
COMMENTARY

The Japan Multi-institutional Collaborative Cohort Study (J-MICC Study) to Detect Gene-environment Interactions for Cancer

The J-MICC Study Group*

Abstract

The Japan Multi-institutional Collaborative Cohort Study (J-MICC Study) launched in 2005, 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. Although the main purpose is to confirm and detect gene-environment interactions of lifestyle-related diseases, mainly of cancer, through the cohort analyses, it includes cross-sectional analyses on lifestyle factors, biomarkers, and genotypes, as well as confirmation/screening of new biomarkers usable for early diagnosis of cancer. The endpoints are cancer diagnosis and death. The participants diagnosed as cancer will be identified through population-based cancer registries, hospital cancer registries, mail questionnaires, questionnaires at repeated visits, death certificates, health insurance data, and second survey questionnaires. Subjects are individuals aged 35 to 69 years enrolled from respondents to study announcements in specified areas, inhabitants attending health checkup examinations by local governments, visitors at health checkup centers, and patients at a cancer hospital. The number of subjects was set to be 100,000 throughout Japan. The enrollment period is from April 2005 to March 2010. The second survey is scheduled 5 years after their enrollment. The participants will be followed until 2025. The J-MICC Central Office is placed at Nagoya University Graduate School of Medicine. Ten participating research groups (Cohort Study Executing Groups) send baseline data and blood samples (buffy coat, serum, and plasma) anonymized with an identification number (J-MICC ID) to the Central Office. The data of second survey and follow-up will be linked using J-MICC ID. This study is expected to produce many findings on lifestyle and genetic traits associated with lifestyle-related diseases including cancer among Japanese.

Key Words: Cohort study – gene-environment interactions – biomarkers \ lifestyle-related diseases \ cancer

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Introduction

According to the vital statistics of Japan, the deaths in 2004 were 1.08 millions, 30% of which were from malignant neoplasms. The estimated cumulative incidence of malignant neoplasms for 0 to 84 years of age was 44.8% for males and 26.5% for females, based on the incidence data in 1998 by cancer registries (Inoue et al., 2003). These figures indicate the importance of studies for cancer prevention, especially among those in age to support society. The prevention is actually effective to reduce the burdens of society. We have learned many risk/preventive factors of cancers from the past epidemiologic studies. The low-risk lifestyle includes no smoking, no or adequate amount of alcohol drinking, frequent physical exercises, balanced diet, keeping body clean, no infections with cancer-related microorganisms, and so forth. The above information is definitively correct, but we have to continuously measure the impact of each lifestyle on the diseases among Japanese.

The great majority of cancers are caused through the combinations of genetic traits and environmental factors. Along with the development of genotyping techniques, many studies on gene-environment interactions have been reported. Some genotypes have an elevated or reduced function relative to the counterpart genotypes, which cause different responses to stimuli from environment. For example, carcinogens from smoking are activated with cytochrome p450 enzymes such as CYP1A1, and metabolized with detoxifying enzymes such as glutathione S-transferases. Functional polymorphisms of these enzymes could interact with carcinogen exposures from tobacco smoke (Wu et al., 2004). The elucidation of gene-environment interactions is the important step for cancer prevention. Information on genotypes interacting environment factors would be useful to identify high risk individuals, not only for cancer but also for other lifestyle-related diseases. The high risk individuals could accept appropriate frequency of health checkups or would try to avoid high risk lifestyle/environment interacting

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with their own genetic traits. Cohort studies focusing on gene-environment interactions are expected to produce many fruits for disease prevention.

After the brief description on relevant cohort studies in the world and Japan, the present article describes the outline of the Japan Multi-institutional Collaborative Cohort Study (J-MICC Study) launched in 2005, 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. Since the J-MICC Study is a union of independent cohort studies conducted by Cohort Study Executing Groups, its protocol covers the common rules among the different study groups.

Cohort studies with DNA samples

Several cohort studies with DNA samples are on going in the world. The EPIC (European Prospective Investigation into Cancer and Nutrition) launched in 1993, and has been managing the data of 480,000 participants from nine European countries, as well as blood samples of 390,000 participants (Riboli, 2001). In England, UK Biobank (www.ukbiobank.ac.uk) is on going to enroll half million subjects (Protocol for the UK Biobank, 2002). In the United States, several cohort studies, such as CPS-II (Cancer Prevention Study II) and Nurses' Health Study, preserve blood samples, having been reporting the associations between genotypes and cancer risks.

