoka Study, in which visitors aged 35 to 69 years to the Seirei Preventive Health Care Center in Hamamatsu were enrolled. Among 13,740 visitors matching eligibility criteria, 5,040 persons (36.7%) were enrolled from January 2006 to December 2007. Their lifestyle, disease history, and family history were surveyed using a self-administrated questionnaire. Blood and urine were collected from the participants. By the end of December 2008, 8 withdrawers and 1 ineligible participant had been removed, leaving 5,031 participants (3,419 males and 1,612 females) as the baseline dataset. Current smokers were 23.3% among males, and 4.4% among females, and those who drank once or more per month were 76.9% and 38.6%, respectively. Those with a cancer history were 3.0% for males and 3.8% for females. Measurements out of a normal range in males and females were 11.3% and 4.0% for diastolic blood pressure $\geq$ 90 mmHg, 11.0% and 7.6% for systolic blood pressure $\geq$ 140 mmHg, 5.9% and 1.7% for fasting blood glucose $\geq$ 126 mg/dl, respectively. Collected information and specimens will be cooperatively used to examine the associations of biomarkers with lifestyle, genotypes, and their combinations, as well as for a part of the J-MICC Study.

Key Words: Cohort study, Gene-environment interaction, J-MICC Study, Shizuoka Study

INTRODUCTION

The Japan Multi-Institutional Collaborative Cohort (J-MICC) Study launched in 2005, was supported by a research grant for Scientific Research on Special Priority Areas of Cancer from the Japanese Ministry of Education, Culture, Sports, Science and Technology.[1,2)] The main purpose is to confirm and detect gene-environment interactions in lifestyle-related diseases, mainly cancer,

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through the cohort analysis. However, the study includes cross-sectional analysis of lifestyle factors, biomarkers, and genotypes, as well as confirmation/screening of new biomarkers useful for the early diagnosis of cancer. The endpoints for follow-up are cancer diagnosis and death from any cause. The participants diagnosed as cancer will be identified through population-based cancer registries, hospital cancer registries, mail questionnaires, questionnaires administered during repeated visits, death certificates, health insurance data, and second survey questionnaires. The Study is expected to enroll 100,000 participants throughout Japan and follow the participants up until 2025.

The J-MICC Study Group consists of 10 research groups. Each group is to conduct a cohort study for the J-MICC Study, but is allowed to collect additional information and to analyze specimens for their own research purposes. Our group is one of the 10 research groups and forms one component of the J-MICC Study called the Shizuoka Study. We enrolled the participants at Seirei Preventive Health Care Center from January 30, 2006 to December 27, 2007. The Center is located in Mikatahara of Hamamatsu City, in Shizuoka Prefecture, whose catchment area is mainly the west half of Shizuoka Prefecture. This paper describes the study design and the characteristics of participants, in order to provide baseline information about this cohort. The J-MICC Study and Shizuoka Study were both approved by the ethics committee of Nagoya University School of Medicine (approval number 253 and 288, respectively).

MATERIALS AND METHODS

Subjects

Subjects of the J-MICC Study were individuals aged 35–69 years whose address was registered at a local government in the area predetermined by each research group. In Shizuoka Study, local governments in the west half of Shizuoka Prefecture were selected, including 12 cities (Shizuoka, Fujieda, Yaizu, Makinohara, Kikukawa, Omaezaki, Kakegawa, Shimada, Fukuroi, Iwata, Hamamatsu, and Kosai) and 6 towns (Okabe, Oigawa, Yoshida, Kawane, Kawanehon, and Arai). The visitors to the Center with matching criteria were invited to participate in the study. They were selected from a one-night stay course in the first year, and from a one-day course in the second year.

Informed consent process

Sets of documents explaining the study were mailed to the eligible visitors before the checkup day. On the day of the health checkup, a video outlining the J-MICC Study was presented in a waiting room. In addition, about a 15-minute face-to-face explanation was provided for 9 visitors at maximum for one session. For those who accepted the invitation, each item for agreement was explained individually to obtain the participant's consent in writing. For the one-night stay course, a 10-minute briefing was provided to screen potential participants. Then participants, who ticked the check box "would like to listen further explanation" on a card to confirm their intention, had the 15-minute face-to-face explanation.

The contents of the agreement included 1) permission to use information on lifestyle, disease history, and family history collected with the self-administered questionnaire, 2) permission to use laboratory data obtained through the health checkup, and 3) the donation of blood and urine specimens. The contents also included the follow-up until 2025 for diagnosis of cancer and death from any cause, and additionally for diagnosis of cardiovascular and cerebrovascular diseases solely for the Shizuoka Study.

