AGENDA

What should we do to raise awareness on the issue of cancer in the global health agenda?

3C Intelligence

Contextual Intelligence
Collective Intelligence
Continuous Intelligence

12:00 Opening remarks

Tetuichiro Muto	President, NPO Health and Medical care Promotion
Hideyuki Akaza	President, APCC
Norie Kawahara	Organizer, Asia Cancer Forum

12:10 Global Challenges in Cancer Control. Video Letter

Ala Alwan
WHO Assistant Director-General - Noncommunicable Diseases and Mental Health"

Session 1: What will shape the global health agenda?

Contextual Intelligence
From the view point of top down

12:25 The Challenges in The Global Health.

Keizo Takemi, Senior Fellow
Japan Center for International Exchange Professor, Tokai University
Special Advisor, Sasakawa Health Memorial Foundation

12:40 Cancer as a Global Health Agenda.

Hajime Inoue, Executive Advisor,
Department of Health and Welfare, Chiba Prefecture,

12:50 How could the issue of cancer be justified as a global health agenda?

Hiroyoshi Endo, Professor
Department of International Affairs and Tropical Medicine,
Tokyo Women's Medical University

Discussion

13:15 Research platform to formulate cancer prevention strategies in Asian-region.

Manami Inoue, Section Head
Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center

Session 2: Where are we really?

What activity can we do against Health Equity?
-Collective Intelligence –
From the view point of bottom up

13:30 On dispatch as expert adviser in Thailand

Eitaka Thuboi, Former President of World Medical Association

Asian Network of Childhood Cancers Tumor Banks: Aiming for Better Cure of the Sick Children

Akira Nakagawara, Director
Chiba Cancer Center,

Role of Traditional Medicine for Cancer Patients.

Kenji Watanabe, Associate Professor, Center for Kampo Medicine,
Keio University School of Medicine

Discussion

Session 3: What should be incorporated in future agendas?

-Continuous Intelligence-

14:05 Health information in my hand.

Mamoru Iwabuchi, Associate Professor, RCAST, the University of Tokyo

14:10 Cancer: from Personal to Societal.

Tohru Masui, Chief, Division of Bioresources Research,
National Institute of Biomedical Innovation

Special Comments

David Hill Australia President, UICC/Cancer Council Victoria
Tomoyuki Kitagawa Chiarn, UICC Japan
Jae Kyung Roh Yonsei University,Korea

The Challenges of Cancer Prevention in China.

Xi Shan Hao President, Chinese Anti-Cancer Association

Expanding Need of Cancer Medicine in Asia.

Hideyuki Akaza President, APCC

14:55 Closing Remark

Masanori Nishiyama President, Medical Platform Asia
Norie Kawahara Organizer, Asia Cancer Forum

III. 研究成果の刊行に関する一覧

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
椙村春彦、松田友成	喫煙	病理と臨床増刊号		文光堂	東京	2009	124-130
増井　徹	バイオバンク	玉井真理子、大谷いづみ	生命倫理	有斐閣	東京	2010	印刷中

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Imai Y, Tamura S, Tanaka H, Hiramatsu N, Kiso S, Doi Y, Inada M, Nagase T, Kitada T, Imanaka K, Fukuda K, Takehara T, Kasahara A, Hayashi N.	Reduced risk of hepatocellular carcinoma after interferon therapy in aged patients with chronic hepatitis C is limited to sustained virological responders.	J Viral Hepat.	17	185-191	2010
Tanaka H, Tanaka M, Chen W, Park S, Jung KW, Chiang CJ, Lai MS, Mirasol-Lumague MR, Laudico AS, Sinuraya ES, Nishino Y, Shibata A, Fujita M, Soda M, Naito M, Tsukuma H, Moore MA, Ajiki W.	Proposal for a Cooperative Study on Population-based Cancer Survival in Selected Registries in East Asia.	Asian Pac J Cancer Prev.	10 (6)	1191-8	2009
Kawase T, Matsuo K, Suzuki T, Hiraki A, Watanabe M, Iwata H, Tanaka H, Tajima K.	FGFR2 intronic polymorphisms interact with reproductive risk factors of breast cancer:Results of a case control study in Japan.	Int J Cancer.	125 (8)	1946-52	2009
Ito Y, Ioka A, Tsukuma H, Ajiki W, Sugimoto T, Rachet B, Coleman MP.	Regional differences in population-based cancer survival between six prefectures in Japan: application of relative survival models with funnel plots.	Cancer Sci.	100 (7)	1306-11	2009

Matsuda T, Marugame T, Kamo KI, Katanoda K, Ajiki W, Sobue T.	Cancer Incidence and Incidence Rates in Japan in 2003: Based on Data from 13 Population-based Cancer Registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project.	Jpn J Clin Oncol.	39 (12)	850-858	2009
Baba S, Ioka A, Tsukuma H, Noda H, Ajiki W, Iso H.	Incidence and survival trends for childhood cancer in Osaka, Japan, 1973–2001.	Cancer Sci.	101 (3)	787-792	2010
Kim HJ, Lim SY, Lee JS, Park SH, Shin AS, Choi BY, Shimazu T, Inoue M, Tsugane S, Kim JS.	Fresh and pickled vegetable consumption and gastric cancer in Japanese and Korean populations: A meta-analysis of observational studies.	Cancer Sci.	101 (2)	508-16	2010
Tanaka M, Tanaka H, Tsukuma H, Ioka A, Oshima A, Nakahara T.	Risk factors for intrahepatic cholangiocarcinoma: A possible role of hepatitis B virus.	Journal of Viral Hepatitis	in press		2010
Truong T, Matsuo K et al.	Internatinal Lung Cancer Consortium: Replication of susceptibility loci on chromosome 15q25, 5p15 and 6p21.	J Natl Cancer Inst.	in press		2010
Truong T, Matsuo K et al.	International Lung Cancer Consortium: Coordinated association study of 10 potential lung cancer susceptibility variants.	Carcinogenesis	in press		2010
Yamada, H., Sugimura, H.et al.	Identification and characterization of a novel germline p53 mutation in a patient with glioblastoma and colon cancer.	Int J Cancer	125 (4)	973-6	2009
Goto, M., Sugimura, H.et al.	Altered expression of the human base excision repair gene NTH1 in gastric cancer.	Carcinogenesis	30 (8)	1345-52	2009
Okudela, K. Sugimura, H.et al.	Down-Regulation of DUSP6 Expression in Lung Cancer --Its Mechanism and Potential Role in Carcinogenesis.	Am J Pathol	175 (2)	867-881	2009

Seike, M., Sugimura, H.et al.	MiR-21 is an EGFR-regulated anti-apoptotic factor in lung cancer in never-smokers.	Proc Natl Acad Sci U S A	106 (29)	12085-90	2009
Goto, M. Sugimura, H. et al.	Three novel NEIL1 promoter polymorphisms in gastric cancer patients.	World Journal of Gastrointestinal Oncology	2	117-20	2010
Kazumi Hakamada, Satoshi Fujita, Jun Miyake.	Onset timing of transient gene expression depends on cell division.	J. Biosci. Bioeng.	109	62-66	2010
T. Sugitate, T. Kihara, X.Y. Liu, J. Miyake.	Mechanical role of the nucleus in a cell in terms of elastic modulus	Current Applied Physics	4S1	e291-e293	2009
Kihara T., Nakamura C., Suzuki M., Han S.W., Fukazawa K., Ishihara K., Miyake J.	Development of a method to evaluate caspase-3 activity in a single cell using a nanoneedle and a fluorescent probe, J.	Biosens. Bioelectron.	25	22-27	2009
The International Cancer Genome Consortium: Masui, T. as an International Data Access Committee.	International network of cancer genome projects.	Nature	in press		2010
Kawahara N.	Perspectives on Strategies for Establishing Cancer on the Global Health Agenda:Discussion on the possibilities and significance of creating infrastructure for cancer prevention information using school health classes.	Asian Pac J Cancer Prev.	8(1)	in press	2010
田中政宏、津熊秀明	胆管細胞がんの疫学	日本臨床	67 (supl. 3)	278-282	2009
増井徹.	バイオバンクの現状と将来.「遺伝子診断学」	日本臨床	印刷中		2010

IV. 研究成果の刊行物・別刷り

COMMENTARY

Proposal for a Cooperative Study on Population-based Cancer Survival in Selected Registries in East Asia

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Abstract

Reliable population-based cancer survival data are essential for assessment of the effectivenes of cancer screening programs, distribution of cancer therapy and prevalent cancer cases. International comparisons are useful to allow societies, mass media and health authorities to gain a real appreciation of the cancer problem in their own country and provide an impetus to improve registration and cancer control planning. Since directly comparable survival data among East Asian countries are presently very limited, a comparative study on population-based cancer survival involving China, Indonesia, Japan, Korea, the Philippines and Taiwan, with Nepal as an observer, was proposed. At the 1st Working Group meeting in Tokyo on March 18th, 2009, it was decided to publish the present Commentary as a step towards realization of truly comparable cancer survival statistics in the region. Included are general information and quality of data of cancer registration at each participating registry and five-year relative survival rates of cancer of the stomach, colo-rectum, liver, lung, breast and cervix.