In Japan, there are several cohort studies with blood samples with or without DNA. Among them, large cohort studies are as follows. The Japan Collaborative Cohort Study (JACC Study; <http://www.med.nagoya-u.ac.jp/yobo/jacc/>) with 130,000 participants started in 1988 (Ohno et al., 2001). The study has blood samples to be measured for serum biomarkers (Wakai et al., 2002), but it does not have DNA. In 1990, the Japan Public Health Center-based Cohort Study (JPHC Study; <http://epi.ncc.go.jp/jphc>) with 140,000 participants started (Iwasaki et al., 2003), which has blood samples for genotyping (Yoshimura et al., 2003). Another notable cohort study is Life Span Study 'http://www.rerf.or.jp' or 93,000 atomic bomb survivors and 20,000 controls (Shimizu et al., 1990). The latter two cohort studies have a potential to examine gene-environment interactions. In 2003, as a leading project of the Japanese Ministry of Education, Culture, Sports, Science and Technology, the Biobank Japan Project on the implementation of personalized medicine launched to collect blood samples for genotyping and other biomarker measurements from 300,000 patients 'http://www.biobankjp.org/index.html'.

Purposes of the J-MICC Study

The J-MICC study aims to produce the fundamental information for prevention of lifestyle-related diseases, mainly of cancer, based on the genetic traits. It consists of 1) cross-sectional analyses on lifestyle, biomarkers, and genotypes, 2) confirmation/screening of biomarkers usable for early diagnosis of cancer, and 3) confirmation/detection of gene-environment interactions with the

follow-up data.

In the cross-sectional analyses, all the combinations among the data derived from lifestyle questionnaires, health checkups, and genotypes can be examined. The analyses will confirm and detect the lifestyle associated with biomarkers such as blood pressure, serum cholesterol, and CRP, and further genotypes modifying the associations between lifestyle and biomarkers. The detection of the genotypes with a potential to cause biomarker changes due to lifestyle changes will be useful to identify the targets for preventive intervention.

The plasma and serum of participants diagnosed as cancer after enrollment and corresponding controls will be used for screening of new molecules useful for early cancer diagnosis. In the present study, the samples two years before the diagnosis will be used for the analyses, as well as the controls cancer-free at analysis. In the cohort analyses, all collected data and predetermined measurements (about 70 molecules in blood, DNA methylation, mutation/defect/amplification using serum DNA, and about 400 polymorphisms) from blood samples can be used. Future approval by ethics committees could extend the measurements.

We had to define the diseases/conditions for analysis, because generally ethics committees in Japan do not approve study protocols without specification of target diseases. They are cancer, precancerous lesions, other lifestyle-related diseases (circulatory diseases, arteriosclerosis, hypertension, diabetes mellitus including insulin resistance, obesity, hyperlipidemia, hyperuricemia, liver diseases, diseases of gallbladder and bile ducts, kidney diseases, respiratory diseases, hematological diseases, and osteoporosis), and total deaths. The results of laboratory tests are also included as outcome conditions.

Study Subjects

The subject sources are 1) volunteers residing in the areas defined by local governmental administration, 2) health checkup examinees run by local governments, 3) visitors of health checkup facilities, and 4) visitors of a cancer hospital. The candidates are those aged 35 to 69 years at enrollment, whose resident records are at the local government offices of the target areas. Those who do not accept the follow-up or those who cannot complete the lifestyle questionnaire are excluded. Other inclusion or exclusion criteria can be made in each Cohort Study Executing Group.

