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 country5,6). 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. Multinstitutional case-control studies and randomized clinical trials have been often performed by alert clinicians who recognize the importance of epidemiology. However, the number of biostaticians 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 became 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 199310,11). 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...
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 occurrence. Segi, Fujimoto, Hanai, and others have contributed significantly to establish the population-based cancer registration in Miyagi and Osaka prefectures. Osaka
cancer registry, which has been continued for more than 30 years, produced many epidemiological work by linking hospital data and registered patients\textsuperscript{17-20).}

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 rates\textsuperscript{4).} 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 published\textsuperscript{13).}

### 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 1946\textsuperscript{21).} 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 studies\textsuperscript{22-24).} 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 cancer\textsuperscript{25-28).}

Unusual cluster of special type of diseases could sometimes lead to the discovery of causal agent. Adult T-cell leukemia/lymphoma is such an example\textsuperscript{29).} Geographic clustering of a peculiar form of leukemia led to the discovery of human T-lymphotropic virus type I\textsuperscript{29).} 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\textsuperscript{30,31).} Cohort of atomic bomb survivors provided useful data for determining the association between the dose of irradiation and the risk of cancer\textsuperscript{32,33).}

Currently three large population based cohort studies are being conducted\textsuperscript{8) (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\textsuperscript{34,35).}

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

| Purpose | Kankyocho* Cohort | Monbusho* Cohort | Koseisho* Multipurpose Cohort |
|---------|-------------------|------------------|-----------------------------|
| Target population | Air pollution and lung cancer | Risk of cancer | Risk of chronic diseases Preventive factors |
| | 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) |
| Base line survey | Miyagi ; 1984 Aichi ; 1985 Osaka ; 1983, 1985 | 1988-1990 | Cohort I ; 40-59 Cohort II ; 40-69 Tokyo and Osaka ; Health check-up examinees (40,45,50) |
| 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 none | 10 years 5th year (optional) serum ; 40,000 | 10 years 5th year serum and buffy coat 45,460 |
| Interim survey | none | Link to annual health checkup data to know changes of individual condition |
| Blood sample | none |

* 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 cancer. Spirit and tobacco smoking are the risk factor for oral and esophageal cancer. Fat intake, alcohol, and constipation were risks for colorectal cancer. HBV and HCV infection consistently showed high odds ratio for liver cancer.

Lung cancer death rate exceeded that of stomach cancer in males in 1993. The lag-time effect of smoking should appear. Several case-control studies on lung cancer etiology in Japan showed a similar risk of tobacco smoking as compared to the western countries. Smoking effect on adenocarcinoma of the lung was also clarified. 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.

Low incidence rate of prostate cancer, despite of the high prevalence of latent cancer, was observed by several researchers. Case-control study on prostate cancer did show different dietary effect in Japanese. 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.

Immigrant Study:

Immigrant study clarified the effect of altered life style. Stimmerman and Kurihara 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 others. Another large Japanese immigrant population is in Brazil. Tsugane and Watanabe 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. Korean-Japanese in Kansai area was an unique population for hepatoma study.

**Molecular Epidemiological Study:**

Introduction of biomarkers to epidemiological studies is rapid. 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 example. Such methods are more vigorously applied to cancer predisposition studies.

**EVALUATION OF MASS-SCREENING**

Evaluation of mass-screening is one of the important fields of clinical epidemiology in Japan. 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). 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 II. 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 cancer.

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

**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

| 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 3. Cumulative rates for local governments which started mass-screening.
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. 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 cancer. For example, tea consumption has been suggested as a remedy to improve chronic atrophic gastritis which is considered to be precancerous lesion. Beta-carotene has also employed for those with chronic gastritis until the recommendation of NCI to quit trail 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 polyps. Synthetic retinoids are also employed for patients with hepatitis to prevent hepatoma. 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 continuously. Cross sectional study on dietary factors and colon, breast and ovarian cancers suggested a preventive effect from tofu and tofu products consumption (Fig. 4). Thus the phytoestrogen study is initiated to study the effect.

Tobacco control in Japan was relatively slow and reluctantly sponsored by the government. The effect of tobacco cessation was clearly shown by the case-control study conducted on ex-smokers. Economical analysis showed apparent external diseconomy, and if no measurement were taken nation’s burden would increase 4 times more in 2030. 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. Environmental Agency also adds to the data set, the measurement of air pollution, water pollution, ultraviolet ray, and etc. 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 epidemiology. Autopsy records include more than 40,000 autopsies performed every year. This additional information also provides histological data of the tumor. Multiple primary cancer cases can be detected by linking hospital registries. Drug-related carcinogenesis has also listed, and used in the clinical epidemiological study. 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 risk. Other models including cancer growth need basic knowledge in biology.

