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Large-scale, Population-based Prospective Studies in Japan

Shaw Watanabe

Large scale, population-based prospective studies have increasing importance for the study of common cancers in view of the possibility of advancing the understanding of different risk factors in the initiation, promotion and progression phases during what is thought to be the long process of human carcinogenesis. The permanent registration system in Japan ("Koseki") simplifies the follow-up of registered participants of such cohorts. The population-based cohort studied by Hirayama and the cohort of the atomic bomb survivors started during the 1960s are examples of such possibilities in Japan. Rapidly changing patterns of disease and lifetyles during the last 30 years require new population-based prospective studies focusing on a different set of exposures and with increased detail of exposure assessment. We have established a new population-based prospective study, the "Koseisho" cohort, between 1990 to 1992, following a cross-sectional study, using various biomarkers in five health centre districts. The Koseisho cohort comprises approximately 170 000 people aged 40–59 or 40–69 in 12 different health centre districts. The data are linked with the mass screening program registry data every year, and the sera and buffy coats collected at the beginning of the study will be stored at −80°C for at least 10 years. We intend to integrate various sources of information about health conditions for the prevention of chronic diseases in these cohort areas. Nutritional practices are one of our main interests, and repeated surveys by different methods are planned. Although all death certificates are collected through the health centres, disease registration committees were established in each district to register incident cases of both cancer and certain cardiovascular diseases. Representative population-based prospective studies in Japan are briefly reviewed and introduced.
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INTRODUCTION

FOR CHRONIC diseases, such as cancer and cardiovascular diseases, prospective population-based studies (frequently called cohort studies) are effective epidemiological study designs [1]. Longitudinal surveillance and recording of these events is a natural model of the study that will allow us to better understand the mechanisms of disease causation and progression. Long-term follow-up is necessary in cancer epidemiology, because the clinical appearance of most cancers can take 20 or more years from the initiation phase. The cases which occur in the few years after the establishment of the cohort portray the risk of progression only (Fig. 1). The hypothesis of initiation, promotion and progression in human carcinogenesis becomes plausible, because the multistage carcinogenesis theory has obtained generality and showed a close correspondence between the age–incidence curves predicted from this theory and those actually observed [2]. Cases that occur during the mid-period of

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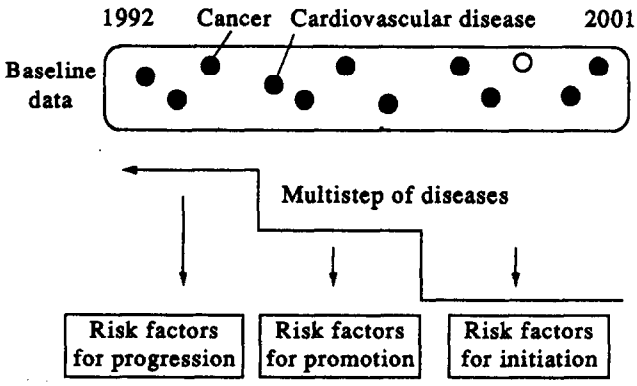

Fig. 1. Risk factors for initiation, promotion and progression obtained from the cohort study, based upon the multistep carcinogenesis. Cases which occurred after a short interval from the set-up can only show risk factors for progression.

the follow-up may show the risk of promotion, and those that happen at least 10 or more years later may show the risk of initiation. The accumulation of multiple genetic alterations is common in human cancer cells, so that it is important to clarify what environmental factors could cause each genetic alteration.

Since it is often easier and cheaper to obtain information on a sample rather than on the entire cohort, case–control studies have become widely adopted in cancer epidemiology as an alternative to cohort studies. This retrospective study design is still the only one feasible for all but the very commonest cancers. In Japan, all vital demographic events such as births, deaths and marriages are registered at the legal address of the family ("Honseki") [3]. This registration system ("Koseki") has been operating for more than 100 years. It is possible to ascertain accurately the vital status of any individual by checking the family register through the permanent address (Honseki) regardless of the actual residence. All deaths are verified through the Koseki check, and the cause of death is obtained from death certificates kept in the Ministry of Health and Welfare. The permanent registration system in Japan has produced many possibilities to follow up registered residents, but in recent times the use of Koseki has become more difficult because of laws introduced to protect privacy. In addition, the registration system of the target cancer or disease under study became necessary particularly because of the increased cure rate from many forms of cancer [4–7].

In this review article, I will describe briefly recent studies in cancer epidemiology in Japan, mainly those of large-scale, population-based prospective studies.