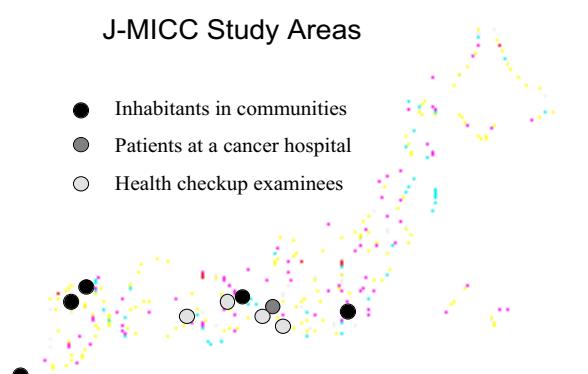


Figure 1. The Study Areas for the J-MICC Study

Table 1. Expected Numbers of Cancer Cases by 2025

Primary site	Males	Females	Total
All sites	7,993	4,796	12,789
Oral and pharynx	173	56	229
Esophagus	348	52	400
Stomach	1,860	733	2,593
Colon	947	615	1,562
Rectum	558	275	833
Liver	738	275	1,013
Gallbladder and bile ducts	199	74	373
Pancreas	274	178	452
Lung	1,186	397	1,583
Prostate	448	-	448
Breast	-	795	795
Cervix uteri	-	122	122
Corpus uteri	-	140	140
Ovary	-	154	154
Bladder	294	73	367
Kidney	181	77	258
Thyroid	36	136	172
Malignant lymphoma	172	113	285
Leukemia	94	65	159

Figure 1 shows the locations of the study areas. From east to west, Chiba supported by Chiba Cancer Center, Shizuoka by Seirei Yobo Kenshin Center and Nagoya University, Okazaki by Nagoya City University, Aichi by Aichi Cancer Center, Takashima by Shiga University of Medical Science, Kyoto by Kyoto Prefectural University of Medicine, Tokushima by Tokushima University, Fukuoka by Kyushu University, Saga by Saga University, and Kagoshima by Kagoshima University.

Study Period, Sample Size and Statistical Power

It was planned to enroll 100,000 participants at the baseline survey from April 2005 (actually, the study started on October 12, 2005 in Kagoshima) to March 2010. The second survey from April 2010 to March 2015 will be

conducted for the participants in the baseline survey. The starting point of follow-up is the date of enrollment. Although it was provisionally planned that they would be followed until 2024, the final decision on the end of follow-up will be determined after 2019. The chief investigator can quit the follow-up at any point of time, if necessary. When the participants move their resident record outside the study areas, they are treated as being censored at the time when they move out.

Based on the person-years and cancer incidence rate in 1999 (The Research Group for Population-based Cancer Registration in Japan, 2004), the number of cancer cases was estimated. For the person-year calculation, 50,000 males and 50,000 females with the age distribution estimated for year 2003 were assumed to be followed up for 17.5 years, taking account of their aging and censoring due to deaths from causes other than cancer. The reduction of person-years due to moving out from the study areas was not considered.

As shown in Table 1, the expected number of all cancer cases is about 8,000 in males and 4,800 in females, in total 12,800. Under the condition of alpha error = 0.05 (two-sided test), the statistical power was calculated to detect relative risk = 2 for dichotomous exposure situation (unexposed and exposed). In case of the proportion for the exposed = 0.1, 0.3, or 0.5, the power exceeded 80% for any cancer except thyroid and leukemia in males. In females, the corresponding power was more than 80% except oral and pharynx, esophagus, cervix uteri, bladder, kidney, malignant lymphoma, and leukemia.

Table 2 shows the statistical power to detect interaction according to exposure frequency and relative risk of the two factors. Under alpha error = 0.05 (two-sided test), the power was more than 80% for common cancers in case of interaction = 2, and for any cancer excluding rare cancers in case of interaction = 3. For these calculations, the following conditions were assumed; 1) factors X and

Table 2a. Statistical Power to Detect Interactions According to Factor Frequencies and Relative Risk (RR) of Two Factors X and Y - Males. 0.1, X possessing (Upper); 0.3, Y possessing (Middle); and 0.5, RR (Lower)

