HISTORICAL REVIEW

Early History of Cancer Epidemiology and Prevention in Japan

Kunio Aoki

Abstract

Cancer epidemiological research has a long and distinguished history and as we continue our work in ever expanding new fields, molecular or otherwise, it is perhaps worthwhile to take time out occasionally to ponder what lessons we can learn from the past. Many of the paradigms which are presently accorded respect in fact were hinted at by very early work and it is fitting that we take a look at how previous developments knit with the present status of cancer research in different areas of the world. For this purpose the present review focuses on cancer epidemiology in Japan, in the hope of gleaning advantage from past experience in planning future programs.

Key words: General epidemiology - early descriptive studies of cancer in Japan - early analytical studies - risk factors

Asian Pacific J Cancer Prev, **7**, 170-176

Prologue

The paradigm of epidemiology was already introduced into Japan in the 1880s, when studies on cholera and other infectious diseases were conducted. First I would like to introduce a unique intervention study on beriberi (vitamin B1 deficiency disease) conducted in Japan. Dr. Kanehiro Takaki was a navy surgeon who graduated from Medical School of St. Thomas Hospital, England. During the course of his studies he noted a significant difference in the incidence of beriberi between the sailors and the officers. However, they were exposed to the same socio-medical factors related to living and working conditions, microenvironment, including clothing, drinking and other habits, except for their daily meals. The sailors took a traditional Japanesemenu of much polished rice and small amount of animal proteins, so that nitrogen containing foods were limited. The officers received more animal proteins and other nutrients so Dr Takagi advised the Navy to increase more milk, meat and bread, and less rice for sailors, recollecting about the diet provided for the British navy.

On learning of a tragic disaster that occurred in 1882, whereby 169 of 371 crew suffered from beriberi during a training ocean voyage from Japan to Australia, South America and Hawaii, resulting in 25 deaths, Dr. Takaki managed to persuade the government to permit an intervention study for the same voyage with a modified diet, the first human experiment of this type in Japan. The trial was successfully ended, recording only 15 cases of beriberi with no deaths among 287 crew (Takaki, 1906; Hirohata, 1996). As a result the Navy changed their dietary practices and the beriberi incidence dramatically decreased and eventually vanished.

However many researchers and the relevant persons in Japan still suspected the evidence from epidemiological studies like Dr. Takaki conducted and no dietary changes were carried out in the army. The leading physicians had studied under Pettenkofer, an environmentalist, or under Robert Koch, a bacteriologist, in Germany, and believed that beriberi might be due to some microorganism. Experimental work based on Dr. Takaki's nutritional balance such as the ratio of N to C unfortunately did not clarify the exact preventive agent for beriberi. Without any effective preventive measures epidemics continued throughout the country for more than 20 years. It should be noted that army soldiers were recorded to have very high incidences at the front in the Japan-Russian War in 1907-8. It was a time when most medical researchers did not approve of epidemiology as a scientific approach in Japan.

Descriptive Epidemiological Studies on Cancer in Japan

In the beginning of the 20 century, the proportion of cancer deaths among all causes of deaths was only 2% in Japan, so that major concerns for the physicians, politicians and lay people were acute infectious and parasitic diseases causing death at relatively young age (Ministry of Health & Welfare of Japan, 1950-1999). Fortunately, a small number of physicians and researchers were interested in cancer patients, examining clinical features, frequency of cancer by site and trying to clarify etiological factors. Their main aims were to find effective treatments and preventive measures for the range of neoplastic diseases (Abe, 1907; Sato,1907).

Emeritus President of Aichi Cancer Center, Emeritus Professor of Nagoya University, Japan Fax +81-52-802-6873
Email: n-meikoi@poem.ocn.ne.jp

Photo 1. Dr Mataro Nagayo

Statistical Studies on Cancer at the Beginning of the 20th Century

The Japanese Government has issued annual mortality statistics by major disease since 1882. From 1899, mortality statistics were published with cause of death, age-sex, present and permanent residence, occupation and other characteristics, adopting the International Classification of Deaths (ICD) (Segi et al., 1955). Regarding cancer, the ICD classification showed only two categories in the first issue of 1899, but this was changed to 9 categories in 1909 (see Table 1). However, these major sites of cancer were not sufficient for physicians and researchers to actually do their work, so that data were published for frequency distributions of cancer patients by more sites, after examining clinical and autopsy records in hospitals around 1900 (Abe, 1907; Sato,1907).

