RESEARCH ACTIVITIES OF EPIDEMIOLOGY IN JAPAN

Cancer

Research Activities of Cancer Epidemiology in Japan

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Cancer epidemiology in Japan has been led by the large-scale population based cohort studies. Permanent registration system has made follow-up easier and more efficient. Low cancer incidence and mortality rates led the researchers to investigate possible preventive factors in diet and life style, in addition to the study of risk factors. The on-going large sized prospective cohorts should be a fruitful resource for future cancer epidemiological studies. Various studies of cancer epidemiology are introduced from a methodological aspect.
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Cancer epidemiology in Japan has been supported by the large volume of registries¹⁻³⁾. Mortality data have accumulated continuously for more than 100 years except for a few years of interruption during the Second World War. This system contributed to build the population-based and organ-specific cancer registries⁴⁾. Geographically Japan is a long country from North to South. Cultural and geographic differences contribute to significant variation in mortality and life style between different regions of the country^{5,6)}. Cross-sectional study comparing SMRs and different life style and environmental factors often sheds light on factors relating etiology of cancer. Accurate registry data are available for such analysis. Different cancer mortality rates in the world were also observed⁷⁾. Recent knowledge of cancer prevention suggests that the low incidence and the mortality rate of cancer in Japan could be a result from dietary intake of cancer preventive chemicals. This hypothesis could be confirmed by two current on-going large population based prospective studies⁸⁾. Recent development in clinical epidemiology is another feature in Japan. Multiinstitutional case-control studies and randomized clinical trials have been often performed by alert clinicians who recognize the importance of epidemiology. However, the number of biostatisticians in this field is rather insufficient. Despite of this shortage, mathematical models are proposed in theoretical epidemiology for tasks such as estimating the effect

of intervention and to calculating power to detect risks, etc.⁹⁾. This chapter discusses the features of some current Japanese cancer epidemiological studies.

DEMOGRAPHIC DATA FOR CANCER EPIDEMIOLOGY

In Japan, permanent registration system has been conducted since 1869. All death certificates should be reported to the Information Bureau of Vital Statistics, Ministry of Health and Welfare, and annual data have been published as Vital Statistics¹⁾. This gives a great advantage for descriptive epidemiology²⁻⁶⁾. After the Second World War, causes of death had dramatically changed from infectious diseases such as tuberculosis to chronic diseases. Cancer has steadily increased to become the primary cause of death since 1950s (Fig. 1). Stomach cancer has been the primary cause of cancer in both males and females until the lung cancer death rate in males exceeded the stomach cancer death rate in 1993^{10,11)}. Mortality rates of stomach and uterine cancer have decreased steadily during the last 20 years (Fig. 2). Instead, colon and lung cancer in both males and females, and breast cancer in females have increased. In addition, liver cancer in males showed a birth-cohort effect, probably due to the poor nutritional state by the Second World War during their teenage¹²⁾.

According to the advance of cancer therapy, collection of

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Figure 1. Changes of causes of deaths in Japan. 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.

Figure 2. Changes of the age-adjusted mortality rates for malignant neoplasms by site, standardized on the population for each sex in 1935 in Japan.

incidence data are mandatory for detecting the change of cancer occurrence¹³⁻¹⁵. Segi, Fujimoto, Hanai, and others have

contributed significantly to establish the population-based cancer registration in Miyagi and Osaka prefectures^{2,3,16}. Osaka

Table 1. Number of patients in each cancer registry and estimated coverage rates in 1992

Registry	Year	Total No registered patients	Annual No. registered	Estimated No of patients	Coverage rate
1. Head & Neck	1979-	18,716	1,000	7,000	14.2%
2. Esophagus	1969-	21,402	1,500	8,000	18.8
3. Stomach	1963-	253,382	12,000	78,000	15.4
4. Large intestine	1974-	24,234	4,000	57,000	7.0
5. Liver	1965-	46,952	10,000	25,000	40.0
6. Bile duct	1987-	5,293	1,000	19,000	5.3
7. Pancreas	1981	13,498	1,300	15,000	8.7
8. Lung	1967-84	33,989	2,100	62,000	3.4
	1989-	5,000			
9. Bone, soft tissue	1964-	49,000	3,000		
10. Skin	1987-93	9,439			
11. Breast	1975-	45,885	4,000	24,000	16.7
12. Uterine cervix	1965-	122,000	2,100	10,400	20.2
13. Uterine body	1966-	2,600			
14. Ovary	1967-	1,954			
15. Bladder	1982-	10,600	2,000	8,000	25.0
16. Brain	1969-	46,002	4,500	13,000	34.6
17. Thyroid	1979-	19,446	1,500		
18. Childhood cancer	1975-	29,446	1,500	2,000	75.0
Total		758,804	51,500	328,400	15.4

cancer registry, which has been continued for more than 30 years, produced many epidemiological work by linking hospital data and registered patients¹⁷⁻²⁰⁾.