Primary site	0.1						0.3						0.5						
	0.1		0.3		0.5		0.1		0.3		0.5		0.1		0.3		0.5		
	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	
All sites	A/A*	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
Oral/pharynx	D/D	C/B	C/B	C/A	C/B	C/B	C/B	C/A	C/A	B/A	B/A	B/A	C/B	C/B	B/A	B/A	B/A	B/A	B/A
Esophagus	D/C	C/A	C/A	B/A	C/A	B/A	C/A	B/A	B/A	A/A	A/A	A/A	C/A	B/A	A/A	A/A	A/A	A/A	B/A
Stomach	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
Colon	C/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
Rectum	C/B	B/A	B/A	A/A	B/A	A/A	B/A	A/A	A/A	A/A	A/A	A/A	B/A	A/A	A/A	A/A	A/A	A/A	A/A
Liver	C/A	A/A	B/A	A/A	A/A	A/A	B/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
Gallbladder	D/C	C/B	C/B	C/A	C/B	C/A	C/B	C/A	B/A	B/A	B/A	B/A	C/B	C/A	B/A	B/A	B/A	B/A	B/A
Pancreas	D/C	C/A	C/B	B/A	C/A	B/A	C/B	B/A	B/A	A/A	B/A	B/A	C/A	B/A	B/A	B/A	A/A	B/A	B/A
Lung	B/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
Prostate	C/B	B/A	B/A	A/A	B/A	B/A	B/A	A/A	A/A	A/A	A/A	A/A	B/A	B/A	A/A	A/A	A/A	A/A	A/A
Bladder	D/C	C/A	C/B	B/A	C/A	B/A	C/B	B/A	B/A	A/A	B/A	B/A	C/A	B/A	B/A	B/A	A/A	B/A	B/A
Kidney	D/D	C/B	C/B	C/A	C/B	C/B	C/B	C/A	C/A	B/A	B/A	B/A	C/B	C/B	B/A	B/A	B/A	B/A	B/A
Thyroid	D/D	D/D	D/D	D/C	D/D	D/C	D/D	D/C	D/C	D/C	D/C	D/C	D/D	D/C	D/C	D/C	D/C	D/C	D/C
Malignant lymphoma	D/D	C/B	D/B	C/A	C/B	C/B	D/B	C/A	C/A	B/A	B/A	B/A	C/B	C/B	B/A	B/A	B/A	B/A	B/A
Leukemia	D/D	D/C	D/C	C/B	D/C	C/C	D/C	C/B	C/B	C/B	C/B	C/B	D/C	C/C	C/B	C/B	C/B	C/B	C/B

*A for 0.80 to 1.00, B for 0.50 to 0.79, C for 0.20 to 0.50, and D for 0.00 to 0.19, and gallbladder includes bile ducts. The power is for the cases of interactions = 2/3

Table 2b. Statistical Power to Detect Interactions According to Factor Frequencies and Relative Risk (RR) of Two Factors X and Y - Females 0.1, X possessing (Upper); 0.3, Y possessing (Middle); and 0.5, RR (Lower)

Primary site	0.1						0.3						0.5						
	0.1		0.3		0.5		0.1		0.3		0.5		0.1		0.3		0.5		
	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	
All sites	A/A*	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
Oral/pharynx	D/D	D/D	D/D	D/C	D/C	D/C	D/D	D/C	D/C	C/B	C/C	C/C	D/C	D/C	C/C	C/C	C/B	C/C	C/C
Esophagus	D/D	D/D	D/D	D/C	D/D	D/C	D/D	D/C	D/C	C/B	C/C	C/C	D/D	D/C	C/C	C/C	C/B	C/C	C/C
Stomach	C/A	A/A	B/A	A/A	A/A	A/A	B/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
Colon	C/B	B/A	B/A	A/A	B/A	A/A	B/A	A/A	A/A	A/A	A/A	A/A	B/A	A/A	A/A	A/A	A/A	A/A	A/A
Rectum	D/C	C/A	C/B	B/A	C/A	B/A	C/B	B/A	B/A	A/A	B/A	B/A	C/A	B/A	B/A	B/A	A/A	B/A	B/A
Liver	D/C	C/A	C/B	B/A	C/A	B/A	C/B	B/A	B/A	A/A	B/A	B/A	C/A	B/A	B/A	B/A	A/A	B/A	B/A
Gallbladder	D/D	C/B	C/B	C/A	C/B	C/B	C/B	C/A	C/A	B/A	B/A	B/A	C/B	C/B	B/A	B/A	B/A	B/A	B/A
Pancreas	D/D	C/B	C/B	C/A	C/B	C/B	C/B	C/A	C/A	B/A	B/A	B/A	C/B	C/B	B/A	B/A	B/A	B/A	B/A
Lung	D/B	B/A	C/A	B/A	B/A	B/A	C/A	B/A	A/A	A/A	A/A	A/A	B/A	B/A	A/A	A/A	A/A	A/A	A/A
Breast	C/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A
Cervix uteri	D/D	D/C	D/C	C/B	D/C	C/B	D/C	C/B	C/B	C/A	C/B	C/B	D/C	C/B	C/B	C/B	C/A	C/B	C/B
Corpus uteri	D/D	D/C	D/C	C/B	C/C	C/B	D/C	C/B	C/A	B/A	C/A	C/A	C/C	C/B	C/A	C/A	B/A	C/B	C/B
Ovary	D/D	C/B	D/C	C/B	C/B	C/B	D/C	C/B	C/A	B/A	B/A	B/A	C/B	C/B	B/A	B/A	B/A	C/B	C/B
Bladder	D/D	D/C	D/D	D/C	D/C	D/C	D/D	D/C	C/B	C/B	C/B	C/B	D/C	D/C	C/B	C/B	C/B	C/B	C/B
Kidney	D/D	D/C	D/C	D/C	D/C	D/C	D/C	D/C	C/B	C/B	C/B	C/B	D/C	D/C	C/B	C/B	C/B	C/B	C/B
Thyroid	D/D	D/C	D/C	C/B	C/C	C/B	D/C	C/B	C/B	B/A	C/A	C/A	C/C	C/B	C/A	C/A	B/A	C/B	C/B
Malignant lymphoma	D/D	D/C	D/C	C/B	D/C	C/B	D/C	C/B	C/B	C/A	C/B	C/B	D/C	C/B	C/B	C/B	C/A	C/B	C/B
Leukemia	D/D	D/C	D/D	D/C	D/C	D/C	D/D	D/C	D/C	C/B	C/B	C/B	D/C	D/C	C/B	C/B	C/B	C/B	C/B