THE LARGE-SCALE COHORT STUDY OF HIRAYAMA

An influence of lifestyles on the risk of various diseases in Japan was first shown by a large-scale, population-based cohort study conducted by Hirayama and Soda [8]. Initial surveys were carried out from October to December in 1965 for 265 118 adults aged 40 and above residing in 29 health centre districts of six prefectures; 42 132 in Miyagi, 45 619 in Aichi, 49 386 in Osaka, 43 201 in Hyogo, 43 441 in Okayama and 41 339 in Kagoshima. These people were first surveyed for their lifestyle practices, such as cigarette smoking, alcohol consumption, broad dietary practices, their occupation and their reproductive histories by an interview conducted by public health nurses with a participation rate of 94.8%. Follow-up has been conducted for 17 years from 1966 to 1982 by death certificates collected by each health centre. The rate of follow-up was almost 100% as long as the study subjects remained in the same health centre districts. Each person who moved out from the districts, however, was deleted from the cohort: this accounted for 10–20% depending on the health district.

Of the lifetyle risk factors studied, daily cigarette smoking significantly raised the risk of dying from 29 out of 44 selected causes of deaths in the ICD-9 [9]. Population attributable risks were calculated [10–13]. This study was among the very first to demonstrate a possible effect of environmental tobacco smoke: non-smoking wives with smoking husbands were found to carry a significantly higher risk of lung cancer [14]. Since then many studies have been conducted on passive smoking: 20 out of 25 studies reported by the end of 1990 showed elevated risks of lung cancer in never-smoking wives with smoking husbands [15, 16]. Hirayama recently reported that the risk of ischaemic heart disease, cancers of the nasal sinus, breast and brain were also positively related to passive smoking [10]. It is essential to consider possible confounding factors especially for the latter tumours.

On the contrary, daily consumption of green-yellow vegetables and fish were found to be most important in reducing the risk of dying from 15 and 14 of the 44 causes of death examined, respectively. Relative risks for cancers of the stomach, colon, lung, uterine, cervix, prostate, those for ischaemic heart diseases, hypertension, atherosclerosis and liver cirrhosis were lowered according to the increased intake of green-yellow vegetables [11, 12].

Hirayama's reports have contributed significantly to health education in Japan, especially for tobacco control and improvement of dietary habits. However, it is possible to criticise this study because the information obtained at the beginning of the study was limited, changes of life style during the relatively long period were not evaluated, and the end points were only confirmed by death certificates. When the number of deaths is relatively small, the accuracy of diagnosis becomes very important, otherwise serious bias becomes an issue. The accuracy of diagnosis differed according to the cause of death. The accuracy rate was high (70–80%) for leukaemia, lung cancer and stomach cancer, but it was poor for cancers of the pancreas and liver [17].

However, such criticism is possible in 1993 but it should not detract from the importance and originality of a study started three decades earlier, when epidemiology was a fledgling.

CHANGES IN LIFESTYLE AND DIETARY HABITS IN JAPAN

Lifestyle habits in Japan have dramatically changed during the last 30 years. Life expectancy continuously increased after World War II, rising from 50 years in 1945 to 88 years for males and 89 years for females in 1991. Food consumption has also changed during this period. A National Nutrition Survey is conducted every year by the Health Promotion and Nutrition Division in the Ministry of Health and Welfare, which started in Tokyo in 1946 and has become nationwide since 1948 [18]. The first aim of this survey was to know the nutritional state of the nation for urgent food supplies from other countries after World War II. Emphasis has subsequently shifted to the improvement of dietary habits and health promotion in the 1960s [19].

About 7000 households in 300 randomly selected districts participate in this survey every year. The food intake in each household is calculated by weighed records on three consecutive

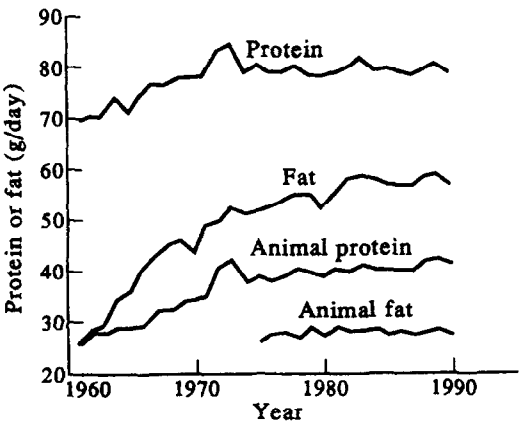

Fig. 2. Trend in nutritional intake by National Nutritional Survey in Japan. Protein and fat intake per capita is steadily increasing, in which consumption of animal protein is noteworthy.

days, except Sundays and holidays, in mid November [20]. Because of geographical differences, the data were summarised to seven large districts from Hokkaido to Kyushu. The 5-year cumulative data were re-calculated to yield valuable data, such as food consumption and other nutritional state, by prefecture [21]. This led to a cross-sectional study of cancer mortality and food intake or other indices by the prefecture.