Key Words: Cancer registration - survival - data quality - international comparisons

Asian Pacific J Cancer Prev, **10**, 1191-1198

Introduction

Survival estimates of patients registered in population-based cancer registries reflect the average prognosis in a given region, since they are based on unselected patients with a variety of socioeconomic status, natural histories, and circumstance of cancer detection as well as treatment procedures. Data on population-based cancer survival are, therefore, useful for evaluating cancer control planning for early detection and distribution of cancer therapy in a given region. Survival statistics are also useful as comparative measures; they can show how survival differs between different populations over time and between subgroups defined by ethnicity, socioeconomic status, hospital volume, etc. An international comparative study on cancer survival mainly consisting of EU countries and North American countries, has been conducted, namely the "CONCORD STUDY", with standardized study subjects and identical analytic methods (Coleman et al., 2008).

In East Asia, population-based cancer survival rates were studied in Qidong (Chen et al., 1998) and Shanghai (Jin et al., 1998) in China, Rizal (Esteban et al., 1998) in the Philippines, and Chiang Mai (Martin et al., 1998) and Khon Kaen (Vatanasapt et al., 1998) in Thailand, and were published in the book entitled, "Cancer Survival in Developing Countries", in 1998. Improvement of infrastructure and/or legislative conditions as well as technical advances in cancer registration have resulted in the ability to obtain better cancer survival estimates in East Asian countries. Five-year relative survival rates (RSRs) were published from seven registries in Japan in 2006 (Miyagi, Yamagata, Niigata, Fukui, Osaka, Tottori and Nagasaki) (Tsukuma et al., 2006), in Korea in 2007 (Jung et al., 2007) and in Manila and Rizal in the Philippines in 2009 (Redaniel et al., 2009). However, these

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Figure 1. Members and Observers at the Working Group Meeting Held in Tokyo on March 18th, 2009

population-based cancer survival data in East Asian countries did not have comparability with each other.

In 2008, a study group for "Cancer Epidemiology and Statistics in East Asia" in the Third-term Comprehensive Ten-year Strategy for Cancer Control was launched through a grant-in-aid from the Japanese Ministry of Health Labour and Welfare. The study group planned to make a platform for conducting a cooperative study using population-based cancer registry data in East Asia. The study group held a meeting with researchers who were in charge of cancer registries that had relatively good quality of data in the region in March 2009 in Tokyo (Figure 1), and decided to perform a cooperative study of cancer survival estimates. As the first stage of the cooperative study, we intended to describe registration procedures and the validity of the participating registries as background information, and collected data on five-year relative survival rates among patients with cancer of the stomach, colorectum, liver, lung, breast and uterine cervix in a designated format.

Background Information on the Registries Participating in this Cooperative Study

(1) Characteristics of the Catchment Areas and Populations

1) Korea Central Cancer Registries (KCCR) The Republic of Korea lies between longitudes 124° and 131°E and latitudes 33° and 38°N, and has an area of 99,500 km^2 including about 3,000 islands. There are seven metropolitan cities with provincial status and nine provinces. The population of the Republic of Korea is 4.8 million (2005 estimates), which is covered by the KCCR.

Most people living in the Republic of Korea are ethnically Korean and their national language is Korean. Buddhism and Christianity are the largest religions in South Korea. Due to rapid urbanization of the country, 80 percent of the population are now classified as living in an urban area. Aging of the population is proceeding very quickly. The 2003 population estimate revealed that 8.3 percent of the total population was 65 years old or over. In 2004, the economically active population was 23.3 million. Of this figure, 8 percent were engaged in agriculture, forestry, or fishing, 27 percent in industry, and 65 percent in services.

2) The Six Cancer Registries in Japan in the Present Cooperative Study. Japan consists of four major islands (approximately 378,000 square km in total area) and has a population of 127 million (2005 national census data). Its population density is 338/square km (2005), which is one of the highest in East Asia. The annual population growth was nearly zero in 2007. The population is aging very quickly, with 21.5% of the population being 65 years old or over (2007). The proportion of the working-age population (aged 15-64 years) is 65.0% (2007). Among the working population, 4.2% were engaged in agriculture, forestry or fishing, 27.9% in industry, and 67.9% in services. Japan is one of the most ethnically homogeneous countries in the world, where almost all of the people with Japanese nationality are ethnic Japanese. About 2% of the residents in Japan are foreigners by nationality (2008).

Japan has 47 prefectures (principal administrative divisions equivalent to provinces), of which 35 have their own cancer registry. There is no legislative basis at the national level that mandates cancer registry. The registry in each prefecture is an activity based on a prefectural ordinance. Six prefectural cancer registries provided data to the present cooperative study, namely, the cancer registries of Miyagi, Yamagata, Niigata, Fukui, Osaka, and Nagasaki. The prefectures of Miyagi and Yamagata are located in the northeastern part of the main Honshuu islabd. The prefectures of Niigata and Fukui are located in central Japan along the coast facing the Japan Sea. The prefecture of Osaka is located at the geographical center of Honshuu, and most of the residents live in urban areas. The prefecture of Nagasaki is located in the westernmost part of the main island. Data on the populations covered by the six participating registries are shown in Table 1.

Table 1. Background Information and Characteristics of the Six Cancer Registries in Japan

	Miyagi	Yamagata	Niigata	Fukui	Osaka	Nagasaki
Pop[1]	2.34	1.20	2.43	0.82	8.67	0.87
Area	7,286	9,323	12,583	4,189	1,897	4,095
Case[2]	1	2	2	2	2	1,3
Follow[3]	Y	Y	N	Y	Y	N
Prognosis[4]	2	1 and 2	2	1 and 2	1 and 2	2

Pop[1], Target population (million) obtained from the National Census in 2005; Area, (square km);[2]Case finding: 1) mainly by active data search, 2) mainly by passive data search, 3) combined with pathological data search; [3]Follow back: Y) follow back conducted, N) follow back not conducted; [4]Prognosis investigation, 1) by referring to the information in residential registration, 2) by referring to the information in the vital statistics database with personal identifying information

3) Registries in Manila and Rizal. The first formal cancer registration activity in the Philippines was started in 1959 by the Philippine Cancer Society (PCS) when it established the Central Tumor Registry of the Philippines (CTRP). The CTRP collected data from 26 hospitals, of which 25 were located in Metropolitan Manila and one in Cebu, completely relying on notifications from these hospitals. The CTRP was converted into a population-based registry in 1983. It covered the population of four cities included in the Metropolitan Manila area (Manila, Quezon City, Pasay City and Caloocan City) and was renamed the Philippine Cancer Society-Manila Cancer Registry (PCS-MCR). The total population in the 4 cities was 5.08 million in a total area of 635 sq.km in 1995. Metro Manila is the major urban center of the country.

The first population-based cancer registry in the Philippines was established in 1974 as one of the activities of the Community Cancer Control Program of the province of Rizal. At that time, Rizal was composed of 26 municipalities, 12 of which were subsequently incorporated into Metropolitan Manila in 1975. In 1984, the Department of Health-Rizal Cancer Registry (DOH-RCR) started a cooperative effort with the Philippine Cancer Society-Manila Cancer Registry in covering 134 hospitals within the National Capital Region and Rizal Province. Currently, the two registries cover over 169 hospitals within the Metro Manila area and Rizal Province. Both registries use the same forms and the same method of active data collection. The total population size in the catchment area of Rizal Cancer Registry was 5.25 million in an area of 1,039 sq.km in 1995. Rizal Province is 75% urban.

4) Taiwan Cancer Registry. Taiwan consists of Taiwan Island proper, Penghu, Kinmen, Matsu, and dozens of small islands (approximately 36,000 square km in total area). Taiwan has a population of 22 million (2008). Its population density is 637/square km (2008), which is the second highest figure in the world after that of Bangladesh. The annual population growth is 3.4%, and 10.4% of the population are 65 years old or over (2008). About 98% of the Taiwanese are Han Chinese, and the rest of the population consists of native Taiwanese with Malayo-Polynesian origin and others. About 2% of the residents in Taiwan in 2008 were foreigners by nationality.

National household registration was implemented in Taiwan in 1906. Information is recorded mandatorily and double-checks performed annually by household registration officers. It is considered to be quite complete and accurate. Also, each Taiwanese has a unique identification number (citizenship ID number), which is used for governmental services. The Taiwan Cancer Registry, a population-based cancer registry, was founded in 1979. The registry became a compulsory system with implementation of the Cancer Control Act of 2003, which mandates hospitals with greater than 50-bed capacity providing outpatient and hospitalized cancer care to report all newly diagnosed malignant neoplasms to the registry. The registry is organized and funded by the Department (Ministry) of Health of the executive branch of the central government. The National Public Health Association has been contracted to operate the registry and organized an advisory board to standardize definitions of terminology, coding, and procedures of the registry's reporting system. The central cancer registry office is located at National Taiwan University, and the professor of Institute of Preventive Medicine heads the registry.

(2) Data Processing at the Registries

1) The Korea Central Cancer Registry (KCCR). The KCCR is responsible for collection, analysis and management of national cancer statistics; providing technical and financial support to regional cancer registries including cancer registrar training; analyses and summarization of data from the central and regional cancer registries; and carrying out administrative tasks related to cancer registry as required by the minister of the Ministry of Health and Welfare.

