Proceedings of Asian Cancer Conference in Shizuoka, 2000

Main Theme
Characteristic Cancers in Asian Countries

October 8th (Sunday), 2000
Shizuoka Convention & Arts Center, GRANSHIP

Organizer : Shizuoka Prefectural Government

Scenes from the Forum

PROGRAM

Asian Cancer Conference in Shizuoka, 2000

Main Theme :"Characteristic Cancers in Asian Countries"

〈 Youlin Qiao／China 〉

〈 Mony Eng Khuon／Cambodia 〉

October 8th (Sunday), 2000
"Granship", Shizuoka City

〈 Sukardja Gede I Dewa／Indonesia 〉

〈 keun-Young Yoo／Korea 〉

PROGRAM

Asian Cancer Conference in Shizuoka, 2000

October 8th(Sunday), 2000
"Granship", Shizuoka City

Main Theme
"Characteristic Cancers in Asian Countries"

Chairperson ; Ken Yamaguchi
Deputy Director, National Cancer Center Research Institute; and Staff Physician, The Department of Internal Medicine, National Cancer Center Hospital, Japan

Co-chairperson ; Suketami Tominaga
Director, Aichi Cancer Center Research Institute, Japan

Kazuki Ito
Chief, Department of Hepato-Gastroenterology and Interventional Radiology, Shizuoka General Hospital, Japan

9 : 30～9 : 40 **Opening Remarks**
Hideyuki Harada
(Director General of Department of Health and Welfare of Shizuoka Prefectural Government)
Ken Yamaguchi
(Chairman of Steering Committee of Shizuoka Cancer Conference 2000)

9 : 40～10 : 10 Speaker 1
Mony Eng Khuon (Cambodia)
: Bureau Chief, Dept of Preventive Medicine, Ministry of Health, Cambodia
Title : How to Improve Cancer Situation In Cambodia

10 : 10～10 : 40 Speaker 2
Keun-Young Yoo (Republic of Korea)
: Professor Dept of Preventive Medicine, Seoul National University College of Medicine, Korea
Title : Epidemiologica Characteristics of Breast Cancer in Korea : Hormonal Risk Factors and Genetic Susceptibility

10 : 40～11 : 00 **Break**

11 : 00～11 : 30 Speaker 3
Sukardja Gede I Dewa (Republic of Indonesia)
: Professor Dept of Surgery, School of Medicine, University of Airlangga, Indonesia / Dr. Soetomo Hospital
Title : Gastric Cancer in Indonesia

11：30～12：00 **Speaker 4**

Santoso Cornain (Republic of Indonesia)

: Professor Dept of Anatomic Pathology, Faculty of Medicine, University of Indonesia, Jakarta and Institute for Genetic Medicine, Hokkaido University, Sapporo

Title : Pathological Studies of Low Incident Gastric Cancer in Indonesian Population : Interest for Molecular Epidemiological Analysis in Multicenter Study

12：00～13：00 **Lunch break**

13：00～13：30 **Speaker 5**

Youlin Qiao (China)

: Professor and Chief, Dept. of Cancer Epidemiology, Cancer Institute/Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China

Title : Mortality Rate and Trends for Cervical Cancer in China, 1970's vs.1990's

13：30～14：00 **Speaker 6**

Kazuo Tajima (Japan)

: Chief, Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Japan

Title : Adult T-cell Leukemia/Lymphoma in Japan : Epidemic Pattern and Prevention Strategy

14：00～14：20 **Break**

14：20～14：50 **Speaker 7**

Rubjir Sanduijav (Mongolia)

: Consultant Surgen, National Cancer Center, Ulaanbaator, Mongolia

Title : The Present Rate of Incidence and Mortality of Cancer Diseases in Mongolia

14：50～15：20 **Speaker 8**

Chawalit Pairojkul (Thailand)

: Associate Professor, Consultant in Pathology, Faculty of Medicine, Khon Kaen University, Thailand

Title : Liver Fluke-Associated Cholangiocarcinoma in Thailand

15：20～16：50 **General Discussion**

16：50～16：55 **Closing Remarks**

Suketami Tominaga

(Director of Aichi Cancer Center Research Institute)

CONTENTS

PREFACE

Deaths caused by such infectious diseases as pneumonia, tuberculosis, and gastroenteritis were common among Japanese people until the middle of the 20th century. Since the end of the World War II, however, the incidence of such diseases has declined rapidly, resulting in one of the highest average life expectancies in the world. This phenomenon is probably attributable to the traditional lifestyle of the Japanese and their interest and knowledge in maintaining their own health. At the same time, the success of health of its population has forced Japan to confront a new issue: the aging of the population. Demographic surveys in 1995 indicated that senior citizens aged 65 years and older accounted for 14.5% of the population, people aged 75 years and older for 5.7%, and those aged 85 years and older for 1.3%. The same estimates also projected that in 2025 the percentage of people aged 65 and older, 75 years and older, and 85 years and older would be 27.4%, 15.5%, and 4.8%, respectively. As this trend accelerates, there will be a rapid increase in the number of people developing such adult or geriatric diseases as cancer, heart disease, and cerebrovascular disease.

This is particularly true of cancer, which since 1981 has been the leading cause of death in Japan. The incidence of cancer of all types in 1994 was estimated to be 440,000, and in 1997, the number of cancer-related deaths was 275,413. It is estimated that cancer is a contributory factor in a third of all deaths nationwide. Projections for 2015 indicate that 740,000 people will develop cancer and 450,000 will die as a result. We believe it is no exaggeration to say that Japan has entered the "Cancer Era," and this trend seems to be spreading throughout many Asian countries.

Under the auspices of Shizuoka Prefecture, the Shizuoka Forum on Health and Longevity has been held every year since 1995 with the aim of accumulating advanced scientific knowledge useful for promoting healthy longevity and diffusing such knowledge among the general public. Since 1998, when a satellite conference focused on cancer, the Asian Cancer Conference in Shizuoka was inaugurated with the main theme of mutual information exchange on cancer control in Asian countries. In the first conference in 1998 entitled, "Cancer in Asia: Present and Future," we learned about the present status of cancer control in 13 Asian countries—Australia, China, India, Indonesia, Japan, Korea, Malaysia, New Zealand, Philippines, Singapore, Taiwan, Thailand, and Vietnam.
At midnight the day before the conference, I wondered about the population of those 13 countries. I phoned my son and asked him to send me a table of worldwide population statistics from one of his junior high school textbooks. I found that aggregate population of these 13 countries was three billion people, or half of world's population. At that time, I realized that this conference plays a very important role in controlling cancer not only in Asia but also around the world. In the second conference in 1999, entitled, "Present Status and Issues Confronting Oncological Nursing in Asia," we learned the status of nursing for cancer patients in seven Asian countries-China, Japan, Malaysia, Nepal, Singapore, Sri Lanka, and Thailand.

The Third Asian Cancer Conference in Shizuoka 2000 was held on October 8, 2000, under the main theme of

"Characteristic Cancers in Asian Countries." The conference was planned by steering committee members, including Dr. Suketami Tominaga (Aichi Cancer Center, Nagoya), Dr. Kazuki Ito (Shizuoka General Hospital, Shizuoka) and myself, with the aim of promoting information exchange on efforts to control endemic cancers and to improve the system for combating cancer in Asian countries.

Researchers were invited from seven countries—Cambodia, China, Korea, Indonesia, Japan, Mongolia and Thailand. The presentations were divided into four topics. The Cambodian and Korean participants discussed cancer control systems and future plans in their countries. Two participants from Indonesia described the low incidence of stomach cancer there. A researcher from China discussed esophageal cancer and typical chemopreventive studies in Linxian. Additionally, in the section on infection and cancer, the topics discussed included adult T-cell leukemia in Japan, liver fluke-associated hepatocellular carcinoma in Thailand, and hepatitis virus-associated hepatocellular carcinoma in Mongolia. All presentations and subsequent discussions offered detailed and distinctive information to all participants on the present status of cancer control in each country.

In this conference as well as previous ones, we learned about unique and effective measures in various fields of cancer control, which I think has proved to be very informative for conference attendees. Through these conferences, I believe we have succeeded to compiling "the collective Asian wisdom on cancer control."

Ken Yamaguchi, M.D., Ph.D.
Chairperson, Steering Committee of Asian Cancer Conference in Shizuoka, 2000
Deputy Director, National Cancer Center Research Institute, Japan

How to Improve Cancer Situation in Cambodia

Mony Eng Khuon
Preventive medicine department technical

Born in: 1954
Past Records: 1986 Medical Doctor
1996 Master Degree of Primary Health Care Management
1996 Diploma in Health Emergency Prepareness & Crisis Manager

Certificate in CBR
Certificate in CB Cancer Prevention

Background

In Cambodia , there is a wide variety of non communicable diseases such as diabetis, cardio-vascular diseases, cancer that are actually one of the preoccupation of the health workers and health services. Since 1979 till 1997 there was not yet policy or guideline concerning on cancer prevention and control . There is no available guideline for cancer treatment and diagnosis . Concerning knowledge and skill for cancer prevention and treatment there is very few available at national hospitals , some provincial hospitals and not available at all at district referral hospital. Surgery treatment , palliative care and pain relief have been provide to cancer patients by individual hospital protocol.

Regarding the registry of cancer, the health information system still not include non communicable into the system . Diseases seen as priority for the health information system are mostly communicable diseases
(Malaria, Tuberculosis, Dengue heomorragic fever, Diarrhea , ARI, sexual transmitted diseases and HIV/AIDs).

In March 1997 , based on the hospital and anapathology laboratory based some common cancer data was gathered by the Department of Preventive Medicine. With the technical and financial support from World Health Organization , Dr. Adriano Laudico, the short term consultant of WHO in collaboration with the Preventive Medicine Department conducted one workshop to discuss on the problems of cancer prevention and control in Cambodia. The two days workshop and the finding of Dr. Laudico came up with the recommendation to Ministry of Health to develop national policy on Cancer Prevention and Control and establish the National Program on Cancer Prevention and Control who will be responsible for define strategies to identify , prevent , management of therapy and diagnosis and control common cancer in Cambodia.

After that two days workshop the department of Preventive Medicine has develop the national policy on cancer prevention and control and as well the establishment of the national program on cancer prevention and control.

On the 26 to 27 November with the technical and financial support from World Health Organization , one workshop on WHO Method on Cancer Pain Relief was held at the Ministry of Health with the assistant of Dr. Fukimazu takeda , the WHO short term consultant.

The Policy on Cancer control and Prevention were developed and approved in 1999. The NCPCP is

initiating by formating a task force that members composed of representative from national hospitals, MCH, Preventive Medicine and the Director General for Health is the president of the task force. To raise awareness of the people and health staff on cancer prevention the manual on cancer prevention and control common cancer is on the process of translating into khmer version. Health education campaign will be done and health center staff will be train on the primary prevention .

The community based cancer prevention will be implemented in collaboration of national program on cancer prevention and control with MCH and Health Promotion Center .

According to the 1998 census the population of Cambodia with both sex are 11,426,223 which female range 0f 5,917,019 (51.80%) and male 5,509,204(48.20 %). The sex ratio-male for 100 female(93.1)

The distribution of population by age group:

0-4 y	13.40%
5-14	30.50%
15-64	52-60%
>64	3.50%

Percentage of females aged 15-49 years 9 to a total population) : 24.77%

Single (female aged over 15) :26.00 %

Married (female aged over 15) :56.60%

Population growth rate :24%

Crude deathj rate(per 1000) : 12%

Crude birth rate (1000) : 38%

Total fertility rate 5.2%

Density (person per km2 : 64

Urban population : 15.70%

Rural population : 84.30%

Under five mortality rate in 1998 (per 1000 live births) : 115

Infant mortality rate in 1997 (per 1000 live birth) :89.90

Causes of death

Health problems	Cases	Death	CFR %
Malaria	26,529	836	3.15 %
Diarrhea	8701	103	1.18 %
Dysentery	2,266	7	0.31 %
ARI	20,351	454	2.23 %
DHF	1175	50	4.26 %
Meningitis	824	117	14.20 %
Measle	261	1	0.38 %
AFP	27	1	3.70 %
Neonatal Tetanus	94	43	45.74 %
Other tetanus	139	36	25.90 %
TB	30,793	335	1.09 %
Gyneco Obst	8,304	232	2.79 %
Mine Accidents	376	6	1.60 %
Road Accidents	10,206	45	0.44 %
Others	85,744	3,285	3.83 %
Total	195,790	5,551	2.84 %

Maternal Mortality rate in 1997 (per 100,000 live birth) : 473

Life expectancy at birth male : 50.34

Life expectancy at birth female : 58,62

Due to the Cambodian people just getting free of civil war and conflict, there many diseases that cause death in Cambodia. Based on the registration within the hospital show that cancer is the second cause of death in Cambodia.

As showed in the tables above , death caused by cancers is not yet registered in the health information system. Almost of cancer cases came to the hospital in a very late stage and often send back for home care or traditional healers.

Time Trend Of Cancer Cases

Based on the hospital based registration , it is showed that

In 1996 at MCH:

- Total admission for cancer cases : 37
  - Durty cervix : 05
  - Cervix cancer : 18
  - Chorio Carcinoma : 04
  - Breast cancer : 12
  - Ovary cancer : 03
  - Other cancer : 03
- In 1998 the registration noted :
  - Cervix cancer : 46
    - Stage 0 : 01
    - stage 1 : 10
    - Stage 2 : 10
    - stage 3 : 08
    - stage 4 : 17

    Only 18 cases were operated
  - Uterus cancer : 12with 7 cases operated
  - Chorio carcinoma : 12 , almost with metastasist
  - Ovary cancer : 10 with only 2 that can be operated
  - Vaginal cancer : 04
  - Breast cancer : 03

- At Calmette hospital, registration done from 1995 to 1997 showed :
  - Liver Tumor : 74 cases (26,72%)
  - Blood : 35 cases (12.41%)
  - Stomach : 34 cases (12.05%)
  - Lung cancer : 22 cases (7.80%)
  - LNH : 19 cases (6.78%)
  - Pancreas : 18 cases (6.42%)
  - Oeusophagus : 10 cases (3.57%)
  - Colon : 10 cases (3,57 %)
  - Brain : 06 cases (2.14%)
  - Abdominal tumors : 06 cases (2.14%)
  - ORL : 05 cases (1.78%)
  - Bladder cancer : 04 cases (1.42%)
  - Cervix cancer : 04 cases (1.42%)
  - Hodgkin : 04 cases (1.42 %)
  - Ovary cancer : 04 cases (1.42%)
  - Metastatic of nodes : 04 cases (1.42 %)
  - Born cancer : 03 cases (1.07 %)
  - Hepatic metastic : 03 cases (1.07 %)
  - Pleural cancer : 03 cases (1.07 %)
  - Skin cancer : 02 cases (0.71%)
  - Tongue cancer : 02 cases (0.71 %)
  - Mediastin cancer : 02 cases (0.70 %)
  - Rectum cancer : 02 cases (0.70%)
  - Myeloma : 02 cases (0.70%)
  - Thyroide cancer : 01 case (0.25 %)
  - Breast cancer : 01 case (0.25%)
  - Gold bladder cancer : 01 case (0.25 %)
  - Kidney cancer : 01 case (0.25%)
- At Preah Kossamak hospital :
  - 1997 1998
    - Oral cancer : 02 00
    - esophageal cancer: 01 02
    - Stomach cancer : 02 02
    - Liver cancer : 04 02
    - mesenteric cancer: 01 00
    - Cervix cancer : 01 01
    - others : 01 05

- In 1997 clinically suspected cancers specimens collected from 8 national hospitals in Phnom Penh

show 1084 per year which 224 were histologically confirmed as cancer.

- The incident of cancer is 11 cases/ 100,000 population
- The distribution by sex : male : 37%
  Female : 63%
- The distribution by age group :
  - 0-16 y : 13%, female is mostly affected
  - 17-60 y: 60%, female is mostly affected
  - > 60y : 27% , female remain the more affected

- Distribution by organe :
  - Genito-urinary : 17%, female were mostly affected
  - ENT : 13%, female were mostly affected
  - GI : 13% , both sex
  - Hematology : 13%, female were mostly affected
  - Breast ; 12%
  - Lung : 6% , male were most affected
  - Liver : 1%, male is most affected
  - Others : 14%, both sex
  - Carcinoma with unknown origin :11% and male are mostly affected.
- Cervix cancer is the leading cancer in Cambodia
- Distribution by residential areas : urban : 33%
  : country side : 67%

In 1999 statistically reported from national histology laboratory 252 cases were detected as cancer :

- Breast cancer : 64 cases (25.3%)
- Ovary cancer 20 cases (8%)
- Lung cancer 18 cases (7.1%)
- Oral cancer 18 cases (7.1%)
- Bone cancer : 18 cases (7.1%)
- Colon cancer 15 cases (6%)
- Thyroid cancer : 12 cases (4.8%)
- Cervix and Uterus : 8 cases /10 cases (3.8%)/ (4%)
- Bronchus cancer : 4 cases (1.5%)
- Other : 57 cases (22.6 %)

At Preah Bath Sihanouk Hospital in 1999 the most common cancer seen was breast cancer following by other cancer. The majority of those cancer were already in the advantage stage while present to the health facility. Out of the 77 cancer cases in 1999 24% underwent surgery treatment and 7% received chemotherapy. Palliative treatment were given to 37% of patient while 10% received no treatment. Among them 81% have give up the follow up.

The survival rate observed in this hospital is only 9% of 1 year survival.

All those patients treated by surgery in Cambodia and continue the radiotherapy in Viet Nam. Some of them went to hospitalised in Vietnam (see attached annex 1).

- The prevention and control program have being started since 1997 : National program again smoking .
  :National Cancer Prevention and Control Program which
  :Policy has been developed
  :Health education will start 2000 with the plan to conduct

Community Cancer Prevention.

- **Smoking Rate**

Base on the survey done by the national center for health promotion, we can know that among 300 respondents, 90% know that tobacco damage health. Among the male population 74.5 % are smokers and female is rate of 35%. Nearly 50% 0f male and 21.6% of female smok regularly. 20.41% of male and 10% of female smoke occasionally. A very small percentage of both gender have given up smoking. 30% of smokers smoke kmer hand roll cigarettes and 44% smoked manufactured cigarette. 32% smoke less than 10 cigarette per days and less than 1% smoke more than two packs/ day.

Smoking control program is under the National Health Promotion Center . The implementation is currently taken by health education.

- **Self Breast Examination**

The program just start in 1999 with the financial

support from WHO. Nurses at national hospitals and provincial hospitals in Siem Reap and Battambang were trained on self breast examination. a campaign was done at this two provinces by educate women in the community to practice on self breast examination. Develop leaflet for distributing to population.

- **Typical Dietary Habit**

Rice is staple food for Cambodian people. Most of the Cambodian dishes are made mostly by fresh vegetable and fish as well meat. Daily meals of rural population are rice and preserve fish usually made it steamed or burned and eat with vegetable and also farmer like pickle vegetable as side dishes with fish or meat . Fruits are also available in all seasons but Cambodian people also like desert and jam. It is notable that diet change such as nutrient content and method of food production and processing increase the risk factors of non communicable diseases .