Since the 1960s, problems of malnutrition have been resolved for reasons mainly related to rapid economic growth, but increasing trends in deaths from chronic diseases, perhaps associated with excess of certain nutrients, have emerged as a new public health problem. Animal protein and fat intake have increased and carbohydrate intake has decreased (Fig. 2). Mean daily caloric intake reached 2226 kcal in 1975. Increasing trends in the average intake of milk and dairy products, meat and fruits were noteworthy. In contrast, the intake of green-yellow vegetables decreased. In 1990, the total calorific intake per day per capita was 2026 kcal, protein intake was 78.7 g (animal protein 41.4 g) and fat intake was 56.9 g (animal fat 27.5 g). The intake of most nutrients exceeded the Japanese Recommended Dietary Allowance except for calcium. Since 1989, blood examinations, such as haemoglobin, iron, SGOT, SGPT, gamma-GTP, cholesterol, HDL-cholesterol, triglyceride, protein, uric acid and glucose, have been added to the nutritional survey. Average serum cholesterol levels exceeded 200 mg/dl in both males and females, although there is some diversity by age. Such changes in dietary habits were often referred to as "westernisation of dietary habits", which is believed to be related to the increasing trends in mortality of some cancers, such as those of the colon and the breast.

Japanese people, however, still like fish, which contains many nutrients, as well as rice (Table 1). The intake of fish is one focus in our new population-based prospective study which is described later.

CHANGES IN CANCER AND MASS SCREENING PROGRAMS

Changes of lifestyle could influence the causes of death, and increase the risk of chronic diseases, "adult diseases", such as cancer and ischaemic heart disease (Fig. 3). The decreased risk of cerebral haemorrhage is considered to be due to decreased salt intake as a result of the nationwide campaign and education through health centres to prevent hypertension [22]. Popularisation of refrigeration has probably contributed effectively to decreasing the consumption of salted fish and other preserved foods. Salt intake per capita was 25 g in 1950, and fell to 13.7 g in 1977, and decreased further to 12.5 g in 1990.

Changes in cancer incidence and/or mortality rates were predicted from the study of Japanese immigrants in the U.S.A. [23–26]. Some cancer patterns were identified to be influenced by the western-type diet and lifestyle. Mortality among Japanese immigrants in Brazil was studied in collaboration with Dr Lorenti and others. This showed a different pattern of cancer occurrence from that found among migrants to the U.S.A. [27–29]. Increases of lung, skin and prostatic cancers in the first generation, and breast cancer in the second generation were observed, but stomach cancer decreased only slightly. Gastric

Table 1. Order of sources of nutrients in Japanese diets (from ecological study in five different areas)

										Vitamin			
	Weight	Energy	Protein	Fat	Carbohydrate	Ca	P	Fe	Na	A	B1	B2	C
Rice	1	1	2		1		1	5			2		
Bread					4								
Noodles					2								
Potato													4
Cakes					3								
Oil and fat		4		1									
Pulses			4	4		2	4	1	2				
Fruits	4				5								3
Vegetables*						5		3		1	5	5	2
Other vegetables†	2					4			4				1
Salt, sauce									1				
Drinks										5			
Fish	5	3	1	3		3	2	2	3	4	3	2	
Meat		2	3	2			3	4		2	1	1	5
Eggs			5	5						3		3	
Milk						1	5					4	

*Green-yellow vegetables, containing more than 600 μg beta-carotene per 100 g. †Other vegetables.

