MEETING REPORT

Public Symposium on “Forefront of Cancer Epidemiology and Prevention” by Study Area of Cancer Epidemiology (SACE) in the Special Priority Area (C) Sponsored by the Japanese Ministry of Education, Science, Culture, Sports and Technology

Kazuo Tajima, Chairman of the SACE

Introduction

This symposium was the first projected for general population to provide comprehensive information on research subjects in the Study Area of Cancer Epidemiology (SACE) newly established in the Special Priority Area (C) sponsored by the Japanese Ministry of Education, Science, Culture, Sports and Technology. This (SACE) consists of five research branches functionally divided into: 1) Ethnoepidemiology; 2) Cohort studies; 3) Case-control studies; 4) Molecular epidemiology; and 5) Clinical epidemiology.

In this symposium eight scientists selected on the basis of these five different research branches presented work in four sections: 1) Ethnoepidemiologic topics regarding the cancer pattern in the world and Japan; 2) Cancer risk factors in general lifestyles analyzed by case-control and cohort studies in Japan; 3) Viruses and cancer with special reference to the original relationship between human evolution and virus infection; 4) New strategies of prevention and treatment taking into account individual characteristics.

The final goal of epidemiological research is to establish a prevention strategy after clarifying risk and protective factors for human cancer by long-term observation of large populations. In general, the pattern of human cancers varies with change in actual exposure to specific carcinogenic agents, e.g., quality and quantity of environmental factors, over time and space. On the other hand, the biological risk of cancer related to a specific agent varies with genetic background among different ethnic groups in the world, and even among individuals in the same ethnic group.

We human beings have established our own cultures adapting to the given environment in each area in the world. Unfortunately, in some cases, this has had a negative outcome in generating culture-specific diseases. Now we need innovative, comprehensive and multidisciplinary ideas to build up new prevention strategies to fight against cancer. In this symposium we presented general information on cancer epidemiology as clearly and succinctly as possible to promote discussion with audience about goals in the 21st century.

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Cancer in the World and Japan

Global Cancer Pattern and Its Characteristic Distribution
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On a grand scale, the earth is divided into the Asian Pacific and Atlantic areas or generally into the developed and developing regions in terms of socioeconomic conditions, as well as geographic and cultural parameters. The cancer pattern in the world varies in accordance with the background environment. For example, upper G-I tract cancer (pharyngeal, esophageal and stomach cancers) is relatively common in Asian Pacific countries, like Japan, China and Korea. In contrast, lower G-I tract cancers (colo-rectal) are more frequent in the Atlantic countries, including the USA and the UK. Furthermore, the incidences of different cancers have been drastically changing over time in each area in the world in accordance with modification of diet because of outside influence. The recent progressive globalization is homogenizing lifestyles in different ethnic groups across the world. On the other hand, there are still some opposing dynamics, functioning to maintain specific cultures and ethnic independence.

As a model international collaborative study in the Asian...
Pacific area, we have just started the “three countries (Japan, China and Korea) collaborative study on risk and protective factors for G-I tract cancer” this year. Before commencing this large, systematic collaborative effort, we conducted a “comparative epidemiological study on esophageal and stomach cancer in high and low incidence areas in Jiangsu, China” during the last five years. From the ecological evidence, in general, people in the low incidence area intake more fruit and green-yellow vegetables, especially allium vegetables, than people in the high incidence area. A case-referent study on esophageal and stomach cancer in the high incidence area showed that higher consumption of fruit and green-yellow vegetables lowers the risk of both sites of cancer in males and females. However, clear evidence was not obtained from the corresponding case-referent study in the low incidence area, because most people, including patients with cancer, all take a lot of fruit and green-yellow vegetables everyday and the difference in the lifestyles between cancer cases and referents were diluted by a common lifestyle. We thus learned the importance of evidence obtained from both ecological and analytical epidemiological studies if we want to clarify risk and protective factors for human cancer only by observation.