Lifestyle data and sample collection

The self-administered questionnaire was distributed after confirming their consent to participation. The questionnaire used in the Shizuoka Study included questions on employments, eating habits, stress, dental health, and forest-air bathing and walking, as well as questions common to the J-MICC Study.[1)] The administered questionnaire was examined by an accompanying staff member in an isolated room, who asked the participant to respond to all unanswered questions except those the participant had already refused to answer. The staff indicated their refusal with a checkmark on the question number. The rule to put the checkmark on the numbers of the questions unwilling to answer was stated on the front page of the questionnaire.

Venous blood was drawn into a 7 ml of vacuum tube including serum separation, and a 7 ml EDTA-Na added vacuum tube on the day of the health checkup. Eight tubes with 300μl serum, 8 tubes with 300μl plasma, and 2 tubes with 300μl buffy coat were separated. Half of the blood specimens were stored for the J-MICC Study, and the other half of the blood specimen were for the Shizuoka Study. DNA was extracted from the buffy coat allocated to the Shizuoka Study, and genotyped to confirm the quality of the extracted DNA. A 27-bp VNTR (variable number of tandem repeats) polymorphism of *NOS3*, which encodes endothelial constitutive nitric oxide synthase,[3)] was applied for the DNA quality confirmation; *5 repeats* were a major allele, and *4 repeats*, *6 repeats*, and *longer repeats* were minor alleles. The PCR condition was described in our previous paper.[3)] For the Shizuoka Study, 2 tubes with 1 ml of urine each were additionally collected. All tubes were stored at –80°C in Nagoya University Graduate School of Medicine.

Endpoints and follow-up methods

As stated, the endpoints of the J-MICC Study are cancer diagnosis and death from any cause, while in the Shizuoka Study, diagnosis of cerebrovascular diseases and myocardial infarction were additionally followed. The information on disease onset is collected at the participants' repeated visits to the Center, as well as through a mail questionnaire. When the information is obtained, the details of the diagnosis are asked of the doctors in charge, by mail. Concerning cancer, the research staff members visit main hospitals to identify cancer cases with hospital cancer registries. Moving out from the catchment area (12 cities and 7 towns) is monitored with the residential registries of local governments. Deaths can also be identified through the registry. The causes of deaths can be confirmed with a death certificate.

Statistical analysis

Calculations were conducted with the computer program STATA Version 7 (STATA Corporation, College Station, TX).

RESULTS

Participation rate

Among 13,740 visitors matching the eligibility criteria, 5,040 persons (36.7%) were enrolled from January 30, 2006 to December 27, 2007. In the first year, 596 (39.7%) of 1,500 eligible persons who visited for the one-night stay course, participated in the study. In the second year, 4,444 (36.3%) of 12,240 eligible persons from the one-day course, participated in the study.

Sex and age distributions

Since there were 8 withdrawers and 1 ineligible participant aged 34 years at enrollment until the end of December, 2008, all information on them including their sex and age was deleted.

Table 1 Sex and age distributions of Shizuoka Study participants

Age	Males		Females		Total	
	n	%	*n*	%	*n*	%
35–39	265	7.8	192	11.9	457	9.1
40–44	438	12.8	205	12.7	643	12.8
45–49	547	16.0	291	18.1	838	16.7
50–54	588	17.2	298	18.5	886	17.6
55–59	780	22.8	333	20.7	1,113	22.1
60–64	483	14.1	188	11.7	671	13.3
65–69	318	9.3	105	6.5	423	8.4
Total	3,419	100	1,612	100	5,031	100

Nine participants had withdrawn by the study until December 31, 2008.

Table 2 Proportions of smokers and drinkers according to sex and age group

Age	Males				Females			
	n	Current	Former	Never	*n*	Current	Former	Never
Smoking								
35–39	264	30.3	33.0	36.7	192	3.6	7.8	88.5
40–44	437	31.4	30.7	38.0	205	6.3	4.9	88.8
45–49	547	23.8	41.5	34.7	289	5.5	7.3	87.2
50–54	587	26.4	44.3	29.3	298	6.4	6.4	87.2
55–59	780	23.5	47.7	28.8	332	2.4	5.4	92.2
60–64	482	16.0	58.3	25.7	187	3.7	3.2	93.0
65–69	318	11.0	53.8	35.2	104	1.0	1.9	97.1
Total	3,415	23.3	44.9	31.8	1,607	4.4	5.7	89.9
Drinking								
35–39	265	75.5	0.8	23.8	189	47.1	1.1	51.9
40–44	438	70.5	0.7	28.8	205	48.3	0.0	51.7
45–49	547	78.8	1.1	20.1	289	41.9	0.7	57.4
50–54	586	79.0	1.7	19.3	296	36.5	0.3	63.2
55–59	775	77.4	0.8	21.8	333	33.9	0.9	65.2
60–64	481	79.6	1.7	18.7	185	32.4	0.5	67.0
65–69	313	73.8	3.5	22.7	105	26.7	1.0	72.4
Total	3,405	76.9	1.4	21.8	1,602	38.6	0.6	60.8