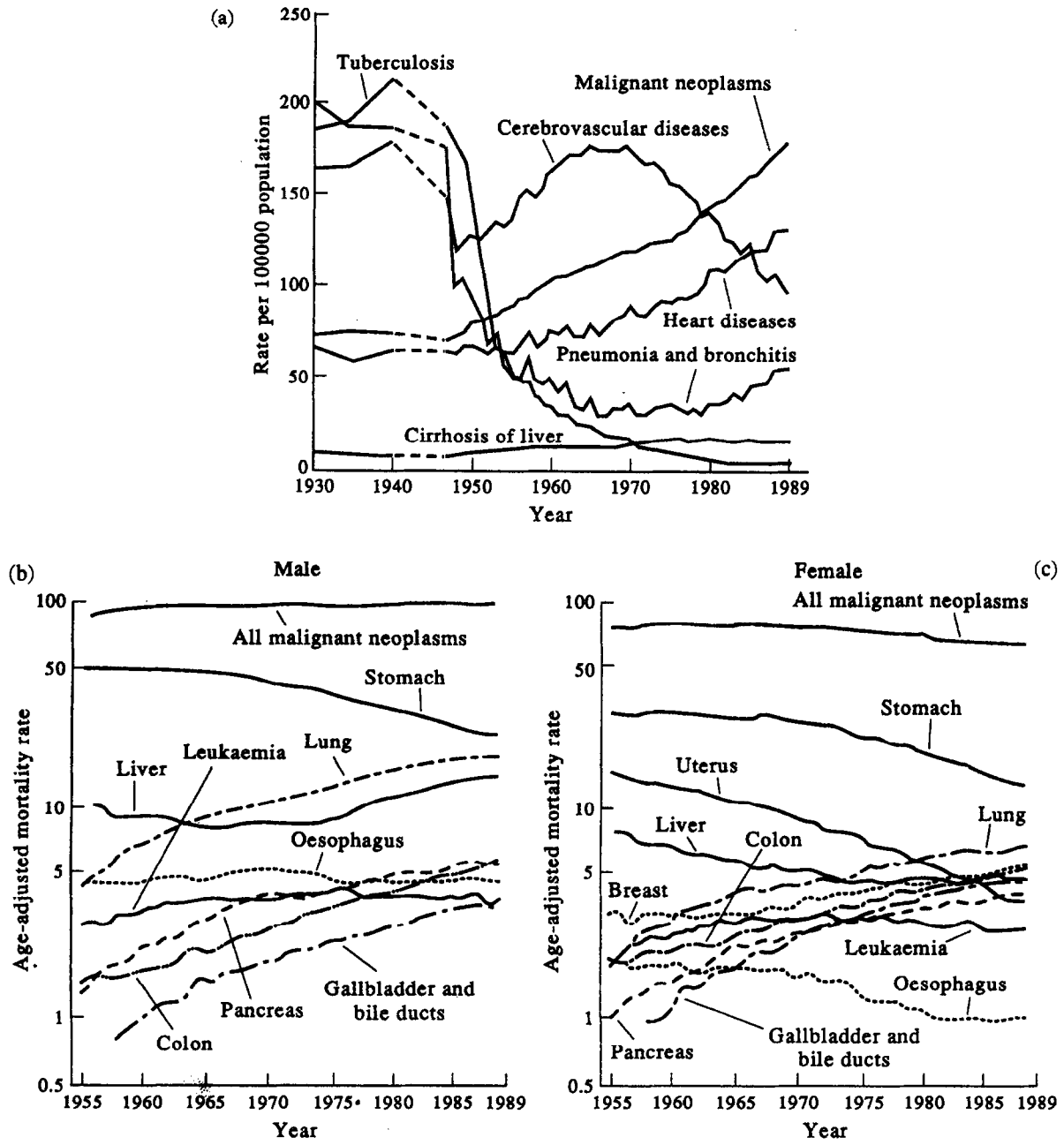

Fig. 3. Changes of causes of deaths. (a) Until the middle of this century, deaths caused by infectious diseases prevailed in Japan. After World War II they have been rapidly decreasing and have been supplemented by adult diseases such as malignant neoplasms, heart disease and cerebrovascular diseases. (b, c) Changes of the age-adjusted mortality rates for malignant neoplasms by site, standardised on the population for each sex in 1935 in Japan.

cancer is, of course, higher in Brazil than in the U.S.A. (Table 2) and may share some common risk factors with Japan.

Since 1958, cancer has become the leading cause of death in Japan [30–32]. Stomach cancer still shows the highest incidence and mortality rate in both males and females, but recently other cancers have increased: lung and colon cancers in both males and females, and breast cancer in females. Increasing trends in several intractable cancers, such as lung, liver, pancreas and certain lymphoreticular cancers have become serious public health problems [32, 33].

Mass screening programs for cancers of the stomach, lung, colon, uterine cervix and breast are conducted by local governments, but the poor prognosis of lung cancer requires the practice of measures of primary prevention, such as anti-smoking programs. Clinical epidemiologists started to work on these programs, and the efficacy of mass screening programs were reported recently (Table 3) [32–42]. Computer simulation models were also developed to evaluate the effect of mass screening and anti-smoking for lung cancer mortality [43, 44].

NECESSITY OF NEW POPULATION-BASED COHORT STUDIES. THE MULTIPURPOSE "KOSEISHO" COHORT

The increased risk of developing cancer as well as cardiovascular disease requires new epidemiological studies to clarify the common risk factors for these chronic diseases and the application of their results to increase prospects for the prevention of these diseases. In accordance with social needs, a new approach

Table 2. Cancer incidence among Japanese and Japanese immigrants in the U.S.A. and Brazil

	Japan			Japanese immigrants		
	Miyagi 1973–1979	Osaka 1973–1977	Fukuoka 1974–1975	Los Angeles 1969–1978	Hawaii 1972–1977	Sao Paulo 1973–1977
Males						
All sites	207.6	203.8	200.7	200.3	240.7	195.2
Oesophagus	13.8	8.6	8.4	4.5	3.9	10.2
Stomach	88.0	78.0	75.0	34.3	34.0	69.3
Colon	8.3	7.7	8.3	30.8	27.5	8.3
Rectum	9.2	7.9	8.8	21.7	21.4	6.6
Pancreas	7.4	5.8	7.5	8.6	4.7	5.0
Lung	25.5	29.4	25.0	30.3	38.3	22.5
Skin	1.3	1.2	1.2	na	na	5.1
Prostate	4.9	3.4	4.1	21.5	35.9	7.1
Females						
All sites	138.1	137.2	143.3	198.6	181.9	147.3
Oesophagus	3.2	2.1	2.0	0.8	0.6	1.8
Stomach	42.0	35.5	38.4	15.6	15.1	32.0
Colon	7.3	6.3	6.7	19.6	18.8	8.4
Rectum	6.5	4.7	5.6	11.7	8.8	3.3
Pancreas	4.2	3.4	4.4	4.5	4.5	3.9
Lung	7.5	8.5	7.3	9.6	11.5	7.2
Skin	0.9	0.6	0.6	na	na	4.0
Breast	17.5	12.7	15.5	57.3	47.1	24.0
Uterine cervix	12.1	17.2	19.4	8.6	6.4	18.0

Adjusted to world population (per 100 000).