To approach interactive phenomena between genetic and environmental characteristics for human cancer risk, we tried cross analysis of a special repair enzyme (hOGG1) polymorphism and intake of pickles in China. Individuals with the polymorphic type of hOGG1 (Cys/Cys homozygotes) showed a 6 times higher odds ratio for stomach cancer. Recently many studies using molecular epidemiologic methods have been conducted, and it is now clear that very many genes can interact in both positive and negative ways. Since establishment of prevention is a final goal for epidemiologists, we have to clarify the environmental risk factors by more sensitive methods such as molecular epidemiology. Now we have concentrating on both genetic and environmental factors and their interactions more precisely in the future.

Is the Cause of Cancer Genetic or Environmental? – Study of Japanese Immigrants and their Descendants Shoichiro TSUGANE

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Stomach cancer is the most frequent cancer in Japan and its age-adjusted incidence rate is still one of the highest in the world, while those of breast and prostate cancers are extremely low as compared to those in Western countries. That of colorectal cancer used to be relatively low, but it has now reached the level seen in some Western countries. Are these differences in cancer occurrence attributable to genetic or environmental factors such as lifestyle and geography? The study of Japanese immigrants and their descendants residing in the United States (1 million) and Brazil (1.3 million) can provide clues to answer these questions, because they have the same genetic background as Japanese in Japan but are exposed to different environments.

We conducted several epidemiological studies in São Paulo, Brazil since 1986 with support of grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology, and determined cancer patterns (mortality and incidence) and lifestyle (dietary habit and health status) among Japanese Brazilians. When the age-adjusted rates of cancer incidence among Japan-born immigrants were compared with those among Japanese in Japan, cancer of the stomach was significantly lower, while breast and prostate were higher. No significant increase of colorectal cancer was recognized. The magnitude of shift in cancer patterns was not so remarkable compared with those reported among Japanese in the United States. A cross-sectional study of randomly selected Japanese residents in the city of São Paulo showed some lifestyle modifications when the results were compared with Japanese in Japan or in the United States. Their dietary habits were more like the pattern seen in Western countries with higher intake of beef and cheese and lower intake of pickled vegetables, miso soup and soy products, though they still consumed these traditional Japanese foods to some extent. These data provided strong evidence that the probability of suffering cancer is modifiable by change of dietary habit and the magnitude reflects the extent of adoption of the new lifestyle among immigrants into Brazil or the United States.

On-going case-control studies of stomach and breast cancer targeting Japanese and non-Japanese Brazilians are now concentrating on both genetic and environmental factors, to elucidate the roles of gene and environmental factors and their interactions more precisely in the future.

Japanese Life-style and Cancer

Case-control Study: Comparison between Cancer Patients and Healthy Individuals

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Case-control and cohort studies are the principal methods for investigating the role of lifestyle factors in human carcinogenesis. In the case-control study, lifestyle factors in the past are compared between cancer patients and controls, usually healthy individuals, and relative risk is estimated. In the cohort study, cancer incidence rates are directly compared among the groups having different levels of a certain lifestyle factor. The case-control study is most valuable especially for etiological research on cancers with
relatively low incidence and combinations of multiple factors, and thus has been most frequently employed. This review illustrates how case-control studies have contributed to understanding the role of lifestyle factors in the occurrence of gastric and colorectal cancers.

A possible anti-carcinogenic effect of green tea has recently attracted much attention, especially as regards gastric cancer. Epidemiologic evidence is largely derived from case-control rather than cohort studies. At least three case-control studies each in Japan and China have consistently shown a protective association between green tea drinking and gastric cancer. In these studies, a decreased risk was generally observed in those with a high consumption of green tea, i.e., 7-10 cups per day. Only one cohort study addressed the relation between green tea and gastric cancer in Japanese living in Hawaii, but this failed to show a protective association probably because individuals with a high consumption of green tea were very few.