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.

ACKNOWLEDGEMENT

The authors appreciate Ms. V. Lee for her kind revision of our manuscript.

REFERENCES

1. Statistics and Information Department, Minister's Secretariat, Ministry of Health and Welfare. Vital Statistics 1950-1990. Kousei Tokei Kyokai, Tokyo, 1950-1990.
2. Segi M, Tominaga S, Aoki K, Fujimoto I (Eds.), Cancer Mortality and Morbidity Statistics. Japan and the World (1981). Japan Scientific Societies Press, Tokyo, 1981.
3. The Research Group for Population-based Cancer Registries in Japan. Cancer Incidence in Japan. In; Gann Monograph on Cancer Research Vol.41. Cancer Mortality and Morbidity Statistics. Japan Scientific Societies Press, Tokyo, 1994: 107-158.
4. Watanabe S, Yamaguchi N, Kinjo Y. History and overview of the site-specific cancer registries in Japan. In; Watanabe S, Tominaga S, Kakizoe T, eds. Cancer Treatment and Survival, Gann Monograph on Cancer Research No 43. Japan Scientific Societies Press, Tokyo, 1995: 1-8.
5. Watanabe S, Arimoto H. Standardized mortality rates of cancer by prefecture in 1979-1981 and 1984-1986 in Japan. Jpn J Clin Oncol 1990; 20: 316-337.
6. Mizuno S, Arimoto H, Yamaguchi N, Watanabe S. Age-standardized cancer mortality by prefecture for the years, 1980 to 1990. Jpn J Clin Oncol 1994; 24 : 51-57.
7. Kurihara M, Aoki K, Tominaga S (Eds.). Cancer Mortality Statistics in the World, University Nagoya Press, Nagoya, 1984.
8. Watanabe S. Large-scale, population-based prospective studies in Japan. Eur J Cancer 1993 ; 29A : 2305-2314.
9. Yamaguchi N, Tamura Y, Sobue T, Akiba S, Ohtaki M, Baba Y, Mizuno S, Watanabe S. Evaluation of cancer prevention strategies by computerized simulation model: Methodological issues. Environmental Health Perspectives 102 : 1994 ; suppl 8 : 67-71.
10. Watanabe S, Arimoto H. Long term trends in cancer mortality rates and cumulative rates from 1955 to 1987 in Japan (2). Jpn J Clin Oncol 1989 ; 19 : 413-425.
11. Kuroishi T, Hirose K, Tajima K, Tominaga S. Cancer mortality in Japan (1959-1990). Gann Monograph on Cancer Research Vol.41. Cancer Mortality and Morbidity Statistics. Japan Scientific Societies Press, Tokyo, 1994 : 1-106.
12. Mizuno S, Yamaguchi N, Watanabe S. Cancer mortality trends in Japan 1960-1990: Three-dimensional graphical presentation. Jpn J Clin Oncol 1992 ; 22 : 433-436.
13. Watanabe S, Tominaga S, Kakizoe T. (eds.), Cancer Treatment and Survival. Gann Monograph. Japan Scientific Societies Press, CRC Press, Tokyo, London, 1995.
14. Takano A, Okuno Y, Miyagi Prefecture Cancer Registries. End results of cancer patients: from population-based cancer registry data. In ; Gann Monograph on Cancer Research Vol 33, Tokyo Scientific Societies Press, Tokyo, 1987 : 81-87.
15. Hanai A, Tsukuma H, Hiyama T, Fujimoto I. Cancer survival in Osaka. In ; Gann Monograph on Cancer Research Vol.41. Cancer Mortality and Morbidity Statistics. Japan Scientific Societies Press, Tokyo, 1994 : 159-166.
16. Hanai A, Fujimoto I. Cancer Incidence in Japan in 1975 and changes of epidemiological features for cancer in Osaka. In ; Trends in Cancer Incidence. Magnus K (ed), Hemisphere Pub. Co., Washington, 1982 : 143-154.
17. Tanaka H, Hiyama T, Hanai A, Fujimoto I. Second primary cancers following colon and rectal cancer in Osaka, Japan. Jpn J Cancer Res, 1991 ; 82 : 1356-1365.
18. Tsukuma H, Hiyama T. Risk factors for hepatocellular carcinoma among patients with chronic liver diseases. New Eng J Med 1993 ; 328 : 1797-1801.
19. Tanaka H, Hiyama T. Primary liver cancer incidence-related to hepatitis C virus infection : a correlational study in Osaka, Japan. Cancer Causes Control 1994 ; 5 : 61-65.
20. Sobue T, Suzuki T, Matsuda M, Horai T, Kajita A, Kuriyama K, Fukuoka M, Kusunoki Y, Kikui M, Ryu S, Fujimoto I. Sensitivity and specificity of lung cancer screening in Osaka, Japan. Jpn J Cancer Res 1991 ; 82 : 1069-1076.