There were clearly problems with accuracy and homogeneity in cancer diagnosis between the statistics reported. Low autopsy rates even in the top ranking hospitals at that time hindered promotion of cancer studies. A total of 932,800 deaths by all causes were registered in 1899, and about 20,000 (2.08% of all cases) were due to cancer. Since many deaths were of patients still active in their communities, correct figures for cancer were strongly requested by researchers and officials responsible for disease control.

Table 1. ICD 2nd Revision Classification, 1909-1922

40 Cancer of the Buccal Cavity
41 Cancer of the Stomach & Liver
42 Cancer of the Peritoneum, Intestines and Rectum
43 Cancer of the Female Genital Organs
44 Cancer of the Breast
45 Cancer of the Skin
46 Cancer of the Other Organs
47 Cancer of Organs Not Specified
48 Other Malignant Tumors

Prevalence and Mortality Data from Autopsy Records

Dr. Mataro Nagayo (Photo 1), pathologist, Professor of Tokyo University, and first Director of the Cancer Institute, Tokyo, devoted himself to obtain more accurate statistics of tumor in Japan. He had carefully examined the pathological records for a total of 1,579 cancer deaths among all autopsied cases of 12,077 in Tokyo University for the period of 1884 to 1934, and established pathological features of tumors and the distribution by site comparing clinical diagnosis and pathological findings in different periods. Selecting 767 cases of cancer among all the 4,592 autopsied for the period from 1915 to 1935, he found that the concordance rate of the clinical diagnoses to the autopsy findings was roughly 82.3% for cancer of all sites, figures, he thought, which were relatively good and allowing gross comparison between different times or different areas. He compared the data for cancer mortality by major site in 1915, 1920, 1924, 1929, and 1930, and confirmed that time trends were evident for proportions of cancer over these15 years. He recognized that the overall mortality, for all sites, in Japan did not show any tendency for increase, remaining at roughly 70 per 100,000. This figure was very similar to those estimated in local studies by others previously. An international comparison of cancer mortality by Dr. Nagayo is shown in Table 2. Checking the figures, he stated that the cancer rate in Japan was relatively low, but in the same range as in the European countries.

Furthermore, he started to examine data for cancer patients in major hospitals throughout Japan in 1928, asking for the active cooperation of physicians of 43 cancer related departments of major institutes like university hospitals, and one cancer hospital. He requested that they notify the numbers of all patients treated first and then ask for further information on cancer cases by site secondarily. He repeatedly asked physicians to send new records of the cases to him for 7 years until 1935, this being the first occasion for most to

Table 2. Cancer Mortality in Japan and Some European Countries (per 100,000 in 1929)

England-Wales	14.4
Denmark	14.4
Switzerland	14.1
Germany	11.4**
USA	9.9*
Australia	9.8
France	9.7
Hungary	7.1
Spain	7.0
Japan	6.8
Italy	6.3

*1927,**1928

Table 3. Proportion of Cancers by Site

	Deaths	Cases
Oral,upperjaw etc	2.7%	6.7%
Stomach,Liver & Esophagus	67.8%	56.7%
Colon-rectum	6.0 %	7.3%
Female genital	16.3 %	20.6%
Skin, Penis	0.5 %	2.8%
Others	5.7 %	5.8%

collaborate in such a study. This method was a kind of questionnaire study in epidemiology. The reported cancer patients totalled 20, 782 cases, which was 2.8% of all patients, 730,984, who presented the clinics. This rate was a little bit higher than that with mortality statistics. The distributions of cancer patients by site among this survey and for mortality were shown in Table 3. Major cancers such as the stomach, liver, cervix uteri and esophagus were similar between the mortality statistics and the patient survey, although the oral and upper jaw was higher in the cancer survey than in cancer deaths. The fatality rate with oral cancer was lower than in the other sites.