Detailed Description Of The Work Of Preventive Department:

The main responsibility of the department is to facilitate monitor and evaluate the impact of public health in relation to the activities of NMCH , non-communicable disease a, oral health, medical rehabilitation , health care for the Elderly, and disaster management.

a/ Develop policies and plan of action for :

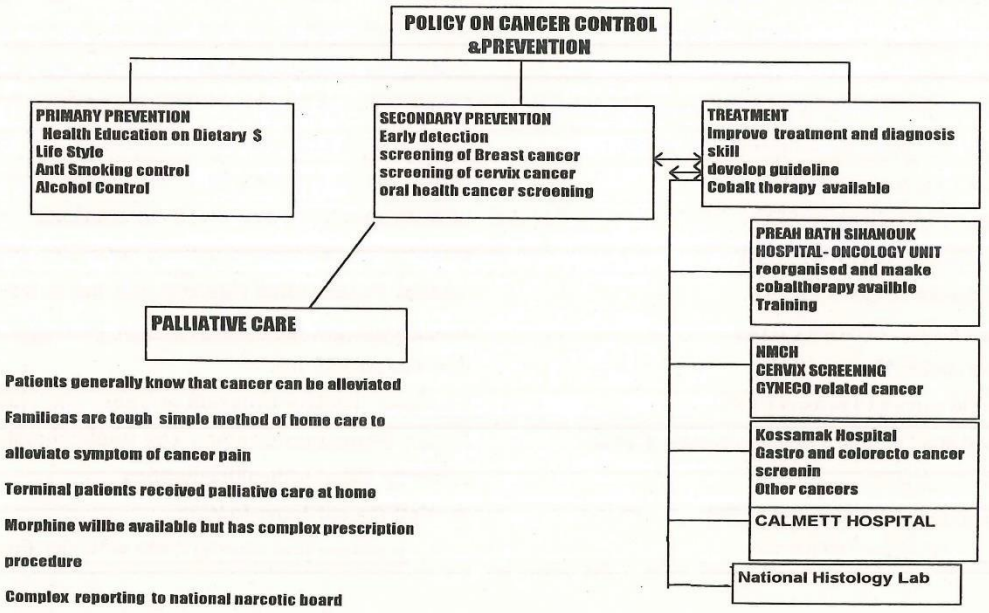
- Health Care for the Elderly and disable people
- Community Based rehabilitation
- Cancer prevention and control which included community based cancer prevention
- Health Emergency/disaster management
- Mass casualty management
- Disaster Medicine
- Community bases awareness on emergency/ disaster situation
- Oral health
- and quarantine services

b/ Coordinate with all concern institution to implement policies and plan of actions as well develop strategies to success those programs activities.

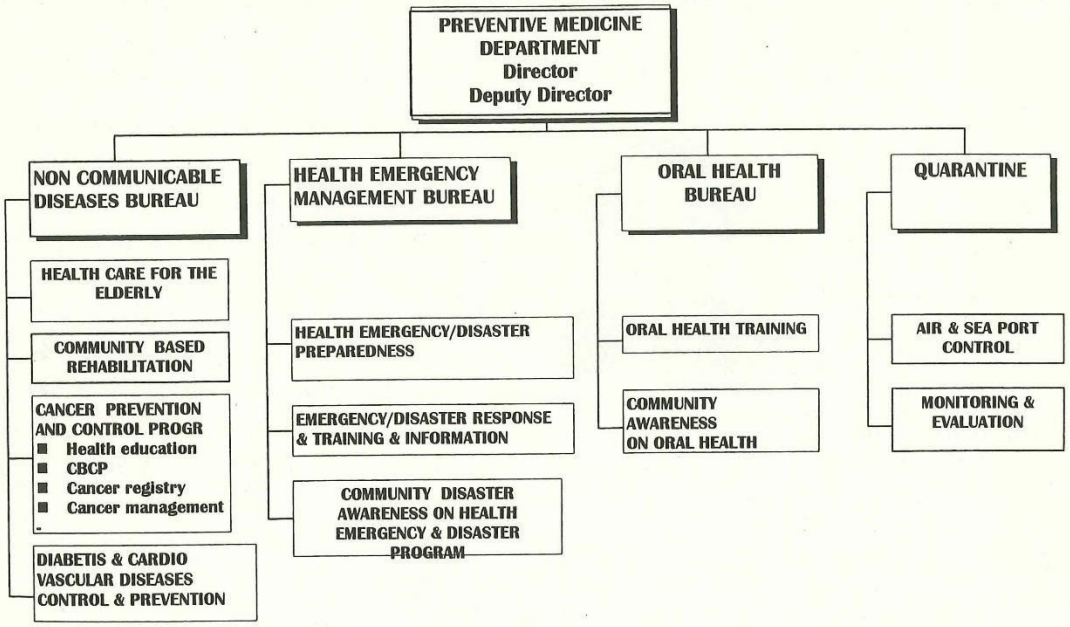
C/ Find fund to assist those institution to implement the programs and as well activities.

d/ Monitoring and Evaluation .Currently the national program of cancer control has being implemented their strategies to improve the cancer situation in Cambodia.

HOW TO IMPROVE CANCER SITUATION IN CAMBODIA ?



PREVENTIVE MEDICINE DEPARTMENT ORGANOGRAM



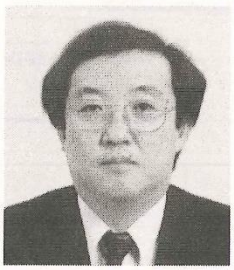
PREAH BAT MORODOM SIHANOUK HOSPITAL
DEPWRTMENT OF GENERAL SURGERY-ONCOLOGY

CANCER CASES RECRUITED IN 1999

N°	Name of Cancer	N° of Case	Surgery	Chemotherapy		Supportive Care	No Treatment	Follow-up		Adress		Age	Sex	
				Comp.	Incomp			Lose.F-up	1Y.DFS	PP	Pro.		M	F
1	Breast Cancer	12	8	1	0	3	1	10	2	7	5	41(20-66)	0	12
2	Ca .unknown origin	10	0	1	2	5	2	7	3 dead .8,7,6 m	4	6	55(28-74)	3	7
3	ENT Cancer	9	1	0	2	6	0	8	1	2	7	53(29-67)	7	2
4	Liver Cancer	7	0	0	0	6	1	6	1dead ,1 m	3	4	52(17-71)	6	1
5	NHL	6	1	0	4	1	1	6	unknown	4	2	35(22-54)	4	2
6	Colorectal Cancer	5	4	1	0	0	1	4	1	2	3	46(34-60)	3	2
7	Cervical Cancer	4	0	1	1	2	0	3	1	2	2	48(41-61)	0	4
8	Stomach Cancer	4	2	1	0	2	0	2	2 dead,1y ,3m	3	1	53(43-64)	2	2
9	Lung Cancer	3	0	0	3	0	0	3	0	1	2	63(60-66)	3	0
10	STS	3	3	0	2	0	0	3	0	1	2	29(5-63)	1	2
11	Leukemia	3	0	0	2	0	1	3	unknown	1	2	27(11-53)	3	0
12	Oesophagous Cancer	2	0	0	1	1	0	2	unknown	1	1	52(33-72)	1	1
13	Thyroid Cancer	2	0	0	0	1	1	2	unknown	0	2	61(51-71)	0	2
14	Penis Cancer	2	0	0	2	0	0	2	unknown	0	2	66	2	0
15	Testicular Cancer	2	0	0	1	1	0	2	unknown	0	2	34(33-36)	2	0
16	Ovarian Cancer	1	0	1	0	0	0	0	1 dead ,9m	1	0	54	0	1
17	Prostate Cancer	1	0	0	0	1	0	0	1	0	1	58	1	0
18	Bone Sarcoma	1	0	0	1	0	0	0	1	1	0	49	0	1
	Total	**77**	**19**	**6**	**21**	**29**	**8**	**63**	**7**	**33**	**44**		**38**	**39**
		100%	**24%**	**7%**	**27%**	**37%**	**10%**	**81%**	**9%**	**42%**	**58%**		**49%**	**51%**

* Lose.F-up : Lose Follow-Up
* 1Y.DFS : 1 Year Disease Free Survival
* PP : Phnom Penh
* Pro : Provinces
* Comp : Complete
* Incomp : Incomplete
* Ca : Cancer
* ENT : Ear Nose Throat
* NHL : Non-Hodgkin Lymphoma
* STS : Soft Tissue Sarcoma

Epidemiologic Characteristics of Breast Cancer in Korea: Hormonal Risk Factors and Genetic Susceptibility



Keun-Young Yoo
Department of Preventive Medicine
Seoul National University College of Medicine, Seoul, Korea

Born in: 1955
Past Records: 1978 Graduated Seoul Nat`l Univ. Coll. of Med. (MD)
1985 Graduated Seoul Nat`l Univ.(PhD)
1989 Visiting Researcher, Yale Univ. LEPH
1990 Visiting Scientist, Aichi Cancer Center, Nagoya
1999 Professor, Seoul Nat`l Univ. Coll. of Med.

The leading causes of death in Korea have shifted from infectious diseases to chronic degenerative illnesses since the end of the 1960s. Malignant neoplasm has become an important cause of death, next to cerebro-vascular accident (1).

1. Magnitude of the problem of breast cancer in Korea

Breast cancer ranks third to uterine cervix cancer and stomach cancer in Korea as a cause of death in women, and as a common site of primary cancer based on National Cancer Registry (2). A nation-wide survey estimated that the age-adjusted incidence rate for breast cancer in women was 10.9 per 100,000 in 1992 (3). It was estimated that about 4,000 new cases of female breast cancer were diagnosed and approximately 1,000 women died of breast cancer in a year (1).

2. International comparison of incidence rates for breast cancer

For many years, breast cancer incidence and mortality rates have been highest in North America and Northern Europe, intermediate in Southern Europe and Latin America, and lowest in Asia and Africa (Table 1) (4-5). In recent years, a steep increase in breast cancer incidence and mortality rates have been reported in several Asian and Central European countries. Thus, the differences in the incidence rates of countries such as Korea or Japan and the United States are less than they were previously.

In fact, one of the most dramatic features of breast cancer is that there is a large difference in its incidence of westernized and non-westernized countries. Environmental changes within a country may be the keys to the different risk levels found in the United States and in the Asian countries.

3. Studies in migrants to the United States

Studies in migrants to the United States suggest that environmental factors rather than genetic factors are mainly responsible for the variation in the breast cancer rates between countries (6). The speed with which the incidence rates of migrants and their offspring, who were potentially exposed to a new environment and culture at an early age, has varied considerably from one ethnic group to another.

Table 2 shows that both Japanese and Chinese migrants have fundamentally higher incidence rates than women in their mother countries, and that these approach those of their adopted country. Even though Korean migrants to L.A. have slightly higher breast cancer incidence rates than women in their mother country, they still maintain a relatively lower level of

Table 1. International comparison of age-standardized mortality rates for breast cancer, OECD countries selected, 1996

Countries	Age-standardized incidence rate (per 100,000 persons)
Germany	44.5
Italy	39.0
France	36.6
United States	32.7
Spain	29.3
Poland	23.6
Japan	11.3
Mexico	6.6
Korea	4.2

Source : WHO (1998)

Table 2. Age-standardized incidence rates for breast cancer by ethnic groups

Population groups	Age-standardized incidence rate (per 100,000 persons)
Japanese, LA (1983-1987)	72.2
Japanese, Miyagi (1983-1987)	27.8
Japanese, Osaka (1983-1987)	21.9
Chinese, LA (1983-1987)	48.7
Chinese, Shanghai (1983-1987)	21.2
Korean, LA (1983-1987)	16.9
Korean, Seoul (1991-1992)	17.0
Korean, nationwide (1988-1989)	10.9

Source : Parkin et al. (1997); American Cancer Society (1995)

breast cancer incidence (4,7). These facts suggest that either some protective factor in the former cultures is carried over into the second generation or that these migrants successfully avoid some risk factor.

4. Trends in mortality and morbidity for breast cancer in Korea

Although the magnitude of the breast cancer problem seems not to have become too serious to date, relative to those of Western countries, there is an increasing trend in mortality and morbidity for breast cancer in Korea. Age-standardized mortality rates for breast cancer have been steadily increasing over the last two decades, showing an increment ratio of more than three. Proxy estimates of incidence show that the age-standardized admission rates for breast cancer have increased since 1981 in Korea (8). These findings also suggest that some underlying factors, which are directly or indirectly associated with the development of breast cancer have consistently existed in the population.

5. Age-specific incidence curve of breast cancer

The variation in incidence rates from one part of the world to another has been associated with the different shapes of age-specific incidence curves. In

areas of high incidence, as illustrated by the United States, a slight leveling off in the increase of the age associated incidence rate occurs during the menopausal years, and this is followed by a continued rise during the postmenopausal years, but at a lower rate of increase. In regions with low incidence rates, however, the rates decline after about age 50 years. In Korea, breast cancer incidence rates increase steeply with age until the late forties, then decrease less steeply with age for the remainder of the life span (Fig. 1). Similar features in the shape of age incidence curves can be seen over time in Japan, in spite of the relatively steep increase in breast cancer incidence rates over the past few decades.

International differences in both breast cancer incidence rates and age incidence curves have been hypothesized to be partially related to variations in the risk factors, such as body weight, some aspect of diet, hormonal levels, and reproductive characteristics. Therefore, changes in both incidence and the age incidence curve may be predicted by observing such factors, which may contribute to the burden of future disease in Korea.

6. Risk factors of breast cancer in Korea

The key epidemiologic hormonal risk factors for breast cancer are all explicable in terms of the estrogen-augmented-by-progesterone hypothesis (9). Older age, family history of breast cancer, early menarche, late menopause, late full-term pregnancy, and never-having had a breast-fed child are the primary risk factors of breast cancer, identified by epidemiologic studies in Korea (10). A case-control comparison revealed that postmenopausal obesity is an important risk factor for breast cancer in Korea, which is relevant to the estrogen-augmented-by-progesterone hypothesis (11). In addition, we found that obesity is closely related to the early menarche, and with late menopause (12). An ecological correlation study observed that age-adjusted mortality rates for breast cancer positively correlated with protein/lipids intakes, but were inversely associated with vegetable and cereal intakes in Korea (13).

Table 3 lists the high-risk breast cancer group on the basis of epidemiological findings in Korea. In spite of the lower level of breast cancer incidence in Korean women, these findings suggest that there seems to be no difference in the breast cancer risk factors of Korea and Western countries.

7. Levels of female sex hormones

In spite of no differences in risk factors in case-

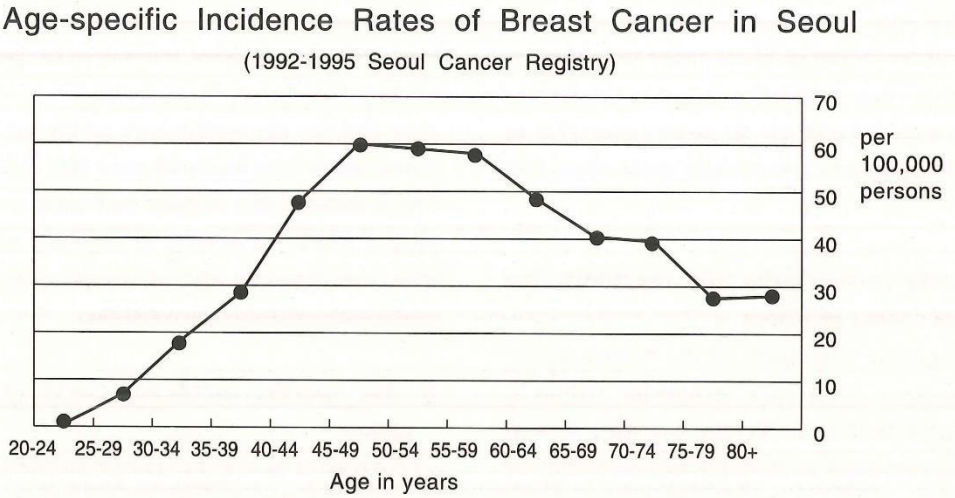


Fig. 1. Age-specific incidence rates for breast cancer, 1992-1995, Seoul, Korea.

Table 3. High-risk group for female breast cancer in Korea

Risk factors	High-risk group
Family history	Women with age over 50 Women who have a family history of breast cancer among the first-degree relatives
Menarche	Women with age at menarche before 14
Pregnancy	Nulliparous women Women with age at first full-term pregnancy after 35
Breast feeding	Women who have never experience breast feeding
Obesity	Women with body mass index over 25 kg/m2 or with body weight more than 64 kg

Source : Yoo et al. (1998)

control comparison, breast cancer rates in the United States are still approximately 6- to 8-fold higher than rates in Korea. Some innate biological facts may be the keys to the different risk levels of breast cancer around the world.

The two risk factors that were previously used to attempt an explanation for this substantial difference were age at menarche and postmenopausal weight. Mean age at menarche in young Korean girls has been steadily decreasing over the last two decades, reaching menarche at 12.1 in 1999. It has been reported that predicted US breast cancer incidence with a 2-year delay in menarche and a low postmenopausal weight is 2.5-fold higher than in Japanese rate (14). For reasons not fully understood, Chinese women reach menarche on average at age 17, while U.S. women do so at 12.8 years. But, 200 years age, North American women were like the Chinese, reaching menarche at 17 (15).

The other biologic fact that can be used to explain the difference is the level of female sex hormones, since ovarian hormones, estradiol and progesterone, play important roles in increasing breast cancer risk. A cross-sectional survey reported estradiol, progesterone and sex hormone binding globulin concentrations among healthy adolescent girls and postmenopausal women in Korea (16). The estradiol levels in Korean postmenopausal women were similar to those of Japanese women (17), and these were much lower than those of American women. These results, along with difference in age at menarche, could provide an important part of the explanation why Asian and American breast cancer rates differ.

8. Differences in genetic susceptibility

However, a large proportion of breast cancer cases cannot be fully explained by the above risk factors. Inherited differences in the capacity to metabolize environmental carcinogens have been suggested to modify the individual's susceptibility to human cancer. The identification of susceptibility factors that predispose individuals to cancer, if they are exposed to particular environmental agents, could possibly give further insight into both the etiology and the prevention of this malignancy.

Inherited metabolic capacity of glutathione S-transferases (GSTs), for example, has been related to individual breast cancer risk. GSTs play an important role in the detoxification of endogenous and exogenous toxicants, and may also have a role in the metabolism of lipids and the DNA products of oxidative stress.

Recent molecular epidemiologic works conducted in our laboratory revealed that both GSTM1 and GSTT1 enzyme activities are absent from approximately half of the study subjects due to homozygous deletion of the respective genes. These findings are relevant to those from other Asian studies. More specifically, both GSTM1 and GSTT1 null genotypes are significantly associated with breast cancer risk in Korea, particularly in high-risk postmenopausal women, i.e., nulliparous women or women experiencing pregnancy in later age. These results are suggesting a novel gene-environmental interaction which plays an important role in the individual susceptibility to breast cancer (18).

Another types of enzymes, N-acetyltransferase (NAT1, NAT2) and catechol-O methyltransferase (COMT) are currently under investigation to explore a new gene-environment interaction in breast carcinogenesis in Korean women. Of these, preliminary results on genetic polymorphism of COMT, which is possibly involved in estrogen metabolism, suggest that women with low-activity COMT genotype might have increased the risk of breast cancer in Korea. Moreover, a gene-gene interaction between GSTs and COMT on breast cancer development was recently demonstrated in premenopausal Korean women.

9. Concluding remarks

Knowledge of the descriptive epidemiology of breast cancer is useful both in suggesting etiologic hypothesis and in delineating high-risk groups to be targeted for preventive efforts. Incidence of female breast cancer is still in lower level in Korea, like most other Asian countries. However, the most notable feature of the descriptive epidemiology of breast cancer in recent years is perhaps the rapidly increasing incidence rates in Korea. Identification of reasons for this increasing pattern would contribute substantially to our understanding of the magnitude of the problem in the future.

Although female sex hormonal levels are estimated to be much lower than those of American women are, there is no substantial difference in the risk factors of breast cancer between Korea and Western countries. Epidemiological features, i.e., trends in mortality and morbidity for female breast cancer, and incidence patterns of breast cancer in other Asian migrants to the United States, suggest that the incidence of breast cancer might further increase in Korea. The age-specific incidence curve is also expected to change in-line with those of countries with higher incidences when the incidence rate in Korea reaches around 50 per 100,000. Given this likely scenario, control strategies that include screening guidelines against breast cancer has been established to counter this malignancy in Korea. Finally, identification of susceptibility factors that predispose individuals to breast cancer may give further insight into both the etiology and the prevention of this malignancy.