21. Yamaguchi M, Suzue R, Watanabe S. Summary of National Nutrition Survey 1980-1984 by prefecture. Jpn J Clin Oncol 1990 ; 20 : 113-120.

22. Tsugane S, Gey F, Ichinowatari Y, et al. Cross-sectional epidemiological study for assessing cancer risks at the population level I. Study design and participation rate. J Epidemiol 1992 ; 2 (2) : 75-81.

23. Tsugane S, Gey F, Ichinowatari Y, et al. Cross-sectional epidemiological study for assessing cancer risks at the population level II. Baseline data and correlation analysis. J Epidemiol 1992 ; 2 (2) : 83-89.

24. Yamaguchi N, Watanabe S, Okubo T, Takahashi K. Work-related bladder cancer risks in male Japanese workers : Estimation of attributable fraction and geographical correlation analysis. Jpn J Cancer Res 1991 ; 82 : 624-631.

25. Kabuto M, Imai H, Tsugane S, Watanabe S. Correlation between atrophic gastritis prevalence and gastric cancer mortality among middle-aged men in 5 areas in Japan. J Epidemiology 1993 ; 3 (1) : 35-39.

26. Kabuto M, Imai H, Tsugane S, Watanabe S. Does high gastric cancer risk associated with low serum ferritin level reflect achlorhydria ? An examination via cross-sectional study. Jpn J Cancer Res 1993 ; 84 : 844-851.

27. Tsugane S, Kabuto M, Imai H, Gey F, Tei Y, Hanaoka T, Sugano K, Watanabe S. Helicobacter pylori, dietary factors, and atrophic gastritis in five Japanese populations with different gastric cancer mortality. Cancer Causes Control 1993 ; 4 : 297-305.

28. Tsugane S, Tei Y, Takahashi T, Watanabe S, Sugano K. Salty food intake and risk of helicobacter pylori infection. Jpn J Cancer Res 1994 ; 85 : 474-478.

29. Watanabe S, Mukai K, Shiomoyama M. Adult T cell leukemia/lymphoma. In ; Knowles DM, ed. Neoplastic Hematopathology. Williams & Wilkins, 1992 : 1281-1294.

30. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer ; a study from Japan. Br Med J 1981 ; 282 : 183-185.

31. Hirayama T. Life Style and Mortality, A large-scale census based cohort study in Japan. Contribution to Epidemiology and Biostatistics. Vol 6. Kruger, Basal, 1990.

32. Shigematsu I, Kagan A. (Eds). Cancer in atomic bomb survivors. Gann Monograph on Cancer Research 32. Japan Scientific Societies Press, Tokyo, 1986.

33. Shigematsu I. Ionizing radiation and health. J Epidemiol 1992 ; 2 : S21-S30.

34. Murakami R, Tsukuma H, Kanamori S, et al. Natural history of colorectal polyps and the effect of polypectomy on occurrence of subsequent cancer. Int J Cancer 1990 ; 46 : 159-164.

35. Kono S, et al. Relationship of diet to small and large adenomas of the sigmoid colon. Jpn J Cancer Res 1993 ; 84 : 13-19.

36. Honjo S, Kono S, Hirohata T, Tokunaga S. Geographic correlation between stomach cancer mortality and food consumption in Japan. J Epidemiol 1992 ; 2 : 41-50.

37. Kamiyama S, Oshima H, Shimada A, et al. Urinary excretion of N-nitrosamino acids and nitrate by inhabitants in high-and low-risk areas for stomach cancer in northern Japan. IARC Sci Pub No. 84, IARC, Lyon, 1987 : 497-502.

38. Tajima K, Tominaga S. Dietary habits and gastrointestinal cancers : a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. Jpn J Cancer Res, 1985 ; 76 : 705-716.