Dr. Nagayo described in his monograph (1935) how the three statistics, including pathology data, were independently collected and examined, but stressed that they showed little difference in diagnoses. Each had some weakness in quality but the different approaches allowed for compensation. Thus, collectively real figures could be surmised. He also referred to cancer mortality data in Korea and some parts of China in his book. A summary of his study results is shown in Table 4. He emphasized that the data suggested significant roles for environmental factors in causation of cancer, which had already been indicated from animal studies on cancer including experimental tar cancer by Drs Yamagiwa & Ichikawa. That meant cancer is preventable. He added that Professor Virchow's irritation theory on tumor development might be endorsed by the statistical data. His keen insight into the cancer entity and possible preventive strategies is highly evaluated even at present, and his statements have stimulated many physicians and researchers in the intervening period.

Photo 2. Dr Akira Fujinami

Analytical Epidemiologic Studies on Malignant Tumors and Risk Factors

Professor Akira Fujinami (Photo 2) and his colleague S Nakari (1907) made plans to study cancer frequency with more accurate cancer mortality figures by examining death certificates of some towns and villages in Kyoto prefecture, and then to detect risk factors of cancer in comparison with the level of mortality. Pathological findings with clinical records were firstly compared to confirm degree of accuracy clinical diagnosis, which was based on the autopsy specimens in Kyoto University. Then, they tried to estimate actual mortality rates for cancers by town and village and the proportion of cancer by site.

Dividing cancer mortality by area into three groups, low, moderate and high, relationships with some living conditions, as well as geographical, climatic and geological features could be examined. This was the first trial to detect risk factors for cancers in local areas of Japan, to my knowledge. Dr

Table 4. Summary of Dr. Nagayo's Results from Autopsy Records, Mortality Statistics and Prevalence Surveys

1. About 90% of cancer deaths are registered in the national statistics, after examining pathological and clinical comparisons
2. Mortality statistics in Japan are useful, but must be carefully interpreted considering misdiagnosis , especially with cancers of the inner organs
3. Mortality statistics are useful for observing time trends of cancer and also to compare frequency distributions of cancers by site
4. Mortality of cancer in Japan is lower than in many European countries, with big differences in frequency of cancer by the anatomical site. Stomach cancer is highest rate in Japan and liver cancer with liver cirrhosis is also high, compared with European countries
5. Cancer incidence increases with aging - the longer the life, the higher the cancer incidence to be expected
6. The statistical data indicate that environmental factors are more improtant than congenital factors in carcinogenesis. Experimental studies endorse the roles of environmental factors. For example, female genital cancer is closely associated with sexual and reproductive histories and stomach cancer is related to stimulative foods and drinks. This points the way for cancer prevention.

Table 5. The Contents of the Study Items of Suzuki

1. Frequency and distribution of cancer deaths by town and village, sex, age for 10 years
2. Constitutional characteristics of cancer including sex and age
3. Hereditary factors by organ from the data based on familial aggregation
4. Cervical cancer and reproductive history of the patients
5. Occupation and cancer
6. Pathological findings of cancer cases, such as distribution of cancer by site, age- sex and area
7. Comparison of clinical features with pathologic findings, and metastasis of cancer by site
8. Co-morbidity such as other cancers, benign tumors, tuberculosis and pneumonia
9. Causes of deaths
10. Risky factors in causation of cancer, such as population density, climatic factors as temperature, humidity, rainfall, topographic and geological background including water, soil, draining, living conditions including housing, personal hygiene, labour conditions and so on
11. Cancer and lifestyle habits such as eating, alcohol drinking, and other behavioral patterns