The mass media often quote remarkable results from a single study reported in a scientific meeting with no consideration of other findings. It is most important to bear in mind the totality of epidemiologic findings for the prevention of cancer. In 1997, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) jointly published a report regarding diet and cancer on the basis of a comprehensive review of epidemiologic studies throughout the world. The WCRF/AICR report concluded that vegetable and fruit consumption is definitely protective against gastric cancer and that high intake of salted foods probably increases the risk. The above-mentioned decreased risk of gastric cancer associated with green tea was regarded as possible. As regards colorectal cancer, it is considered that vegetable consumption is definitely protective and that red meat probably increases the risk. It was also concluded that physical activity definitely confers a decreased risk of colon, but not rectal cancer. While high-fat and low-fiber diet has generally been linked with an increased risk of colorectal cancer, epidemiologic findings are not sufficiently consistent to draw unequivocal conclusions. These are based on a large number of case-control studies and a limited number of cohort studies, although the latter have increased in number recently. Japanese studies are very few, especially with respect to colorectal cancer, and none has addressed the relation of fat or fiber to colorectal cancer.

Case-control studies of colorectal adenomas, which are well-established precursor lesions for colorectal cancer, have generally supported the conclusions drawn regarding colorectal cancer. However, a unique finding has emerged from studies of colorectal adenomas, and it is not widely known even among cancer researchers. As illustrated in the Self Defense Forces study in Japan, cigarette smoking is consistently related to increased risk of colorectal adenomas. Although more evidence needs to be accumulated, cigarette smoking is beginning to be considered a risk factor for colorectal cancer.

Findings from a Large-scale Cohort Study (JACC study): Longitudinal Follow-up of the General Population
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The Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC study) was initiated in 1998-1999, involving 34 investigators (epidemiologists and epidemiology-oriented clinicians) and one statistician in 24 institutions (universities and hospitals), by establishing a basic cohort population of approximately 127,500 healthy inhabitants in 45 areas throughout Japan, for which 46,465 men and 64,327 women, aged 40-79 years, were to be followed up for a minimum of 10 years. At the entry of the cohort population, each person was asked to fill, with written informed consent, a self-administered questionnaire which requested such epidemiological information as demographic and health conditions, life-style habits, dietary practices, physical exercise, and behavioral attitude/stress. In addition, about 40,000 cohort members donated blood specimens, and their sera were stored at around –80 °C in several deep freezers. With these sera, we have recently started to measure, at one reliable laboratory, superoxide-dismutase (SOD) activity, insulin-like growth factor-I (IGF-I), insulin-like growth factor-II (IGF-II), insulin-like growth factor-binding protein 3 (IGF-BP3), soluble Fas (sFas), and transforming growth factor-α1 (TGF-α1) among all the deceased and incident cancer sufferers as well as three times their number of healthy controls (about 15,000 samples in total).

At the moment, follow-up data are available as of the end of 1997 (mean follow-up period: 8.1 years) with a review of all deaths and move-outs among those aged 40-79 years old at entry. As of the end of 1997, we could identify 5,472 and 3,653 total deaths among men and women, including 2,145 and 1,313 cancer deaths, respectively. So far, we could examine the associations of basic life-style habits with total deaths, all cancer deaths and deaths from such sites of cancer as the lung, stomach, pancreas, gallbladder and bile duct. Associations with each life-style habit were analyzed by Cox proportional hazard regression model, regarding those who moved out as censored cases and adjusting for age alone.

Major findings obtained from these particular analyses are as follows:

1) Current smoking habit at entry significantly increased the risk of dying from all causes (by 1.6 times in men and 1.3 times in women), all cancers (by 2.0 times in men and 1.6 times in women), and lung cancer (by 4.5 times in men and 2.5 times in women) as well.

2) Current alcohol drinking habit at entry significantly decreased the risk of dying from all causes (by 0.9 times in men and 0.8 times in women) as well as all cancers (by 0.8 times in women), but increased the risk of dying from gallbladder cancer (by 3.0 times in men).

3) Current physical exercise habit at entry significantly decreased the risk of dying from all causes (by 0.7, 0.7 and 0.9 times for the exercise of 5 hours or more, 3-4 hours and 1-2 hours per week, respectively, in both men and women).