39. Inoue M, Tajima K, et al. Life style and subsite of gastric cancer- Joint effect of smoking and drinking habit. Int J Cancer 1994 ; 56 : 494-499.

40. Hanaoka T, Tsugane S, Ando N, et al. Alcohol consumption and risk of esophageal cancer in Japan : A case-control study in seven hospitals. Jpn J Clin Oncol 1994 ; 24 : 241-246.

41. Kato I, Tominaga S, Ikari A. A case-control study of male colorectal cancer in Aichi Prefecture, Japan : with special reference to occupational activity level, drinking habits and family history. Jpn J Cancer Res, 1990 ; 81 : 115-121.

42. Oshima A, Tsukuma H, Hiyama T, Fujimoto I, Yamano H, Tanaka M. Follow-up study of HBs Ag-positive blood donors with special reference to effect of drinking and smoking on development of liver cancer. Int J Cancer 1984 ; 34 : 775-779.

43. Oshima A, Hiyama T, Fujimoto I, Song K, Yamano H, Tanaka M. The epidemiology of liver cancer. Jpn J Cancer Clin 1982 ; 28 : 962-971.

44. Tobe T, Kameda H, Okudaira M, et al (eds.), Primary Liver Cancer in Japan. Springer-Verlag, Tokyo, 1992.

45. Mizuno S, Akiba S, Hirayama T. Lung cancer risk comparison among male smokers between the “six prefecture cohort” in Japan and the British physicians’ cohort. Jpn J Cancer Res 1989 ; 80 : 1165-1170.

46. Sobue T. Association of indoor air pollution and life style with lung cancer inOsaka, Japan. Int J Epidemiol 1990 ; 19 : S62-S66.

47. Yamaguchi N, Kido M, Hoshuyama T, Manabe H, Kikuchi Y, Nishio T, Ohshima LHK, Watanabe S. A case-control study on occupational lung cancer risks in industrialized city of Japan. Jpn J Cancer Res 1992 ; 83 : 134-140.

48. Tsugane S, Watanabe S, Sugimura H, et al. Smoking, occupation and family history in lung cancer patients...
under fifty years of age. Jpn J Clin Oncol 1987; 17: 309-317.

49. Suzuki T, Sobue T, et al. Association of adenocarcinoma of the lung with cigarette smoking by grade of differentiation and subtype. Cancer Res 1990; 50: 444-447.

50. Nakachi K. Polymorphisms of the CYP1A1 and glutathione S-transferase genes associated with susceptibility to lung cancer in relation to cigarette dose in a Japanese population. Cancer Res, 1993; 51: 2994-2999.

51. Sugimura H, Suzuki I, Hamada G S, Iwase T, Takahashi T, Nagara K, Iwata H, Watanabe S, Kino I, Tsugane S. Cytochrome P-450 1A1 genotype in lung cancer patients and controls in Rio de Janeiro, Brazil. Cancer Epidemiol Biom Prev 1994; 3: 145-148.

52. Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K, Ohyanagi H, Fujiki T, Motojima K. A multi-institute case-control study on the risk factors of developing pancreatic cancer. Jpn J Clin Oncol 1992; 22: 286-291.

53. Yatani R, et al. Geographic pathology of latent prostatic carcinoma. Int J Cancer 1982; 29: 611.

54. Ohno Y, Yoshida O, Oishi K, et al. Dietary beta-carotene and cancer of the prostate: a case-control study in Kyoto, Japan. Cancer Res 1988; 48: 1331-1336.

55. Kato I, et al. Alcohol consumption and cancers of hormone-related organs in females. Jpn J Clin Oncol, 1989; 19: 202-207.

56. Wakai K, Ohno Y, Watanabe S, Sakamoto G, Kasumi F, Suzuki S, Kubo-Fujiwara N. Risk factors for breast cancer among Japanese women in Tokyo: A case-control study. J Epidemiol 1994; 4: 65-71.

57. Haenzel W, Kurihara M. Studies of Japanese immigrants. J Epidemiol 1994; 4: 65-71.

58. Wakai K, Ohno Y, Watanabe S, Sakamoto G, Kasumi F, Suzuki S, Kubo-Fujiwara N. Risk factors for breast cancer among Japanese women in Tokyo: A case-control study. J Epidemiol 1994; 4: 65-71.