*A for 0.80 to 1.00, B for 0.50 to 0.79, C for 0.20 to 0.50, and D for 0.00 to 0.19. The power is for the cases of interactions = 2/3

Y are independent dichotomous variables with the minor category frequency = 0.1, 0.3, or 0.5, 2) cancer cases are under a Poisson distribution, and 3) normal approximation of logarithm of odds ratio is applied for hypothesis testing. As references for applicable gene-environment interaction, genotype frequencies among Japanese are listed in Table 3 (Hamajima et al., 2002; Kawase et al., 2003).

Data and Blood Samples Collected

The J-MICC dataset consists of J-MICC ID number, demographic data, lifestyle data and health checkup laboratory data at baseline survey, lifestyle data and health checkup laboratory data at second survey, and follow-up data. The dataset does not include name, birthday, address, and telephone number. Accordingly, the Central Office cannot identify the participants; the linkage of the additional data is possible only through J-MICC ID.

1) Lifestyle data: The core questions in the questionnaire are common among all cohorts, but extra questions can be added by each Cohort Study Executing Group. The responses for the common questions are sent to the Center Office. The common questionnaire includes 1) sleeping and exercise, 2) alcohol drinking, 3) smoking, 4) psychological stress, 5) medication and supplements, 6) food intake frequency, 7) family disease history, 8) past disease history, and 9) female reproductive history.

2) Physical checkup and laboratory data: In case that health checkup is conducted at the enrollment, the results of health checkup are also subjects of the J-MICC Study. Table 4 shows the items to be sent to the Central Office. The other information can be collected and used for the analyses in each Cohort Study Executing Group.

3) Blood samples: When the participants agree the blood donation for the J-MICC Study, 14 ml of blood is drawn

by a 7ml of plain tube for serum and a 7ml EDTA-2Na added tube for plasma and buffy coat. Usually, 3ml of serum, 3ml of plasma, and 0.8 ml of buffy coat can be obtained from the 14 ml of blood. Blood samples to be sent to the Center Office are 1) one tube including 300 microliter of buffy coat, 2) four tubes including 300 microliter of serum, and 3) four tubes including 300 microliter of plasma. The rest is used for the researches by each Cohort Study Executing Group.

4) Follow-up data: The endpoints are incident cancer diagnosis and death from any cause. Data are collected through population-based cancer registries if available, lists of patients at main hospitals in the areas, mail questionnaires sent to the participants, questionnaires at repeated visits to health checkup facilities, notes from death certificates, information from health insurance data, and second survey questionnaires. The incident data from the mail questionnaires, questionnaires at repeated visits, death certificates, health insurance data, and second survey questionnaires, are confirmed by the hospital record.