Nakarai presented a preliminary result of the study at the Scientific Meeting of Cancer in 1908. He suggested that some risky areas of cancer were such as in high humidity places, the low land near lake and swamp, places of bad water draining, and that risky factors were such as to drink bad quality of water, to take much alcohol, much foods, less consumption of vegetables and others. He confirmed familial aggregation of cancer, but stated that familial cancer might be affected by environmental factors (Nakarai, 1913) Dr. Fujinami emphasized in another paper (1929) that studies should be performed in various areas because the results should be compared with those obtained in other ones, and also he hoped to develop better methods of studying such statistical and geographical investigations for the inhabitants.
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Dr Nobuyoshi Suzuki, a graduate student of Prof. Fujinami, tried to confirm his teacher's working hypothesis. He carried out a check in all death certificates in Kyoto prefecture by town and village during 10 years from 1905 to 1914, obtaining the assistance of local government officers. The autopsy records on cancer cases in Kyoto University were also examined for 14 years to clarify accuracy of clinical diagnosis and specific characteristics of cancer from the pathological point of view. Then, he made laborious efforts on examine the social, and medical factors related to cancer onset, going from town to town and from village to village collecting data on risk factors of natural and artificial environments, lifestyles and/or behavioral pattern of the inhabitants by himself for 5 years. He classified the towns and villages examined into 3 categories as high, moderate and low mortality of cancer like Dr Nakarai, and compared natural and environmental factors, and lifestyles and other living conditions (see Table 5). His first treatise of 137 pages was published in a medical journal in 1918 (Suzuki, 1918), entitled "Statistical study on malignant tumors", and this was succeeded by second and third reports in 1921 (Suzuki, 1921). In his last paper, the results of a similar study in Shiga prefecture next to Kyoto was added for comparison.

The summary of his work can be stated as follows: mortality rates in the towns or villages of Kyoto prefecture ranged from 19 to 43 per 100,000, increasing with age and peaking at 61 to 70 years. Stomach cancer was the most common neoplasm in both sexes and familial aggregation was seen in 9.7% for all sites, the risk elevation for the same site being 3.1 times higher than without cancer in any kin. Cervical cancer was closely associated with a previous history of reproductive experiences, such as multiple pregnancies and deliveries. Environmental risk factors for cancer are listed in Table 6. He confirmed previous reports of Drs Fujinami and Nakarai regarding geographic and climatic factors and in addition noted the association betweeen hot tea/gruel and oesophageal cancer. These findings were compared with those in European countries and discussed. It is very interesting that many risk factors detected in this study are very reminiscent of those detected by modern epidemiological studies and experimental research since 1965. They were also the subjects of European literature at the end of the 19th century and Dr. Fujinami might have learned about these results from Europe and therefore examined equivalent factors in Japan.

After Dr Suzuki there were no students in Dr. Fujinami's Department for more than 10 years but then a series of studies were performed by graduate students, Nakagawa S in Kagawa prefecture (Oyama, 1930) and Kajikawa T in Nara prefecture (1930). Summarizing the four studies conducted in Kyoto, Shiga, Kagawa and Nara, Dr. Fujinami conclusively stated at the Scientific meeting of Japanese Pathological Association

Table 6. Environmental Risk Factors for Cancer

Low risk area	Highland, mountainous district, Good drainage places, Dry climate. Areas without lakes or swamps and with good quality water
High risk area	Low land near lakes and swamps, with bad drainage sites, wet climate, and bad quality drinking water Tendency to drink much alcohol, and to eat much food, with low consumption of vegetables and tea
Specific finding	Esophageal cancer is associated with very hot drinks / foods and/or hot tea gruel.

in 1929 that cancer mortality rate in Japan was in the range of 60-90 per100,000, although there were some differences by prefectures. He estimated that the cancer incidence in Japan was not so different from those of European countries, although the pattern of other causes of death was clearly different from in Europe, in line with Dr. Nagayo's findings later in 1935. The following conclusion should be noted, that is, that there are big differences in cancer mortality among organ sites between countries, suggesting the effects of different environmental factors. Familial aggregation of cancer was observed at about 10% in the cancer group, but environmental factors appeared much more important for causation of neoplasia. Cancer susceptibility to specific organ might be determined by the repeated stimuli from external factors in each country. To obtain more objective evidence, studies should be done in many areas, and also more adequate scientific methods in geographical and statistical study should be developed (Fujinami, 1929).