Table 3. Efficacy of mass screening certified by case–control studies

Target site	Criteria of cases	Odds ratio	Condition	Reference
Stomach	Death	0.60 (M) 0.18 (F)	History of mass screening	Oshima [35]
	Advanced carcinoma	0.34	Mass screening 1 year ago	Fukao [36]
	Advanced carcinoma	0.25	Mass screening 1 year ago	Yamasaki [37]
Large intestine	Death	0.36	History of mass screening	Hisamichi [41]
Lung	Death	0.72	Mass screening 1 year ago	Sobue [40]
Breast	Death	0.76	History of mass screening	Kuroishi [79]
Uterus	Death	0.22	History of mass screening	Sobue [38]
	Invasive carcinoma	0.11	Mass screening 1 year ago	Makino [39]

to molecular epidemiology has been developed in the study of human carcinogenesis [45–49].

In our cross-sectional study from 1988 to 1990 of five different health centre districts, we used some biomarkers to test the efficacy of molecular epidemiology [50–52]. Each area, such as Ninohe, Yokote, Saku, Katsushika and Ishikawa, showed a different mortality rate, i.e. Ninohe has high cerebrovascular but low stomach cancer deaths, Yokote showed high mortality in both cerebrovascular and stomach cancer, Ishikawa showed low stomach cancer but high lung cancer deaths, Saku showed low mortality rates for many diseases, and Katsushika showed high cardiovascular death rates (Fig. 4). Each local health centre district includes several cities, towns and/or villages, and covers more than 100 000 people, therefore, it is easy to compare mortality rates between these areas. One hundred and seventy men, aged in their 40s, were randomly selected in each area, and asked to participate in our study. More than 70% of the surveyed men and 66% of their spouses participated in the study [51]. In addition to interviews by trained public health nurses or nutritionists, biochemical blood analyses of hormones, vitamins, trace elements and antioxidants, such as beta-carotene, lycopene, alpha-tocopherol, retinol, ascorbic acid, etc. were meas-

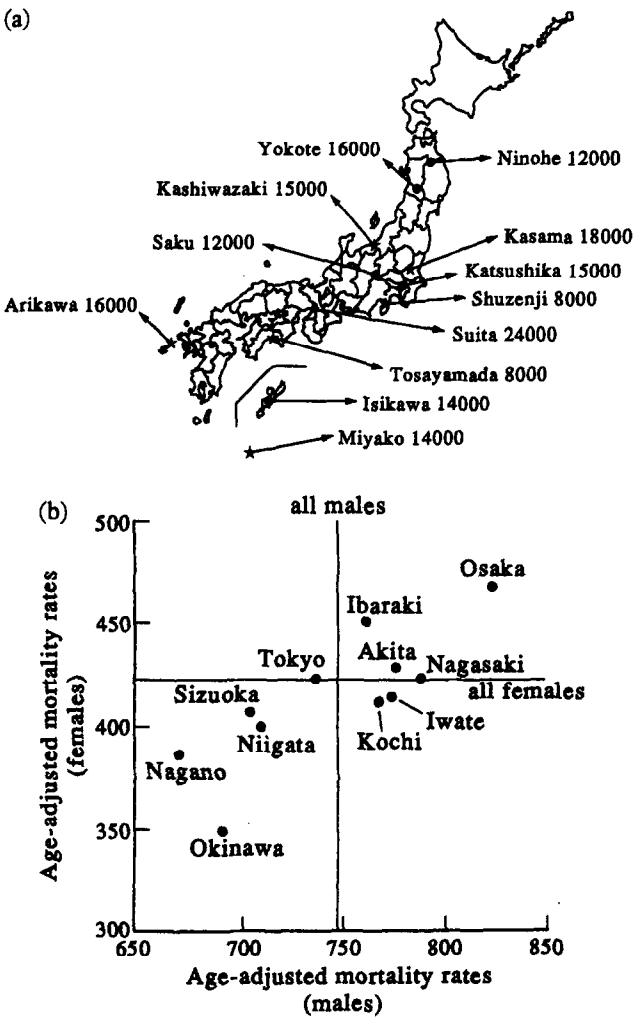

Fig. 4. Cohort study areas. (a) Round circles show cohort areas started in 1990, and stars show those started in 1992 and 1993. The target population was whole residents, aged 40–59, in the former cohort areas, and it is from age 40 to 69 in the recent cohorts. The participants in Katsushika, Tokyo, and Suita, Osaka, are screenees who applied for the health screening program. (b) The mortality rate of each prefecture where health centres for the cohort study are included. Mortality rates for all causes of death are highest in Osaka, and lowest in Okinawa and Nagano in Japan. Names of health centres and their location in prefectures are shown in Table 4.

ured. Antibody titres of hepatitis B and C viruses, HTLV-1 and *Helicobacter pylori* were also measured. Twenty-four-hour urine samples were collected, and a 3-day nutritional survey accompanied by weighing of food items was conducted.