Study Organization

The J-MICC Study is an integration of the data and samples collected by Cohort Study Executing Groups. Each group has its own independent enrollment field. The chief investigator of the J-MICC Study is the chairperson of the Steering Committee. The Central Office in Nagoya University Graduate School of Medicine where all J-MICC data and blood samples are preserved, makes effortsto standardize the process of each cohort study, supplies common tools, such as data input system, sample management system, posters, and brochures, and maintains Internet homepage (<http://www.jmicc.com/>).

The Steering Committee is responsible for the whole J-MICC Study. The responsibility covers the approval of

Table 3. Genotype Frequencies among Japanese

Gene	Polymorphism	N	Genotype frequency*		
ALDH2	Glu487Lys	241	52.3%	39.9%	7.9%
BAR2(ADRB2)	Gln27Glu	239	83.3%	16.3%	0.4%
BAR3(ADRB2)	Trp64Arg	239	64.4%	32.2%	3.3%
COMT	Val158Met	123	46.3%	38.2%	15.4%
CYP17	T-34C	123	27.6%	57.7%	14.6%
CYP19	Trp39Arg	241	90.5%	9.1%	0.4%
GSTM1	present/null	234	46.6%	53.4%	0.0%
GSTT1	present/null	234	56.0%	44.0%	0.0%
IL-1B	C-31T	241	17.4%	55.2%	27.4%
IL-10	T-819C	241	45.6%	44.8%	9.5%
LEP	A-2548G	237	60.8%	36.3%	3.0%
L-myc	L/S	241	24.5%	55.6%	19.9%
MPO	G-463A	241	79.7%	19.5%	0.8%
MTHFR	C677T	241	34.0%	51.0%	14.9%
NQO1	C609T	241	35.7%	44.4%	19.9%
OGG1	Ser326Cys	240	28.2%	49.2%	22.5%
p53	Arg72Pro	239	37.7%	44.4%	18.0%
SRD5A2	Val89Leu	237	28.7%	44.3%	27.0%
TGF-B1	Leu10Pro	115	22.6%	49.6%	27.8%
TNF-A	G-308A	240	97.5%	2.5%	0.0%
TNF-B(LTA)	A252G	241	36.5%	48.1%	15.4%
XPD	Lys751Gln	240	90.4%	8.8%	0.8%
XRCC1	Arg399Gln	241	47.7%	44.8%	7.5%

* The percentages are for former allele homozygous, heterozygous, latter allele homozygous of the polymorphism symbols, respectively. Data are derived from Hamajima et al., 2002 and Kawase et al., 2003

1) participation of new Cohort Study Executing Groups and new collaborating institutions, 2) the details of the second survey, 3) extended analyses of J-MICC data and samples, 4) supplies of data and samples to outer research groups, 5) authorships of papers on the J-MICC study, 6) revision of J-MICC study protocol, and 7) financial supplies from new resources.

The Cohort Study Executing Groups are the teams to enroll participants, collect data and samples, and follow the participants. The teams can conduct researches using the data and samples collected by themselves, independently of the J-MICC Study. For their own purposes of researches, they can add the questions in the questionnaire, reserve remaining blood samples, and collect different specimen such as urine. Some Cohort

Study Executing Groups have different age criteria for enrolment, but those aged 35 to 69 years are subjects of the J-MICC Study. They must submit the data and blood samples to the Central Office through linkable anonymization (Hamajima et al. 2004). Each group is expected to enroll more than 5,000 participants.

We have 1) Committee on Social Issues, which analyzes the social issues pertaining to the J-MICC Study and advises the Steering Committee on them, 2) Monitoring Committee, which examines ethical aspects and scientific validity of the Study and monitors the study process, and 3) External Evaluation Committee, which evaluates the planning, execution, and management of the Study from the outsiders' viewpoint. The image of the J-MICC study organization is depicted in Figure 2.