4) Almost every-day intake of green-yellow vegetables at entry significantly decreased the risk of dying from all causes (by 0.9 times in men) and lung cancer (by 0.7 times in men).

5) Intake of oranges (once or more per week) at entry significantly decreased the risk of dying from all causes (by 0.8 times in both men and women) and all cancers (by 0.9 times in men) as well as lung cancer (by 0.6 times with intake 3 times or more per week in men).

6) Current coffee drinking habit at entry significantly decreased the risk of dying from all causes and all cancers (both by 0.8 times in men as well as women). Almost every-day coffee drinking at entry significantly decreased the risk of dying from lung cancer (by 0.8 times in men) and gallbladder cancer (by 0.5 times in men).

7) Stressful daily life at entry significantly increased the risk of dying from all causes (by 1.3 times in men and 1.2 times in women).

Such sites of cancer as the liver, colon and rectum will be examined in relation to life-style habits and biological markers from the fiscal year 2002. For the sites of cancer such as the lung, stomach, pancreas, gallbladder and bile duct, nested case-control studies will be conducted using both epidemiological information and site-specific biological markers in the next fiscal year of 2001. Detailed analysis for total and all cancer deaths will be finished within the fiscal year of 2000.

Virus Infection and Cancer

Genetic Interactions between Oncogenic Viruses and Human Host Genes

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Human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell leukemia virus type I (HTLV-I) and Epstein-Barr virus (EBV) are causatively associated with cervical cancers, laryngeal papillomatosis, hepatocarcinomas, adult T-cell leukemia, nasopharyngeal carcinomas, malignant lymphomas and a kind of gastric carcinoma. The viruses infect human hosts and persist within the target organs life-long to cause organ-specific malignancies. Malignant transformation of the target cells is a reflection of a multi-step interaction between host and viral genes (or products). The outcome of the virus-host interaction varies with genetic polymorphism of host factors to recognize viral antigen epitopes, that is determined by individual human leukocyte antigen (HLA) alleles. Each virus encodes a particular protein called an oncoprotein, acting to trans-activate host genes and enhance cell cycle and malignant transformation.

Human T-cell leukemia virus type I (HTLV-I) and human papillomavirus (HPV) encode the virus-specific oncoproteins, Tax and E6/E7, respectively. HTLV-I Tax protein induces outgrowth of CD4+ T-cells to cause adult T-cell leukemia (ATL) while HPV E6/E7 proteins induce dysplasia of cervical mucous membrane leading to malignant transformation and cervical carcinoma. Both HTLV-I Tax and HPV E6/E7 oncoproteins are expressed on the target cells which are recognized by the individual HLA molecules. Genetic polymorphism of the individual HLA molecules determines efficiency of the antigen peptide recognition. In fact, HLA-A*26, B*4002 and B*4006 molecules have no binding motifs to recognize HTLV-I Tax peptides. The HLA-DRB1*0901 molecule is also incapable of recognizing HPV E6/E7 peptides. It is thus conceivable that individuals born with HLA-A*26, B*4002 and B*4006 are at high risk of ATL and those born with HLA-B1*0901 are at risk for HPV-associated cervical carcinoma.

Most oncogenic viruses are transmitted via breast milk and sexual intercourse as well as intimate contact between mother and infants, husband and wife, so that these viruses are kept within particular genetic groups whose HLA alleles are often incompatible with recognition of the viral antigen epitopes as mentioned above. Such low immune responders are naturally selected by genetic interaction between virus and human host. This new paradigm of viral oncogenesis in human hosts was first established by ethnoepidemiological studies on HTLV-I infections and diseases.

Prevention of Virus – Related Hepatocellular Carcinoma

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In Japan, approximately 30,000 patients die of hepatocellular carcinoma every year. In 1988, HCV (Hepatitis C Virus) was discovered, and immediately blood from patients with hepatocellular carcinoma was tested. It turned out that 11% and 83% of the patients with cancer were positive for HBV (Hepatitis B Virus) and HCV, respectively. This indicates that 94% of our patients with hepatocellular carcinoma are currently infected with either of the two hepatitis viruses. In contrast, only 3% (1.5% for HBV and 1.5% for HCV) of the general population are infected with the viruses. Our follow-up study indicates that there is a difference between B-viral and C-viral disease with regard to development into hepatocellular carcinoma, i.e., C-viral hepatocellular carcinomas often develop with a background of advanced fibrosis and/or cirrhosis, whereas B-viral HCCs
may sometimes occur without such a regenerative stimulus.