A simple correlation analysis of each lifetyle factor with the age-adjusted mortality of selected cancer sites showed a very good positive correlation between oesophageal cancer and both smoking and weekly intake of alcohol, between gastric cancer rates and salt and calcium levels in the 24-h urine samples, between colon cancer and HDL cholesterol levels and between lymphoma and triglyceride levels. Negative correlations were observed between pancreatic cancer rates and triglycerides. These correlations were, in many ways to be expected, following the review of many case–control studies [53], but such a good correlation was unexpected in a cross-sectional study. Stomach cancer mortality was also well correlated with the prevalence of chronic gastritis, which was determined by the measurement of pepsinogen I and II, and by the titre of anti-helicobacter antibodies (Fig. 5) [54–57]. These factors confirm that multiple factors may influence multiple steps in the carcinogenesis of stomach cancer.

It is well known that one factor may influence the risk of multiple diseases [58–60]. For example, salt intake is thought to be related to hypertension and its resultant cerebrovascular disease, renal disease and stomach cancer. Low calcium and prostaglandin levels are related to the risk of colon cancer as well as hypertension. Population-based prospective studies in these areas with different disease patterns could help clarify the role of environmental factors in the phases of initiation, promotion and progression of chronic diseases and test the accuracy of the associations by the cross-sectional study of cancer and the aforementioned biomarkers.

We started a population-based prospective study in four areas; Ninohe, Yokote, Saku and Ishikawa health centres in 1990, and added six more areas, Kasama, Kashiwazaki, Suita, Tosayamada, Arikawa and Miyako health centres in 1992 (Fig. 4). Usually, one health centre covers several cities, towns or villages (there are 3400 local governments and 850 health centres), and at least one city and one town or village were asked to join the cohort study. The total number of participants will be in the region of 170 000. Local governments carry out the mass screening program for basic annual health check-ups and for cancers under the "Law for Elderly Health". We have asked that the data from screening programs be linked to our cohort data. At least 50% of the cohort participants would join that program. Blood sera and buffy coats from 10 ml of peripheral blood from participants will be stored in a deep freezer for 10 years, to be used in a future nested case–control studies. The research funding of this study amounts to 10 billion yen for the core component, and the cost of mass-screening is shared equally between the screenees, local governments and the government. The study has been named the "Koseisho Cohort", because many different sections in the Ministry of Health and Welfare have cooperated to integrate various information and to promote the research. Committees for registration of incident cases of cancer, cardio- and cerebrovascular diseases have been organised in collaboration with the regional medical association and hospitals. The schemes of the research organisation and sources of information are shown in Table 4 and Fig. 6.

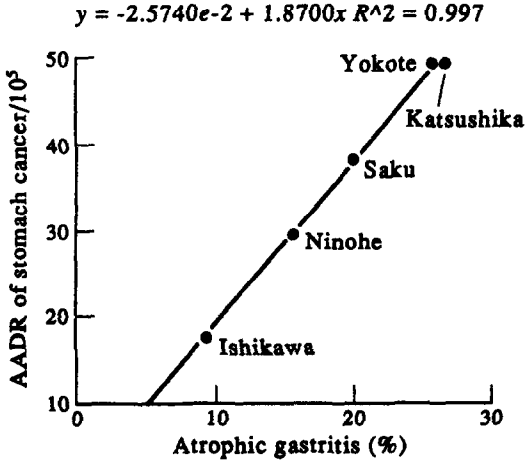

Fig. 5. Relationship between stomach cancer mortality rate and prevalence of chronic atrophic gastritis, determined by serum pepsinogen I being less than 70 ng/ml and pepsinogen I/pepsinogen II ratio being less than 3.0. Data from the cross-sectional study.