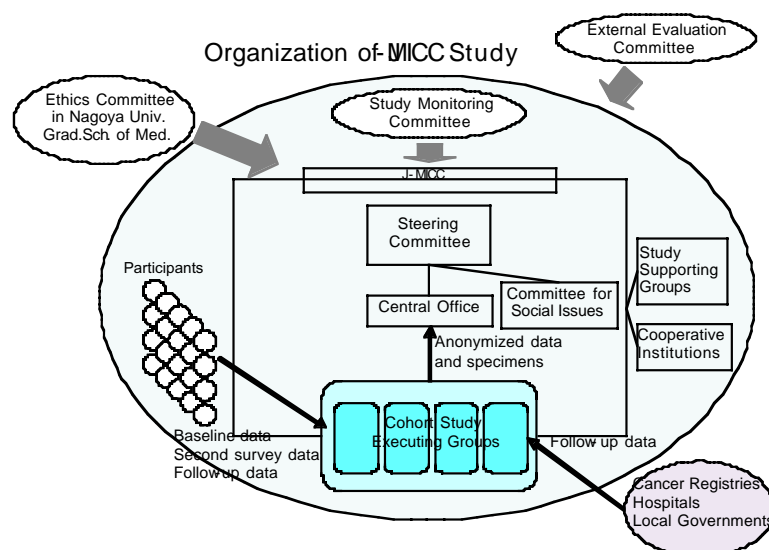
**Figure 2. Organization of Japan Multi-institutional Collaborative Cohort Study (J-MICC Study)**

Table 4. Items to be Collected from Health Checkup

- 1) Date of health checkup
- 2) Physical condition: height, weight, blood pressure
- 3) Urinalysis: protein, glucose
- 4) Serum tests: total protein, albumin, proportion of protein components, albumin globulin ratio, triacylglycerol, total cholesterol, HDL cholesterol, ALT, AST, γ GTP, ALP, LDH, CRP, uric acid, BUN, creatinine
- 5) Blood cell counts: red blood cell, white blood cell, platelet, hemoglobin, hematocrit
- 6) Plasma tests: blood glucose, hemoglobin A1c, PSA
- 7) Bone density

Approval by ethics committees

The main study protocol of the J-MICC Study was approved in July 20, 2005 by Ethics Committee at Nagoya University School of Medicine (Approval number 253). Since actual studies are slightly different from the main J-MICC Study protocol, the study protocol of each Cohort Study Executing Group was approved by ethics committees both of Nagoya University School of Medicine and each institute. The enrollment started after the approval of each institute.

Disclosure of results of laboratory tests conducted for research purposes

The participants have a right to ask researchers to disclose any information on their own, based on Act on the Protection of Personal Information (Law No. 57, 2003) issued on May 30, 2003. Concerning the data stored in the Central Office, the information to identify the individual participants is not attached, so that the requests can be dismissed. The requests to the Cohort Study Executing Groups are treated with the process determined by the law. As a rule of the J-MICC Study, we will not inform voluntarily the participants of the results of laboratory tests conducted with research purposes including genotypes, because 1) the laboratory tests with research purposes will be conducted several years later, and 2) the associations with disease risk are generally not well established. Concerning genotype testing, identification of hereditary disease genotypes is not included in the present study. Since it is an association study including the non-hereditary cases, there is no chance to detect the genotypes of the hereditary diseases.

Perspectives

The J-MICC Study is one of large cohort studies in Japan, which started after "Ethical Guideline for Studies on Human Genome Genetic Analysis" issued on March 29, 2001 by Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, and Ministry of Economy, Trade and Industry. The Study cleared the regulation of the Guideline, but the processes in the study approval needed a long time compared with those of previous studies. The public awareness on privacy is making researchers' burdens of informed consent processes heavier, which increases the costs of the study. For the participation, a large amount of

information, longer documentation, and signature are required. The preliminary observation in the J-MICC Study indicated the participation rate was lower than those in past conventional cohort studies in Japan. However, many researchers involved in this project are paying great efforts to execute it under the study protocol.

We have to pay attentions to produce timely findings for prevention of lifestyle-related diseases. The cross-sectional analyses will be expected to detect gene-environment interactions for biomarkers collected at the baseline survey and second survey. The serum and plasma of patients diagnosed as cancer within two years will provide the evidence how the candidate molecules are effective for early cancer diagnosis. The analyses based on the follow-up data will be performed more than ten years later, but the findings on gene-environment interactions are valid relative to case-control studies.

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Appendix

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