After stomach cancer consistently stayed as the primary cause of cancer death for many years, in 1965, clinicians began to register their patients in order to study method of diagnosis, treatment and survival rates⁴⁾. Since then several other cancers were also registered. By now, 18 site-specific cancer registries are carried out by organization or research groups of expert clinicians (Table 1). Stage specific survival rates are recently published¹³⁾.

STUDIES OF CANCER ETIOLOGY

Cross-Sectional Study :

Accurate statistical data of various areas in Japan could be used for ecological study. National Nutritional Survey has been carried out on 7000 households each year since 1946²¹⁾. This survey provides valuable information about the changes of Japanese diet. Due to the large geographical area covered by the country, the climate in each region and life-style of the inhabitants show considerable difference. Standardized cancer mortality ratios are thus diverted. This variation provides an advantage for conducting ecological studies²²⁻²⁴⁾. For example, frequency of stomach cancer shows three fold difference between prefectures.

Various risk factors were proposed for stomach cancer, and recently helicobacter pylori infection has been investigated as an important etiological risk factor for stomach cancer²⁵⁻²⁸⁾.

Unusual cluster of special type of diseases could sometimes lead to the discovery of causative agent. Adult T-cell leukemia/lymphoma is such an example²⁹⁾. Geographic clustering of a peculiar form of leukemia led to the discovery of human T-lymphotropic virus type I²⁹⁾. Anthropological study on this viral infection has been done worldwide by Dr. Tajima and his group.

Cohort Study :

As cancer may take many years to develop, a large-sized prospective cohort study is the most preferable method to find etiologic factors. "Six prefecture cohort study", which started in 1965 clarified the risk of active and passive smoking and preventive effect of green-yellow vegetables^{30,31)}. Cohort of atomic bomb survivors provided useful data for determining the association between the dose of irradiation and the risk of cancer^{32,33)}.

Currently three large population based cohort studies are being conducted⁸⁾ (Table 2). The outcomes of interest of the multipurpose Koseisho cohort study not only includes cancers but also cardiovascular diseases. It was started in 1990 and in 1993 with nearly 120,000 participants in 11 different health center districts, and will continue until year 2002. Other cohort study consisted of special occupational group is also being investigated currently. Follow-up study on retired soldiers who received sigmoidoscopy showed an association of increased large adenomatous polyp formation in the colon and alcohol consumption^{34,35)}.

Table 2. On-going population based prospective studies in Japan

	Kankyocho* Cohort	Monbusho* Cohort	Koseisho* Multipurpose Cohort
Purpose	Air pollution and lung cancer	Risk of cancer	Risk of chronic diseases Preventive factors
Target population	9 municipalities in 3 prefectures (Total=125,760) Miyagi (31,360) Aichi (33,531) Age 40-59 Osaka (39,118)	34 municipalities working place (25,336) (Total 151,096)	29 municipalities in 11 health center district (Total 140,000) Cohort I ; 40-59 Cohort II ; 40-69 Tokyo and Osaka ; Health check-up examinees (40,45,50) Cohort I ; 1990 Cohort II ; 1993
Base line survey	Miyagi ; 1984 Aichi ; 1985 Osaka ; 1983, 1985	1988-1990	
End point	Mortality Cancer incidence by regional cancer	Mortality Cancer incidence (Optional)	Mortality Incidence of cancer, cardiovascular diseases by direct registry
Follow-up period	10 years	10 years	10 years
Interim survey	none	5th year (optional)	5th year
Blood sample	none	serum ; 40,000	serum and buffy coat 45,460
Others			Link to annual health checkup data to know changes of individual condition

* Kankyocho; Environmental Agency, Monbusho ; Ministry of Education, Science and Culture, Koseisho; Ministry of Health and Welfare.