To reveal the stepwise progression toward hepatocellular carcinoma with chronic hepatitis C virus infection, we took liver biopsies from patients with chronic hepatitis and classified the liver fibrosis according to a scoring system; namely, F1-mild fibrosis, F2-moderate fibrosis, F3-advanced fibrosis and F4-cirrhosis. The risk of developing hepatocellular carcinoma was calculated by our follow-up study as follows; in cases of F1, the chance of getting hepatocellular carcinoma is approximately 0.5% per year, with F2 1.5%, F3 3.0%, and F4 7.0%. In addition, there is a simple biochemical parameter to assess fibrosis scores without taking a liver biopsy, that is, the platelet count. A value of approximately 170,000 per ml correlates with F1, 150,000 with F2, 130,000 with F3 and below 100,000 with F4. Thus, with this parameter, we can define a super high risk group in the Japanese population with HCV infection. If the platelet count is below 130,000 a prevention strategy might thus be implemented such as interferon treatment. In the last 8 years, interferon treatment was given to approximately 2,000,000 patients with chronic hepatitis C. We have studied the incidence of hepatocellular carcinoma among approximately 3,000 patients; 2,400 treated with interferon, and 600 untreated. After follow-up for an average of 5 years, the incidence of cancer in the group with interferon treatment was reduced by half, as compared to the untreated group. Of the treated individuals, 1/3rd showed a complete response (eradication of the virus). Among these cases, the risk of the development of cancer was reduced to 1/5th. In addition, we studied the histological fibrosis score before and after the treatment by taking paired biopsies. It turned out that the natural progression in the group without treatment (fibrosis progression per year) was +0.1, indicating it may take 10 years to one step up, for example from F1 to F2. In contrast, if a complete response was obtained, the fibrosis score reduced by –0.28 per year, suggesting that interferon treatment may induce resolution of fibrosis by eradicating virus even in the patients with cirrhosis.

The same strategy can be applied for patients who already have a hepatocellular carcinoma. There are several treatment options, including surgery and percutaneous tumor ablation (percutaneous ethanol injection therapy, microwave ablation, and radio frequency ablation). Even though cancer nodules can successfully treated by these procedures, because of the fibrotic and cirrhotic background, the cancer recurrence rate sometimes reaches 20% per year. After treatment of cancer nodules, we treated those patients with interferon and found that 5-year survival for the patients with virus eradication by interferon reached 83% which is extremely high for patients with cancer. The overall 5-year survival for the patients of hepatocellular carcinoma in our country is in the range of 40-60%. Liver transplantation was recently introduced, and the 5-year survival rate for HCV liver disease is reported to be 60% to 80% with this approach. Treatment for both cancer nodules and background fibrosis may even be compatible with liver transplantation.

Since HCV related liver diseases show gradual step-by-step progression toward cancer, we can define a super high risk group by simple platelet counting which might make it possible to conduct very effective screening and eventually improve the survival of the patients who are suffering from virally induced ailments.

New Strategies for Cancer Prevention and Treatment

Immunological Host Defenses against Cancer: Implications for Lifestyle Intervention for Cancer Prevention
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One of the most critical questions in the immunosurveillance hypothesis is whether inter-individual differences in natural immunological host defenses can predict future development of cancer. Although this question has so far remained open, there are clear indications, from laboratory studies, of significant roles played by the natural cytotoxicity of several lymphocytes in preventing the development of cancer. We therefore began a prospective cohort study among a Japanese general population in 1986, using various immunological and biochemical markers. Natural cytotoxic activity, i.e., natural killer (NK) activity of peripheral blood mononuclear cells, was assessed by isotope-release assay in a total of 3625 residents mostly aged over 40 years living in a Japanese town, 1986-1990. Other immunological and biochemical markers were also measured, and participants were given a questionnaire on lifestyle. We carried out a follow-up survey of the cohort members looking at cancer incidence and death from all causes, and analyzed the association between levels of NK activity of peripheral blood lymphocytes assessed at baseline and cancer incidence found in the subsequent eleven-year follow-up survey (a total of 154 cases used in the analysis). For the survival analysis, we omitted those cancer cases that had arisen within two years after the measurement of NK activity, in order to avoid any possible influence of preclinical cancer on the measurement.