References

1. National Statistical Office, Republic of Korea (1998) Annual report on the cause of death statistics (based on vital registration). Seoul.
2. Ministry of Health and Welfare, Republic of Korea (1999) Yearbook of Health and Welfare Statistics. Seoul.
3. Ahn, Y.O., Park, B.J., Yoo, K.Y., Lee, M.S., Kim, H., Noh, D.Y. and Park T.S. (1994) Incidence estimation of female breast cancer among Koreans. J. Korean Med. Sci. 9, 328-334.
4. Parkin, D.M., Whelan, S.L., Ferlay, J., Raymond, L. and Young J. (1997) Cancer incidence in five continents, Vol. VII, IARC Scientific Publications No.143. Lyon.
5. World Health Organization (1998) 1996 World Health Statistics. Geneve.
6. Kelsey, J.L. and Horn-Ross, P.L. (1993) Breast cancer: magnitude of the problem and descriptive epidemiology. Epidemiol. Rev. 15, 7-16.
7. American Cancer Society (1995) Breast cancer facts & figures. Atlanta, GA.
8. Yoo, K.Y. and Kim, D.H. (1992) Trends in mortality

and morbidity of uterine cervix, female breast, and ovarian cancer in Korea. Seoul J. Med. 33, 175-181.

9. Pike, M.C., Spicer, D.V., Dahmoush, L. and Press, M.F. (1993) Estrogens, progesterones, normal breast cell proliferation, and breast cancer risk. Epidemiol. Rev., 15, 17-35.
10. Yoo, K.Y., Park, S.K., Sung, J.H., Kang, D.H., Kim, Y.C., Kang, H.S., Suh, J.S., Kim, J.S., Yun, I.J., Han, S.W., Noh, D.Y. and Choe, K.J. (1998) High risk group for female breast cancer in Korea. J. Korean Cancer Assoc., 30, 435-439.
11. Joo, J.S., Yoo, K.Y., Shin, M.H., Noh, D.Y. and Choe, K.J. (1994) Overweight related to the risk of breast cancer by menopausal status in Korea. J. Korean Surg. Soc., 46, 937-948.
12. Yoo, K.Y., Bae, J.M., Park, E.S., Ha, M.N., Suh, J.S., Noh, D.Y., Choe, K.J. Park, Y.S., Lee, H.K., Lee, K.S., Kim, C.Y., Kim, Y.I. and Shin, Y.S. (1995) Obesity as a determinant of age at menarche and age of menopause in a cross-sectional survey in Yonchon County, Korea. Seoul J. Med., 36, 137-154.
13. Yoo, K.Y., Kim, D.H., Shin, M.H., Noh, D.Y. and Choe, K.J. (1993) Ecologic correlation study on nutrients/foods intake and mortality for female breast cancer in Korea. Seoul J. Med., 34, 17-25.
14. Pike, M.C., Krailo, M.D., Henderson, B.E., Casagrande, J.T. and Hoel, D.G. (1983) "Hormonal" risk factors, "breast tissue age" and the age-incidence of breast cancer. Nature, 303, 767-770.
15. Marshall, E. (1993) Search for killer: Focus shifts from fat to hormones. Science, 259, 618-621.
16. Yoo, K.Y., Kim, H., Shin, H.R., Kang, D.H., Ha, M.N., Park, S.K., Lee, B.O. and Cho, S.H. (1998) Female sex hormones and body mass in adolescent and postmenopausal Korean women. J. Korean Med. Sci., 13, 241-246.
17. Shimizu, H., Ross, R.K., Bernstein, L., Pike, M.C. and Henderson, B.E. (1990) Serum oestrogen levels in postmenopausal women: comparison of American whites and Japanese in Japan. Br. J Cancer, 62, 451-453.
18. Park, S.K., Yoo, K.Y., Lee, S.J., Kim, S.U., Ahn, S.H., Noh, D.Y., Choe, K.J., Strickland, P.T., Hirvonen, A. and Kang, D.H. (2000) Alcohol consumption, glutathione S-transferase M1 and T1 genetic polymorphisms and breast cancer risk. Pharmacogenetics, 10, 301-309.

Gastric Cancer in Indonesia

Sukardja Gede I Dewa
Department of Surgery, School of Medicine, University of Airlangga / Dr. Soetomo Hospital-SURABAYA, INDONESIA

Born : 1934

Past Records : 1962 Medical Doctor,School of Medicine,University of Airlangga,Surabaya
1969 General Surgeon,School of Medicine,University of Airlangga,Surabaya
1971 Surgical Oncology,Netherland Cancer Institute,Amsterdam
1973 Early Gastric Cancer Detection National Cancer Center,Tokyo,Japan
1982 Cancer Control Program,Netherland and France
1984 ph.D.Post Graduate School of University of Airlangga

Head of Cancer Team,Shool of Medicine Univ.of Airlangga Dr.Sutomo Hospital
Head of Surgical Oncology Division of the Department of Surgery
Member of Indonesian National Cancer Committee of Ministry of Health of the Republic of Indonesia

Abstract

The frequency of gastric cancer is low in Indonesia, rank 26th. of all cancer or the 5th. of digestive cancer . At Dr. Soetomo hospital Surabaya, the teaching hospital of the School of Medicine of the University of Airlangga which has capacity of 1500 beds, the average annual admission of all diseases is ± 55000 patients, of neoplasm is±3500 (6.32% of all diseases), of cancer is±2300(65.16% of neoplasm), of digestive cancer is ±260 (11.29% of cancer), of gastric cancer is ±9 (0.37% of all cancer or 3.27% of digestive cancer). Among the digestive cancer the frequent cancer encountered are cancer of the liver (66.58%), followed by cancer of the rectum (13.64%), of the colon (8.18%), of the pancreas (3.37%), and than of the stomach (3.27%).

Gastric cancer is more frequent in male than in female with the ratio of 3 to 1. The most frequent site is in the lower third or anthrum-pyloric part of the stomach (63.63%) along the lesser curvature, with the majority adenocarcinoma (95%). The patients mostly come in an advanced stage (75%).

The etiology of gastric cancer is still unclear. It is closely related the carcinogenes, ethnic groups, food habit, smoking, infection, atrophy, metaplasia, dysplasia, achlorhydria and environmental factors. The well known carcinogens such as polycyclic aromatic hydrocarbon, N-nitroso-compound may appear during food processing, for instance from salted, smoked, roasted, prickled food or meat, high nitrate or nitrite, etc. Helicobacter pylori has been implicated in the development of chronic gastritis and play a rule in the possible etiologic factor of gastric cancinogenesis. Food containing much fibers, fresh fruits, vegetables, carotinoid, flavinoid, or drink green tea, which contain much vitamin A,C,E, antioxidant, catechin may protect the development of gastric cancer.

The low frequency of gastric cancer in Indonesian may be in part related to the natural food processing, which facilitate digestion as high consumption of rice, fiber diets, vegetables, fresh fruits, spices and all kind of side dishes, and moderate consumption of fat and protein

The diagnosis of gastric cancer is based on the history, physical examination, Upper GI studies with

double contrast, gastroscopy and biopsy.

The treatment of gastric cancer in early stage is curative and in advanced stage is palliative, mainly with surgery, radiotherapy, chemotherapy and nutritional support, depend on the operability of the tumor and the condition of the patients.

I. Introduction

Gastric cancer is malignant neoplasm originating from the stomach, mostly from the gastric gland and mucous membrane lining the stomach. Malignant neoplasm originating from muscle or soft tissue part of stomach is rare. Pathological appearance mostly adenocarcinoma. (95%)

The frequency of gastric carcinoma in Indonesia is low, take the rank of 26th of all cancer and the 5th. among the digestive cancer.

Indonesia is a country in the tropic, along the equator from 95° to 141° east latitude a distance more than 5100 km and from 6° north to 11° south lratitude a distance more than 1900 km, occupying an area of 2.000.000 km², consisted more than 1300 islands. There are 5 big islands, i.e.: Sumatra, Java, Kalimantan, Sulawesi and Papua. About 80% of the area consist of sea and 20% of land and divided into 26 provinces. The population in the year 2000 more than 200 million consists of more the 300 ethnic groups which difference dialect, cultural and food habit.

The province of East Java covered an area of 47922 km², or 2.5% of Indonesia, with the population of 30 million and the main ethnic group are Javanese and Madurese. Surabaya is a capital of East Java province, with the population of 3 million, is the second largest city of Indonesia after the capitol of Indonesia Jakarta. Dr. Sutomo hospital is the teaching hospital of the School of Medicine of the University of Airlangga. It has 1500 beds capacity, with the average annual admission of all diseases is about 55000 patients, of neoplasm is about 3500 (6.32%), of cancer is about 2300 (65.16% of neoplasm), of digestive cancer is about 260 (11.29% of cancer), of gastric cancer is about 9 (0.37% of all cancer or 3.27% of digestive cancer).

This paper will discuss mainly the probability cause of low frequency of gastric cancer in Indonesia.

II. Epidemiology

In Indonesia the frequency of gastric cancer is low in comparison with that in Japan, Korea and Chinese.

Hospital based data for 20 years, 1975-1994 from Dr. Soetomo Surabaya revealed the high frequency of cancer are the cancer the cervix (36.61%), cancer of the liver (7.52%), cancer of the breast (6.25%), the leukemia (6.17%), cancer of the ovary (4.41%), etc. The digestive cancer accounted for 11.29% of all cancer which the average annual admission of about 260 cases. Among the digestive cancer the high frequency are the cancer of the liver (66.58%), cancer of the rectum (13.64%), cancer of the colon (8.18%), cancer of the pancreas (3.37%), and than come cancer of the stomach (3.27% of the digestive cancer or 0.37 of all cancer).

Pathological based data from the Department of pathology School of Medicine University of Airlangga revealed that Gastric cancer rank the 27th. accounted for 0.66% all cancer. Pathological based data from the Department of Health of Indonesia which collected data from 13 pathological centers throughout Indonesia, i.e. from Medan, Padang, Palembang, Jakarta, Bandung, Semarang, Surakarta, Yogyakarta, Surabaya, Malang, Denpasar, Makasar, and Menado revealed the frequency of gastric cancer actually low, accounted for 0.84% and take the rank of the 22nd. The first 10th. high ranked were cancer of 1). the cervix (18.80%), 2). the breast (12.60%, 3). the skin (8.37%), 4). the nasopharynx (5.95%), 5). the ovary (4.68%), 6). the malignant lymphoma (4.48%), 7). the thyroid (3.42%), 8). the rectum (3.32%), 9). the colon (2.88%), and 10). the soft tissues (2.73%).

At dr. Sutomo Hospital Surabaya, the average annual admission of gastric cancer is only about 9 cases, which is take the rank of the 26th. of all cancer and the 5th. of digestive cancer. The colorectal cancer is much more frequent, about 7x than that of gastric cancer. The gastric cancer predominantly in male, with the ratio of male to female is 3 to 1. The peak frequency is

in age of 55-54 year (21.14%). In the age of 50-65 year is 57.14%

The most frequent site of gastric cancer is in the 3rd. distal part of the stomach (63.63%), i.e. in the anthral and pyloric regions, mostly along the lesser curvature.

The patients usually come to see the hospital in advanced stage[3] (75%), in stage II, III or IV. according to UICC TNM system.

The etiology of gastric cancer is multifactorial and still unclear. It is closely related the carcinogens, ethnic groups, food habit, smoking, infection, atrophy, metaplasia, dysplasia of the stomach, achlorhydria and environmental factors.

In the nature there are many pro-carcinogens discovered, which converted in the body into carcinogens, such as polycyclic aromatic hydrocarbon (benzanthracene, dibenanthracene, benzopyrene, methylcholanthrenne), dromatic amine(naphthylamine, benzidine), nitosamine (dimethylnitrosamine, N-methyl-nitrozourea), aflatoxin, arsen, chrome, nitrate, nitrite, etc.

Carcinogens may also appear during food processing, such as polycyclic aromatic hydrocarbon from smoked or roasted organic food, nitrosamine from preservation of food composed of protein with preservative, with salt, nitrite, nitrate, prickled, etc.

In the food there are also many substances which may promote or inhibit the development of cancer. Food containing much fibers, carbohydrate, vegetables, fresh fruits, rich in vitamin, carotinoid, flavinoid, drink much tea are less susceptible to get gastric cancer. It is supposed the antioxidant property the fruits or foods, such as vitamin A,C,E, carotinoid and catechin may prevent the transformation of proto oncogen to oncogene so inhibit the development of gastric cancer. The Epigallocatechin gallate (EGCG) a mayor constituent of tea have been reported to inhibit cancer development in mice induced by chemical carcinogens through activating the alkylguanine-DNA alkyltransferas (AGT) an enzym which is necessary to repair the damaged DNA.[5].

While salty, prickled, roasted, smoked, or hot food prone to stimulate the development of gastritis and gastric metaplasia and to gastric cancer.

It is supposed that the high pH of gastric juice promotes the growth of bacteria, that reduced the protein or dietary nitrate to nitrite and converted into dietary amine and than into carcinogenic N-nitroso compounds. It is also known that most carcinogens are fat soluble and so high fat diet may provoked the development of cancer.

Helicobacter pylori has been implicated in the development of chronic gastritis and play a rule in the possible etiologic factor for gastric carcinoma.

Environmental factors such as coal mining, nickel refining, rubber worker, asbestos exposure may also play a rule in the development of gastric cancer

The frequency of gastric cancer in Indonesia is low. There are many factors which probability play a rule in the cause low frequency of gastric cancer, such as: low incidence of cancer in general in Indonesia, which also influent the gastric cancer. It is supposed that the food habit may play a rule in the development of gastric cancer and is still much to study about the real cause of gastric cancer. The consumption of balanced food with high carbohydrate, low protein and fat, high fibers, enough vitamins, antioxidants, much water and minerals, fresh prepared food, traditionally consuming food seasoning, spices, juices, drink tea, originating from herbs that might prevent the development of cancer. The daily recommended allowance of energy consumption for adult depend on the activities, about 2500 to 3500 calorie, composed of about 1/2 of the calorie needed from carbohydrate, 1/4 each from protein and fat. The food passage in the digestive tract is fast with low frequency of constipation, so that the contact of carcinogens to the mucosa in the stomach have no much time.

Food consumption pattern in Indonesia as the main menu usually rice but in some regions or ethnic groups also the substitute of rice such as maize, cassave, sagu, etc. The Department of Health of Indonesia recommended **"4 healthy and 5 perfect food"**

that is 4 kinds food for healthy life consisted of rice or its substitute, dishes, vegetables, fruits and one additional milk especially for children and mother which contain all kind of nutrients (see table 1 and figure 1).

Table 1 : Composition of daily menu of most Indonesian.

NO	M E N U	N U T R I E N T	S O U R C E
1	Main menu	Carbohydrate	Rice in nearly all Indonesian. Some regions or ethnic used substitute of rice, such as: ● maize in Madura and Timor ● cassave in Bagelen, Gunung Kudul ● *sagu* in Maluku, Papua ● *ubi* (sweet potato) in Nias, Papua ● *tales* (black radish) in Maluku, Papua.
2	Dishs	Protein and fat	● Animal origin: egg, meat, fish, chicken, sea food, etc ● Plant origin : tofu, tempe (soya bean cake), coconut, palm, peanut, spices, etc.
3	Vegetales Fruits	Protein, fat and fibers	cabbage, spinach, salad, celery, tomato, green leave, spruts, bean, pea, peanut, kangkung, cucumbar, terong (solanum), etc.
4		Vitamin, water, mineral	banana, orange, papaya, pine apple, manggo, melon, grape, jambu, rambutan, duku, etc.
5	Milk	Especially recommended for children and mother. Contain all kind of nutrients.	

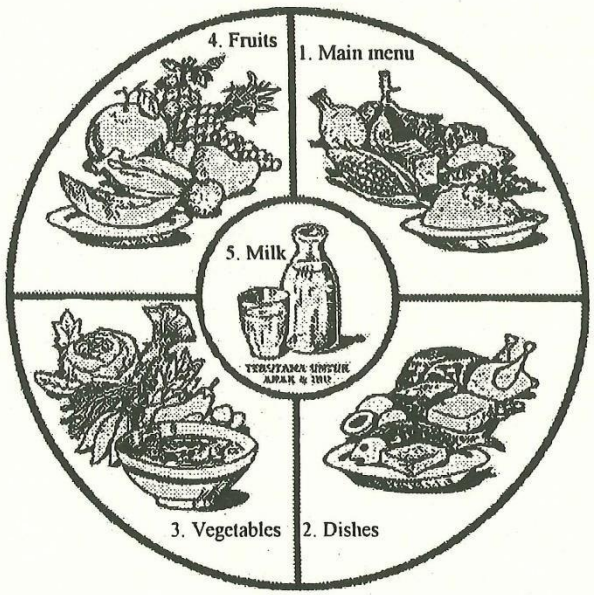


Figure 1: Composition of daily menu of 4 healthy & 5 perfect food

It is also known that many kinds of herb in Indonesia that could stimulate or modulate the immunity and may play a rule in the prevention of cancer. These herbs some of which have been proven in vitro could inhibit the development or growth of cancer cells and are used traditionally by the people as food supplement, food seasoning, spices, juices, fruit salads, traditional medicine, etc. such as:

1. Tea with its mayor constituent Epigallocatechin gallate (EGCG) which could activate the enzym alkylguanine-DNA alkytransferas (AGT), which is necessary for repaire the damaged DNA caused by chemical carcinogene[5].
2. Family cruciferae of the genus brassica such as cabbage (*kubis*), brassica rugosa (*sawi*), black radish (*lobak*) , brocoli, cauliflower, etc. contains indoylmethyl glucosinolate or glucobrassin as indole-3-cabinol which retard the growth of cancer, stimulate the TNF and interleukin-1
3. Gynura procumbens i.e. Gynura procumbens Merr (*daun dewa*) and Gynura pseudo-china (*daun sambung nyawa*) contain many flavinoid, fenolic acid, benzapyrene etc. which inhibit the growth of cancer cells
4. Vinca rosea contains vinca alkaloid which inhibit polarizatin of microtubuli and is act as anti mitosis. Vinca alkaloid has been used as chemotherapy in the name of vincristine, vinblastine, vinorelbine
5. Curcuma longa (*kunyit*), contain curcumin which has anti inflammation activities, antioxidant, induction of apoptosis, and inhibit tumorigenesis.
6. .Curcuma zedoaria (*temu putih*) contains zedoarone , curdione etc. which has anti tumor activities, hepatoprotector, and anti inflammation
7. Solanum nigrum (*terong ranti*) contains solanigrin a protease inhibitor, anti tumori-genesis, immuno-modulator, and hepatoprotector
8. Aloe vera (*lidah buaya*) contains polysaccharide as immunomodulator and anti inflammation
9. Allium sativum (*bawang putih*) contains garlic acid which inhibits mutagenesis, immunomodulator and anti inflammation
10. Kaempferia rotunda (*kunir putih*) as immuopmodulator
11. Nigella sativa (*jinten hitam*) as anti inflammation, immunomudulator, growth inhibitor
12. Morinda citrifolia (*mengkudu / pace*) contain xeronine, 1-methoxy-2-formyl-3-hydroxy-anthra-quinone, as anti tumor activity, anti-angiogenesis, immunomodulator. In the USA it is used a food supplement in the name of NONI and has been patented in Japan as anti Helicobacter pylori by Hazegawa in 1996, as anti-AIDS by Kayono in 1994 and as anti cancer by Umezawa in 1994
13. Manihot esculenta Crantz (*ketella gendruwo*) contains many glicosides as lotaustralin, linamarin, HCN, and is used as cytotoxic
14. Viscum album (*benalu*), a parasitic plant mistletoe contains lectin and used is as cytotoxic, immonomodulator which increases the TNF-.
15. Andographis paniculata Ness (*sambiloto*) as immunomudulator, hepatoprotector and has been patented in the USA as anti-HIV with the brand name AndroVir.

III. Clinic of Gastric Cancer

The clinical manifestation of gastric cancer may be as:

1. Epigastric discomfort 2. Epigastric tumor
3. Dyspepsia 4. Dysphagia 5. Hematemesis
5. Melena 6. Anemia
7. Peritonitis due to gastric perforation.

The diagnosis of gastric cancer is based on finding of history, clinical examination, upper GI study with double contrast, and gastroscopy with biopsy.