The KCCR established the Korea National Cancer Incidence Database (KNCIDB) by merging the KCCR database and the databases of all eight population-based regional cancer registries (Busan, Daegu, Seoul, Daejeon, Gwangju, Inchon, Ulsan, Jejudo). The KCCR dataset was further refined by confirming multiple primary cancers and removing duplicates with the help of experts from various fields including clinicians, pathologists and medical recorders.

2) The Six Japanese Registries. An outline of the registration procedures at the 6 Japanese registries in this report follows, although there are differences in the implementation of case finding, prognosis investigation, and follow back of death certificate notification (DCN) cases. The differences in these procedures, as well as characteristics of the catchment area, are summarized in Table 1.

a) Health care facilities send information on cancer patients who have been diagnosed or treated at their facility, to the cancer registry office of the prefecture.

b) The registry office collects information in death certificates from the local prefectural office. As a follow-back survey, for DCN cases, a request for information is sent to each health care facility that issued the death certificate. Also, some other data source, such as data on

pathological services provided at health care facilities or information on patients who received governmental financial support for cancer care, may be utilized for case finding by some registries.

c) The incidence, mortality, and prognostic information are organized, verified, and consolidated in the central database. It usually takes about 3-4 years to complete all of these procedures.

3) Registries in Manila and Rizal. Manila Cancer Registry (MCR) clerks are assigned to collect and abstract data from 109 hospitals (active registration) which include 26 hospitals that also send reporting forms to the MCR (passive registration). At the Rizal Cancer Registry (RCR), initially data collection was entirely passive, relying on notification from physicians and hospitals, from 1974 to 1979. This system was highly unsatisfactory and active registration was started in 1980. At present, the Rizal Cancer Registry covers 60 hospitals using an active method of registration. Research assistants at both the MCR and RCR review death certificates from the office of the Local Civil Registries. Data received are checked for completeness and consistency as well as for duplication, both manually and with the aid of a computer. Checking for consistency and validity of codes is performed with the IARC/IACR CanReg 4 software.

4) The Taiwan Cancer Registry. Taiwan has several social infrastructures that allow efficient cancer registry, such as the National Cancer Act of 2003 which mandates nationwide cancer registry, citizenship ID numbers, nationwide health insurance system since 1995, and digitized database of vital statistics, health insurance claims, and cancer screening programs. With these tools, cancer registry is conducted very efficiently with excellent quality indices. An outline of the registration procedures in Taiwan follows.

a) All hospitals with more than 50 beds (approximately 230 facilities in 2008) are mandated to report newly diagnosed cancer cases within 12 months after confirming the diagnosis. Required information on these cases includes patients' basic information (age, sex and citizenship ID numbers), information on the diagnosis and administered therapies, and prognosis if known. Also, hospitals that diagnose or treat more than 500 cases per year are mandated to report more detailed information on cases of cancer at 6 major sites (liver, lung, colon, female breast, oral cavity, and cervix uteri).

b) A database on potential cancer cases is created each year from the death certificate database, catastrophic illness database (health insurance claim data for serious illnesses), and cancer screening program database (data from screening programs for cancers of the cervix, female breast, colorectum, and oral cavity). This database is compared with the database of cancer cases reported by health care facilities each year. Unreported cases of potential cancer are followed-back to the hospitals where the cases had received care or been screened. These cases are added to the cancer registry database if confirmed as a cancer case.

c) For prognosis investigation (follow-up), the cumulated database of cancer cases since 1979 is record-linked to the death database in vital statistics. Cancer death cases matched in the two databases are consolidated with the cancer registry database.

(3) Quality Indicators of the Registries

Table 2 shows the percentage of morphologically verified cases (MV%), percentage of death certificate only cases (DCO%), and the mortality vs. incidence ratio (MI%) of the six cancer sites in this study at the participating registries in 1997-99. The MV% of stomach cancer ranged from 64% in Manila & Rizal to 96% in Taiwan. The MV% of liver cancer was relatively lower (except in Osaka) than those of the other types of cancer. The DCO% was relatively lower in Korea, Yamagata, Fukui, Nagasaki and Taiwan in comparison with Miyagi, Niigata, Osaka and Manila & Rizal, with some exceptions. The M/I% for stomach cancer and lung cancer in Taiwan were relatively higher (70%, 96%, respectively) than those in Korea and the Japanese registries. The Japanese registries had relatively higher M/I% for cervical cancer (24%~38%) than that in Korea (16%) and Taiwan (16%).

Method of Prognosis Investigation and Calculation of Survival

The task force of the study group required the participating registries to submit data on the 5-year relative survival rate of cancer of the stomach, colon, rectum, colorectum, liver, lung, female breast and cervix diagnosed from 1997 through 1999 or the nearest available years, which were already published or officially reported.

The survival data submitted from Indonesia were the 5-year cumulative survival rate among cancer patients who were diagnosed at Dharmais National Cancer Center in Jakarta in 1997-1999, which was calculated by the Kaplan-Meier method. Therefore, we introduced the data from Indonesia separate from the data from population-based registries.

(1) Korea Central Cancer Registries. Prognosis investigation was performed: by referring to the death certificate information; by referring to the inhabitant registry information;and for patients identified as potential cancer cases, by reviewing the medical records at the hospital through linking with the national medical health insurance data, national death certificate data and national population registration data. Passive follow-up was performed by linkage with several national databases using the unique personal identification number assigned to all residents in Korea. The national incidence database was linked to the national death certificate data from the Korea National Statistical Office and the national inhabitant registration data from the Ministry of Public Administration and Security, for follow-up of their vital status.

Cases with carcinoma in situ and subsequent tumors were excluded from the survival analysis. All cases with follow-back were included in the analysis. The Ederer II method was used for relative survival analysis with life

Table 2. Quality Indicators for the Registries

Organ/Registry	MV%	DCO%	M/I%
Stomach			
Korea	84.6	8.2	54.4
Miyagi	82.8	12.1	43.2
Yamagata	89.6	6.8	46.4
Niigata	77.9	20.5	45.9
Fukui	92.1	3.6	43.0
Osaka	78.5	18.8	57.4
Nagasaki	92.5	5.5	44.8
Manila & Rizal	63.7	14.3	
Taiwan	95.7	9.0	70.1
Colorectum			
Korea	87.5	4.4	38.1
Miyagi	83.1	11.1	39.2
Yamagata	88.2	6.1	37.8
Niigata	80.8	16.5	39.1
Fukui	89.4	4.1	41.9
Osaka	77.6	16.8	49.8
Nagasaki	90.1	6.3	40.6
Manila & Rizal	80.0	6.0	
Taiwan	94.0	5.7	45.9
Liver			
Korea	25.5	11.5	73.8
Miyagi	29.5	26.3	76.4
Yamagata	23.7	16.5	81.0
Niigata	20.9	43.8	82.1
Fukui	18.7	6.1	76.5
Osaka	90.4	26.4	82.2
Nagasaki	33.2	19.5	84.7
Manila & Rizal	30.4	26.7	
Taiwan	35.8	13.6	76.9
Lung			
Korea	69.7	10.8	79.1
Miyagi	74.6	16.2	73.1
Yamagata	76.4	16.8	80.3
Niigata	59.6	34.2	75.4
Fukui	73.9	8.5	82.2
Osaka	73.0	24.0	81.5
Nagasaki	74.5	15.3	75.2
Manila & Rizal	57.8	14.6	
Taiwan	84.0	14.3	96.0
Breast			
Korea	94.8	1.7	20.0
Miyagi	91.5	3.5	21.3
Yamagata	94.3	2.4	23.2
Niigata	91.3	7.6	24.6
Fukui	95.3	2.0	24.7
Osaka	91.0	5.8	29.6
Nagasaki	96.7	1.8	23.6
Manila & Rizal	88.0	5.1	
Taiwan	97.6	2.7	25.9
Cervix			
Korea	95.0	0.7	15.5
Miyagi	87.4	4.8	36.2
Yamagata	93.1	6.3	37.5
Niigata	90.2	9.3	27.2
Fukui	94.7	0.8	34.8
Osaka	89.4	8.0	37.9
Nagasaki	97.2	2.0	23.7
Manila & Rizal	89.0	4.9	
Taiwan	98.1	1.7	15.5

MV, morphologically verified; DCO, Death certificate only; M/I, mortality incidence ratio

tables through 1999 to 2006 in the Korean population.

(2) The Six Japanese Registries. For prognosis investigation, the vital status of registered persons for whom no cancer death was reported for five years, was confirmed by the information in the residential registration and/or the vital statistics database (non-cancer death database) (Table 1).

Calculation of relative survival was largely based on the method used in the EUROCARE study except that cases that had been followed-back using information in death certificates were excluded. In short, DCO cases, in situ cancer cases and mucosal cancer cases of the large bowel (when identified in the database) were excluded from the analysis (mucosal cancer cases were included in the Niigata registry because we could not identify them in the database). In the case of multiple cancers, only the first-diagnosed tumor was analyzed.