Case-Control Study :

Number of clinicians who are interested in etiologic study collaborated with epidemiologists in many case-control studies. They have conducted case-control studies in many fields ; i.e. esophageal cancer, stomach cancer, colon cancer, liver cancer, pancreatic cancer, lung cancer, prostatic cancer, and breast cancer. Salty foods, such as pickles, fish eggs, etc. are often associated with the risk of stomach cancer³⁶⁻³⁹. Spirit and tobacco smoking are the risk factor for oral and esophageal cancer⁴⁰. Fat intake, alcohol, and constipation were risks for colo-rectal cancer⁴¹. HBV and HCV infection consistently showed high odds ratio for liver cancer⁴²⁻⁴⁴.

Lung cancer death rate exceeded that of stomach cancer in males in 1993. The lag-time effect of smoking should appear⁴⁵. Several case-control studies on lung cancer etiology in Japan showed a similar risk of tobacco smoking as compared to the western countries⁴⁵⁻⁴⁸. Smoking effect on adenocarcinoma of the lung was also clarified⁴⁹. Introduction of molecular biology for case-control study has been introduced to clarify genetic predisposition ; the different susceptibilities for tobacco smokers to develop lung cancer^{50,51}. Effect of pas-

sive smoking during childhood was recognized as a risk of pancreatic cancer by a multiinstitutional case-control study⁵².

Low incidence rate of prostate cancer, despite of the high prevalence of latent cancer, was observed by several researchers⁵³. Case-control study on prostate cancer did show different dietary effect in Japanese⁵⁴. Other hormone-related cancers were also studied, and high concentration of serum isoflavonoids, which are typical dietary phytoestrogens is considered to have preventive effect on estrogen-related carcinogenesis^{55,56}.

Immigrant Study :

Immigrant study clarified the effect of altered life style. Stimmerman and Kurihara⁵⁷ showed a decreased mortality from stomach cancer and an increased colon cancer among Japanese immigrants in Hawaii. Japanese-American study was continued by Hirohata, Henderson and Shimizu, and others⁵⁸⁻⁶². Another large Japanese immigrant population is in Brazil. Tsugane and Watanabe⁶³⁻⁶⁵ studied the mortality and the incidence rates of cancers among Japanese-Brazilians with Laurenti et al, and found a less decrease of stomach cancer, an

increased prostate cancer even in the first generation, and also increased breast cancer in the second generation, when comparing Japanese Brazilian and Japanese in Japan. The prevalence of hepatitis B virus is the same between immigrants and those in the mother country. But lower liver cancer incidence may indicate a preventive modification of high protein diet in Brazil^{66,67)}. Korean-Japanese in Kansai area was an unique population for hepatoma study^{68,69)}.

Molecular Epidemiological Study :

Introduction of biomarkers to epidemiological studies is rapid⁷⁰⁾. As the full development of cancer needs 20-30 years, risk evaluation by mid-term markers is convenient and reliable. Alteration of p53 gene in premalignant solar keratosis was such example⁷¹⁾. Such methods are more vigorously applied to cancer predisposition studies^{50,51)}.

EVALUATION OF MASS-SCREENING

Evaluation of mass-screening is one of the important fields of clinical epidemiology in Japan⁷²⁾. Mass-screening program has been introduced before the epidemiological evaluation ; stomach cancer detection program in 1965, uterine cervical cancer

in 1967, breast cancer in 1978, lung cancer in 1985, and colon cancer in 1990 (Fig.3). The effectiveness of screening was measured mostly by case-control studies and each program is shown to be effective (Table 3)⁷³⁻⁸⁰⁾. The high stomach cancer mortality rate in Akita prefecture decreased accordingly with increased proportion of population been screened. New biomarkers used to identify high risk group are employed in some studies ; i.e. helicobacter pylori antibody and plasma pepsinogen I and II⁸¹⁾. Other new detection methods are under study ; mammography for breast cancer, helical computed tomography for lung cancer, sigmoidoscopy for colon cancer, and rectal ultrasonography or prostate-specific antigen for prostate cancer⁸³⁾.

Neuroblastoma screening in infants has also been introduced in 1984, and the treatment method for Stage IVs is under debate now⁸²⁾.

STUDIES ON CANCER PREVENTION

It is noteworthy that the totaled cancer incidence among Japanese has been relatively low, except for the stomach cancer. As described earlier, the standardized mortality rates showed great variation in Japan. Lowest area and highest area

Figure 3. Cumulative rates for local governments which started mass-screening.