The oesophago-gastro-doudenoscopy may revealed

1. Mucosal defect, 2. Erosion, 3. Ulcer,
4. Bleeding, 5. Polyp or tumor
6. Diffuse contraction (linitis plastica), etc

In early gastric cancer the defect is limited to the mucosa and submucosa as protuded lesion (type I), superficial lesion (type II) which may elevated (type IIa), flat (IIb) or depressed (IIc) and excavated lesion (type III). The gastric folds may radiate to the lesion. In advance gastric cancer the gastroscopic finding may be lesion as polypoid, ulcerative, or infiltrative

(linitis plastica).

Biopsy or cytologic examination discovers the morphology of the lesion, whether it is a cancer or no.

Clinically gastric carcinoma is divided into 9 categories according to ICD (International Classification of Diseases) of WHO, depend on the location of the primary tumor.(see table 2). For seek of simplicity the stomach may be divided into 3 categories. To delimit these sub-sites the lesser curvature (C16.0-C16.4) and the greater curvatures (C16.0-C16.4) are divided at two equidistant points and these are joint. The tumor is assigned to the region in which the bulk of its is situated. (see table 3).

The stage of gastric cancer according to UICC TNM system can be divided into 5 stages: i.e: stage 0, I, II, III and IV. What is called early gastric cancer is cancer limited to the mucosa and submucoca i.e. in stage 0 and I, which is still curable and has the 5 year

Table 2 : Clinical classification of Gastric cancer according to ICD-10.

NO	SITE	ICD. NO	NO	SITE	ICD. NO
1	Cardia	C16.0	6	Lesser curvature	C16.5
2	Fundus	C16.1	7	Greater curvature	C16.6
3	Corpus	C16.2	8	Overlapping lesion	C16.8
4	Anthrum	C16.3	9	Unspecified	C16.9
5	Pylorus	C16.4			

Table 3 : Clinical classification of Gastric cancer according to ICD-10.

NO	REGION	SITE	ICD-10	SITE	ICD-10
1	Upper third	cardia	C16.0	includes fundus	C16.1
2	Middle third	corpus	C16.2		
3	Lower third	Anthrum	C16.3	includes pylorus	C16.4

Table 4: Stage of gastric cancer (UICC)

Stage	T N. M.	Description	
0	$T_{is}. N_0. M_0$	T_0	= No evidence of primary tumor
IA	$T_1. N_0. M_0$	T_{is}	= intraepithelial cancer without invasion of lamina propria
IB	$T_1. N_1. M_0$	T_1	= Tumor invades lamina propria or submucosa
	$T_2. N_0. M_0$	T_2	= Tumor invades lamina muscularis or subserosa
II	$T_2. N_2. M_0$	T_3	= Tumor penetrate the serosa
	$T_2. N_1. M_0$	T_4	= Tumor invades adjacent structures
	$T_3. N_0. M_0$		
IIIA	$T_2. N_2. M_0$	N_0	= No regional node metastasis
	$T_3. N_1. M_0$	N_1	= Metas in perigastric nodes ≦ 3 cm of the edge of tumor
	$T_4. N_0. M_0$	N_2	= Metas in perigastric nodes > 3 cm from the tumor, or
IIIB	$T_3. N_2. M_0$		in lymphnodes along the gastric, splenic, hepatic or
	$T_4. N_1. M_0$		coeliac arteries
IV	$T_4. N_2. M_0$	M_0	= No evidences of distance metastasis
	$T_{any} N_{any}. M_1.$	M_1	= There is evidences of distance metastasis

survival rate of about 90%

IV. Pathology

1. Macroscopic appearance

Macroscopic appearance of gastric cancer in early stage may be as protruded lesion (type I), superficial mucosal defect (type II) as elevated (IIa), flat (IIb) or depressed (type IIc), and excavated lesion (type III), with gastric fold radiating into the lesion or as erosion.. In advanced gastric cancer the tumor may be polypoid, ulcerated, or as diffuse infiltration of the gastric wall.(linitis plastica).

2. Microscopic appearance

Mostly the gastric cancer appears as adenocarcinoma (95%), in the form of papillary, tubular, signet ring or undifferntiated carcinoma. Some are as adenosquamous carcinoma, squamous cell carcinoma, leomyosarcoma, malignant lymphoma, carcinoid and others. (see table 5)

According to WHO gastric tumor may be classified into epithelial, non epithelial and carcinoid tumor. The epithelial tumor, comprising malignant and benign, in situ and uncertain behavior. The epithelial tumor may be the papillary, tubular, mucinous, signet ring or undifferentiated carcinoma.

V. Treatment of Gastric Cancer

The treatment of gastric cancer may be curative or palliative.

1. Curative treatment

1). Surgery to excise radically the tumor and to establish continuity by anastomosis.

(1).Total gastrectomy with or without nodal dissection. The continuity is reestablished by oesophago-duodenostomy or oesophago-jejunostomy,

Table 5 : WHO classification of gastric carcinoma

NO	TYPE OF TUMOR				
I	EPITHELIAL TUMOR				ICD.M
	A	BENIGN			
		1. Adenoma			8140/0
			a.	Papillary	8260/0
			b.	Tubular	8211/0
			c.	Papillotubular	8263/0
	B	MALIGNANT			
		1.	Adenocarcinoma		8140/3
			a.	Papillary	8260/3
			b.	Tubular	8211/3
			c.	Mucinous	8480/3
			d.	Signet ring cell carcinoma	6490/3
		2.	Adenosquamous carcinoma		8560/3
		3.	Squamous cell carcinoma		8070/3
		4.	Undifferentiated carcinoma		8020/3
		5.	Unclassified carcinoma		8010/0
II	CARCINOID TUMOR				8240/1
III	NON EPITHELIAL TUMORS				
	A	Smooth muscle tumors			
		1. leomyoma			8890/0
		2. Leiomyoblastoma			8891/1
		3. Leiomyosarcoma			8890/3
	B	Others			

(2). Partial gastrectomy at least 3-5 cm from the margin of the tumor, with or without nodal dissection. The continuity is reestablished by gastro-gastrostomy and pyloroplasty, oesophago-gastrostomy and pyloroplasty, or gastro-doudenostomy

2). Adjuvant chemotherapy

2. Palliative treatment

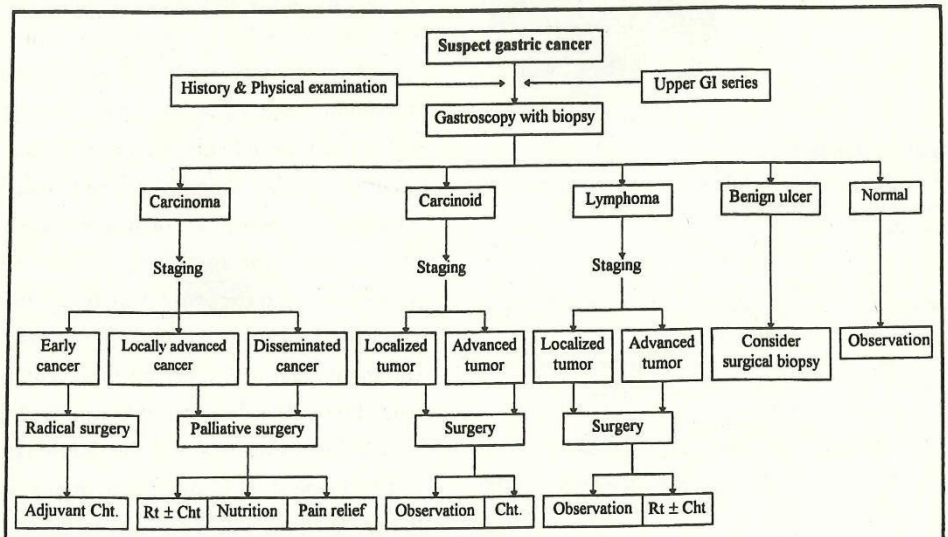
1). Surgery to overcome the obstruction or closed the perforation, with bypass operation, such as gastrostomy, jejunostomy, gastro-duodenostomy, oesophago-jejunostomy

2). Radiotherapy

3). Chemotherapy

4). Pain relief

5). Nutrition



Algorithm of diagnosis and treatment of gastric cancer

VI. LITERATURES

1. Alexander HR, Kelsen DP and Tepper JE.: Cancer of Stomach. In: Cancer Principles & Practice of Oncology. Pp. 818-848. Ed. DeVita Jr. VT, Hellman S and Rosenberg SA. Pp. JB. Lippencoatt Co, Phyladelphia, 1993.

2. Department of Health of Indonesia:. Cancer in Indonesia in the year 1988 and 1989. Histopathological data.

3. Jayaprata I.: Endoscopic evaluation of patients with upper gastrointestinal ulcer. Proc National congress of Indonesian Gastroenterology association, pp 49-59, 1987.

4. Pok Kim, J. Cancer of the stomach. In. pp.439-452. UICC Manual of Clinical Oncology, 7nd. Ed. Edit. Pollock RE, et al. Wiley-Liss Publ., New York 1999

5. Purwanto DA.: Inhibition of carcinogenesis by (-)-epigalocatechin gallat through increasing the activity of 0^6-alkylguinine-DNA transverase. Dissertation, Post Graduate School, University of Airlangga, 2000.

6. Sukardja IDG: Hospital Cancer Registration at. Dr. Sutomo Hospital Surabaya, Indonesia. In. Cancer Epidemiology and Control in the Asia-Pacific Region. pp. 113-127. Kobe University School of Medicine, Mahidol University, 1999.

Pathological Studies of Low Incident Gastric Cancer in Indonesian Population: Interest for Molecular Epidemiological Analysis in Multicenter Study

Santoso Cornain
Dept of Anatomic Pathology, Faculty of Medicine, University of Indonesia, Jakarta and Insitute for Genetic Medicine, Hokkaido University, Sapporo

Born in:	1942	
Past Records:	1968	M.D., University of Indonesia, Jakarta, Indonesia
	1971-1973	Research Fellow, The Netherlands Cancer Institute, Amsterdam, The Netherlands
	1974-1977	D.Sc. (PhD) in Tumor Biology, Karolinska Institute, Stockholm, Sweden
	1987	Bone Marrow Transplantation Histocompatibility Lab, Hospital Saint Louis, Paris, France
	1992,1996	Molecular Genetic of Tumors, Hokkaido University School of Medicine, Sapporo, Japan

Co-authors :
Vera Damayanti
Ening Krisnuhoni
Wirasmi Marwotro
Siti Oetarini Sri Widodo
Rukmini Rashid
Dept of Anatomic Pathology, Faculty of Medicine, University of Indonesia, Jakarta.

Abstract

Relatively low incidence of gastric cancer has been observed in Indonesian population, with estimated age standardized cancer rate from 1988 to 1999 of 0.71, 0.60, 0.70, 0.58, 0.58 per 100.000 population annually. It occurred more frequently among males (male to female ratio =1.9). Histopathological study on 109 cases (1985-1998) revealed that adenocarcinoma was found in 64.2 %, signet ring carcinoma in 28.4 %, sarcoma in 3.7 %, maltoma in 2.8 % and carcinoid in 0.9 % of cases. The age distribution peaked at 50-59 years age group. It is noteworthy to indicate that signet ring carcinoma occurred more frequently in older than 50 years in contrast to such type of colon cancer occurring more often in younger age group (20-39 years). The presence *of Helicobacter pylori* infection was examined in the biopsy specimen of gastric carcinoma and precancer lesions. The preliminary data showed the infection in low percentage (1/6) of both the intestinal type and the diffuse type or signet ring cell type (1/6) of gastric carcinoma, as compared to intestinal metaplasia (7/21). Our earlier study on biopsies of chronic inflammation detected *H. pylori* in 9/27 gastritis, in 4/18 gastric ulcer and in 2/2 duodenal ulcer. It is of interest, that the infection tend to occur preferentially to certain ethnic groups, namely Bataknese and Javanese with 50 % positivity. Such findings might have certain clue to the detailed analysis of risk factors with ethnic difference within heterogenous Indonesian population and between different races. In respect to contrasting risk in different populations, comparative study between populations with low and high, e.g. Indonesia and Japan, would be worthwhile. Possible difference in various genetic and environmental factors, namely inactivation of *p53* and APC, activation of *c-met*, reduction of *E-cadherin*, interaction with bcl-2 anti-apoptosis, certain growth factors and *Epstein-Barr* virus, might further elucidate different behaviors of gastric malignancy. Both molecular pathological and molecular epidemiological study could be proposed

in a multicenter structure and international collaboration, as exemplified by the Japan-Indonesia joint studies in breast and skin cancers.

Introduction

Gastric cancer occurs in relatively low incidence in Indonesia in contrast to that in Japan. Recently, the incidence of cancer in Indonesia has been attempted to be made using nearly nationwide pathology based cancer registry by collection of cancer cases in thirteen university pathology centers spread throughout the country. Relative frequency of stomach cancer in Indonesia ranked far below the 10 most frequent cancers from 1988 to 1992, namely cancers of uterine cervix, breast, ovary, skin, thyroid, corpus uteri, rectum, nasopharynx, lymph gland and colon, among females with estimated age standardized incidence rate per 100,000 of 30.03, 18.13, 7.63, 6.44, 4.9, 3.5, 3.22, 2.94, 3.71 and 2.1, respectively; while among males were cancers of the skin, nasopharynx, lymph gland, rectum, lung, prostate, soft tissue, colon, urinary bladder and nasal cavity with the figures of 6.3, 6.02, 5.39, 4.27, 2.45, 2.38, 3.29, 2.73, 2.52 and 2.66, respectively. Estimated age standardized rate of stomach cancer in Indonesia from 1988 to 1992 were 0.71, 0.60, 0.70, 0.58 and 0.58 per 100,000 population annually (1). In Japan, by 1995, the age standardized rate of stomach cancer was 66.5 as calculated based on world population or 93.4 as calculated based on Japanese model population of 1985 (2). Such contrasting rates of stomach cancer in two different population might be determined by different risk factors, including both external or environmental and internal factors, in particular genetic factors. A number of studies have reported the importance of nutritional risk factors, infectious agents, *i.e. Helicobacter pylori and Epstein-Barr* virus and genetic factors, *i.e.* inactivation of *p53* and APC, activation of *c-met*, reduction of *E-cadherin*, in interaction with *bcl-2* anti-apoptosis and certain growth factors (6,7).

It is of interest to elucidate the difference of the incidence in respect to possible difference in various genetic and environmental factors. Various clinicopathological aspects of stomach cancer in Indonesia and its relationship with the presence of *H. pylor*i have been studied in order to obtain preliminary data. The following paper will present the preliminary results and discuss the possible different behaviors of gastric malignancy due to different risk factors in two populations with contrasting incidence rate, such as Indonesia and Japan with low and high incidence rate, respectively. Therefore, a comparative study including both molecular pathological and molecular epidemiological study could be proposed between Japan and Indonesia.

Materials and Methods

Pathology based cancer registry was performed by collecting cancer cases diagnosed in the pathology laboratories of 13 university centers spread over Indonesia, namely Medan, Padang, Palembang, Jakarta, Bandung, Yogyakarta, Solo, Semarang, Surabaya, Malang, Denpasar, Ujung Pandang and Menado. Five years database from 1988-1992 were analyzed for relative frequency, ASCAR (age standardized cancer ratio) and estimated age standardized incidence rate using both the Indonesian population and adjusted to world population (1,3). The estimated incidence rate was derived by applying correction factor of 7, based on overall estimated coverage around 15%. The latter was compared to the data of limited population based cancer registry in Semarang (Central Java) in 1985-1989 (4). The changes of the incidence rate during five years were calculated according to log-linear model (5).

Histopathological study was performed on biopsy and surgical specimens collected from 1985 to 1998, standard morphological typing was used. The adenocarcinoma was subtyped into intestinal type and diffuse gastric type according to Lauren classification (6). The gastritis and the premalignant lesions were included as controls. The presence of *Helicobacter pylori* infection was analyzed in biopsy specimens collected from 1977 to 1999 by Giemsa staining; the

location was determined: cardia, corpus, fundus or pyloric antrum of the stomach. The data was analyzed according to gender, age group and local ethnic groups.

Results

Pathology based cancer registry of stomach cancer in Indonesia from 1988 to 1992 revealed 182 cases as collected from 13 university centers. Estimated age standardized cancer rates during five years were 0.71, 0.60, 0.70, 0.58, 0.58 per 100,000/year. The trend curve is given in figure 1. Males to females (M/F) ratio was 1.9. A rise of frequency occurred at age group of 34 to 44 years and peaked at 55 to 64 years.

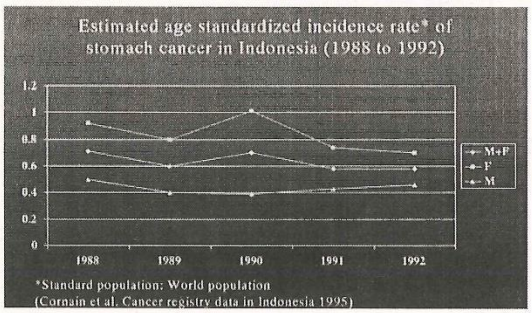


Figure 1. Age standardized incidence rate of stomach cancer in Indonesia (1988-1992)

The incidence rates of gastric carcinoma in Indonesia were significantly low as compared to the incidence rates in Japan, as shown in figure 2.

The age standardized rate per 100,000 population in 1995 was 66.5 according to world population or 63.4 according to Japanese 1985 model population.

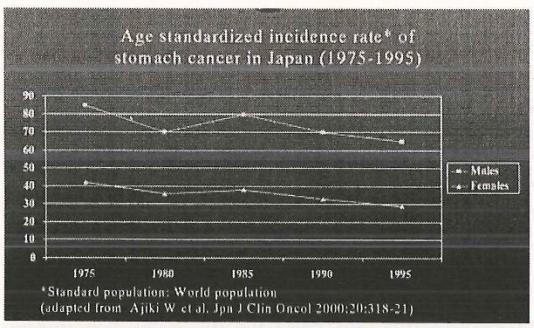


Figure 2. Age standardized incidence rate of stomach cancer in Japan (1975-1995)

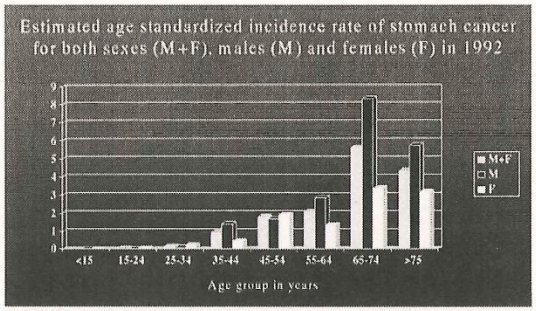


Figure 3. Age standardized incidence rates of stomach cancer in 1992 according to age distribution forboth sexes in Indonesia

Estimated age standardized incidence rate for both sexes and for males and females in 1992 are given in figure 3. It is of interest, that significant rise of cases has been started to be detected in the younger age group, namely 35 to 44 years.

The age distribution of stomach cancer in 1995 is given in figure 4.

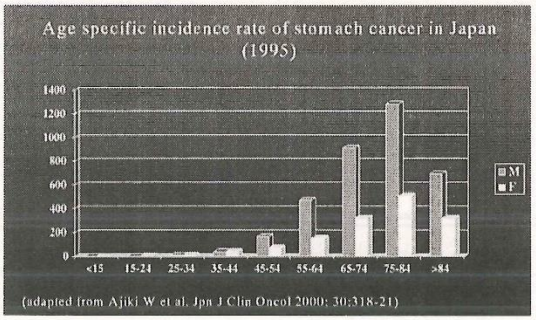


Figure 4. Age standardized incidence rate of stomach cancer in Japan (1995)

Histopathological study on 108 cases of gastric carcinoma collected from 1985 to 1998 at Department of Anatomic Pathology, Faculty of Medicine, University of Indonesia, Jakarta, revealed 64.2% adenocarcinoma, 28.4% signet ring cell carcinoma, 3.7% sarcoma, 2.8% maltoma (lymphoma) and 0.9% carcinoid. The age distribution peaked at 50 to 59 years group. Adenocarcinoma among individuals younger than 44 years was found in 30 cases, while

among individuals older than 50 years was found in 39 cases. Signet ring cell type was distributed differently, namely in 11 cases and in 20 cases respectively. The frequency distribution is given in figure 5.