In calculating survival, cumulative 5-year survival rates were calculated starting from the date of diagnosis. Cases whose status was unknown at 5 years after diagnosis, were assumed to be alive as of the last known date of living. Expected survival rates were calculated using the cohort survival table based on life tables of the Japanese population and afterwards using the survival probability in the general population similar to the patients in sex, birth-year and age. The former was divided by the latter to obtain relative 5-year survival rates in an Ederer II method.

(3) Registries in Manila and Rizal. Prognosis investigation was performed: by referring to the death certificate information, through home visits, and by calling the patient's telephone number at home. The process of prognosis investigation was as follows: A summary of all cases abstracted in each hospital was prepared (number of cases collected per hospital/year and the distribution of cases/hospital by site). A summary of all death certificate abstracts gathered per municipality/year was likewise prepared (number of deaths from cancer per municipality/year and the distribution of cases by site, also cases for follow-back and the hospitals for follow-back). Both the hospital and death certificate abstracts were checked for completeness and consistency. To avoid duplication, completed hospital and death certificate abstracts were compared with the Master Patient Index File, Prior to Reference Date Cases, Site Index File, and Case-finding lists from the hospitals to determine if the case was previously seen in a hospital or not. If the case could not be traced back to a hospital or to the physician who signed the death certificate, the case was then registered under the "Death Certificate Only" category (DCO). Home visits are made by the registry assistant on patients who are deemed to be alive based on the status at last contact and whose names do not appear on any death certificate. Abstracts are updated as to status, treatment and current stage based on the information obtained at the home visit.

Cases with carcinoma in situ and subsequent primary cancer were excluded, and the follow-back cases were all included in the survival data. Ederer II, age-standardized

(using the world standard cancer patient population) 5-year RSRs were computed by using the life table for the Metro Manila population through individual years in 1997-1999.

(4) Taiwan Cancer Registry. The Taiwan Cancer Registry obtains follow-up information by data linkage with profiles of death certificates, catastrophic illnesses (included in health insurance program) and cancer screening programs. In the follow-up process, death records from the vital statistics database, catastrophic illnesses records and cancer screening databases for a given year were first matched with cancer registry data. Potential unreported cancer cases, i.e., those recorded as malignant cancer but had never been reported to the national cancer registry, were obtained. After the follow-up process, follow-back cases were included in the registry database except for the DCO and unreported cases.

Cases with carcinoma in situ and subsequent primary cancer except if the first primary cancer was non-melanoma skin, were excluded from the survival data. Bilateral breast cancers and multiple colon cancers were included as a single cancer if synchronous. The follow-back cases were all included.

The life tables of the national population of Taiwan from 1997 to 1999 were used to calculate the expected number of surviving patients or survival years. The Ederer II method was performed to calculate the 5-RSRs.

Survival Data (Tables 3 and 4)

(1) Stomach Cancer. The five-year relative survival rate (5-RSR) for stomach cancer ranged from 27% in Manila & Rizal to 70% in Niigata. All of the six Japanese registries showed a 5-RSR for stomach cancer among males of greater than 50%, followed by that in Korea (48%) and Taiwan (37%). Osaka had the lowest 5-RSR among the six Japanese registries. Similar geographic differences in stomach cancer survival were observed in female patients.

(2) Colorectal Cancer. The 5-RSR for colorectal cancer ranged from 40% in Manila & Rizal to 79% in Niigata. Relatively high 5-RSRs were observed in the Japanese registries in both males and females (59%~79%). The 5-RSRs for colorectal cancer in males and females in Korea (59% and 58%) were close to those in Taiwan (56% and 57%).

(3) Liver Cancer. Most of the 5-RSRs for liver cancer in the Japanese registries were between 20% and 30%. The 5-RSR in Taiwan was 18% among males and 20% among females, which was followed by that in Korea (13% and 15%). Manila & Rizal showed a 5-RSR for liver cancer of 8.5%.

(4) Lung Cancer. The 5-RSR for lung cancer in the six registries in Japan varied from 18% to 29% in males and from 25% to 48% in females. The 5-RSR of females was higher than that of males in all of the registries, and the difference was as much as 19 points in Yamagata and

Table 3. Five-year Relative Survival Rates (RSRs)

Organ/Registry	N	Diagnostic year(s)	PA* (%)	5-year RSR No (%)	SE (%)
Stomach Male					
Korea	12,421	1999-1999	98.3	48.1	0.5
Miyagi	3,203	1997-1999		67.6	1.0
Yamagata	2,607	1997-1999	98.8	66.0	1.2
Niigata	4,513	1997-1999		70.3	0.9
Fukui	1,402	1997-1999	95.6	65.7	1.6
Osaka	7,923	1997-1999	98.0	55.3	0.6
Nagasaki	2,242	1997-1999		59.2	1.3
Manila & Rizal (both sexes)					
	792	1993-2002		27.3	4.9
Taiwan	6,519	1997-1999	99.9	36.8	0.7
Stomach Female					
Korea	6,453	1999-1999	99.1	46.9	0.7
Miyagi	1,431	1997-1999		64.8	1.5
Yamagata	1,349	1997-1999	99.3	67.9	1.5
Niigata	2,028	1997-1999		69.0	1.2
Fukui	758	1997-1999	95.3	60.3	2.1
Osaka	3,697	1997-1999	98.2	53.7	0.9
Nagasaki	1,222	1997-1999		59.9	1.6
Taiwan	3,432	1997-1999	99.9	41.1	0.9
Colorectum Male					
Korea	4,949	1999	97.1	59.0	0.8
Miyagi	2,088	1997-1999		69.8	1.4
Yamagata	1,643	1997-1999	98.8	76.6	1.4
Niigata	2,820	1997-1999		78.7	1.1
Fukui	737	1997-1999	95.7	63.2	2.3
Osaka	5,226	1997-1999	97.2	60.6	0.8
Nagasaki	1,653	1997-1999		67.3	1.5
Manila & Rizal (both sexes)					
	1,635	1993-2002		40.2	4.4
Taiwan	10,265	1997-1999	99.8	56.1	0.6
Colorectum Female					
Korea	4,089	1999	97.6	57.6	0.9
Miyagi	1,566	1997-1999		69.8	1.4
Yamagata	1,278	1997-1999	99.2	69.0	1.6
Niigata	1,998	1997-1999		71.1	1.2
Fukui	606	1997-1999	94.4	68.5	2.4
Osaka	3,828	1997-1999	97.6	59.4	0.9
Nagasaki	1,305	1997-1999		67.0	1.6
Taiwan	7,790	1997-1999	99.9	57.0	0.6
Liver Male					
Korea	8,743	1999-1999	97.9	13.0	0.4
Miyagi	625	1997-1999		24.0	1.8
Yamagata	400	1997-1999	99.5	22.3	2.2
Niigata	541	1997-1999		22.7	1.9
Fukui	422	1997-1999	99.1	32.5	2.5
Osaka	4,766	1997-1999	97.6	23.4	0.7
Nagasaki	935	1997-1999		22.1	1.4
Manila & Rizal (both sexes)					
	772	1993-2002		8.5	1.9
Taiwan	16,325	1997-1999	99.9	17.6	0.3
Liver Female					
Korea	2,765	1999-1999	98.0	14.7	0.7
Miyagi	307	1997-1999		22.8	2.4
Yamagata	239	1997-1999	99.6	19.5	2.6
Niigata	252	1997-1999		21.7	2.6
Fukui	200	1997-1999	98.0	20.4	2.9
Osaka	1,752	1997-1999	97.4	21.3	1.0
Nagasaki	368	1997-1999		25.8	2.3
Taiwan	5,793	1997-1999	99.9	20.3	0.6

N, number of cases; PA, Prognosis available

Table 3 (continued). Five-year RSRs

Organ/Registry	N	Diagnostic year(s)	PA* (%)	5-year RSR No (%)	SE (%)
Lung Male					
Korea	8,612	1999-1999	97.7	11.5	0.4
Miyagi	1,883	1997-1999		24.9	1.1
Yamagata	1,066	1997-1999	99.2	23.7	1.4
Niigata	2,077	1997-1999		29.0	1.1
Fukui	701	1997-1999	98.7	21.5	1.7
Osaka	5,358	1997-1999	99.1	18.3	0.6
Nagasaki	1,652	1997-1999		24.0	1.2
Manila & Rizal (both sexes)					
	840	1993-2002		12.0	3.7
Taiwan	12,313	1997-1999	99.9	12.4	0.3
Lung Female					
Korea	2,899	1999-1999	98.0	17.8	0.8
Miyagi	730	1997-1999		37.7	1.9
Yamagata	366	1997-1999	99.2	43.2	2.8
Niigata	761	1997-1999		48.0	2.0
Fukui	247	1997-1999	97.2	33.6	3.2
Osaka	2,171	1997-1999	98.5	25.1	1.0
Nagasaki	688	1997-1999		34.5	2.0
Taiwan	5,398	1997-1999	99.9	15.0	0.5
Breast Female					
Korea	5,537	1999-1999	98.8	83.7	0.5
Miyagi	2,029	1997-1999		88.1	0.9
Yamagata	939	1997-1999	98.0	86.3	1.4
Niigata	1,708	1997-1999		86.4	1.0
Fukui	606	1997-1999	93.7	88.2	1.7
Osaka	5,816	1997-1999	97.5	83.6	0.6
Nagasaki	1,236	1997-1999		86.6	1.2
Manila &Rizal	1,615	1993-2002		58.6	4.1
Taiwan	11,723	1997-1999	99.9	79.7	0.4
Cervix Female					
Korea	4,333	1999-1999	98.2	81.1	0.7
Miyagi	262	1997-1999		69.6	3.2
Yamagata	122	1997-1999	94.3	73.3	5.0
Niigata	342	1997-1999		81.2	2.6
Fukui	114	1997-1999	93.9	65.9	5.3
Osaka	1,068	1997-1999	96.5	67.3	1.6
Nagasaki	336	1997-1999		77.2	2.7
Manila &Rizal	1,580	1993-2002		45.4	3.7
Taiwan	8,593	1997-1999	99.9	77.4	0.5

N, number of cases; PA, Prognosis available

Niigata. The female dominance in 5-RSR was also observed in Taiwan and Korea, although the difference was less marked. The 5-RSR in both genders in Manila & Rizal was 12%.