Table 4. Organisation of "Koseisho" cohort study

Executive committee
- Shaw Watanabe, National Cancer Center
- Masamitsu Konishi, National Cardiovascular Center
- Suketami Tominaga, Aichi Cancer Center
- Shigeaki Baba, Hyogo Adult Diseases Center
- and Head of each subcommittee

Field survey committee
- Shoichiro Tsugane, National Cancer Center (Head)
- Shunroku Baba, National Circulatory Diseases Center
- Keigo Miyagawa, Ninohe Health Center, Iwate prefecture
- Yoshimichi Miyajima, Yokote Health Center, Akita prefecture
- Akira Murata, Kasama Health Center, Ibaragi prefecture
- Heihachiro Yazawa, Katsushika Health Center, Tokyo
- Kazumitsu Matsui, Kashiwazaki Health Center, Niigata prefecture
- Fumimune Kobayashi, Saku Health Center, Nagano prefecture
- Shuzenji Health Center, Shizuoke prefecture
- Fujiko Horii, Suita Health Center, Osaka
- Mitsunori Doi, Tosayamada Health Center, Kochi prefecture
- Hiraku Sueta, Arikawa Health Center, Nagasaki prefecture
- Masako Kinjo, Ishikawa Health Center, Okinawa prefecture
- Hachiro Sakiyama, Miyako Health Center, Okinawa prefecture

Nutritional survey committee
- Masayuki Akabane, Tokyo Agricultural University (Head)
- Momoko Yamaguchi, National Nutrition Institute
- Tosei Takahashi, National Cancer Center

Data standardisation committee
- Minoru Iida, Osaka Adult Diseases Center (Head)
- Local committee members

Data linkage committee
- Naohito Yamaguchi (Head)

Diseases registration committee
- Shosui Matsushima, Saku General Hospital Health Center
- Local committee members

Cooperative groups in the Ministry of Health and Welfare
- Statistics and Information Department
- Health Service Bureau
- Health Policy Bureau
  - Health Planning Division
- Department of the Health and Social Welfare Service for the Aged
- Planning office of the National Cancer Center
- Planning office of the National Cardiovascular Center

Data linkage of annual health check-up data was attempted by us in the SAKUCESS (Saku Cancer Etiology Surveillance Study) project in the Nagano prefecture. We integrated health data from more than 90 000 residents during the 15 years since 1978, into a retrospective cohort which will now be followed-up prospectively [61]. Such continuous data, with both epidemiology and laboratory medicine, can clarify the effects of aging present in laboratory data and other biological signs. It was found that the serum globulin and albumin levels were lowered a few years before the diagnosis of gastric cancer [62]. Such early changes, if specific, could be used to identify individuals at high risk of stomach cancer, and to define the population that should be targeted for screening.

OTHER POPULATION-BASED COHORT STUDIES IN JAPAN

"Monbusho" cohort

Another large-scale population-based cohort study has been operating in Japan since 1988 supported by the Ministry of Education, Science and Culture (Monbusho) [63]. The chief investigator is Dr Kunio Aoki of the Aichi Cancer Centre. The objective of this cohort were people aged over 40, from nearly 50 local towns and one city, and three occupational groups (about 25 000 workers) investigated by 24 and 3 epidemiologists, respectively. Most areas have been studied for the epidemiology of circulatory diseases. The total number of participants was 125 760. Baseline data were collected in 1988, and an intermediate survey will be carried out in 1993. Life-styles of participants were surveyed by a questionnaire and the biochemical data of the sera, as in our cohort study, were obtained from the mass screening program by local governments. The remaining sera were kept in a deep freezer for future biomarker analyses. Information about smoking, drinking and dietary habits are comparable to ours, and one area (Saku city) is neighbouring to our area and covered by the same health centre. This compatibility makes it possible to compare the results between the Koisisho and Monbusho cohort studies. The follow-up in this system should be done by participants themselves because of the insufficient registration system in each area, even though death certificates are available.

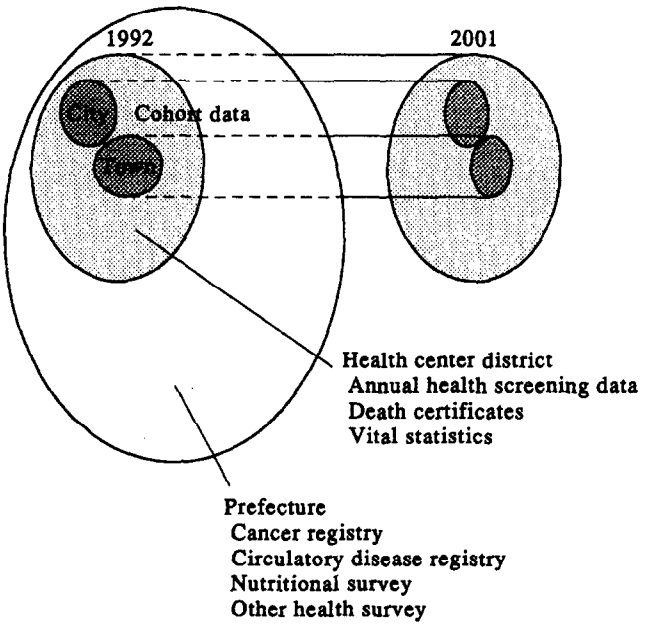

Fig. 6. Sources of information for linkage study in the Koseisho cohort study. In addition to the cohort data, annual health screening data could be integrated by linkage analysis. Death certificates and vital statistics are also sent from the health centers. Cancer registry, circulatory disease registry, nutritional survey and other data being related to the health program from the prefecture are all linked to the cohort data. An intermediate questionnaire survey for the cohort participants is also being planned.