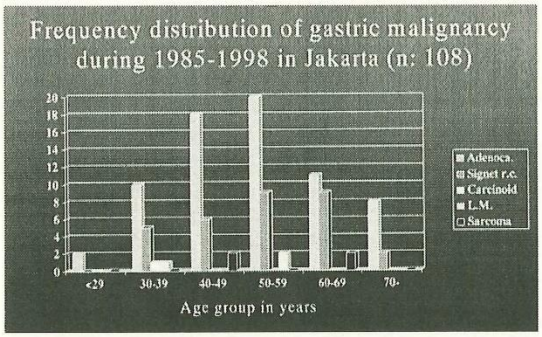


Figure 5. Frequency distribution of gastric malignancy in Jakarta

The distribution of signet ring cell carcinoma of gastric cancer was rather different from that of colon carcinoma. See figure 6. The cases were frequently encountered in younger age, namely in 20 to 29 years group.

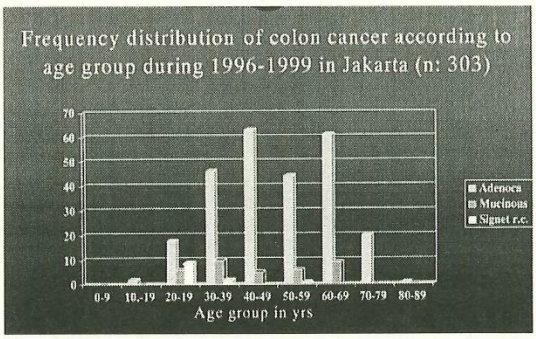


Figure 6. Frequency distribution of colon cancer in Jakarta (1996-1999)

During 1997 to 1999, a study on gastric malignancy and precancer lesion was performed. The distribution according to location is given in table 1.

Teble 1. Distribution of gastric malignancy and precancer lesion

Distribution of gastric malignancy and precancer lesions according to location (1997-1999)

	Antrum py.	Corpus	Cardia
Gastric ca. intestinal type	10	1	6
Gastric ca. diffuse type	2	1	1
Intestinal metaplasia	23	-	-
Severe dysplasia	1	-	-
Maltoma	1	1	-
Gastritis with lymph. follicle	1	-	-

The relationship to Helicobacter pylori infection is given in table 2. The infection was found in small proportion of gastric carcinoma, i.e. 3/17 of the intestinal type and 1/4 of the diffuse type. In contrast, the infection was frequently found in intestinal metaplasia, i.e. in 17 out of 23 cases.

Teble 2. Helicobacter pylori infection in gastric malignancy and precancer lesion

Helicobacter pylori infection in gastric malignancy and precancer lesions (1997-1999)

	-ve	+ve	Proportion +ve
Gastric carcinoma intestinal type	14	3	3/17
Gastric carcinoma diffuse type	3	1	1./4
Intestinal metaplasia	6	17	17/23
Severe dysplasia	0	1	?
Maltoma	0	1	?
Gastritis with Lymph. Follicle	0	1	?

The distribution of gastric malignancy and precancer lesion was also analyzed against local ethnic groups and the results are given in table 3. Both the intestinal type and the diffuse type of gastric cancer seemed to occur more frequently among Bataknese (North Sumatra Island) and Javanese (Java Island). However, the intestinal metaplasia were spread among Bataknese, Javanese, Sundanese and others.

Teble 3. Distribution of gastric malignancy and precancer lesion according to ethnic groups

Distribution of gastric malignancy and precancer lesions according to ethnic groups (1997-1999)

	Bataknese	Javanese	Sundanese	Others
Gastric ca. intestinal type	5	4	-	-
Gastric ca. diffuse type	3	-	1	-
Intestinal metaplasia	6	2	3	7
Severe dysplasia	-	1	-	-
Maltoma	1	-	-	-
Gastritis with lymph. follicle	1	-	-	-

In 1995, using another series of patients (n=79), the H. pylori infection was studied in relation to various mucosal pathological changes, *i.e.* minimal change (edema & hyperemia), chronic active gastritis, chronic non-active gastritis, gastric ulcer, signet cell ring carcinoma and adenocarcinoma. The location was distinguished whether in the fundus, antrum or undefined. The results showed that the infection occurred in more than half (18/34) of chronic active gastritis, 13 at antrum, 4 at fundus and 1 undefined. The infection in minimal change was in lower proportion (4/14), 2 at antrum, 1 at fundus and 1 undefined. H. pylori was not detected in limited number of the other pathological changes. The details are given in Table 4.

Teble 4. H. pylori infection in various mucosal pathological changes

Helicobacter pylori infection in various gastric mucosal pathological changes (1995)

	Antrum		Fundus		Undefined		Proportion
	-ve	+ve	-ve	+ve	-ve	+ve	+ve
Min. change (edema/hyperemia)	6	2	3	1	1	1	4/14
Chr. Active gastritis	23	13	8	4*	3	1	18/34
Chr. Gastritis nonactive	3	-	-	-	1	-	0/4
Gastric ulcer	1	-	-	-	2	-	0/3
Signet r.ca.	1	-	-	-	-	-	0/1
Adenocarcinoma	-	-	-	-	2	-	0/2

* : 1 at Antrum-Fundus boundary

The data was also analyzed against gender and age, as shown in Figure 7. *H. pylori* positive cases were detected among both males and females started from age group 20-29 years. The highest proportion (about the half) of female cases infected were of 30-39 years of age, while the highest proportion (about two third) among males were of 50-59 years of age.

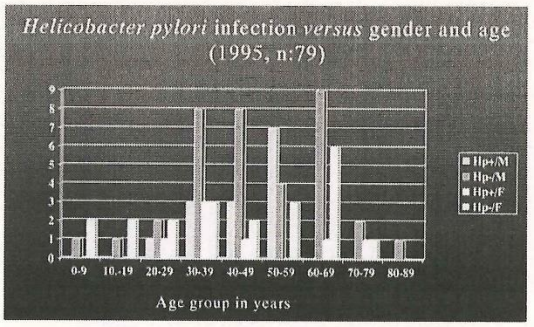


Figure 7.The distribution of H. pylori infection according to gender and age.

Discussion

From comparable data of cancer registry presented from Indonesia and Japan, we could see a contrasting risk of gastric cancer in two different populations, i.e. low in Indonesian and high in Japanese. Such difference might be due to different risk factors, including the host related factors (genetic, hormonal and immunological), lifestyle and environment. The incidence of stomach cancer varied worldwide, namely classified as low, i.e. less than 20; moderate, i.e. 20 to 50; and high, i.e. more than 50 per 100,000 annually. For instance, the figures for males and females in Senegal were 3.7 and 2.0, India were 8.9 and 6.0, USA were 10.0 and 4.3, England & Wales were 18.5 and 7.8, Slovakia were 31.7 and 14.5, Colombia were 48.4 and 25.5, China were 58.3 and 24.6 and Japan were 66.5 and 27.1 (2,9). It is of interest, that preliminary findings indicated certain degree of difference in the frequency of gastric cancer among different local ethnic groups in Indonesia. Further study using larger number of cases is required to elucidate further about the ethnic

difference. Since the Indonesian population is highly heterogenous, consisting of many ethnic groups living in well spread geographical areas with different environments, an expanded epidemiological study in a multicenter study is necessary. Such study is deemed important since the death rates of stomach cancer worldwide also varied relative to the above mentioned incidence rates. The decreasing trend of the death rates during the last 5 decades has been observed (10). However, the present incidence of stomach cancer remains high in certain areas and the decreasing death rate might be conceivable to the advances in diagnostic, treatment and screening procedures. The mass screening in Japan using barium photofluorography conducted since 1960 has been recently evaluated which revealed 70-90% sensitivity and 80-90% specificity, with 15-30% higher five-year survival for patients with screen-detected cancer compared to those with symptomatic cancer (11).

The data of the histopathological study revealed several interesting findings as well. The gastric cancer in Indonesian population tended to occur in relatively lower age group (5 to 10 years lower) as compared to other ethnic group. A special attention has been paid on the signet ring cell carcinoma, which occurred more often in the older group (older than 44 years); while this histological type in colon cancer occurred in younger age group (mostly in 20-29 years). *Helicobacter pylori* infection studied on the biopsy and surgical specimens was less frequent in gastric cancer as compared to gastritis and intestinal metaplasia. *Helicobacter pylori* has been known to be growing in the site without metaplastic changes. The data might show certain difference from other studies in other populations with high incidence of gastric cancer. *H. pylori* carriage, namely individuals with persisting exposure to the microorganism without gastric epithelial cell invasion, is an established risk factor for non-cardia gastric cancer. Controversial results remains to be observed in attempting to see its association with the risk of cardia gastric cancer.

In order to clarify such contrasting risk, molecular epidemiological study could be expected to obtain better assessment of risk factors. In parallel molecular pathological study is necessary for better identification of factors playing roles in the pathogenesis and its malignant behavior. Previous studies by others have revealed several lines of evidences, *inter alia*: 1). Inactivation of tumor suppressor genes p53 and APC versus loss of cell growth control; 2). Activation of c-met, K-sam, s-erb-2 versus proliferation and malignant behavior; 3). Reduction of E-cadherin versus invasion & metastasis potential; 4). The above mentioned factors and its interaction with: bcl-2 anti apoptosis, certain growth factors e.g. HCGF, FGF, infectious agents i.e. *Helicobacter* pylori and Epstein-Barr Virus. (6,12-23). Further studies have been going on to analyze further the association of *H. pylori* and the risk of gastric cancer in population with high incidence, i.e. China, using serological study against *H. pylori* whole cell and CagA antigens in well-characterized cohort (24). The results showed that seropositivity was associated with increased risks for both gastric cardia cancer and non-cardia gastric cancer. Recently, CagA positive *H. pylori* strains have been analyzed for its association with the pathogenesis of gastric mucosa-associated lymphoid tissue (MALT)-type lymphoma as well (25). Further evidence on the relationship of *H. pylori*-associated antibodies and the involvement of virulent type in the pathogenesis of gastric adenocarcinoma has been also reported (26). Finally, great concern about the length of chronic *H. pylori* infection in causing gastric cancer has been analyzed by reviewing all data of acquired infection in childhood. The study revealed that *H. pylori* infection seems to be associated with an increased risk of developing gastric cancer albeit in only small number of infected individuals, less than 1% (27).

Acknowledgement:

The present paper was prepared during the tenure of Visitng Prefessorship of S.C. at the Hokkaido University in 2000 and the travel fellowship has been provided by the Shizuoka Forum. The Pathology

based Cancer Registry has been supported by the Indonesian Cancer Foundation under Long-term Program of Cancer Research and Cancer Registry. We would like to thank Ms.Devieta Sari for assisting in data analysis and word processing.

References

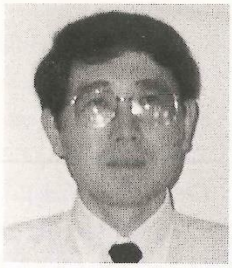
1. Cornain S, Mangunkusumo R, Nasar IM, Prihartono J. Ten most frequent cancer in Indonesia: Pathology based cancer registry data of 1988-1992. *In*: Cancer Registry in Indonesia. National Cancer Registry Center Jakarta Coordinating Board, 1995.
2. Ajiki W, Kinoshita N, Tsukuma H, Oshima A (The research group for Population-based Cancer Registration in Japan). Cancer incidence and incidence rates in 1995: Estimates based on data from nine population-based cancer registries. *Jpn J Clin Oncol 2000; 30:* 318-321.
3. Boyle P, Parkin DM. Statistical method for registries. *In*: Cancer Registration: Principles and Methods. Jensen OM, Parkin DM, MacLennan R, Muir CS and Skeet RG (Eds). IARC, Oxford University Press, Oxford 1991: pp. 126-58.
4. Sarjadi. Cancer Incidence 1985-1989 in Semarang, Indonesia. Indonesian Cancer Society, 1990.
5. Clayton D, Hills M. Statistical Models in Epidemiology. Oxford University Press, Oxford 1996: pp. 197-204.
6. Fenoglio-Preiser CM, Noffsinger AE, Belli J, Stemmermann GN. Pathologic and phenotypic features of gastric cancer. Semin in Oncol, 1996; 23: 292-306.
7. Tahara E. Molecular mechanism of stomach carcinogenesis. *J Cancer Res Clin Oncol 1993; 119:* 265-272.
8. Dekigai H, Murakami M, Kita T. Mechanism of *Helicobacter pylori*-associated dastric mucosal injury. Digestive Diseases and Sciences, 1995; 40: 1332-1339.
9. Tomatis L, et al (Eds). Cancer: causes, occurrence and control. Lyon, International Aency for Research on Cancer, 1990 (IARC Scientific Publication, No. 100).
10. Aoki K, Kurihara M, Hayakawa N, Suzuki S. Death Rates for Malignant Neoplasms for Selected Sites by Sex and Five-Year Age Group in 33 Countries: 1953-1957 to 1983-1987. International Union Against Cancer, The University of Nagoya Coop Press, 1992.
11. Davis P, Hakama M, Hisamichi S, Kakizoe T, Sano T, Sugimura T. Report of the thirteenth international symposium of the foundation for promotion of cancer research: Cancer screening-Past, present and future. *Jpn J Clin Oncol 2000;* 30: 322-31.
12. Dekigai H, Murakami M, Kita T. Mechanism of *Helicobacter pylori*-associated gastric mucosal injury. *Digest Dis and Sci 1995; 40:* 1332-9.
13. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, Sibley RK. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med 1991; 325:* 1127-31.
14. Tahara E. Molecular mechanism of stomach carcinogenesis. *J Cancer Res Clin Oncol 1993; 119:* 265-72.
15. Kitamura S, Kondo S, Shinomura Y, Kanayama S, Miyazaki Y, Kiyohara T, Hiraoka S, Matsuzawa Y. Met/HGF receptor modulates bcl-w expression and inhibits apoptosis in human colorectal cancers. *Br J Cancer 2000; 83:* 668-73.
16. Gulley ML, Pulitzer DR, Eagan PA, Schneider BG. Epstein-Barr virus infection is an early event in gastric carcinogenesis and is independent of bcl-2 expression and p53 accumulation. *Hum Pathol 1996; 27:* 20-7.
17. Sugiura S, Imai S, Tokunaga M, Koizumi S, Uchizawa M, Okamoto K, Osato T. Transcriptional analysis of Epstein-Barr virus gene expression in EBV-positive gastric carcinoma: Unique viral latency in the tumour cells. B*r J Cancer 1996; 74:* 625-31.
18. Tokunaga M, Land CE, Uemura Y, Tokudome T, Tanaka S, Sato E. Epstein-Barr virus in gastric carcinoma. *Am J Pathol 1993; 143:* 1250-4.
19. Saiki Y, Ohtani H, Naito Y, Miyazawa M, Nagura

H. Immunophenotypic characterization of Epstein-Barr virus-associated gastric carcinoma: Massive infiltration by proliferating CD8+ T-lymphocytes. *Lab Invest 1996; 75:* 67-75.

20. Takada K. Epstein-Barr virus and gastric carcinoma. *Epstein-Barr virus report 1999; 6:* 95-100.
21. Becker K-F, Atkinson MJ, Reich U, Becker I, Nekarda H, Siewert JR, Hofler H. E-cadherin gene mutations provide clues to diffuse type gastric carcinomas. *Cancer Res 1994; 54:* 3845-52.
22. Becker K-F, Hofler H. Frequent somatic allelic inactivation of the E-cadherin gene in gastric carcinomas. *J Natl Cancer Inst 1995; 87:* 1082-4.
23. Becker K-F, Kremmer E, Eulitz M, Becker I, Handschuh G, Schuhmacher C, Muller W, Gabbert HE, Ochiai A, Hirohashi S, Hofler H. Analysis of E-cadherin in diffuse type gastric cancer using a mutation-specific monoclonal antibody. *Am J Pathol 1999; 155:* 1803-9.
24. Limburg PJ, Qiao YL, Mark SD, Wanf GQ, Perez-Perez GI, Blaser MJ, Wu YP, Zou XN, Dong ZW, Taylor PR, Dawsey SM. Helicobacter pylori seropositivity and subsite-specific gastric cancer risks in Linxian, China. *J Natl Cancer Inst 2001;* 93: 226-33.
25. Grimley CE, Holder RL, Loft DE, Morris A, Nwokolo Cu. Helicobacter pylori-associated antibodies in patients with duodenal ulcer, gastric and oesophangeal adenocarcinoma. *Eur J Gastroenterol Hepatol 1999;* 11: 503-9.
26. Schmausser B, Eck M, Greiner A, Kraus M, Muler-Hermelink HK. Mucosal humoral immune response to CagA shows a high prevalence in patients with gastric MALT-type lymphoma. *Virchows Arch 2000; 436:* 115-8.
27. Imrie C, Rowland M, Bourke B, Drumm B. Is Helicobacter pylori infection in childhood a risk factor for gastric cancer? *Pediatrics 2001; 107:* 373-80.

Mortality Rate and Trends for Cervical Cancer in China, 1970's vs. 1990's

Liandi Li, Ling Yang, Xiaomei Huangpu, Fengzhu Lu, Siwei Zhang, Xiudi Sun, Ren Mu, Youlin Qiao.



Youlin Qiao

Professor and Chief, Dept.of Cancer Epidemiology, Cancer Institute/Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China

Born in: 1955

Past Records:
- 1976-1980 Medical diploma, Shichuan Medical College, Chengdu, PR Chine
- 1984-1989 Principal Investigator, Lung Cancer Case-Control Study among Tin Miners at Gejiu Yunnan, P.R. China (Grant from China State Science & Technology Commission)
- 1990-1996 Ph.D. The Johns Hopkins University, The School of Hygiene and Public Health, Baltimore, Maryland, USA.
- 1991-1997 Visiting Associate, Cancer Prevention Studies Branch, Division of Cancer Prevention and Control,National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.
- 1992- Scientific director,Co-principal investigator for the development of a Biologic Specimen Bank for the Study of Early Markers of Lung Cancer Among Tin Miners in Yunnan,China (NIH Contract No. NCI-CN-25420).
- 1997- Principal Investigator for A Comparative trial of Multiple Techniques to Detect Cervical Intraepithelial Neoplasia in Shanxi,China (Cleveland Clinic Foundation, USA).
- 1997- Principal Investigator, Environmental and Biological Monitoring Pilot Study for Polycyclic Aromatic Hydrocarbons (NIH Contract No. MQ-914682)
- 1998- Co-Principal investigator, Early Detection and Treatment of Esophageal Cancer in North-Central China (NIH Contract No. NO1-SC-91019)
- 1999- Co-Principal investigator, Follow-up of Nutrition Intervention Trials in Linxian China (NIH Contract No. NO1-SC-91030)
- 1999- Principal investigator, Linxian Parkinson's and Alzheimer's diseases study (NINDS/NIH and University of Rochester,USA)

Abstract

Objective To describe the distribution changes of the mortality rate for cervical cancer in China between the 1970's and 1990's and provide the scientific evidence for the prevention and control strategies for cervical cancer in China in next century.

Methods Data from two National Surveys for the Causes of Death in 1970's and 1990's in China. The crude and adjusted mortality rates for the cervical cancer and the distributions based on age, area were calculated and described. The comparison of the differences between two periods and trends were showed based on the age-standardized mortality rates.

Results During two decades, the mortality rate for cervical cancer was 10.7 per 100,000 in 1970's declined to 3.89 per 100,000 in 1990's, decreased about 63.64%, and from the 3rd ranking among all female malignant tumors to the 6th in 1990's. But the declination was not evenly. There still have some high-risk areas, most located in rural counties in the mid-west of China, with rates remain unchanged and even at the highest level in the world, such as Wudu in Gansu and Yangcheng in Shanxi. A big difference was showed between rural county and city, but in both of them, the mortality rates in 1990's were significantly much lower than in 1970's (P=0.001) at each five-year age group. And in the city, there was a much sharper increased trend in young women in 1990's.

Conclusions The mortality rate for cervical cancer in China has been substantially declined during past twenty years, but it's still a major health problem for women, especially in rural China. The focus of the

prevention and control for the cervical cancer in the next century should put on rural areas, especially in mid-west of China and young women in the city.