(5) Female Breast Cancer. In each registry, the 5-RSR for female breast cancer showed the highest figure among all cancer sites. The 5-RSR ranged from 58% (Manila & Rizal) to 88% (Fukui) among all of the registries.

(6) Cervical Cancer. The 5-RSR for cervical cancer was the highest in Korea and Niigata (81%), followed by Taiwan (77%). Miyagi (70%), Osaka (67%) and Fukui (66%) had lower rates than Korea and Taiwan. Manila & Rizal showed a 5-RSR for cervical cancer of 45%.

(7) Survival Data from Jakarta. One of the authors (E.S.) prepared 5-year cumulative survival rates in patients who were diagnosed at Dharmais National Cancer Hospital between 1997 and 1999. Table 4 shows the results along with the percentage of subjects who did not drop out during the 5-year period of prognosis investigation. Data for stomach cancer are not presented because of the small number of subjects. Note that the percentage of patients whose prognosis at 5 years after diagnosis was available, was low (ranging from 54% to 77%). Therefore, the estimated 5-year cumulative survival rate was possibly overestimated.

Table 4. Five-year Cumulative Survival Rates for Patients Diagnosed at Dharmais National Cancer Hospital, Indonesia between 1997 and 1999

Organ	Sex	Age range	N	PA (%)	No/Total	Survival No(%)	SE(%)
Colon	Male	25-80	41	75.6	(31/41)	36.6	6.31
	Female	21-83	39	64.1	(25/39)	28.2	5.49
Rectum	Male	24-81	36	69.4	(25/36)	38.9	6.61
	Female	26-79	24	54.2	(13/24)	37.5	2.07
Liver	Male	30-84	55	83.6	(46/55)	34.6	1.20
	Female	25-78	20	55.0	(11/20)	30.0	1.05
Lung	Male	27-82	250	73.2	(183/250)	33.2	1.66
	Female	21-88	80	77.5	(62/80)	31.3	3.61
Breast	Female	19-95	475	73.7	(350/475)	48.6	3.43
Cervix	Female	18-84	487	66.5	(324/487)	50.5	0.96

N, number of cases; PA, Prognosis available; SE: standard error

Discussion

Our results revealed that there were substantial differences in quality indices among different cancer registries in East Asia in the late 1990s. These differences partly reflect differences in the social system and health care infrastructure.

The DCO% in Taiwan and Korea were among the lowest of the nine registries for all cancer sites. This is, at least in part, due to the fact that the two countries have excellent social infrastructures for cancer registry, such as citizenship ID number, digitized vital and health statistics database, and a universal health insurance system. On the other hand, the Japanese registries showed great variation in DCO%, which is partly due to the facts that there is no nationwide legal basis or social infrastructure for cancer registry in the country and that each registry developed its system.

Our study results also showed that there was substantial variation in the reported RSRs among the six registries in Japan in the late 1990s. These differences should reflect not only differences in cancer control activities and cancer care, but also differences in cancer registration system. Therefore, we need to consider all of these factors in the interpretation of the results. Besides health care quality, there are three major factors that can influence RSRs, namely the characteristics of the subjects, the patient follow-up system, and the method of calculation of RSR. "The characteristics of the subjects" refers to the combination of different patient groups such as: i) hospital-reported cases, followed-back cases, and DCO cases, ii) primary cancer cases and subsequent cancer cases, iii) symptom-diagnosed cases and cancer screening-

diagnosed cases. The survival rates of these patient groups are usually different; therefore, the proportion of each patient group in the subject population can affect the survival rate. The follow-up system varies from registry to registry, and if it is not exhaustive, RSRs may be over-estimated. There are three different methods of calculation of RSR, i.e., the Ederer I, Ederer II or Hakulinen method, each of which produces somewhat different results. In the current study, all of the registries adopted the Ederer II method. Also, for better comparability across cancer patient populations, we need age-adjusted and clinical stage-specific calculation.

The RSR for cervical cancer in Japan tended to be lower than that in Taiwan or Korea. This finding may be explained by a difference in the clinical stage of cervical cancer cases coming from a difference in cervical screening coverage. In Japan, cervical screening has been offered mainly by the population-based program, and its coverage has been fairly low (approximately 15% in the 1990s). Taiwan introduced a population-based cervical screening program in 1996, which achieved a higher screening coverage than that in Japan by 1999. A recent publication on international comparison of cancer survivals reported that the 5RSR for cervical cancer in the three registries from Korea (Busan, Incheon and Seoul) was 76 ~79 % (Sankaranarayanan et al., 2009). Korea introduced a population-based screening program in 1999, but voluntary screening might have achieved good coverage by the introduction. Therefore, the proportion of screening-diagnosed cases in the Japanese registries might have been lower than that in Korea or Taiwan, in contrast to the screening coverage for stomach, colon and lung. In addition, cervical cancer survival rate is largely differed by age at diagnosis (Ioka et al., 2009) which was possibly attributed in relatively lower survival observed in the Japanese even in the RSR. We need to validate this hypothesis by comparing the clinical stage of reported cases and screening coverage for cervical cancer.

Our study has some limitations. First, as explained earlier, the RSRs at some registries may have been overestimated due to the difference in follow-up system or exclusion of followed-back cases. Second, the calculation of DCO% at the Japanese registries was based on the Japanese definition of DCO, which may have overestimated the DCO% in the country. Third, it is likely that there was a difference in age distribution of the patient population across different registries, but we could not age-standardize the calculation of RSRs at this time, which might have reduced the comparability (Cprazziari et al., 2004). Fourth, the results from Manila and Rizal were on subjects who were diagnosed between 1993 and 1999 in both genders, which had less comparability with the other registries. Last, we did not collect information on clinical stage or histology for each cancer site, and potential differences in this critical information could not be analyzed.

Even with the above-described limitations, this study is worthwhile as the first attempt to calculate population-based cancer survival in selected registries in East Asia, with disclosing data quality. To improve the comparability for assessment of cancer survival difference in East Asia, we need further efforts to standardize the definition of study subjects and to obtain individualized data items attributed to the survival time.

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References

Chen J-G, Li W-G, Shen Z-C, et al (1998). Population-based cancer survival in Qidong, People's Republic of China. In Sankaranarayanan R., Black RJ and Parkin DM eds. Cancer Survival in Developing Countries. IARC Scientific Publications No. 145, Lyon, 27-35.

Coleman MP, Quaresma M, Berrino F, et al (2008). Cancer Survival in five countries: a worldwide population-based study (CONCORD). *Lancet Oncol*, **9**, 730-56.

Corazziari I, Quinn M, Capocaccia R (2004). Standard cancer patient population for age standardising survival ratios. *Eur J Cancer*, **40**, 2307-16.

Esteban D, Ngelangel C, Lacaya L, Robies E (1998). Cancer survival in Rizal, Philippines. In Sankaranarayanan R., Black RJ and Parkin DM eds. Cancer Survival in Developing Countries. IARC Scientific Publications No. 145, Lyon, 101-8.

Ioka A, Ito Y, Tsukuma H (2009). Factors relating to poor survival rates of aged cervical cancer patients: a population-based study with the relative survival model in Osaka, Japan. *Asian Pacific J Cancer Prev*, **10**, 457-62.

Jin F, Xiang Y-B, Gao Y-T (1998). Cancer survival in Shanghai, People's Republic of China. In Sankaranarayanan R., Black RJ and Parkin DM eds. Cancer Survival in Developing Countries. IARC Scientific Publications No. 145, Lyon, 37-50

Jung K-W, Yim S-H, Kong H-J, Hwang S-Y, Won Y-J, Lee J-K, et al (2007). Cancer survival in Korea 1993-2002: a population-based study. *J Korean Med Sci*, **22 (suppl)**, s5-10.

Martin N, Srisukho S, Kunpradist O, Suttalit M (1998). Cancer survival in Chiang Mai, Thailand. In Sankaranarayanan R., Black RJ and Parkin DM eds. Cancer Survival in Developing Countries. IARC Scientific Publications No. 145, Lyon, 109-22.

Redaniel MT, Laudico A, Mirasol-Lumague MR, et al (2009). Cancer survival discrepancies in developed and developing countries: Comparison between the Philippines and the United States. *Br J Cancer*, **100**, 858-62.