Data were not available for 9 participants regarding smoking and 24 participants regarding drinking

Accordingly, Table 1 shows the distributions for the remaining 5,031 participants, who were fixed as the first baseline dataset. In this cohort, the males were dominant; 3,419 males and 1,612 females. The 55–59 year age group was the largest both in males and females, while the 35–39 year age group was smallest in males and the 65–69 year age group in females.

Smoking and drinking

Smoking habit was classified into "current," "former," and "never." Never smokers were not defined in the questionnaire, so it was defined by each participant. Former smokers included those who quit smoking from 1 month to 46 years ago. Two females explicitly refused to answer the smoking question, and 4 males and 3 females did not respond to it. Smoking habits of the

remaining 5,022 participants were shown in Table 2. The current smokers accounted for 23.3% in 3,415 males and 4.4% in 1,607 females. The highest percentage was observed in the 40–44 year group among males (31.4%) and the 50–54 year group among females (6.4%). Among the 797 current male smokers, 796 specified the number of cigarettes smoked per day; 9.0% smoked 1–9 cigarettes per day, 17.5% 10 cigarettes per day, 20.7% 11–19 cigarettes per day, 37.6% 20 cigarettes per day, and 15.2% smoked 21 cigarettes or more per day. Seventy out of 71 current female smokers specified the number of cigarettes smoked per day; 28.6% smoked 1–9 a day, 31.4% 10 a day, 21.4% 11–19 a day, 14.3% 20 per day, and 4.3% smoked 21 or more a day.

Drinking habit was similarly classified into "current," "former," and "never." Drinkers were defined as those who drank once or more a month. Three females explicitly refused to answer the drinking question, and 14 males and 7 females did not respond. Drinking habit of the remaining 5,007 participants is shown in Table 2. Among 3,405 males, 76.9% answered they are current drinkers, while 38.6% did so among 1,602 females. There was no marked trend in drinking habit among different age groups in males, but a slight reduction in the current drinker percentage was observed in females along with age. The frequency of drinking was questioned with 5 possible replies: "everyday," "5–6 days per week," "3–4 days per week," "1–2 days per week," and "1–3 days per month." Five male drinkers and 2 female drinkers did not respond to the question of frequency. Male drinkers responding to the respective frequencies were 24.7%, 18.0%, 14.1%, 11.0%, and 9.0% of 3,405 respondents, and the female drinkers were 3.7%, 5.6%, 7.6%, 10.2%, and 11.3% of 1,602 respondents, respectively.

Cancer history

The participants were asked about their cancer history using 3 response options: "No," "Yes at present," and "Yes in the past." Refusal to answer the question was indicated by a checkmark on the question number. Among 3,419 males, 19 answered "Yes at present" and 82 answered "Yes in the past." Four participants used the checkmark, and 19 participants did not answer. In 1,612 females, the corresponding numbers were 15 and 46. Six participants (5 males and 1 female) stated two different sites of primary cancers and 1 male participant stated three different sites of cancers (stomach, prostate, and testis). Majority of cancer history consisted of stomach cancer (28 males and 7 females), colorectal cancer (16 males and 4 females), breast cancer (17 females), prostate cancer (16 males), thyroid cancer (10 males and 5 females), lung cancer (11 males and 4 females), and uterine (cervical, endometrial, and unspecified) cancer (14 females).

Laboratory data

Tables 3 and 4 present the mean, standard deviation, minimum, and maximum values from the selected laboratory tests, as well as the percentages of those with measurements outside the normal range, in males and females, respectively. Those with a body mass index (BMI) $\geq$ 25 were 26.0% in males and 15.9% in females. Those with BMI $\geq$ 30 were 2.4% and 1.7%, respectively. Since they were health checkup examinees, the great majority were normal. The cut-off points for laboratory data were arbitrarily determined to calculate the percentages of individuals with measurements out of the normal range in Tables 3 and 4. They were applied similarly to both sexes. For example, 70U/l and 100U/l were used for γGTP, though the normal range was usually less than 70 U/l for males and less than 30 U/l for females. Women with γGTP between 30 U/l and 69 U/l accounted for 14.9% of the participants.