Keywords Cervical cancer Mortality Trends Survey

Cervical cancer is the third most common woman cancer. There are 371,200 new cases per year comprise 9.8% of all cancers in the world (1). In general terms, it is much more common in developing countries, where 78% of cases occur and cervical cancer accounts for 15% of female cancers, with a lifetime risk of about 3%, whereas in developed countries it accounts for only 4.4% of new cancers, with a lifetime risk of 1.1%.

China is the third largest country in the world and has a population of about 1.3 billion, comprising of 1/4 world population, most of whom live in the east or south areas more developed than west and north. Although China has a very long history of medical care and the data about cancer incidence and mortality have been collected for several decades, the resulting information had mainly been published in locally circulated printouts before. Cancer registration in China started in 1950's and was organized into a national scheme in late 1960's when National Cancer Research and Control Office been established. Since then, two national surveys of the causes of death were organized (2,3). The first one was undertaken in 1973-1975. It has gotten such great success as said that 'Few medical projects can ever have been successfully carried through that compare in scale with it. That immense task, which involved identification of about 20 million deaths in the three previous years and retrospective diagnosis of their causes, provided for the first time in indication of the sex- and age-specific mortality rates for the principal diseases affecting a fifth of the world's population.' (4) And the geographical distribution of cancer mortality in the country has been described in detail. The second survey was carried out in 1990-1992. It is a sample survey, the stratification was based on the mortality rate's distribution of the results of 1970's survey (2,3).

During these two decades, China had gotten a huge change due to the innovation and opening policy. The life style and health status was improved a lot. In this paper, we used the data from both of two national-wide surveys in 1970's and 1990's to describe the distribution of the mortality for cervical cancer in 1990's sampling survey. Then based on the comparison results between two periods, showed the changes of cervical cancer in China during that two decades and provide the scientific evidence for the prevention and control strategies for cervical cancer in China in next century.

MATERIALS AND METHODS

Data were extracted from national computer files on the two national mortality surveys from National Cancer Research and Control Office in China. Survey for causes of death in 1970's was a national-wide investigation and covered about 850 million people in China at that time. The 1990's survey covered 27 provinces and 1/10 population (about 100 million people). Two-stage stratified cluster randomized sampling method was used. The basic unit is county or a district in large city. 263 such units had been sampled, 74 units were cities and 189 were counties (2-4).

The crude and age-specific mortality rate for cervical cancer was estimated. Age-standardized mortality rates were calculated for each five-year age group, standardized by the Chinese standard population in 1982 and world standard population (announced in 1985, WHO). If the mortality rate for cervical cancer in one place is more than twice of national average level, that area was defined as a high-risk area. The age and geographic distribution of mortality rates for cervical cancer, especially in these high-risk areas were described here. The differences of mortality for cervical between two calendar periods and between city and rural were compared. In this paper, the comparing analysis between two periods was based on the age-standardized mortality rate data from the

same sample units as 1990's.

RESULTS

In 1970's, the mortality rate for cervical cancer was 10.7 per 100,000, age-standardized rate was 10.28 per 100,000, comprising 15.28% in all cancer death and ranked the 3rd among all female malignant tumors. But in 1990's the number corresponding changed to 3.89 per 100,000, 3.29 per 100,000, 4.86% and 6th rank respectively. The decreased rate was 63.64% (68.39% after age standardized) during that two decades.

As for the age-specific mortality rates for cervical cancer in two decades were also different (showed in Fig. 1): in 1990's, the rates increased from 20-year age and achieved a peak point at 70-year age then declined as well as in 1970's. But in 1990's, all of the age-specific mortality rates for each age group were all much lower than in 1970's. And from these two curves, the increasing and declining trends were all flatter in 1990's than in 1970's.

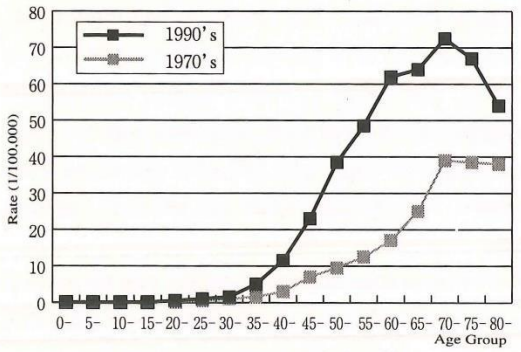


Fig.1 Tha Age-specified mortality raues for cervical cancer in China. 1970's and 1990's

Based on the data from 1990's survey, the frequency on different mortality level was showed in Fig. 2: two thirds of mortality rates were between 1~8 per 100,000. And from Table 1, the first three highest provinces, Shanxi, Gansu and Shaanxi were all located in the mid-west of China. The geographical distribution of cervical cancer was not evenly in China, most of rates in western and middle areas were much higher than in eastern of China.

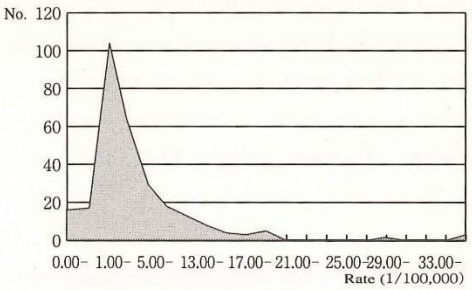


Fig.2 Tha frequency of samplinng sites by mortality rate for cervical cancer, China 1990-1992

Table.1 Tha mortality rates of cervical cancer per100,000 for some provinces in China,1990-92

Province	Crude rate	ASRC#	ASRW&
Shanxi	12.41	11.23	14.46
Gansu	11.44	11.88	15.17
Shaanxi	7.73	7.28	9.66
Hunan	7.74	6.63	8.80
Jiangsu	3.19	2.09	2.84
Guangdong	2.85	2.27	2.93
Beijing	2.04	1.34	1.88
Jilin	1.16	1.14	1.62

: Age-standardized Rate by Chinese standerd population; &: Age-standardized rate by world population

Table 2 showed the first ten high-risk areas in 1990's survey. There were 38 high-risk areas comprising 14.45% of all sampling areas and almost distributed among county or countryside. Most of these areas are located in the mid-west of China as showed in Table 1. The rates in some places among them were even at the highest level in the world, such as Wudu in Gansu and Yangcheng in Shanxi.

Table.2 Age-stsndardized mortality rates for the ten high-risk areas in Chinna, 1990-92 (per 100,000)

County	Mortality Rate
Wudu, Gansu	36.15
Yangcheng, Shanxi	35.71
Yuanba, Sichuan	27.57
Pingshun, Shanxi	18.66
Jingchuan, Gansu	18.27
Wuning, Jiangxi	17.58
Liuyang, Hunan	16.67
Heshui, Gansu	15.18
Shanyang, Shaanxi	14.59
Longxian, Shaanxi	13.54

* Age-standardized rate by world population;
# the mortality proportion for cervica cancer among all cancers

As compare the rates in rural county and in the city of China, according to the age-standardized rate by Chinese standard population, the rates in 1990's were 2.45 per 100,000 in city and 3.60 in rural area. The proportion and rank in cancer were 3.93% and 8th in city and 4.71% and 5th in rural respectively. During these two decades, the distribution for the mortality rate for cervical cancer was also much different from each other. Fig. 3 and Fig. 4 showed the age-specific logrithmic mortality rates for cervical cancer for two calendar periods among female in city and in rural of China. During these two periods, the difference for the cervical cancer in city is much bigger than in rural, but in both of them, the mortality rates in 1990's were significantly much lower than in 1970's (P=0.001). And in the city, there was a much sharper increased trend in young women (20 to 25-year age group) in 1990's than in 1970's. Fig. 5 showed the cervical cancer age-standardized mortality rates decreased from 1970's to 1990s. Only Gansu Province where cervical cancer mortality rate increased, all of others declined. The most declined is in Hunan Province, from 20.61 to 6.63 per 100,000. But in some areas, especially in mid-west of China where the SES was much lower than others, the rate remains unchanged or not significant.

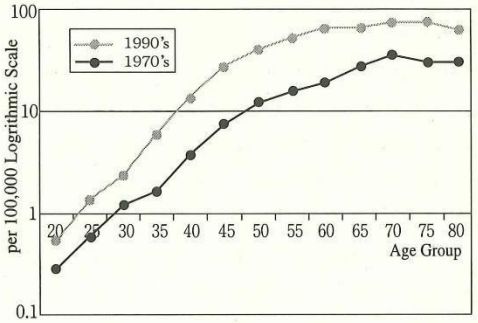


Fig.4 Mortality rate for cervical cancer for the two calender periods by birth, in Rural of China

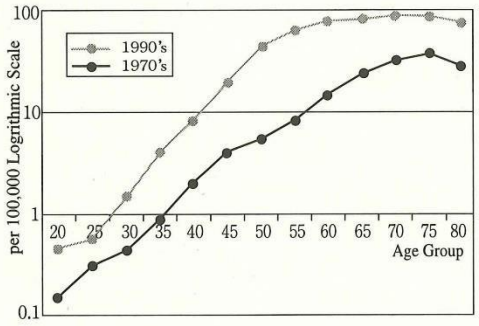


Fig.3 Mortality rate for cervical cancer for the two calender periods by birth, in City of China

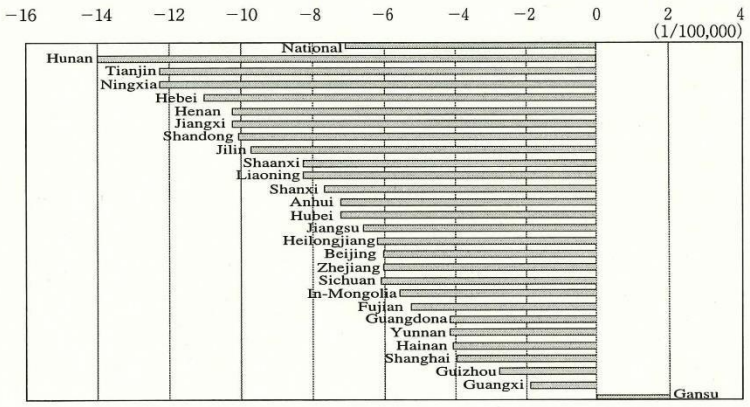


Fig.5 The decreased mortality rate (China age-standardized) for cervical cancer mortality rate decreased from 1970's to 1990's in China

DISCUSSION

Based on the comparison results from 1970's and 1990's, the mortality rate for cervical cancer declined by about 68% during last 20 years in China. Compared with other countries, the rank for the cervical cancer mortality in China also declined from high level in 1970's to mid-level in 1990's(5). This result significantly showed that the prevention and control for cervical cancer in China had gotten a compelling success, the introduction of organized mass screening programs played an important role (2,3).

Now there is growing evidence that cervical cancer is sexually transmitted. The major risk factors for cervical cancer include age at first intercourse, multiple sexual partners, oral contraception, and low social class (1,6-8). And the HPV has been convincingly identified as the most likely agent responsible for the disease (9). Screening for cervical cancer has been demonstrated to be effective and the implementation of mass screening programs is likely to be responsible for the decline observed in both mortality and incidence of invasive cancer in several countries (10-16).

During that two decades, the rates in city decreased (78%) more than in countryside (64%). This largely accounted for using more Pap smear screening and having higher social economic status (SES) in city than in rural. By now, there are still more than 100,000 new cases per year at present, comprising 1/4 of world incidence of cervical cancer, and more than 20,000 death per year due to cervical cancer in China. Nearly 1/3 regions in county or countryside still had very high-level mortality rate for cervical cancer. Some rates among them remaining unchanged and at the top level of the world such as Wudu in Gansu and Yangcheng in Shanxi. And most of the high-risk areas were located in the mid-west of China where in the backland of China and with much lower social-economics status (SES) than other areas. Local people there have not enough health care facilities and knowledge. Aimed at that problem, some researchers are now studying some feasible and highly effective screening methods, such as HPV self-test or highly sensitively cytological techniques for different developing statuses (17,18).

The death constituent ratio for each age group suggested that cervical cancer often occurred after middle age, the mortality between 45-75 year age represents 81.5% of total death. So the emphases of prevention and control for cervical cancer should focus on 45-65 year age in China. And since cervical cancer related with smoking, the increased number of young smoking-women in China, especially in the city, was also play an important role for the rates. The sharply increased trend for cervical cancer in young women in city was showed in Fig. 3. Thus for the prevention strategy for cervical cancer in city, we suggest that prevention for cervical cancer should be begun earlier than 45, maybe at 35 or 40 year old.

CONCLUSION

Although the overall mortality rate for cervical cancer in China has been substantially declined during past twenty years, but according to the unbalanced declination between city and rural areas, cervical cancer is still a major health problem for women in rural China. By now, there still have some counties where the rate remaining unchanged and young patients of cervical cancer increasing in the city. So the focus of the prevention and control for the cervical cancer in next century should put on rural areas, especially in mid-west of China and young women in the city. Mass and efficient screening program should be used in national wide to decrease the cervical cancer incidence and mortality rate in next century.

[Supported by National Program for Key Medical Science and Technology Projects, the 8th Five-year Plan, PR China (Grant # : 85-914-01-07)].

REFERENCES

1. D. Max Parkin, Paola Pisani, J. Ferlay Global Cancer Statistics. CA Cancer J Clin, 1999, 49(1): 33-64
2. L.D. Li, F.Z. Lu, S.W. Zhang, et al. Analysis of variation trend and short term detection of

Chinese malignant tumor mortality during twenty years. Chin J Oncol, 1997. 19(1): 3-9

3. L.D. Li, F.Z. Lu, S.W. Zhang, et al. Analysis of cancer mortality and distribution in China from year 1990 through 1992. An Epidemiologic study. Chin J Oncol, 1996. 18(6): 403-7
4. J.S. Chen, T.C. Campbell, J.Y. Li, et al. Diet, Life-style and Mortality in China. A study of the characteristics of 65 Chinese counties. Oxford Univ. Press; Cornell Univ. Press; People's Medical Publishing House, 1991.
5. WHO. World Health SAnnal. Annals. Geneve, 1994.
6. Isabel dos Santos Silva. Cancer Epidemiology: Principles and Methods. 1999, IARC Lyon, France
7. N. Munoz, Ex Bosch, K.V. Shah, et al. The Epidemiology of Cervical Cancer and Human Papillomavirus. 1992, Lyon, International Agency for Research on Cancer
8. Schiffman MH, Brinton LA. The Epidemiology of Cervical Carcinogenesis. Cancer Suppl.,1995,76(10)
9. David M. Eddy. Screening for Cervical Cancer. Annals of internal medicine,1990,113,214-226
10. M.P. Coleman, J. Esteve, P. Dammecki Trends in Cancer Incidence and Mortality. IARC Scientific Publication, No. 121, LYON, 1993
11. Christopherson WM, Lundin FE, Mendez WM, et al. Cervical cancer control. A study of morbidity and mortality trends over a twenty-one year period. Cancer, 1976; 38:1357-66.
12. S.E. Munoz, L Chatenoud, C La Vecchia, et al. Trends in cancer mortality in Argentina, 1966-91. Eur J Cancer Prevention, 1998, 7(1): 37-44
13. Tiiu Aareleid, Eero Pukkala, Heldi Thomson, et al. Cervical cancer incidence and Mortality trends in Finland and Estonia: a screened vs. an unscreened population. Eur J Cancer, 1993, 29A(5): 745-49
14. AJ Swerdlow, I dos Santos Silva, A Reld, et al. Trends in cancer incidence and mortality in Scotland: description and possible explanations. British J of Cancer, 1998, 77(Supp. 3): 1-16
15. Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: Association with organized screening programmes. Lancet, 1987;1(8544): 1247-49.
16. Cancer Prevention and Control Office in China Health Ministry. Investigate for Malignant tumor Mortality in China. People's Health Publish House, 1979.
17. L Yang, WH Zhang, QJ Pan, et al. A pilot study for cervical cancer screening in Shanxi Province. Bulletin of Chinese Cancer, 2000, 9(9): 391-2.
18. J Belinson, YL Qiao, R Pretorius, et al. Shanxi Province Cervical Cancer Screening Study, A Cross-Sectional Comparative Trial Of Multiple Techniques To Detect Cervical Intraepithelial Neoplasia. (J) (Submitted to Lancet)

Adult T-cell Leukemia/Lymphoma in Japan: Epidemic Pattern and Prevention Strategy

Kazuo Tajima
Div. of Epidemiol. and Prev., Aichi Cancer Center Res. Inst., JAPAN

Born:	1947	
Past Records:	1966-1972	Osaka University,Faculty of Medicine
	1972-1973	Resident,Osaka Univ.Hosp.,Dept.of Orthopedic Surgery
	1973-1977	Surgeon,Seirei Mikatabara Hosp.,Hamamatsu,Dept. of Surgery
	1977-1979	Fellow,Aichi Cancer Cent.Hosp.,Dept.of Clin.Pathol.& Lab.
	1981-1987	Research Staff,Aichi Cancer Center Res.Inst.,Div.of Epidemiol.
	1985-1986	Ohns Hopkins University,School of Hygiene and Public Health
	1987-1990	Section Head,Aichi Cancer Center Res.Inst.,Div.of Epidemiol.
	1990-1999	Chief,Aichi Cancer Center Res.Inst.,Div.of Epidemiol.
	2000-	Chief,Aichi Cancer Cent.Res.Inst.,Div.of Epidemiol.& Prev.

Summary

Human T-cell leukemia virus type I (HTLV-I) and its related disease, adult T-cell leukemia/lymphoma (ATL), are distributed all the world over but mainly clustered in isolated ethnic groups, Mongoloids in Asia and South America, Blacks in Africa and the Caribbean, and Melanesians in Oceania. In Japan approximately 1.2 million HTLV-I carriers may exist and 700~1,000 new cases of ATL are generally found with the biennial nationwide hospital-based surveillance. Most HTLV-I carriers and patients with ATL are detected in South Japan, Kyushu Island and South Shikoku. The micro-geographical distribution of HTLV-I carriers on a typical ATL endemic Japanese island mirrors that in Japan in general and the world. A cross-sectional sero-epidemiological survey of HTLV-I carriers among several groups in Japan showed distinctive features for age- and sex-specific distribution. ATL has been classified into four subtypes, acute, lymphoma, chronic and smoldering, with refer to clinico-pathological features. The lifelong risk of ATL among persistent HTLV-I carriers in men is estimated at 4-6% while risk in females is relatively low. In line with the aging of HTLV-I carriers, the average age of ATL patients is becoming older, e.g., from 58.2 years in 1988-89 to 60.3 years in 1994-95. With regard to the risk of ATL after HTLV-I infection, host-specific factors, e.g., genetic character, are more likely than environmental factors. Ethnicity-based epidemiological studies on HTLV-I and its related disease can provide important evidence for the risk of virus-associated cancers. The major transmission routes of HTLV-I under natural conditions are vertical transmission from mother-to-child through breast milk and horizontal transmission from man-to-woman through semen. The most effective preventive measure against HTLV-I is control of the manner of breast-feeding of HTLV-I carrying mothers. From the main result of long-term prevention trial against mother-to-child transmission of HTLV-I in ATL endemic islands, we recommend two available choices for HTLV-I carrying pregnant women, complete quitting of breast-feeding or short-term (3-6 months) breast-feeding.

Introductlion

Human T-cell leukemia virus type (HTLV-I)[1,2] is the main causal agent of adult T-cell leukemia/lymphoma

(ATL)[3] which is spread throughout the world, whereas HTLV type II (HTLV-II)[4] is detected in very limited groups in America and Africa[5]. Phylogenetically, three subtypes of HTLV-I, which were defined as groups of viral strains with common nucleotides at any provirus portion of DNA sequence, are assigned as the cosmopolitan, central African and Melanesian[6]. HTLV-II is classified into two main subtypes as to IIa and IIb which are commonly found in drug users and American natives, respectively[7]. The unique ethnic clusters of patients with HTLV-I associated diseases in the world could be explained by the natural history of familial transmission of HTLV-I which is limited via mother-to-child (breast feeding) and man-to-woman (sexual contact). The present study reviews the geographical and demographic distribution of HTLV-I, clinico-pathological features of ATL, its risk factors and essential preventive measures.