59. Haenzel W, Kurihara M. Studies of Japanese immigrants. J Epidemiol 1994; 4: 65-71.

60. Wakai K, Ohno Y, Watanabe S, Sakamoto G, Kasumi F, Suzuki S, Kubo-Fujiwara N. Risk factors for breast cancer among Japanese women in Tokyo: A case-control study. J Epidemiol 1994; 4: 65-71.

61. Shimizu H, Mack TM, Ross RK, Henderson BE. Cancer of the gastrointestinal tract among Japanese and white immigrants in Los Angeles County. JNCI 1987; 78: 223-228.

62. Shimizu H, Mack TM, Ross RK, Henderson BE. Cancer of the gastrointestinal tract among Japanese and white immigrants in Los Angeles County. JNCI 1987; 78: 223-228.

63. Shimizu H, Ross RK, Bernstein L, et al. Cancer of the prostate and breast among apes and white immigrants in Los Angeles County. Br J Cancer, 1991; 63: 963-966.

64. Shimizu H, Ross RK, Bernstein L, Pike MC, Henderson BE. Serum oestrogen levels in postmenopausal women: comparison of American whites and Japanese in Japan. Br J Cancer 1990; 62: 451-453.

65. Tsugane S, Gotlieb SLD, Laurenti R, Souza JMP, Watanabe S. Mortality and cause of death among first-generation Japanese in Sao Paulo, Brazil. Int J Epidemiol 1989; 18 (3): 647-651.
78. Watanabe S. Breast cancer in Japan-Trends and recent researches in biology and epidemiology. Asian Med J, 1993; 36: 486-494.
79. Endo T, Kido T, et al. Breast cancer screening using OMR. Clinical Medicine of Breast Cancer 1990; 5: 424-430.
80. The Japan Society of Obstetrics and Gynecology. Registration of Gynecological Malignancies. In: Cancer Treatment and Survival. Site-specific Registries in Japan. Watanabe S, Tominaga S, Kakizoe T (Eds.), Japan Scientific Societies Press, CRC PRESS, Tokyo, London. 1995, pp. 169-180.
81. Kitajima S, Inaba Y, Wada O, Miki K, Tenjin H, Kaneko E, Mizukoshi H. Should age, sex, subjective symptoms in the stomach and past history of peptic ulcer be regarded in the evaluation of efficacy of serum pepsinogen values for use in gastric cancer mass-screening? J Epidemiol 1993; 3: 71-76.
82. Nishi M, Miyake H, Takeda T, Hanai J, Kikuzaki Y, Takaasagi N. Comparison of patients with neuroblastoma screened at 6 months of age and those screened at 7 to 10 months. Int J Pediatr Hematol/Oncol 1995; 2: 321-324.
83. Watanabe O. Present status of mass-screening for prostate cancer in Japan. Nihon Iji Shinpo 1993; 3600: 27-34.
84. Watanabe S. Changing cancer strategy in Japan. Radiology Japan 1992; (28): 1-7.
85. Kono S, Ikeda M, Tokudome S, Kuratsune M. A case-control study of gastric cancer and diet in northern Kyushu, Japan. Jpn J Cancer Res 1988; 79: 1067-1074.
86. Nakachi K. Significant reduction of cancer incidence by drinking green tea observed in a Japanese population. In: Proc Int Conf, Food Factors (in press).
87. Ishikawa H, Akedo 1, Suzuki T, Otani T, Sobue T. Lung cancer incidence rate for male ex-smokers according to age at cessation of smoking. Jpn J Cancer Res, 1993; 84: 601-607.
88. Goto K, Watanabe S. Social cost of smoking for the 21st century. J Epidemiol 1995; 5: 31-34.
89. Ohkawa M, Kim D-K, Munaka M, Yamaguchi N, Watanabe S. An exploratory analysis of mortality with an age-period model and its application to stomach cancer in Japan. Jpn J Biometrics 1992; 13: 87-97.
90. Mizuno S, Watanabe S, Iwama T, Mishima Y. Colorectal cancer incidence linking model in familial adenomatous polyposis and the general population. J Epidemiol 1993; 3 (2): 109-115.
91. Endo T, Kido T, et al. Breast cancer screening using OMR. Clinical Medicine of Breast Cancer 1990; 5: 424-430.
92. Adlercreutz H, Fotsis T, Watanabe S, Lampe J, Wahala K, Makela T, Hase T. Determination of lignans and isoflavonoids in plasma by isotope dilution gas chromatography-mass spectrometry. Cancer Detect Prevent 1994; 18: 259-271.