Sankaranarayanan R, Swaminathan R, Brenner H, et al (2009). Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol*, Published online December 10,2009, doi:10.1016/S1470-2045(09)70335-3.

Tsukuma H, Ajiki W, Ioka A, et al (2006). Survival of cancer patients diagnosed between 1993 and 1996: a collaborative study of population-based cancer registries in Japan. *Jpn J Clin Oncol*, 36, 602-7.

Vatanasapt V, Sriampom S, Kamsa-ard S, et al (1998). Cancer survival in Khon Kaen, Thailand. In Sankaranarayanan R., Black RJ and Parkin DM eds. Cancer Survival in Developing Countries. IARC Scientific Publications No. 145, Lyon, 123-34.

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FGFR2 intronic polymorphisms interact with reproductive risk factors of breast cancer: Results of a case control study in Japan

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Recently, 2 genome-wide association studies demonstrated that single nucleotide polymorphisms (SNPs) of the *fibroblast growth factor receptor 2* (*FGFR2*) gene at intron 2 are significantly associated with the risk of female breast cancer. As the next step, it is necessary to evaluate the interaction between these SNPs and known risk factors of breast cancer because such an evaluation could elucidate mechanisms of carcinogenesis and lead to preventive advances. We conducted a case-control study of 456 newly and histologically diagnosed breast cancer cases and 912 age- and menopausal status-matched noncancer controls. The impact of 5 *FGFR2* intronic SNPs on the risk of breast cancer and the interactions between these SNPs and various known risk factors of breast cancer were evaluated in both pre and postmenopausal women. We observed a statistically significant association between 4 SNPs and breast cancer risk and these 4 SNPs were in strong linkage disequilibrium in the Japanese population. rs2420946 was associated with a population-attributable risk of 17.7%. We found that *FGFR2* polymorphisms interact with family history of breast cancer (interaction $p = 0.003$) and reproductive risk factors, namely, age at menarche (interaction $p = 0.019$) and parity (interaction $p = 0.026$). Of note, a significant association between body mass index (BMI) ≥ 25 and *FGFR2* polymorphism was observed among postmenopausal women (trend $p = 0.012$), but not among premenopausal women. In contrast, BMI < 25 had no significant association with this polymorphism regardless of menopausal status. These findings suggest that *FGFR2* intronic SNPs affect the reproductive hormone-related pathway and contribute to the development of female breast cancer in the Japanese population.
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Key words: breast cancer; reproductive hormone; *FGFR2* intronic polymorphisms

Breast cancer ranks first among cancers affecting women worldwide.[1] The incidence rate of breast cancer in the Japanese population is generally lower than that in Caucasian populations and higher than that in other Asian populations.[2] In the Japanese population[3] and in other Asian populations,[4] the incidence of breast cancer increases rapidly until menopause, and then it reaches a plateau or decreases.

Recently, 2 large genome-wide association studies demonstrated that intronic single nucleotide polymorphisms (SNPs) of the *fibroblast growth factor receptor 2* (*FGFR2*) gene are significantly associated with the risk of female breast cancer,[5,6] although 1 study was conducted in sporadic postmenopausal women and the other was conducted in women who had a strong family history of breast cancer in the first stage of the study. Subsequently, the association of *FGFR2* polymorphisms with breast cancer was reported in Jewish and Arab Israeli populations,[7] Chinese population[8] and European-American but not African-American population.[9] Several other studies indicated that FGFR2 is associated with carcinogenesis of some types of cancer; that is, overexpression or missense mutation of FGFR2 occurs in breast, lung, gastric and ovarian cancers.[10–13] However, the mechanism through which these intronic SNPs increase the risk of developing breast cancer remains unknown, although an association between these SNPs and reproductive hormones has been suspected by 2 epidemiological studies.[8,9] In the first study, a significant additive interaction between *FGFR2* intronic polymorphisms and menopausal status was found in Chinese women,[8] and in the second study, a significant interaction between *FGFR2* intronic polymorphisms and combined hormone replacement therapy use was found in European-American women.[9] These evidences of interaction with specific risk factors of breast cancer may play a key role in elucidating the carcinogenic mechanism of *FGFR2* polymorphisms.

Recently, genome-wide association analysis using high-throughput genotyping technology has improved the efficiency of detection of loci that are associated with the risk for developing various diseases. Even if a susceptibility locus that is detected by a genome-wide association study has a modest effect, the predisposing allele is common and the population-attributable risk is considered to be relatively high. *FGFR2* intronic polymorphisms are the first example that was detected using this technology in the cancer area.[5] The population-attributable risk was estimated to be 16.0% among the white population.[6]

Here, we conducted a case-control study to evaluate the association of SNPs in intron 2 of *FGFR2* with breast cancer in the Japanese population and to clarify whether and how these SNPs interact with various known environmental risk factors for breast cancer, which may lead to elucidation of mechanisms of carcinogenesis involving the *FGFR2* gene and preventive advances.

Material and methods

Subjects

The cases were 456 female patients (217 premenopausal women and 239 postmenopausal women) with no previous history of cancer who were newly and histologically diagnosed with breast cancer between January 2001 and June 2005 at Aichi Cancer Center Hospital (ACCH) in Japan.[14] As controls, 912 female subjects (434 premenopausal women and 478 postmenopausal women) who were noncancer patients at ACCH were randomly selected and matched by age (±3 years) and menopausal status (pre or postmenopause) to the cases in a 1:2 case:control ratio. Even though the ACCH is called a cancer hospital, only 19% of all new outpatients have cancer.[15] About 66% of noncancer outpatients at ACCH have no specific medical condition, and the remaining 34% have a specific disease such as benign tumors, nonneoplastic

Additional Supporting Information may be found in the online version of this article.

Abbreviations: ACCH, Aichi Cancer Center Hospital; BMI, body mass index; CI, confidence interval; *FGFR2*, *fibroblast growth factor receptor 2*; HERPACC, hospital-based epidemiologic research program at Aichi Cancer Center; ORs, odds ratios; SNPs, single nucleotide polymorphisms.

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polyps or both (13.1%), mastitis (7.5%), gastrointestinal disease (4.1%) or benign gynecologic disease (4.1%). The medical background of the controls may have introduced bias into the study; however, our previous study focusing on women demonstrated that this would have had only limited impact.[16] All subjects were recruited within the framework of the hospital-based epidemiologic research program at Aichi Cancer Center (HERPACC), as described elsewhere.[17,18] In brief, in the HERPACC, information on lifestyle factors was collected using a self-administered questionnaire and checked by a trained interviewer. Outpatients were also asked to provide blood samples. Each patient was asked about her lifestyle when healthy or before the current symptoms developed. They were also asked to provide information on their lifestyle including body mass index (BMI) and regular exercise at the time of about 1 year before the interview or 1 year before the current symptoms developed. Approximately 95% of eligible subjects complete the questionnaire and 60% provide blood samples.[17] We used noncancer patients at our hospital as controls given the likelihood that our cases arose within this population base. We previously confirmed the feasibility of using noncancer outpatients at our hospital as controls in epidemiological studies by showing that their general lifestyles were accordant with those of a general population randomly selected from the electoral roll in Nagoya City, Aichi Prefecture.[15] All participants gave written informed consent. This study was approved by the Ethics Committee of Aichi Cancer Center.

Genotyping of intronic SNPs of FGFR2

Five SNPs of *FGFR2* at intron 2 were genotyped in this study. One SNP (rs2981582) reported by Easton *et al.*[5] and 4 other SNPs (rs11200014, rs2981579, rs1219648 and rs2420946) by Hunter *et al.*[6] were elucidated as significant risk factors for female breast cancer in the respective genome-wide association study. The quality of genotyping in our department is routinely assessed by conducting re-genotyping of randomly selected 5% of samples, and we confirmed complete concordance of the results of the genotyping. We also confirmed that there were no allelic distributions among the controls that departed from the Hardy-Weinberg frequency.

DNA from each subject was extracted from the buffy coat fraction with BioRobot EZ1 with an EZ1 DNA Blood 350 μL kit or QIAamp DNA blood mini kit (Qiagen K. K., Tokyo, Japan). Genotyping was based on Taqman Assays from Applied Biosystems (Foster City, CA).[19]

Assessment of environmental factors

Total alcohol consumption was estimated as the summarized amount of pure alcohol consumption. Drinking habit was classified into never, former, and current low, moderate and heavy drinking (heavy drinkers, those currently consuming alcoholic beverages in a daily amount of 15 g of ethanol or more; moderate drinkers, those currently consuming between 5 g of ethanol and less than 15 g of ethanol per day; low drinkers, those currently consuming less than 5 g of ethanol per day). The amount of alcohol consumption in Japanese females is lower than that in white females[20]; therefore, the boundary for each category in current drinkers was set relatively low. Cumulative smoking dose was evaluated as pack-years (product of the number of packs consumed per day and years of smoking). Smoking habit was classified into the 4 categories of never, former and current smokers of <20 and ≥20 pack-years. Former drinkers or smokers were defined as those who had quit drinking or smoking at least 1 year before the survey, respectively. BMI was calculated as weight divided by the squared height (kg/m^2). Regular exercise was classified as positive if the subject performed exercise more than once per month regardless of exercise time. In our study, family history was considered positive if either a mother or sister had had breast cancer.