DNA samples

Among the 5,031 participants, blood draw for buffy coat was not successful for 6 individuals. From extracted DNA, *NOS3* 27-bp VNTR at intron 4 was genotyped, so all but 2 samples were

Table 3 Mean, standard deviation (SD), minimum (Min), and maximum (Max) of laboratory tests, as well as proportion of those with measurements outside normal range in males

	n	Mean	SD	Min	Max	Subnormal %			
BMI	3,418	23.5	2.9	15.4	47.0	<18.5	2.7	25.0≤	26.0
DBP	3,419	76.3	10.5	42	120	90–94	7.2	95≤	4.1
SBP	3,419	121.0	15.3	80	186	140–159	9.5	160≤	1.5
FBG	3,419	102.1	18.6	72	410	110–125	11.6	126≤	5.9
T-C	3,419	202.3	31.4	99	349	220–279	26.2	280≤	1.2
HDL-C	3,419	57.6	15.3	12	159	40–49	4.9	<40	8.9
TG	3,415	124.8	78.7	22	1079	150–199	13.4	200≤	11.5
AST	3,419	22.4	12.9	8	533	40–49	1.8	50≤	1.5
ALT	3,419	25.5	20.6	5	741	40–49	5.3	50≤	6.4
γGTP	3,419	46.9	54.2	2	1799	70–99	7.4	100≤	7.8
UA	3,419	6.1	1.2	0.7	11.4	<3.0	0.6	7.0≤	23.5
Creatinine	3,419	0.9	0.2	0.5	8.9	1.1–1.2	6.4	1.3≤	0.6
BUN	3,419	14.4	3.3	6	50	20–29	6.6	30≤	0.1
Hb	3,419	14.8	1.0	9.2	18.7	10.0–11.9	0.6	<10.0	0.0
RBC	3,419	483	37	338	695	<400	1.4	550≤	3.8
WBC	3,419	5.68	1.48	2.18	16.90	<3.50	2.8	10.00≤	1.4
Platelets	3,419	22.8	4.9	5.0	106.3	40.0≤	0.5	<13.0	0.9

BMI: body mass index (kg/m^2), DBP: diastolic blood pressure (mmHg), SBP: systolic blood pressure (mmHg), FBG: fasting blood glucose (mg/dl), T-C: total cholesterol (mg/dl), HDL-C: HDL cholesterol (mg/dl), TG: triglyceride (mg/dl), AST (U/l), ALT (U/l), γGTP (U/l), UA: uric acid (mg/dl), creatinine (mg/dl), BUN (mg/dl), Hb: hemoglobin (g/dl), RBC: red blood cells (×10^4/μl), WBC: white blood cells (×10^3/μl), and platelets (×10^4/μl)

Table 4 Mean, standard deviation (SD), minimum (Min), and maximum (Max) of laboratory tests, as well as proportion of those with measurements outside normal range in females

	n	Mean	SD	Min	Max	Subnormal %			
BMI	1,612	22.0	3.1	16.1	35.2	<18.5	9.6	25.0<	15.9
DBP	1,612	69.9	10.4	44	110	90–94	2.6	95<	1.4
SBP	1,612	114.4	15.9	80	194	140–159	6.7	160<	0.9
FBG	1,612	93.7	10.9	73	213	110–125	4.2	126<	1.7
T-C	1,612	207.2	32.6	107	320	220–279	32.7	280<	1.7
HDL-C	1,612	71.0	16.6	33	140	40–49	7.6	<40	1.1
TG	1,611	85.1	43.2	19	406	150–199	6.0	200<	9.3
AST	1,612	19.6	6.7	6	119	40–49	0.7	50<	0.5
ALT	1,612	17.2	10.4	5	179	40–49	1.9	50<	1.2
γGTP	1,612	23.3	21.5	7	373	70–99	1.7	100<	1.1
UA	1,612	4.4	1.0	0.5	8.9	<3.0	5.2	7.0<	1.5
Creatinine	1,612	0.6	0.1	0.3	1.2	1.1–1.2	0.2	1.3<	0.0
BUN	1,612	13.2	3.3	6	30	20–29	4.0	30<	0.1
Hb	1,612	12.8	1.2	6.7	15.8	10.0–11.9	15.0	<10.0	3.0
RBC	1,612	437	32	311	545	<400	12.0	550<	0.0
WBC	1,612	5.02	1.34	1.60	14.50	<3.50	8.8	10.00<	0.4
Platelets	1,612	24.3	5.4	8.1	58.0	40.0<	1.2	<13.0	0.7