Cohort of atomic bomb survivors

Another large-scale population-based cohort study is the cohort of the atomic bomb (A-bomb) survivors [64–67]. The number of A-bomb-related acute deaths which occurred before the end of December 1945 was estimated to be between 90 000 and 120 000 out of a population of approximately 330 000 in Hiroshima. It was somewhat between 80 000 and 90 000 out of about 250 000 in Nagasaki. These acute deaths were caused by A-bomb radiation, burns and mechanical injuries [67]. The Atomic Bomb Casualty Commission (ABCC) was established in the two cities by the U.S.A. government in 1947 to initiate follow-up studies on the late health effects of A-bomb radiation [64]. A nationwide survey of A-bomb survivors was first conducted in 1950, identifying a total of 284 000 survivors throughout Japan. A sample of about 110 000 subjects was selected from among these survivors and non-exposed controls who were resident in Hiroshima and Nagasaki at the time of the survey. The follow-up study of this sample was named the Life Span Study (LSS). Data concerning lifestyles, such as smoking habits, diet, socioeconomic status, childbearing history, occupation and other details have been collected in a series of interviews and mail surveys of large subsets of the LSS sample conducted at various times between 1963 and 1981.

An important subset of the LSS is the Adult Health Study (AHS) population, which has had extensive and continuing clinical evaluations since it began in 1958. A total of 19 962 persons were selected from the entire LSS population, and over 60% of these were examined at least once within 4 years. All AHS subjects living in or near either city are encouraged to be examined every 2 years for their health, including medical history, physical examination, laboratory evaluations and special clinical studies as needed. By the 11th 2-year cycle of examinations (July 1978–June 1980) over 30% of the original AHS sample had been lost to follow-up due to death or migration out of the Hiroshima and Nagasaki areas. By the end of 1982, the LSS population contained 120 132 subjects, of whom 38 890 were deceased.

A number of case–control studies have been undertaken, i.e. studies of cancer of the female breast, the lung, the colon and rectum, etc [68–71]. For leukaemia, with about 90 out of 220 deaths attributable to radiation exposure, adequate statistical power is available for detailed inference concerning the radiation dose–response, its time course, and modification of the dose–response by other factors. So far from 1950 to 1985, attributable risk of irradiation more than 0.01 Gy was 55.4% for leukaemia, 7.9% for all cancers except leukaemia, 32.5% for multiple myeloma, 22.7% for urinary cancer, 22.1% for breast cancer, 15.1% for colon cancer, 11.4% for lung cancer, and 6.3% for stomach cancer [67].

The potential exists for profound changes in currently held notions of human radiation carcinogenesis as the youngest members of the LSS sample reach the ages of greatest cancer risk.

EPILOGUE

In Japan, the cancer registry has played an important role in cancer epidemiology [72, 73]. The tradition is still active, and has contributed especially to clinical epidemiological studies, such as the evaluation of the mass screening program, and studies of second primary cancers [34–41, 74–78]. There are site-specific cancer registries, such as stomach, colon, oesophagus, oral cavity, liver, pancreas, bile duct, lung, bone and soft tissues, breast, uterus, ovary, urinary bladder, brain and childhood cancers in Japan. In addition to those, retinoblastoma and familial polyposis are registered separately. These registries are run by the society or an association of expert doctors, and are mainly used to study the trends in diagnostic and treatment methods, but they are available and suitable for use in epidemiological research, i.e. hepititis virus infection and liver cancer [36, 40, 79, 80]. Joint work between clinicians, pathologists and epidemiologists, and recently molecular biologists may produce more profound understanding in human carcinogenesis.

Baseline data of the Koseisho cohort showed certain differences in lifestyle, such as dietary habits, by prefecture. The high participation rate of residents, and an efficient system to follow-up participants with the collaboration of officials in local governments and health centres, especially nurses and nutritionists, should keep the quality of the cohort study high. Future nested case–control studies in conjunction with analyses of appropriate biomarkers could clarify many aspects about the risk of many diseases.

The Koseisho cohort also aims to integrate as much information related to health not only from the cohort area but also from other areas in the prefecture. This will make it possible to compare the characteristics of the cohort area with those of the remaining area in the same health centre. Accumulation and linkage of this information are not used only to clarify the risks for initiation, promotion and progression in chronic diseases, but they can also be used in making public health policies and in prevention and disease control in high-risk populations [81]. Individuals identified as being at high risk could be invited to comprehensive health check-ups. The cost-effectiveness of health education should be good enough to challenge that of chemical intervention (chemoprevention). This has been confirmed by the WHO Five Country Study [82]. Further

information, such as biological material, may be obtained from regional hospitals and be available for more basic science [83].

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