Worldwide Distribution of HTLV in the World

In Africa, carriers of HTLV-I are clustered in the central and western tropical countries where HTLV-I carriers among general people ranged 0-20%[5]. Highly endemic areas were detected in southern Gabon and northern Zaire. On the other hand, less than 1% of the people showed positive for anti-HTLV-I antibody in northern Africa. HTLV-II is also endemic in specific Pygmy tribes from Zaire and Cameroon[8,9].

In the southeast Asian countries other than Japan, only a hunting-gathering people, the Aeta in the Philippines, show an extremely high rate of HTLV-I carriers[10]. A recent study showed that more than 10% of the Mashadi Jews in northern Iran carried the virus[11]. In other central Asian countries, sporadic distributions of HTLV-I carriers and patients with ATL were disclosed recently among Chinese on the east coast of China, Singapore, and Hong Kong, Koreans in Korea, Indians in Singapore and India, Jewish in Israel[5,12]. We found no evidence of any HTLV-II clustering area and/or ethnic group in Asian countries.

In South America, HTLV-I carriers are widely distributed among Amerindian people who live along the Andes mountains from Colombia to Chile[13,14]. In the Andes of South America, carriers were found only among an isolated indigenous people living in a central hinterland located several hours by jeep from the center of a large city. A recent report suggests that HTLV-II is widely distributed among American natives from the Central America to the southern end of America. As observed throughout the world, HTLV-I/II shows a geographical distribution that is linked to the modern history of human migration.

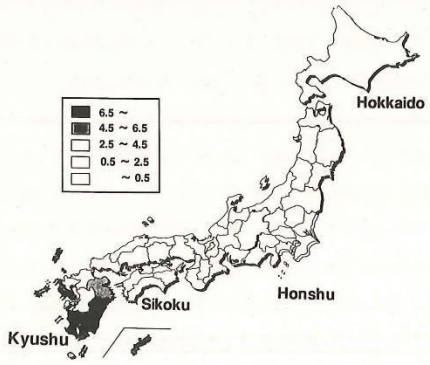
Diagnostic Criteria of ATL

ATL caused by HTLV-I has been classified into four subtypes[15], acute type, lymphoma type, chronic type and smouldering type, by clinico-pathological features. Among 2,123 ATL cases registered in the whole Japan from 1988 to 1995[16-18], more than 60% cases were classified into acute type, and then 24%, 8% and 5% were grouped into lymphoma type, chronic type and smoldering type, respectively Acute type is the most common ATL (prototype of ATL) and its clinico-pathological features are pleomorphic cells infiltration, lympocytosis, hypercalcemia, skin lesion and hepatosplenomegaly. Lymphoma type showed similar clinical course except blood involvement at onset. Chronic type is characterized by persistent T-cell lymphocytosis with atypical cells, but this does not show organomegaly and hypercalcemia. Smouldering type referred to pre-leukemic ATL is characterized by skin lesion and lung infiltration.

Macro- and Micro-Geographic Distribution of ATL and HTLV-I in Japan

According to evidence obtained from a biennial nationwide surveillance of ATL carried out in Japan since 1986, the annual incidence is estimated to be 700 from approximately 1.2 million HTLV-I carriers in Japan. Those patients with ATL and HTLV-I carriers are found mainly in the southern and northern ATL endemic areas (Fig. 1)[18]. Among 2,123 ATL cases newly diagnosed during the 8 years from 1988 to 1995, 70% of the ATL patients were born in the

(Fig. 1)



Geographical distribution of Estimated Incidence Rate of ATL in Japanese prefectures in 1990-95
(Data source : The T- and B-cell Malignancy Study Group,1998)

southwestern districts of Kyushu and Shikoku, and 8.5% in the northern districts of Hokkaido and Tohoku, and thus consistently related to that of HTLV-I carriers (Table 1) in this country.

The microgeographical distribution of HTLV-I carriers on an ATL endemic island of Japan mirrors that in Japan and the world[19]. There were many HTLV-I carriers in places isolated from neighboring villages by steep and rocky forests and where people from different villages did not often visit each other because of the difficulty of transportation. On the other hand, carriers were relatively few in each northernmost and southernmost villages. The proximity of the low-rate village to the highly endemic villages, it is suggested that this virus does not spread easily under natural conditions.

Demographic Features of HTLV-I and ATL

A cross-sectional sero-epidemiological survey on HTLV-I carriers among several ethnic groups in the

Table 1) Distribution of anti-HTLV-I positives [1] in adults in northern and southern ATL-endemic districts of Japan

District	Area	(subarea/Group)	subjects	positive rate(%)
Hokkaido	central south	(Hidaka)	1,434	2.6
		(Ainu)[2]	419	18.4
Shikokusouth coast		(Uwajima)	6,239	7.5
		(Kochi)	2,558	3.6
Kyushu Northwest		(Saga)	2,000	3.9
		(Sasebo)	1,999	9.3
		(Nagasaki)	2,989	6.7
	Northwest island	(Tsushima)	2,585	22.7
		(Goto)	4,079	25.9
	Southeast	(Miyazaki)	2,000	7.4
	South	(Kagoshima)	2,533	11.7
Okinawa	Main island	(North)	2,398	18.3
		(Central)	582	24.1
		(South)	1,454	32.6
	Southern island	(Miyako)	1,254	5.2
		(Yaeyama)	574	33.4

1) Anti-HTLV-Iantibody was confirmed by immunofluorescence test.
2) Blood samples from a native Japanese(Ainu)were collected about 30 years ago (1966-70) Referred from Tajima and Hinuma, 1992

world showed distinctive features in age- and sex-specific distribution: a remarkable discrepancy in carrier rates of HTLV-I between younger and older generation groups as well as between older males and females (Table 2) [12,20-23]. Only in Papua New Guinea there is no discrepancy in HTLV-I distribution between age group and gender. In Japan, more than 96% of the patients are over 40 years old as shown in a survey taken in 1988-1995. The age-specific incidence rate of ATL increases steeply with age of above 40 up to 70 years and then decreases in both sexes (Fig. 2). The epidemic curb of age-specific incidence rate in the 8th surveillance (1994-95) showed a little deviation to the older generation compared with that in the 5th surveillance (1988-89), especially in males.

Natural Transmission of HTLV-I

The primary route appears to be transmission from a mother with HTLV-I antigen-positive lymphocytes in her breast milk to her child[24,25]. This vertical transmission occurs until approximately 1-2 years of age and remains stable until young adulthood. It is rare that antibody expression after transmission of HTLV-I would be delayed for as long as several decades. Therefore, it has been suggested that seroconversion after vertical transmission of HTLV-I occurs during the first 2-3 years. It was reported that the overall infection rate from carrier mothers to their children (younger than 19 years) was 10-30% in Japan.

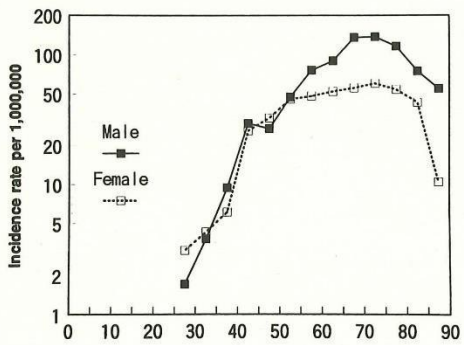
The second important route of natural transmission is horizontal transmission between men and women[24,26]. A study of married couples strongly suggests that HTLV-I is transmitted mainly from husband to wife. Between two partners in a marriage, the limited conditions checked suggest that the infected T cells of the carrier enter the non-carrier's body, so that transmission from wife to husband does not easily occur. The detection of HTLV-I in semen

Table 2) Age -and Sex-specific Positive Rate of anti-HTLV-I Among Epidemic Areas in Asia

Age	Japan			Taiwan	Papua
years	Hokkaido	Uwajima	Tsushima		New Guinea
	(29,516)	(6,651)	(6,615)	(3,541)	(786)
	M/F	M/F	M/F	M/F	M/F
-19	0.1/0.3	1.1/1.3	2.2/2.8	0.0/1.0	3.3/3.6
20-39	0.5/0.7	2.4/4.1	17.4/20.0	2.3/2.4	3.3/3.1
40-59	0.8/1.3	4.4/9.6	21.1/30.0	5.5/9.0	0.0/0.0
60-	1.2/1.6	8.5/10.8	23.5/34.3	9.9/16.8	Unknown

from kondo et al,1989 ; kwon et al,1994 ; Tajima et al,1955;wang et al,1988 ; Imai et al,1990

(Fig. 2)



Chronological change of age-and sex-specific incidence rate of ATL from 1988-89(the 5th surveillance)to 1994-95 (the 8th surveillance)in Kyushu,Japan
(Data source : The T-and B-cell Malignancy study Group,1998)

from carrier males supported the possibility of the one-way transmission from males to females via semen. Possible explanations for the universal increasing trend with age in the carrier rate among women (Table 2) are thought to be the increased transmission risk by cumulative exposure to the virus through repeated sexual contacts.

Risk and Risk Factors of ATL Among HTLV-I Carriers

The annual incidence rate of ATL in Japan was estimated at 0.6 among 1,000 adult HTLV-I carriers in the ATL-endemic areas[27]., approximately 1/1,000 in males and 1/2,000 in females older than 40 years old which was not very different from that in Jamaica (Table 3) [21,23,28]. As pointed out before, age distribution of ATL in Jamaica shifted into younger generation compared to those in Japanese patients. The most important factor of age variation in patients with ATL between two areas may depend on a different life span which influence directly a age distribution of HTLV-I carrying persons as the background population at risk of ATL.

In the southwestern Japan, the preleukemic cases of ATL (pre-ATL) having the monoclonal proliferation of abnormal lymphocytes without clinical signs and symptoms were studied. The prevalence rate of pre-ATL, that is, patients with monoclonal integration of HTLV-I among HTLV-I carriers older than 30 years was estimated at 2% and the age distribution of pre-ATL cases ranged from 30-77 was not different from that of overt cases of ATL[27]. Pre-ATL is presumed to be the clinical stage which precedes ATL, however, the possibility remains that the HTLV-I carrier may develop symptoms of ATL directly, without going through the pre-ATL stage.

As a host-specific risk factor of ATL, family history of ATL and/or lymphoid malignancies was picked up by a case study and a case-control study. The existence of a genetic factor has recently been recognized, and it has been suggested that some host-related background for ATL patients may exist. A genetic factor of ATL was studied with regard to the immune response to HTLV-I by analyzing the HLA haplotype and HTLV-I immune responsiveness. A previous study showed that most ATL patients have specific HLA haplotypes which were detected in a minority of a Japanese subpopulation[30]. This suggested that patients with acute ATL and HAM have different genetic backgrounds.

Several case-control studies on ATL were conducted in Japan. There is no question that HTLV-I is a determinant risk factor for ATL manifestation. Besides HTLV-I, habitual smoking was picked up as a risk factor of ATL. Generally, habitual smoking is one of the common risk factors of many sites of cancers and there is some possibility that some fractions in cigarette smoke enhance the risk of ATL among

Table 3) Age - and Sex-specific Incidence Rate Estimated among 1,000 HTLV - I Carriers in the ATL Endemic Areas

Age	Kondo (Uwajima)		Tokudome (Saga)		Murphy (Jamaica)	
years	male	female	male	female	male	female
30-39	0.95	0.41	0.00	0.48	0.94	1.10
40-49	0.83	0.66	1.19	0.63	1.12	1.10
50-59	2.10	0.33	1.16	0.58	1.26	0.83
60-69	2.00	0.98	1.20	0.78	0.30	0.38
>40	1.50	0.58	1.06	0.61	0.80	0.71
cumulative risk						
in 30-69 years,		59 24		36 25		33 30

from kondo et al,1989;Tokudme et al,1989;Murphy et al,1989

HTLV-I carrying people[31]. There is a similarity in the geographical distribution between the recent ATL-endemic areas and the past microfilaria carriers in Japan[32]. Filarial parasites impair the function of their host immune system, and the immune reactivity of T lymphocytes is strikingly suppressed in parasite-infected hosts. In Okinawa a strong correlation was found between the positive rate of anti-HTLV-I antibody and infection rate of Strongyloides stercoralis (ST) among the general population in the ATL-endemic areas[33]. It was suggested that some specific but unknown antigen from these parasites might have played an important role in the etiology of HTLV-I infection and/or its proliferation in the host.

Practical Prevention Strategy

To establish a desirable measure against vertical transmission of HTLV-I, several prospective studies in highly endemic areas where 5-15% of pregnant women carried HTLV-I have been conducted since 1985. Fundamentally, pregnant women found to be positive against anti-HTLV-I antibody are recommended not to breast-feed their newborn babies and they received bromocriptine mesilate immediately after delivery to stop secretion of breast milk and the other mothers proceeded to breast-fed[34]. The results obtained from 3-year-old children whose anti-HTLV-I antibodies had been confirmed showed that around 2-4% became antibody positives. On the other hand, 10-20% of breast-fed children became positives. Among them only 3-8% of children breast-fed for less than 6 months were infected with HTLV-I. The results obtained from those cohort studies showed breast-fed term-related increment on transmission risk of HTLV-I in babies from mother with HTLV-I (Table 4).

A complete stop to her breast-feeding is most effective prevention strategy, however, maternal antibody through breast milk during the first 5 months protect babies from not only HTLV-I but also other infectious agents which may generate a fatal condition for newborn babies, just as a dilemma of general public health. A short-term breast-fed which still remains a little risk of maternal infection of HTLV-I would be recommendable instead of bottle-fed, especially under the poor nutritional status for newborn babies in the developing countries.

Table 4) Seroconversion rate of HTLV -I antibody among children from HTLV-I carrier mothers by period of breast feeding in two islands in kyushu,japan

Gorup	period of breast feeding (Type of breast feeding)	positives/Subjects	positive rate (95%confidence interval)
A	0 month (Bottle feeding)	4/162	2.5% (0.1-4.9%)
B	1-6 months (Short term feeding)	2/51	3.9% (0.0-9.2%)
C	>6 months (Long term feeding)	13/64	20.3% (10.5-30.2%)

* Difference in the seroconversion rate between group C and group A&B is statistically significant.
from Takezaki et al,1997

Referenes

1. Poiesz, B.J., Ruscetti, F.W., Gazdar, A.F., Bunn, P.A., Minna, J.D. and Gallo, R.C. (1980) Detection and isolation of type-C retrovirus particles from fresh and cultured lymphocytes of patients with cutaneous T-cell lymphoma. Proc. Natl. Acad. Sci. USA 77, 7415-7419.
2. Hinuma, Y., Nagata, K., Hanaoka, M., Nakai, M., Matsumoto, T., Kinoshita, K., Shirakawa, S. and Miyoshi, I. (1981) Adult T-cell leukemia: Antigen in an ATL cell line and detection of antibodies to the antigen

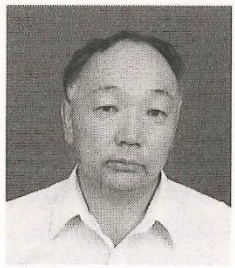
in human sera. Proc. Natl. Acad. Sci. USA 78, 6476-6480.

3. Uchiyama, T., Yodoi, J., Sagawa, K., Takatsuki, K. and Uchino, H. (1977) Adult T-cell leukemia: Clinical and hematologic features of 16 cases Blood 50, 481-492.
4. Kalyanaraman, V.S., Sarngadharan, M.G.,Å@Robert-Guroff, M., Miyoshi, I., Blayney, D., Golde, D. and Gallo, R.C. (1982) A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia. Science 218, 571-573.
5. Tajima, K. and Hinuma, Y. (1992) Epidemiology of HTLV-I/II in Japan and the world. GANN Monogr. Cancer Res. 39, 129-149.
6. Miura, T., Fukunaga, T., Igarashi, T., Yamashita, M., Ido, E., Funahashi, S., Ishida, T., Washio, K., Ueda, S., Hashimoto, K., Yoshida, M., Osame, M., Singhal, B., Zaninovic, V., Cartier, L., Sonoda, S., Tajima, K., Ina, Y., Gojobori, T., and Hayami, M. (1994) Phylogenetic subtypes of Human T-lymphotropic virus type I and their relations to the anthropological background. Proc. Natl. Acad. Sci. USA 91, 1124-1127.
7. Ijichi, S., Tajima, K., Zaninovic, V., Leon, F.E., Katahira, Y., Sonoda, S., Miura, T., Hayami, M., Hall, W.W. (1993) Identification of human T cell leukemia virus type IIb infection in the Wayu, an aboriginal population of Colombia. Jpn. J. Cancer Res. 84, 1215-1218.
8. Gessain, A., Mauclere, P., Froment, A., Biglione, M., Hesran, J.Y.L., Tekaia, F., Millan, J. and de-The, G. (1995) Isolation and molecular characterization of a human T-cell lymphotropic virus type II (HTLV-II), subtype B, from a healthy Pygmy living in a remote area of Cameroon: An ancient origin for HTLV-II in Africa. Proc. Natl. Acad. Sci. USA 92, 4041-4045.
9. Goubau, P., Desmyter, J., Swanson, P., Reynders, M., Shih ,J., Surmont, I., Kazadi, K. and Lee, H. (1993) Detection of HTLV-I and HTLV-II infection in Africans using type-specific envelop peptides. J. Med. Virol. 39, 28-32.
10. Ishida, T., Yamamoto, K. and Omoto, K. (1988) A seroepidemiological survey of HTLV-I in the Philippines. Int. J. Epidemiol. 17, 625-628.
11. Meytes, D., Schochat, B., Lee, H., Nadel, G., Sidi, Y., Cerney, M., Swanson, P., Shaklai, M., Kilim, Y., Elgat, M., Ghin, E., Danon, Y. and Rosenblatt, J.D. (1990) Serological and molecular survey for HTLV-I infection in a high-risk Middle Eastern group. Lancet 336, 1533-1535.
12. Wang C-H, Chen C-J, Hu C-Y, You S-L, Chu C-T, Chou M-J, Essex M, Blattner WA, Liu C-H and Yang C-S: Seroepidemiology of human T-cell lymphotropic virus type I infection in Taiwan Cancer Research 48: 5042-5044, 1988.
13. Zaninovic, V., Sanzon, F., Lopez, F., Velandia, G., Blank, A., Blank, M., Fujiyama, C., Yashiki, S., Matsumoto, D., Katahira, Y., Miyashita, H., Fujiyoshi, T., Chan, L., Sawada, T., Miura, T., Hayami, M., Tajima, K. and Sonoda, S. (1994) Geographic independence of HTLV-I and HTLV-II foci in the Andes Highland, the Atlantic Coast, and the Orinoco of Colombia. AIDS Res. Human Retroviruses 10, 97-101.
14. Fujiyoshi, T., Yashiki, S., Fujiyama, C., Kuwayama, M., Miyashita, H., Ohnishi, H., Blank, M., Zaninovic, V., Blank, A., Cartier, L., Byrnes, J.J., Harrington, W.J., Miura, T., Hayami, M., Tajima, K. and Sonoda, S. (1995) Ethnic segrigation of HTLV-I and HTLV-II carriers among South American native Indians. Int. J. Cancer 63, 510-515.
15. Shimoyama, M. and Members of The Lymphoma Study Group (1991) Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia lymphoma. Br. J. Haematol. 79, 428-437.
16. The T- and B-cell Malignancy Study Group (1988) The third nation-wide study on adult T-cell leukemia/lymphoma (ATL) in Japan: Characteristic patterns of HLA antigen and HTLV-I infection in ATL patients and their relatives .Int. J. Cancer 41, 505-512.
17. Tajima, K., The T- and B-cell Malignancy Study Group and Co-authors (1990) The 4th nation-wide study of adult T-cell leukemia/lymphoma(ATL)in Japan: Estimates of risk of ATL and its geographical and clinical features. Int. J. Cancer 45, 237-243.
18. The T- and B-cell Malignancy Study Group (1998) A report from the 8th nationwide study of adult T-cell leukemia/lymphoma (ATL in Japan). Jpn. J. Cancer Clin. 44, 381-397 (in Japanese).
19. Tajima, K., Kamura, S., Ito, S., Ito, M., Nagatomo, M.,

Kinoshita, K. and Ikeda, S. (1987) Epidemiological features of HTLV-I carriers and incidence of ATL in an ATL-endemic island: A report of the community-based cooperative study in Tsushima, Japan. Int. J. Cancer 40, 741-746.