TABLE I – CHARACTERISTICS OF THE PATIENTS WITH BREAST CANCER AND THE CONTROLS

	Cases (n = 456), n(%)	Controls (n = 912), n(%)	p
Age (yr)			
≤29	5 (1.1)	10 (1.1)	
30–39	46 (10.1)	76 (8.3)	
40–49	125 (27.4)	259 (28.4)	
50–59	148 (32.5)	285 (31.3)	
60–69	101 (22.1)	205 (22.5)	
70–79	31 (6.8)	77 (8.4)	0.80
Mean age (SD)	52.8 (10.7)	53.6 (10.8)	0.25
Drinking habit			
Never	286 (61.7)	563 (61.7)	
Former[1]	8 (1.8)	15 (1.6)	
Current			
Low[2]	73 (16.0)	157 (17.2)	
Moderate[3]	50 (11.0)	103 (11.3)	
Heavy[4]	36 (7.9)	59 (6.5)	0.88
Unknown	3 (0.7)	15 (1.6)	
Smoking habit			
Never	382 (83.8)	724 (79.4)	
Former[3]	24 (5.3)	55 (6.0)	
Current (pack years)			
0–19	34 (7.5)	78 (8.6)	
≥20	14 (3.1)	53 (5.8)	0.11
Unknown	2 (0.4)	2 (0.2)	
BMI			
<18.5	102 (22.4)	209 (22.9)	
18.5–24.9	259 (56.8)	532 (58.3)	
≥25.0	95 (20.8)	166 (18.2)	0.49
Unknown	0 (0)	5 (0.5)	
Regular exercise			
Yes	297 (65.1)	623 (68.3)	
No	157 (34.4)	288 (31.6)	
0.27 Unknown	2 (0.4)	1 (0.1)	
Family history of breast cancer			
Yes	32 (7.0)	47 (5.2)	
No	399 (87.5)	781 (85.6)	0.23
Unknown	25 (5.5)	84 (9.2)	
Menopausal status			
Premenopausal	217 (47.6)	434 (47.6)	
Postmenopausal	239 (52.4)	478 (52.4)	1.00
Age at menarche(yr)			
≤12	132 (28.9)	239 (26.2)	
13–14	218 (47.8)	443 (48.6)	
≥15	103 (22.6)	207 (22.7)	0.68
Unknown	3 (0.7)	23 (2.5)	
Age at menopause (yr) (only in postmenopausal women)			
≤49	83 (34.7)	155 (32.4)	
≥50	155 (64.9)	317 (64.9)	0.59
Unknown	1 (0.0)	6 (1.3)	
Parity			
0	61 (13.4)	133 (14.6)	
1–2	300 (65.8)	541 (59.3)	
≥3	95 (20.8)	232 (25.4)	0.08
Unknown	0 (0)	6 (0.7)	
Hormone use (months)			
Never	395 (86.6)	755 (82.8)	
1–6	32 (7.0)	80 (8.8)	
>6	27 (5.9)	64 (7.0)	0.34
Unknown	2 (0.4)	13 (1.4)	
Referral pattern to our hospital			
Patient's discretion	124 (27.2)	287 (31.5)	
Family recommendation	114 (25.0)	153 (16.8)	
Referral from other clinics	130 (28.5)	177 (19.4)	
Secondary screening after primary screening	84 (18.4)	286 (31.4)	
Others	2 (0.4)	6 (0.7)	<0.01
Unknown	2 (0.4)	3 (0.3)	

SD, standard deviation; BMI, body mass index.
[1]Former smokers and former drinkers were defined as subjects who had quit smoking or drinking, respectively, at least 1 year previously.–[2]Low drinker means ingesting <5 g ethanol/day.–[3]Moderate drinker means ingesting between ≥5 g ethanol/day and <15 g ethanol/day.–[4]Heavy drinker means ingesting ≥15 g ethanol/day.

TABLE II – IMPACT OF *FGFR2* POLYMORPHISMS

	All		Premenopausal		Postmenopausal	
	No. of cases/controls	ORs[1] (95% CI)	No. of cases/controls	ORs (95% CI)	No. of cases/controls	ORs (95% CI)
rs11200014						
GG	217/464	1.00 (ref.)	95/231	1.00 (ref.)	122/233	1.00 (ref.)
GA	191/369	1.11 (0.88–1.42)	100/169	1.44 (1.01–2.04)	91/200	0.87 (0.62–1.22)
AA	45/79	1.24 (0.83–1.86)	19/34	1.26 (0.68–2.36)	26/45	1.19 (0.69–2.04)
Unknown	3/0		3/0			
p_{trend}[2]		0.228		0.104		0.968
rs2981579						
CC	132/310	1.00 (ref.)	64/155	1.00 (ref.)	68/155	1.00 (ref.)
CT	233/461	1.19 (0.92–1.55)	110/219	1.21 (0.83–1.76)	123/242	1.18 (0.82–1.69)
TT	91/141	1.63 (1.16–2.29)	43/60	1.85 (1.12–3.06)	48/81	1.49 (0.93–2.38)
p_{trend}[2]		0.006		0.022		0.098
rs1219648						
AA	169/396	1.00 (ref.)	79/195	1.00 (ref.)	90/201	1.00 (ref.)
GA	227/416	1.29 (1.01–1.64)	110/193	1.39 (0.97–1.99)	117/223	1.19 (0.85–1.68)
GG	60/100	1.48 (1.02–2.15)	28/46	1.49 (0.85–2.58)	32/54	1.44 (0.86–2.41)
p_{trend}[2]		0.015		0.064		0.137
rs2420946						
CC	167/397	1.00 (ref.)	76/194	1.00 (ref.)	91/203	1.00 (ref.)
CT	226/416	1.29 (1.01–1.65)	113/194	1.47 (1.02–2.1)	113/222	1.16 (0.82–1.62)
TT	60/99	1.53 (1.05–2.23)	26/46	1.43 (0.81–2.52)	34/53	1.59 (0.95–2.64)
Unknown	3/0		2/0		1/0	
p_{trend}[2]		0.01		0.061		0.088
rs2981582						
CC	221/502	1.00 (ref.)	98/245	1.00 (ref.)	123/257	1.00 (ref.)
CT	192/347	1.26 (0.99–1.6)	99/161	1.50 (1.06–2.13)	93/186	1.06 (0.76–1.48)
TT	42/63	1.55 (1.01–2.37)	19/28	1.67 (0.87–3.18)	23/35	1.44 (0.81–2.58)
Unknown	1/0		1/0			
p_{trend}[2]		0.014		0.017		0.292

The genotype frequencies of all SNPs among the controls were in accordance with the Hardy-Weinberg law, namely rs11200014 ($p = 0.75$), rs2981579 ($p = 0.16$), rs1219648 ($p = 0.55$), rs2420946 ($p = 0.52$) and rs2981582 ($p = 0.77$).

[1]ORs were matched for age and menopausal status and adjusted for drinking habit, smoking habit, current body mass index, regular exercise, family history of breast cancer, age at menarche, parity, hormone use for contraception, infertility treatment or hormone replacement and referral pattern to our hospital.–[2]Trend of genotype was assessed by score test applying score for each genotypes (0, homozygous genotype for reference allele; 1, heterozygote genotype; and 2, homozygous genotype for nonreference allele).

Statistical analysis

To assess the strength of the associations between SNPs of *FGFR2* at intron 2 and the risk of breast cancer, odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using logistic models adjusted for potential confounders. Although we tried conditional logistic regression as primary analysis, we finally applied unconditional logistic regression to avoid dropping of controls, leading to unstable estimation in stratified analysis. Consistency between conditional and unconditional logistic regression models was confirmed. Potential confounders considered in the multivariate analyses were age, drinking habit (never, former, low, moderate or heavy drinkers), smoking habit (never, former, current smokers of <20 or ≥20 pack-years), current BMI (<20, 20–24.9, ≥25.0), regular exercise (yes, no), family history of breast cancer (yes, no), menopausal status (premenopause, postmenopause), age at menarche (≤12, 13–14, ≥15 years), parity (0, 1–2, ≥3), hormone use for contraception, infertility treatment or hormone replacement therapy (never, 1–6 months, >6 months) and referral pattern to our hospital (patient discretion, family or friend recommendation, referral from another clinic, secondary screening after primary screening or other) and these confounders were included in the model at once. To modify possible differences between cases and controls, we adjusted for referral pattern to our hospital. Menopause was defined as the complete cessation of menstrual bleeding due to natural, chemical or surgical causes.