BMI: body mass index (kg/m^2), DBP: diastolic blood pressure (mmHg), SBP: systolic blood pressure (mmHg), FBG: fasting blood glucose (mg/dl), T-C: total cholesterol (mg/dl), HDL-C: HDL cholesterol (mg/dl), TG: triglyceride (mg/dl), AST (U/l), ALT (U/l), γGTP (U/l), UA: uric acid (mg/dl), creatinine (mg/dl), BUN (mg/dl), Hb: hemoglobin (g/dl), RBC: red blood cells (×10^4/μl), WBC: white blood cells (×10^3/μl), and platelets (×10^4/μl)

successfully genotyped. Among 5,023 samples successfully genotyped, the genotype frequency of the *NOS3* polymorphism was 3,946 for *5/5*, 985 for *4/5*, 3 for *5/6*, 16 for *5/L*, 71 for *4/4*, and 2 for *4/L*. The frequency for the *5 repeat* allele was 0.886. When the three minor alleles (*4 repeats*, *6 repeats*, and *longer repeats*) were combined, the genotype distribution (3,946, 1,004, and 73) was in Hardy-Weinberg equilibrium (χ^2=0.998, p=0.318).

DISCUSSION

In the Shizuoka Study, 5,040 persons (36.7% of 13,740 invited visitors) aged 35 to 69 years were enrolled from January 30, 2006 to December 27, 2007, at the Seirei Prevention Health Care Center. Nine participants had withdrawn up to the end of 2008. Although several participants had abnormal laboratory tests, the great majority was healthy. Data from the questionnaire and health checkup were fixed at the end of 2008 for analysis. Blood and urine specimens were stored in the Nagoya University Graduate School of Medicine.

The main issue regarding subject enrollment involved the representativeness of participants, ie, whether or not this or that cohort indeed reflected the general Japanese population as a whole. In general populations, there are a certain percentage of individuals with disease and cancer history. For the analysis of disease risk in the Shizuoka Study, those with disease are excluded in priciple, resulting in no effects on the estimation of relative risk for lifestyle, genotypes, biomarkers and their combinations. Accordingly, abnormal laboratory tests and cancer history would not compromise the appropriateness of this cohort as a general population.

Current smokers accounted for 23.3% of males and 4.4% of females, relatively fewer than those from nation-wide surveys; the corresponding values for those aged 20 years or over were 40.2% and 12.7% in the Japan Tobacco Company Survey of 2007, and 39.9% and 10.0% in a 2008 survey by the Japan Ministry of Health, Labour and Welfare.[4] Although no data were available, the participation rate of smokers might be lower than for non-smokers among the visitors invited; it was 36.7% as a whole. The fewer smokers in this cohort may reduce the statistical power to detect smoking effects, compared to the populations with more smokers.

A survey by the Japan Ministry of Health, Labour and Welfare reported that 51.1% of males and 15.3% of females aged 20 years or over drank three times or more per week.[4] The corresponding percentage in this cohort was 56.7% and 16.9%, which were almost the same as the estimates from the nation-wide survey.

In this cohort, the allele frequency of *NOS3* 27-bp VNTR was 0.886 for *5 repeats*. Other studies reported a similar frequency (0.875 in Hokkaido with 703 persons[4], and 0.922 in Nagano with 51 persons.[5] In Japan, there were no examples of a group sampled in a large city on the main island (Honshu) with a large deviation in allele frequency from the general populations. Accordingly, it was unlikely that this cohort had a genetic background different from Japanese general populations.

Generally speaking, due to space limitations, the whole picture of a cohort study is rarely presented in papers reporting specific associations obtained from a cohort study. However, many readers may wish to have more details on the study design and baseline data, especially when many papers lack a full description of the background. On the other hand, repeated explanation may be tedious for the readers knowledgeable in the study area. Therefore, it seems useful to report the study design and baseline information of the cohort study in an article. To date, corresponding reports have been published in Japan for the J-MICC Study,[1] JACC Study,[6] JPHC Study,[7] and HERPACC Study.[8] This paper aims to play this role for the Shizuoka Study.

In conclusion, the Shizuoka Study, a component of the J-MICC Study, enrolled 5,040

participants in two years. The observed distribution indicated that this cohort may reflect a general population, although the smoker percentages were lower than those reported by the nation-wide surveys. Collected information and specimens will be cooperatively used to examine the associations of biomarkers with lifestyle, genotypes, and the combinations, as well as with a part of the J-MICC Study.

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