Categorizing the NK activity of peripheral blood lymphocytes by tertiles, age-adjusted relative risk of cancer incidence (all sites) is 0.62 (95%CI, 0.38-1.03) and 0.72 (0.45-1.16) for men with medium and high NK activity, respectively, taking the risk of those with low NK activity as reference; 0.56 (0.31-1.01) and 0.52 (0.28-0.95) for women with medium and high NK activity, respectively; 0.59(0.40-0.87) and 0.63(0.43-0.92) for both sexes with medium and high NK activity, respectively. Although NK activity of peripheral blood lymphocytes was found to be associated with selected lifestyle factors, the results remained almost unchanged even after adjusting for the different factors in question.

Our results from the cohort study thus indicate that medium and high NK activity of peripheral blood lymphocytes is associated with reduced cancer risk, while low NK activity is associated with increased cancer risk, demonstrating the significance of natural immunological host defense mechanisms against cancer. Lifestyle factors associated with high NK activity were found in a cross-sectional analysis of cohort members: 1) not smoking, 2) moderate alcohol consumption, 3) regular life (meal time and sleeping hours), 4) moderate physical activity, 5) adequate body weight, 6) daily consumption of leaf vegetables, 7) frequent intake of milk, dairy products, and soy products, 8) resolution of mental stress. We showed an example of NK activity-oriented lifestyle-intervention trial in women who experienced breast cancer, indicating that NK activity was in fact enhanced by improvement of these lifestyle factors.

New Tailor-made Therapy Based on Molecular Medicine

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Chemotherapy, surgery and radiation are three major therapeutic modalities for a variety of cancers. Besides these three choices, gene therapy and new immunotherapy will be used more effectively in the 21st century. Drawbacks for gene therapy would be the inefficient targeting and severe adverse effects. These should be solved when new vectors, including "modified" adenoviral vectors, are available.

New immunotherapy includes cell therapy in conjunction with cytotoxic T cells (CTL) against cancer "specific" peptides on the HLA class I molecule. Dendritic cells could be used more frequently to present appropriate antigens to CTL. Cancer vaccines may be used to enhance CTL responses in vivo.

It is extremely important to ascertain the behavior of cancer cells such as the capability for invasion and metastasis, since this information may affect the prognosis of the affected patients. For example, matrilysin, a family member of matrix metalloproteases (MMP), is produced by colonic cancer cells and affects (lyses) the extracellular matrix of the submucosal layer of the colonic epithelium. We have recently found that the expression of this molecule in cells of the invasive fronts of colonic tumor islands is associated with a poor prognosis, presumably because such tumor cells have been demonstrated to be more aggressive than their matrilysin-negative counterparts.

More recently, however, systematic gene profiles have made amenable to investigation by the introduction of cDNA array technology. As a matter of fact, the human genome project has revealed almost all the entire genomic profile of human cells. Using this revolution in information gathering, the cDNA array becomes one of the strongest weapons to explore the "secret" of cancer cells. Among more than thirty thousand genes, we can now pick up and select several genes responsible for tumor invasion and metastasis, and hopefully design interventions to improve the prognosis of the patients.

Single nucleotide polymorphisms (SNPs) are individual markers of genes related to some of the adverse effects of drugs. The existence of an SNP may also affect the individual susceptibility to disease. Therefore, the study of genetic profiles using cDNA array method and SNP techniques may give us an important clues to understanding the characteristics of cancers and to appropriately treat them.