The significance of differences in categorized demographic variables between the cases and controls was tested using the chi-squared test; subjects with unknown data were not included in the respective analysis. The ages of cases and controls were compared using Student's *t*-test. To assess for discrepancies between genotype and allele frequencies, accordance with the Hardy-Weinberg equilibrium was checked among the controls using the chi-squared test. Population-attributable risk was calculated using the following formula: $P_{Ho}(OR_{Ho} - 1) + P_{He}(OR_{He} - 1)/(1 + P_{Ho}(OR_{Ho} - 1) + P_{He}(OR_{He} - 1))$, where P_{Ho} and P_{He} are the proportions of homozygotes and heterozygotes of the risk allele, respectively, and OR_{Ho} and OR_{He} are the estimated ORs for homozygotes and heterozygotes of the risk allele, respectively. Gene-environmental interactions between several environmental factors and the genotype of 1 intronic SNP of *FGFR2* (rs2420946) were evaluated under the multiplicative model. Cross products of scores for genotype (0, homozygous genotype for reference allele; 1, heterozygote genotype; and 2, homozygous genotype for nonreference allele) and scores for each factor including drinking habit (0, non drinker; 1, current low and moderate drinker; 2, current heavy drinker), smoking habit (0, non smoker; 1, 0–19 pack-years; 2, ≥20 pack-years), BMI (0, <25; 1, ≥25), regular exercise (0, yes; 1, no), family history of breast cancer (0, no; 1, yes), age at menarche (0, ≥15; 1, 13–14; 2, ≤12), age at menopause (0, ≤49; 1, ≥50 years), parity (0, ≥3; 1, 1–2; 2, 0) or hormone use (0, yes; 1, no) were included in the multivariate logistic regression models as interaction terms. Former drinker and former smoker were excluded in each analysis. Statistical significance was set at $p < 0.05$. All analyses were performed using STATA version 10 (Stata Corp., College Station, TX).

Results

Data from 456 breast cancer cases and 912 controls were available for analysis. Table I shows the distribution of subjects by background characteristics. Age was appropriately matched, and drinking and smoking habits did not significantly differ between the groups. With regard to referral pattern, family recommendation and referral from other clinics were more frequent among the

TABLE III – INTERACTION BETWEEN *FGFR2* POLYMORPHISM (rs2420946) AND ENVIRONMENTAL FACTORS

	rs2420946 [No. of cases/controls, ORs (95% CIs)]			
	CC	CT	TT	p_{int}
Drinking habit				
Never	101/237, 1.00 (ref.)	146/265,1.31 (0.96–1.79)	37/61, 1.48 (0.92–2.38)	
Low[1] + moderate[2]	42/115, 0.86 (0.55–1.32)	60/118, 1.20 (0.81–1.79)	20/27, 1.93 (1.02–3.65)	
Heavy[3]	20/28, 1.87 (0.98–3.57)	13/26, 1.24 (0.6–2.56)	3/5, 1.93 (0.43–8.58)	0.696
Smoking habit				
0 pack-years	137/299, 1.00 (ref.)	191/341, 1.24 (0.94–1.63)	51/84, 1.43 (0.95–2.15)	
0–19 pack-years	13/46, 0.57 (0.29–1.11)	17/30, 1.16 (0.61–2.21)	4/2, 6.58 (1.03–42.17)	
≥20 pack-years	6/32, 0.43 (0.17–1.05)	7/17, 0.95 (0.38–2.38)	1/4, 0.62 (0.07–5.78)	0.136
BMI				
<25	135/320, 1.00 (ref.)	176/335, 1.23 (0.94–1.62)	48/86, 1.41 (0.93–2.13)	
≥25.0	32/77, 0.97 (0.6–1.55)	50/78, 1.53 (1.01–2.32)	12/11, 2.52 (1.07–5.98)	0.210
Regular exercise				
Yes	109/259, 1.00 (ref.)	151/294, 1.22 (0.9–1.64)	35/70, 1.27 (0.79–2.04)	
No	58/138, 1.03 (0.7–1.52)	73/121, 1.50 (1.04–2.18)	25/29, 2.21 (1.22–4.01)	0.204
Family history of breast cancer				
No	141/352, 1.00 (ref.)	202/349, 1.44 (1.1–1.87)	54/80, 1.77 (1.18–2.65)	
Yes	17/16, 2.72 (1.32–5.6)	13/23, 1.37 (0.67–2.8)	1/8, 0.30 (0.04–2.43)	0.003
Age at menarche				
≥15	42/84, 1.00 (ref.)	48/99, 0.98 (0.59–1.63)	12/24, 1.08 (0.49–2.39)	
13–14	87/194, 0.88 (0.56–1.39)	102/202, 1.00 (0.64–1.58)	28/47, 1.22 (0.66–2.24)	
≤12	35/112, 0.62 (0.36–1.08)	76/103, 1.42 (0.86–2.34)	20/24, 1.74 (0.84–3.59)	0.019
Age at menopause (only in postmenopausal women)				
≤49	35/72, 1.00 (ref.)	43/69, 1.32 (0.75–2.33)	5/14, 0.84 (0.28–2.58)	
≥50	56/129, 0.91 (0.54–1.53)	69/151, 0.96 (0.58–1.58)	29/37, 1.75 (0.91–3.33)	0.491
Parity				
≥3	38/96, 1.00 (ref.)	45/101, 1.18 (0.7–1.98)	11/35, 0.82 (0.38–1.8)	
1–2	110/237, 1.18 (0.76–1.84)	150/251, 1.51 (0.98–2.32)	38/53, 1.91 (1.08–3.38)	
0	19/63, 0.78 (0.41–1.49)	31/60, 1.28 (0.71–2.31)	11/10, 3.31 (1.25–8.74)	0.026
Hormone replacement therapy				
No	143/329, 1.00 (ref.)	198/346, 1.32 (1.01–1.72)	51/80, 1.51 (1–2.27)	
Yes	24/65, 0.87 (0.52–1.46)	28/64, 1.00 (0.61–1.64)	7/15, 1.14 (0.45–2.89)	0.559

BMI, body mass index.

ORs were matched for age and menopausal status and adjusted for drinking habit, smoking habit, current body mass index, regular exercise, family history of breast cancer, age at menarche, parity, hormone use for contraception, infertility treatment or hormone replacement and referral pattern to our hospital.

[1]Low drinker means <5 g ethanol/day.–[2]Moderate drinker means ≥5 g ethanol/day and <15 g ethanol/day.–[3]Heavy drinker means ≥15 g ethanol/day.

cases than among the controls, whereas patient discretion and secondary screening were less common in the former group.

Table II shows the genotype distributions of 5 SNPs of *FGFR2* at intron 2, and the OR and 95% CI for each SNP for breast cancer risk in all subjects and the subjects stratified by menopausal status. Four neighboring SNPs (rs2981579, rs1219648, rs2420946 and rs2981582), but not rs11200014, were in strong linkage disequilibrium (under limit of 95% CIs with each D' value >0.9) in the controls. Therefore, the results of the analyses of these 4 SNPs showed the same tendencies. These 4 SNPs revealed significant associations with the risk of breast cancer among all subjects; for example, the multivariable OR for rs2420946 for heterozygotes (CT) compared with homozygotes of the major allele (CC) was 1.29 (95% CI: 1.01–1.65) and the OR for homozygotes of the minor allele (TT) compared with CC was 1.53 (95% CI:1.05–2.23). rs2420946 was associated with a population-attributable risk of 17.7% among the study subjects. Stratified analyses according to menopausal status showed the same tendency as the analyses among all subjects.

The interactions between *FGFR2* polymorphism (rs2420946) and several reproductive and environmental risk factors of breast cancer were analyzed (Table III). Among all of the subjects, age at menarche (≥15, 13–14, ≤12, interaction $p = 0.018$), parity (≥3, 1–2, 0, interaction $p = 0.026$) and family history of breast cancer (No, Yes, interaction $p = 0.003$) showed significant interactions with the rs2420946 polymorphism. There were no statistically significant interactions between the *FGFR2* polymorphism and drinking habit, smoking habit, BMI, regular exercise, age at menopause (only among postmenopausal women) and hormone use. As expected from the strong linkage disequilibrium of the 4 SNPs of interest (rs2981579, rs1219648, rs2420946 and rs2981582), the same significant interactions were seen in the other 3 SNPs (Supporting Information Tables I—III).

Table IV shows the impact of *FGFR2* polymorphism (rs2420946) stratified by reproductive risk factors for breast cancer according to menopausal status. Among postmenopausal subjects, BMI ≥ 25 revealed a significant association with rs2420946 polymorphism (trend $p = 0.012$). In contrast, BMI < 25 had no significant association regardless of menopausal status. Age at menarche ≤12 years demonstrated significant association with rs2420946 polymorphism among both premenopausal (trend $p = 0.003$) and postmenopausal (trend $p = 0.049$) subjects, whereas age at menarche ≥13 years had no significant association in either menopausal status. Among premenopausal subjects, nulliparity had a significant association with rs2420946 polymorphism (trend $p = 0.008$) and among postmenopausal subjects, age at menopause ≥50 years had a marginal association with this polymorphism (trend $p = 0.056$).

As the results of this study suggested that *FGFR2* intronic SNPs contribute to the development of breast cancer through a reproductive hormone-related pathway as discussed in the Discussion section, we calculated the OR and 95% CI for each SNP for breast cancer risk in all subjects and the subjects stratified by menopausal status adjusting for confounders that are expected not to be reproductive hormone-related, namely, adjusted for drinking habit, smoking habit, family history of breast cancer and referral pattern to our hospital. The results hardly changed from the results of the original analysis (Table II); for example, among all subjects, the OR for rs2420946 for heterozygotes (CT) compared with homozygotes of the major allele (CC) was 1.29 (95% CI: 1.01–1.64) and