Collaborative Studies by Professor N Hayashi and Colleagues

Dr. Naosuke Hayashi (Photo 3), Professor of Pathology, Aichi Medical College, who had previously worked under Professor Fujinami in Kyoto University, deeply understood the importance of geographical and statistical studies on cancer. He therefore decided to collaborate such cancer study in his department, although he was very busy with his own research on transplantable fowl sarcoma, Tsutsugamu's disease (Rickettsiosis) and others. Therefore he requested his graduate student, K Nomura, to conduct geographic and statistical studies on cancer in Aichi prefecture, where his Medical College was located (Nomura, 1924). Nomura had advice on his study plan from Dr N Suzuki, who was working in Nagoya after moving from Kyoto University, and the study objects and methods were mostly the same as Suzuki's, multi-phasic and laborious work, as indeed acknowledged in Nomura's paper. Nomura also performed a similar study in Gifu prefecture with his colleague, Yoshida (1925). The frequency of cancer deaths by site and by area were calculated by age-sex and by town and village and clinical and pathological characteristics of cancer were analysed along with the Suzuki's lines, The results were mostly similar to that obtained in Kyoto, but some risky or protective factors found were specific, such as occupational status and some of lifestyle habits.

Dr. Hayashi asked his 7 graduate students to carry out research in 6 prefectures in Chubu district. Dr M Yoshida focused on Shizuoka prefecture (Yoshida, 1926), I Yokoyama on Mie (1932), T Katada on Yamanashi (1926), Y Sugiura on Toyama (Sugiura, 1933), R Tsuda on Fukui 21) and T and S Kato on Ishikawa (1936) successively from 1915 to 1936. Their efforts were mainly to determine frequency distributions of cancer deaths by town and village. They also walked around their prefectures to survey environmental factors, industries and occupation, living conditions, income and/or lifestyle habits of the inhabitants, and established

Photo 3. Dr Naosuke Hayashi

collaborators in local governments and/or volunteers. Voluminous data were analyzed as by Nomura, and new analytic studies were added if necessary. Some eight papers for 8 prefectures were published one after another in the Archives of Pathology issued in the Department of Pathology of Aichi Medical College, entitled ' Geographic and statistical study on malignant tumors in named prefectures'.

Dr Hayashi shortly summarized the results of the 8 studies in Chubu District of Japan conducted according to Dr. Fujinami's methods at the Scientific Meeting of Pathology in 1935, (1935). The mortality rate from cancer of all sites, was 68.7 per 100,000 on average in Chubu district, and the proportion of all causes was 2.99%. Mortality from sarcoma was 0,092% of all causes. Male to female ratio in cancer deaths was approximately one to one, and female cancer mortality exceeded males in younger age groups. Stomach cancer was most common form, accounting for more than 50% of the total. The peak age of cancer deaths was in the 71 to 80 year bracket. These figures were mostly the same as published by Dr. Fujinami's group. Hayashi did not speak on risk factors for cancer, but the Kato brothers, the last workers on this project, summarized the findings of the 8 studies in a paper which was published in 1936 (Kato and Kato, 1936).

Significant Findings in Chubu District

The common characteristics of the natural environment with increased risk of cancer mortality were low land near swamps rivers or the coast with generally wet/humid conditions, bad water draining and high alluvium or diluvium in the soil. Risky lifestyle included much eating and alcohol consumption. Table 7 shows the ratios of alcohol drinking habits and cancer mortality by town and village in 6

Table 7. Risk of Cancer Mortality with Reference to Alcohol Consumption

Alcohol drinking	Much	Moderate	Low
Aichi	2.3	0.3	-
Shizuoka	0.6	3.0	0.2
Gifu	1.4	1.6	0.6
Yamanashi	2.0	0.7	0.7
Mie	3.7	0.4	-
Toyama	11.5	0.6	0.4

Table 8. Drinking Water Quality and Cancer Mortality Risk in Toyama Prefecture

		High risk*	Low risk*
Bad smell/taste		8.32%	1.85%
Nitrate	Trace	4.35	2.05
	Little	1.30	0.19
Nitrite	Trace	1.24	0.19
Fe	Little	0.70	0.50
Organic Compounds		9.82	8.25
Hardness		3.59	4.00
Overall Evaluation			
	Acceptable	42.19	86.05
	Not acceptable	35.19	7.61

*8 areas for each case

prefectures. In 5 prefectures, the relative risks were 0.3 to 0.7 in the areas with drinking less alcohol were shown, but in the areas with much alcohol drinking the risks ranged from 1.4 to 11.5 times higher, except in one prefecture. Consumption of rice as the staple food did not show significant risk, but low intake of vegetables was associated with a higher risk of dying from cancer. The effect of much intake of meats/fishes was not consistent between prefectures. Frequent exposure to very hot tea or hot tea gruel was again found to be a risk factor for cancers of the esophagus and stomach in some districts. Schistosomiasis infestation was furthermore linked to a high incidence of liver cancer in Yamanashi prefecture.