Table 3. Efficacy of mass-screening determined by case-control study

Site	Criteria of cases	Odds ratio	Condition	Reference
Stomach	Death	m=0.6, f=0.18	History of screening	Oshima
	Advanced cancer	0.34	Mass-screening 1 yr ago	Fukao
	Advanced cancer	0.25	Mass-screening 1 yr ago	Yamasaki
Uterus	Death	0.22	History of mass-screening	Sobue
	Invasive cancer	0.11	Mass-screening 1 yr ago	Makino
Lung	Death	0.72	Mass-screening 1 yr ago	Sobue
Large intestine	Death	0.36	History of mass-screening	Hisamichi

Figure 4. Hormone related cancer mortality and per capita consumption of tofu and tofu products. Each point represents each prefecture. Significant reverse correlation was present between principal component being composed of colon, breast and ovary cancer mortality rates Factor 1 and tofu and tofu products by prefecture.

often showed more than three fold difference in most cancers^{5,6}. For example, stomach cancer mortality rates in Nagano and Okinawa is almost one third of highest area like Akita. Low salt consumption and high green-yellow vegetable intake suggested the preventive influence of food chemicals. These knowledge was extended to the intervention study, especially for intractable cancer⁸⁴. For example, tea consumption has been suggested as a remedy to improve chronic atrophic gastritis which is considered to be precancerous lesion^{85,86}. Beta-carotene has also employed for those with chronic gastritis until the recommendation of NCI to quit trial of β -carotene.

Dietary fiber was proven to have preventive influence on colon cancer. Currently, randomized control trial is underway by giving biscuit with high fiber to patients with colonic polyps⁸⁷. Synthetic retinoids are also employed for patients with hepatitis to prevent hepatoma⁸⁸. However, chemical intervention trials are only conducted with high risk individuals, such as patients in the hospital. Knowledge of new chemicals which can be found in food and are beneficial in cancer prevention are being discovered continuously⁸⁹. Cross sectional study on dietary factors and colon, breast and ovarian cancers suggested a preventive effect from tofu and tofu products consumption⁹⁰ (Fig. 4). Thus the phytoestrogen study is initiated to study the effect^{91,92}.

Tobacco control in Japan was relatively slow and reluctantly sponsored by the government⁹³. The effect of tobacco cessation was clearly shown by the case-control study conducted on ex-smokers^{94,95}. Economical analysis showed apparent external diseconomy, and if no measurement were taken nation's

burden would increase 4 times more in 2030⁹⁶. This kind of economical analysis should also be employed for cancer prevention in the future.

NETWORK FOR MULTIDISCIPLINARY STUDIES

As described earlier, there exist many statistical data in Japan in addition to the death certificates. Nutritional survey has been conducted every year, population census is renewed every 5 years, and statistics of various industrial indices are revised annually. Some of these data even require special permission for use from the government. Nonetheless these are valuable data source for epidemiological studies, especially for biostatisticians to deduct statistical models^{97,98}. Environmental Agency also adds to the data set, the measurement of air pollution, water pollution, ultraviolet ray, and etc.⁹⁹. These data are also applicable for epidemiological studies. Cross-sectional or ecological study is always effective as the first step of epidemiological study. With this regard, analysis performed by linking this large stack of information may open new field in epidemiology¹⁰⁰. Autopsy records include more than 40,000 autopsies performed every year. This additional information also provides histological data of the tumor¹⁰¹. Multiple primary cancer cases can be detected by linking hospital registries¹⁰²⁻¹⁰⁶. Drug-related carcinogenesis has also listed, and used in the clinical epidemiological study¹⁰⁷⁻¹⁰⁹. In Japan, randomized clinical trials are carried out under strict regulations, and epidemiologists are called to join the studies in order to assist clinicians. However, this area is not described here.

MODELS

To deduct statistical model is always important in theoretical epidemiology. Non-parametric Markov model needs a lot of epidemiological data in order to calculate transitional rates of risk⁹⁾. Other models including cancer growth need basic knowledge in biology¹¹⁰⁻¹¹³⁾.

EPILOGUE

The number of epidemiologists in Japan occupied about 2% of all cancer researchers. Funding has also stayed at two percent of all cancer fund from the government for many years. Since the establishment of Japanese Epidemiological Association in 1993, however, the number of members in the association has increased continuously. Limited by only one existing public health school in Japan, most epidemiologists are trained in the medical school. Therefore, more than 90% members in this organization have medical degree. It can be said that physician is a term that generally characterize the members in the Japanese Epidemiological Society.

The fields in epidemiology is expanding. We can distinguish four areas in epidemiological development; namely epidemiology for acute infection (first generation), for chronic diseases (second generation), for clinical evaluation (third generation), and for accumulation of large volume of information for epidemiological research (fourth generation). Computer network can open a new field of research in the near future.

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