93. Watanabe S. WHO Collaborating Center, Japan. Tobacco Alert; July 1995, WHO, Geneva, p10.
94. Sobue T, Suzuki T, Fujimoto I, et al. Lung cancer risk among exsmokers. Jpn J Cancer Res 1991; 82: 272-279.
95. Sobue T, Fujimoto I, et al. Lung cancer incidence rate for male ex-smokers according to age at cessation of smoking. Jpn J Cancer Res, 1993; 84: 601-607.
96. Goto K, Watanabe S. Social cost of smoking for the 21st century. J Epidemiol 1995; 5: 31-34.
97. Ohkawa M, Kim D-K, Munaka M, Yamaguchi N, Watanabe S. An exploratory analysis of mortality with an age-period model and its application to stomach cancer in Japan. Jpn J Biometrics 1992; 13: 87-97.
98. Mizuno S, Watanabe S, Iwama T, Mishima Y. Colorectal cancer incidence linking model in familial adenomatous polyposis and the general population. J Epidemiol 1993; 3 (2): 109-115.
99. Environmental Agency. Annual Report, Environmental Agency, Tokyo, 1995.
100. Watanabe S. Why do we need cancer information? Jpn J Clin Oncol 1990; 20: 7-15.
101. Watanabe S, Tsugane S, Arimoto H, Shimosato Y, Suemasu K, Arai H, Urano Y. Trend of lung cancers in the National Cancer Center of Japan and comparison with that of Japanese Pathological Autopsy Records. Jpn J Cancer Res (Gann) 1987; 78: 460-466.
102. Watanabe S, Kodama T, Shimosato Y, Arimoto H, Sugimura T, Suemasu K, Shiraishi M. Multiple primary cancers in 5,456 autopsy cases in the National Cancer Center of Japan. JNCI 1984; 72 (5): 1021-1027.
103. Nagao K, Watanabe S, Tsugane S, Morinaga S, Yoneyama T. Case-control study on histologically determined multiple primary lung cancer. JNCI 1987; 79: 435-441.
104. Kobayashi Y, Arimoto H, Ono I, Watanabe S. Multiple primary cancers in patients with initial laryngeal cancer. Jpn J Clin Oncol 1990; 20: 128-133.
105. Kobayashi Y, Arimoto H, Watanabe S. Occurrence of multiple primary cancer at the National Cancer Center Hospital, 1962-1989. Jpn J Clin Oncol 1991; 21: 233-251.
106. Tsunematsu Y, Watanabe S, Oka T, Tsukamoto T, Kawa-Ha K, Hirata Y, Yamanaka H, Ohira M, Ono M. Familial aggregation of cancer from proband cases with childhood adrenal cortical carcinoma. Jpn J Cancer Res 1991; 82: 893-900.
107. Watanabe S, Mizuno S, Oshima L-H, Tsunematsu Y, Fujimoto J, Komiyama A. Leukemia and other malignancies among GH users. J Ped Endocrinol 1993; 6 (1): 99-108.
108. Watanabe S, Yamaguchi N, Tsunematsu Y, Komiyama A. Risk factors for leukemia occurrence among growth hormone users. Jpn J Cancer Res 1989; 80: 822-825.
109. Watanabe S, Yamasaki S, Tanoe A, Hibi I. Ad hoc committee on Androcur users. Three cases of hepatocellular carcinoma among cyproterone users. Lancet 1994; 344: 1567-1568.

110. Mizuno S, Akiba S. Smoking and lung cancer mortality in Japanese men: Estimates for dose and duration of cigarette smoking based on the Japan Vital Statistics data. Jpn J Cancer Res. 1989; 80: 727-731.

111. Mizuno S, Akiba S, Hirayama T. Lung cancer risk comparison among male smokers between the "Six prefecture Cohort" in Japan and the British Physicians" Cohort. Jpn J Cancer Res, 1989; 80: 1165-1170.

112. Yamaguchi N, Watanabe S, Maruyama K, Okubo T. Estimation of the prevalence of occult cancer and its application to the epidemiology of multiple primary cancer. Jpn J Clin Oncol 1985; 15 (Suppl 1): 313-323. 1986.

113. Yamaguchi N, Watanabe S, Maruyama K, Okubo T. Analysis of stomach cancer incidence by histologic subtypes based on a mathematical model of multistage cancer induction and exponential growth. Jpn J Cancer Res 1990; 81: 1109-1117.