In Toyama prefecture, the association of quality of drinking water with cancer mortality was examined between the higher and lower cancer mortality areas (Sugiura, 1933). Table 8 shows that high risk areas showed higher percentage of bad quality drinking water such as bad smell, bad taste, higher content of nitrate and nitrite. Nitrate and nitrite were recognized as carcinogenic agents in 1970s. Therefore this finding was the first report in the world, but unfortunately because it was written in Japanese the international scientific community was not aware of its existence.

Much intake of foods, much drinking, daily habits to take hot tea gruel were also scientifically confirmed as risk factors of cancer after the 1970s in Japan It was interesting that bathing habit in hot spring was associated with lower incidence of cervical cancer, which suggested some mental or psychological factors in human carcinogenesis.

Epilogue

These geographic and statistical studies in the early period of 20 century with very poor knowledge of cancer, especially for entity of disease and almost no previous etiological studies on cancer in the world should be highly evaluated.

Dr. Fujinami was really unique in his emphasis on studying the cancer entity and its prevention. He planned and executed cancer research from an epidemiological point of view scientifically and pragmatically, although he himself was trained and active as a pathologist. He had learned in Europe how to approach the etiology of diseases, considering prevention. He performed distinguished studies which were awarded top ranking prizes on Schistosomiasis Japonica and Transplantable fowl sarcoma. He was the member of the Society of Geographic Pathology in 1900, immediately after its foundation in Switzerland, which aimed to detect external factors as causes of disease with the stress on the living environment and lifestyle and other personal behavior. He repeatedly stated that the disease was closely associated with environmental factors, even though genetic factors had previously been accorded more attention. It was the reason why he made efforts to obtain accurate statistics of cancer, which allow information on the etiological background of disease development. Regrettably he could not get better mortality records and more sensitive statistical methods, which hindered conclusion of his laborious work at that time. It might be the reason why Fujinami and Hayashi did not strongly emphasize the values of risk factors clarified in his voluminous studies.

Dr. Nagayo's studies should also be highly evaluated considering his speciality. His strong concern on reducing cancer mortality forced his attempt generate accurate cancer statistics. His prevalence study was the first nation-wide survey on cancer in Japan, a method successfully continued after World War II. His insight on cancer was also great at that time. In 1931, Dr Fujinami passed away and Dr Hayashi was retired from the medical college. No further studies were performed for 20 years. The military conflicts discontinued information transfer from abroad to Japan and the main stream of medical research largely changed during the war.

After World War II, cancer mortality began to increase, especially after 1950 and public attention gradually focused increasingly on cancer. In 1953, Professor T Ogata (Tokyo University) carried out a cancer patient survey throughout Japan, supported by a Governmental grant (Ogata, 1955), adopting a similar method for surveying cancer patients as had been applied by Dr. Nagayo. Subsequently, Dr. Mitsuo Segi, responsible for epidemiological study of this Research Committee, conducted case-control studies on some sites of cancer to detect risk factors (Segi et al., 1960). I suppose he had learned many ideas from the past reports since 1908, because the listed items of the questionnaire were similar to those described by Drs. Fujinami & Suzuki and his collaborators. Indeed, Dr. Segi cited most of their papers in the literature as well as foreign papers. He then went on to

intensify his study of cancer epidemiology, periodically compiling and publishing cancer mortality statistics for 23 countries, standardized by the world population in 1950, and published for 12 years biannually.

Acknowledgements

The author thanks Dr Malcolm Moore, APJCP Chief Editor, and Dr Kazuo Tajima, APOCP Chairman, for their helpful advice and English revision. He is also grateful to Ms Keiko Mizutani for her technical assistance.

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