20. Kwon, K.W., Yano, M., Sekiguchi, S., Iwabnaga, M., Fujiwara, S., Oikawa, O., Sugimura, M., Imai, S. and Osato, T. (1994) Prevalence of human T-cell leukemia virus type I (HTLV-I) in general inhabitants in non-adult T-cell leukemia (ATL) endemic Hokkaido, Japan. In Vivo 8, 1011-1014.
21. Kondo, T., Kono, H., Miyamoto, N., Yoshida, R., Toki, H., Matsumoto, I., Hara, M., Inoue, H., Inatsuki, A., Funatsu, T., Yamano, N., Bando, F., Iwao, E., Miyoshi, I., Hinuma, Y. and Hanaoka, M. (1989) Age- and sex-specific cumulative rate and risk of ATLL for HTLV-I carriers. Int. J. Cancer 43, 1061-1064.
22. Imai, J., Terashi, S., Talonu, T., Komoda, H., Taufa, T., Nurse, G.T., Babona, D., Yamaguchi, K., Nakashima, H., Ishikawa, K., Kawamura, M. and Hayami, M. (1990) Geographical distribution of subjects seropositive for human T-cell leukemia virus type I in Papua New guinea. Jpn. J. Cancer Res. 81, 1218-1221.
23. Tokudome, S., Tokunaga, O., Shimamoto, Y., Miyamoto, Y., Sumida, I., Kikuchi, M., Takeshita, M., Ikeda, T., Fujiwara, K., Yoshihara, M., Yanagawa, T. and Nishizumi, M. (1989) Incidence of adult T-cell leukemia/lymphoma among human T-lymphotropic virus type I carriers in Saga, Japan. Cancer Res. 49, 226-228.
24. Tajima, K., Tominaga, S., Suchi, T., Kawagoe, T., Komoda, H., Hinuma, Y., Oda, T. and Fujita, K. (1982) Epidemiological analysis of the distribution of antibody to adult T-cell leukemia-virus-associated antigen (ATLA): Possible horizontal transmission of adult T-cell leukemia virus. Jpn. J. Cancer Res. 73, 893-901.
25. Kinoshita, K., Hino, S., Amagasaki, T., Ikeda, S., Yamada, Y., Suzuyama, J., Momita, S., Toriya, K., Kamihira, S. and Ichimaru, M. (1984) Demonstration of adult T-cell leukemia virus antigen in milk from three sero-positive mothers Jpn. J. Cancer Res. 75, 103-105.
26. Nakano, S., Ando, Y., Ichiro, M., Moriyama, L., Saito, S., Sugimura, K. and Hinuma, Y. (1984) Search for possible routes of vertical and horizontal transmission of adult T-cell leukemia virus. Jpn. J. Cancer Res. 75, 1044-1045.
27. Tajima, K. and Kuroishi, T. (1985) Estimation of rate of incidence of ATL among ATLV (HTLV-I) carriers in Kyushu, Japan. Jpn. J. Clin. Oncol. 15, 423-430.
28. Murphy, E.L., Hanchard, B., Figueroa, J.P., Gibbs, W.N., Lofters, W.S., Campbell, M., Goedert, J.J. and Blattner, W.A. (1989) Modelling the risk of adult T-cell leukemia/lymphoma in persons infected with human T-lymphotropic virus type I. Int. J. Cancer 43, 250-253.
29. Ikeda, S., Momita, S., Amagasaki, T., Tsukasaki, K., Yamada, Y., Kusumoto, Y., Ito, M., Kanda, N., Tomonaga, M., Soda, H., Atogami, S., Kamihira, S., Hino, S., Ito, S., Kinoshita, K. and Ichimaru, M. (1990) Detection of preleukemic state of adult T-cell leukemia (pre-ATL) in HTLV-I carriers. Cancer Detect. Prev. 14, 431-435.
30. Sonoda, S. and Fujiyoshi, T. (1996) HTLV-I infection and HLA Gann Monogr. Cancer Res. 44, 207-217.
31. Tokudome, S., Shimamoto, Y. and Sumida, I. (1993) Smoking and adult T-cell leukemia/lymphoma. E. J. Cancer Prev. 2, 84-85.
32. Tajima, K., Fujita, K., Tsukidate, S., Oda, T., Tominaga, S., Suchi, T. and Hinuma, Y. (1983) Seroepidemiological studies on the effects of filarial parasites of infestation of adult T-cell leukemia virus in the Goto Island. Jpn. J. Cancer Res. 74, 188-191.
33. Nakada, K., Kohakura, M., Komoda, H. and Hinuma, Y. (1984) A high incidence of antibody to a human leukemic virus in the carriers of a parasites, Strongyloides stercoralis. Lancet 633.
34. Takezaki, T., Tajima, K., Ito, M., Ito, S., Kinoshita, I., Tachibana, K., Matsushita, Y. and The Tsushima ATL Study Group (1997) Short-term breast-feeding may reduce the risk of vertical transmission of HTLV-I. Leukemia 11, 60-61.

The Present Rate of Incidence and Mortality of Cancer Disease in Mongolia



Rubjir Sanduijav
Consultant Surgeon, National Cancer Center, Ulaanbaator, Mongolia

Born in: 1950
Past Records: 1975 Graduated from Medical University, Ulaanbaator, Mongolia
1975 Joined National Cancer Center
1985 Advance study on Oncology in Moscow at Russian Cancer Center
1990 Consultant Surgeon, National Cancer Center, Ulaanbaator, Mongolia
1993 Improved Qualification on the Advanced Methods of the Surgical Treatment of Liver Cancer.,National Cancer Center, Tokyo, Japan
1998 Ph. D. Mongolia Medical University
2000 Training course in Community - based cancer prevention. Aichi Cancer Center Research Institute, Nagoya, Japan

Both the rate of incidence and mortality of Primary Liver Cancer [PLC] in Mongolia is consistently increasing year after year and there is a tendency of its increase on the days to come. PLC of the most leading cancer in our country.

THE INCREASING RATES OF INCIDENCE OF PRIMARY HEPATO CARCINOMA DURING LASTTWENTY-SIX YEARS FROM 1973-1999 (%)

Table 1

Years	1973	1978	1982	1987	1994	1999
Male	23.6	26.6	27.7	35.5	40.3	41.5
Female	18.0	19.8	19.6	26.8	27.8	31.6
Total	21.4	23.7	24.1	31.6	34.7	37.06

From 1966 to 1970 primary liver cancer accounts for 15.5% of total rate of mortality and was third cause of death, from 1973-1982 it was 23.2% becoming second position in causing the death, whereas from 1983-1987 it was 31.6% and became the number one cause of mortality among all the cancer diseases. From 1990-1999 it accounts for 37.06% and is increasing year by year.

THE NATIONAL STANDARD RATE OF INCIDENCE OF PRIMARY LIVER CANCER IN 100.000 POPULATION FROM 1973-1999.

Table 2

Years	1973	1978	1993-1996	1999
Male	41.0	56.5	56.09	63.1
Female	17.7	27.8	33.08	39.0
Total	28.6	41.4	44.57	50.8

The number of primary liver cancer registered in 1973 was 293, in 1987 it was 924, and in 1999 it was 1176. For last twenty-six years it has increased by four times from 28.6% to 50.8%.

The standard rate of incidence of primary liver cancer in 100.000 population in relation to provinces and cities.

THE STANDARTIZE AVERAGE INCIDENCE OF LIVER CANCER
ON EVERY 100000 POPULATION OF 1993-1996

Table 3

	Aimak	Total	Male	Female
1	Arhangai	31.66	39.34	24.51
2	Bayan-Oligii	9.39	8.02	10.98
3	Bayanhongor	36.36	41.9	31.91
4	Bulgan	69.65	72.48	67.51
5	Gobi-altai	26.96	34.92	20.22
6	Dornogobi	50.67	63.53	39.49
7	Dornot	54.74	81.77	51.58
8	Dundgobi	24.66	36.4	13.35
9	Zavhan	36.03	52.51	21.93
10	Oborhangai	43.71	55.65	35.76
11	Omnogobi	8.16	10.29	6.54
12	Sukhbaatar	30.78	44.68	18.69
13	Selenge	33.05	42.19	23.72
14	Tob	20.12	24.68	15.34
15	Uvs	53.58	75.00	34.26
16	Hovd	19.89	28.75	11.99
17	Hovsgol	23.16	24.58	22.04
18	Hentii	52.36	62.62	41.99
19	Darhan-uul	57.65	68.97	55.03
20	Ulaanbaatar	85.76	82.16	47.33
21	Orhon	44.78	20.02	31.71
22	Gobisumber	13.56	12.95	14.18
23	Total	44.57	56.29	33.08

From our studies the rate of incidence of primary liver cancer in 100.000 population is 0.5 to 1.0 times more in Ulaanbaatar. Bulgan, Darkhan-Uul and Dornod and the incidence is found comparatively lesser in Omnogobi, Bayan-Ulgii, Khovd provinces.

The different rate of incidence of primary liver cancer in different provinces is related to different rate of incidence of hepatitis in different provinces.

The study has been carried out to show.

THE RATE OF INCIDENCE OF HEPATITIS IN THE VARIOUS PROVINCES AND CITIES IN MONGOLIA FROM 1958-1990.

Table 4

	Aimak	1958-1975	1976-1980	1981-1985	1986-1990	1976-1990
1	Arhangai	93.0	50.42	59.88	60.04	56.9
2	Bayan-Oligii	66.5	44.58	34.16	37.42	38.72
3	Bayanhongor	100.7	45.52	63.48	49.96	52.9
4	Bulgan	137.5	69.72	78.44	71.62	73.26
5	Gobi-altai	83.5	46.42	55.18	52.56	51.38
6	Dornogobi	101.9	50.8	74.82	78.5	68.4
7	Dornot	142.4	55.46	61.34	64.22	60.34
8	Dundgobi	115.5	71.58	67.04	56.1	65.2
9	Zavhan	93.2	37.7	39.8	34.94	37.48
10	Oborhangai	89.3	45.3	48.28	41.38	44.99
11	Omnogobi	143.8	74.8	68.62	43.6	62.67
12	Sukhbaatar	127.9	70.4	79.8	73.4	74.5
13	Selenge	122.9	66.78	85.72	71.0	74.5
14	Tob	100.6	62.4	57.48	72.06	64.16
15	Uvs	88.5	57.36	53.8	57.1	56.88
16	Hovd	75.3	51.84	49.48	57.24	52.85
17	Hovsgol	79.3	52.42	59.24	61.2	57.16
18	Hentii	116.2	54.28	65.58	53.44	57.7
19	Darhan-uul	168.9	122.22	93.94	84.58	100.2
20	Ulaanbaatar	131.8	116.08	87.6	97.82	100.5
21	Orhon	63.22	95.2	120.3	92.5	
22	Gobisumber					
23	Total	121.9	70.22	69.78	67.22	69.07

It is clear from these data that the rate of hepatitis decreases every five years. However where the rate of primary liver cancer is higher such as in Ulaanbaatar, Bulgan, Darkhan-Uul, Dornod and Hentii, the rate of incidence of hepatitis higher as well. The incidence of hepatitis is higher in the provinces like Omnogobi, Sukhbaatar, and Tov, but the rate of incidence of primary liver carcinoma is lower than the average of national level.

Provinces where the rate of incidence of primary

liver cancer is lower such as Omnogobi, Bayan-Ulgii, Hovd, Tov and Huvsgul have also lower rate of hepatitis.

In the last 20 years the mortality of Primary Liver Cancer in 100,000
population was 51,4 in male, 31,6 in female with total 41,3. Of the total rate of mortality in Mongolia the liver cancer alone accounts for 5% in 1995; 6,1% in 1998.

COMPARATIVE STUDY OF PRIMARY LIVER CANCER AND HEPATITIS VIRUSES

Table 5

Marker	Patients	Percent (%)
HBSAg (+)	36	17.1%
Anti-HCV (+)	108	51.4%
HBSAg (+)		
Anti-HCV (+)	66	31.4%
Total	210	100%

From this study it shows that hepatitis does influence the cause of primary liver cancer. In 1992-1996 a study has been carried out among the Mongolian population to identify various hepatitis. It is found that 15% of general population is infected with HBV, and 15% with HCV. 210 patients with primary liver cancer are studied with virus markers, 108 patients or 51.4% are positive with HCV, 36 patients or 17.11% are positive with HBSAg, 66 patients or 31.4% are positive with HCV and HBSAg. From these study it can be concluded that it is not only the B and C viruses, but also combination of B and C viruses cause the primary liver carcinoma.

Particularly HCV causes far more primary liver cancer than HBV. In Mongolian male population suffer from primary liver cancer twice more than female. According to age wise, the incidence of primary liver cancer increases in 40 to 49 years and reach to the highest after the age of 60.

THE RATE INCIDENCE OF PRIMARY LIVERCANCER BETWEEN SEX, BY AGES, ON EVERY 100000 POPULATION OF 1992-1999

Figure1

AGES	0.20	20.29	30.39	40.49	50.59	60 ANDMORE
Male	0.2	0.4	13.1	84.35	283.6	505.7
Female	0.2	0.9	7.3	44.5	153.5	312.3
Total	0.25	1.7	10.2	64.06	217.9	417.9

Figure 1

From the figure it is clear that as far as incidence of primary liver cancer concerned, there is no difference in sex below the age of 29, however the rate of incidence is higher in male from 30-39 ages group.

Having these figures today Mongolia is one of the countries in the world with one of the highest incidence and mortality caused by the liver cancer. Generally Mongolia is one of the country in the world that have highest rate of primary liver cancers in the world.

Liver Fluke-Associated Cholangiocarcinoma in Thailand

Chawalit Pairojkul
Associate Professor, Consultant in Pathology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Born in :	1951	
Past Records :	1975	Medical degree,Mahidol University, Bangkok, Thailand
	1978	Member of Thai Board of Pathology
	1978-	Department of Pathology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
	1989-1995	Head of department

Summary

Epidemiological studies have revealed a coincident high prevalence of cholagio carcinoma (CCA) in Northeast Thailand, which is the endemic region of liver fluke (*Opisthorchis viverrini*). We have demonstrated in animal models that dietary contamination with nitrosamines and Opisthorchiasis are strong predisposing factors for CCA. However there is substantial evidence that nitric oxide synthesis and endogenous nitrosation, which could exert genotoxic effects are elevated as a result of inflammatory response to fluke infection. We compared between CCA in Thai and in Japanese : similarities in tumor phenotypes were found, the incidence of ras mutation differed markedly, but the incidence of *p53* mutation was similar. The findings suggesting that bile duct might proceed to malignancy by similar pathways in these populations. In this article we present an overview of studies aimed at understanding carcinogenesis of fluke-related CCA.

Epidemiological Studies

Cholangiocarcinoma (CCA), the intrahepatic bile duct cancer is infrequently encountered worldwide. It accounts for only an estimated 10-15% of primary liver cancers (Mizumoto and Kawarada, 1988) . In contrast epidemiological studies reveal geographical clusters of CCA in the endemic regions of liver fluke *Opisthorchis viverrini* (OV) or its close relative, *Clonochis sinensis*, such as Northeast Thailand and Hongkong (Parkin et al. 1993). Recent national surveys reported a prevalence of OV infection of 24% among northeast people, indicating at least 5 million people still harboured flukes (Jongsuksantigul et al., 1992). Srivatanakul et al., (1988) conducted a formal geographical analysis and found the incidence of CCA in five regions of Thailand varies at least 12-fold and is correlated strongly with prevalence of OV infection as measured by OV antibody titer, while hepatocellular carcinoma shows no such relation. A similar association between the intensity of OV infection and the risk of CCA has been observed at district level (Vatanasapt el al., 1990). Parkin et al. (1990) found a signigicantly higher frequency of elevated OV antibody among CCA cases compared to controls (Odds ratio = 5.1) and implied at least two-thirds of CCA cases were attributed to OV infection. No association was seen with chronic carriers of hepatitis B nor with recent aflatoxin intake. There was no association with dietary constituents and tobacco use. In Khon Kaen, Northeast Thailand the age standardized incidence rate of CCA is estimated at 84.6 and 36.8 per 100,000 for males and females,

respectively, which is at least 30-fold higher than the regions without fluke infection. Even more striking is that 89% of liver cancers in this region are found to be CCA (Vatanasapt et al. 1993).

Histogenesis Studies

Infection with *Opisthorchis* and *Clonochis* is acquired by consuming uncooked freshwater fish which contains infective encysted metacercariae. In the duodenum the lavae excyst and ascend the common bile duct to establish chronic infection, mainly in the lumen of the intrahepatic large bile ducts and their branches (Hou, 1955). Chronic infection results in chronic inflammation of bile ducts with epithelial changes including hyperplasia, proliferation with acini formation (adenomatous hyperplasia), goblet cell metaplasia and periductal fibrosis (Hou, 1955;Tansurat, 1971;Riganti et al., 1989;Pairojkul et al., 1991). Usually the liver appears normal in light infection but in heavy infection there is subcapsular bile lake dilatation (Hou, 1955;Pairojkul et al., 1991). CCA is generally considered to originate from surface epithelial cells lining bile duct. Atypical hyperplasia and dysplasia that lie adjacent to CCA are potential precancerous lesions which have been reported in both fluke related CCA as well as other CCA (Hou, 1956;Kim, 1984;Nakanuma et al., 1985). Shirai et al. (1992) compared CCA from Thai and Japanese cases, and found marked differences in non-cancerous areas:chronic cholangitis and cholangiofibrosis is more pronounced in Thai cases. However, a similar spectrum of tumor phenotypes was evident; 78-80% of CCA were tubular adenocarcinoma. The observations support that CCA with different etiological backgrounds may have a common histogenesis. Terada et al., (1987) using postmortem cholangiographs and serial sections demonstrated the adnexal glands (peribiliary gland) around the intrahepatic large bile ducts. They also disclosed that the acini formation of the adenomatous hyperplasia in fluke infection is intramural peribiliary gland hyperplasia (Terada et al., 1992). Nakanuma et al., (1994) highlighted a number of pathological changes of the peribiliary gland in studies surveying 1000 autopsies. Findings included that the hyperplasia of peribiliary gland which occurred consistently in hepatolithiasis and liver fluke infection are more varriable in other conditions (e.g.biliary tract infection and submassive hepatic necrosis) and in normal liver. Kurashina et al., (1988) investigating the relationship between intrahepatic bile duct hyperplasia and CCA, reported that most of CCA develops from bile duct hyperplasia, carcinoma in situ is occured in 48.1% of cases on a background of surface epithelial hyperplasia and 7.4% on a background of peribiliary gland hyperplasia. All the above accounts suggest that fluke-related lesions could be precursor lesions in tumor development, and fluke infection were assumed to play epigenetic roles.

Carcinogenic Effect Of Liver Fluke Infection

Analysis of foodstuffs consumed daily among the local Thai people revealed contamination with nitrites and nitrates (Migasena et al., 1980). Syrian hamsters respond to OV infection with proliferative changes in the intrahepatic bile duct similar to those observed in man (Bharmanrapravati et al., 1978). We and other groups have found clear synergistic effects of dimethyl nitrosamine (DMN) and OV infection in inducing CCA in Syrian hamsters (Thamavit et al., 1987;Flavell and Lucus 1982; Lee et al., 1994). Thus all Syrian hamsters receiving a combination of subcarcinogenic doses of DMN and infection with flukes developed cholangiocarcinomas, while chemical administration or fluke infection alone did not cause cancer (Thamavit et al., 1978). Synergistic induction by DMN and OV infection was found to be related to level of exposure to both (Thamavit et al., 1987). OV infected hamsters given precursor forms of nitrosamine, aminopyrine and nitrite had an increased tumor yield (Thamavit et al., 1988). These results indicated that cholangiocarcinogenesis associated OV infection is a multifactorial process. Nitrosamines in food and endogenous nitrosation could be risk factors. The underlying mechanism of

enhancement of neoplasia by OV remains unclear, however epithelial proliferation of bile ducts during the period of DMN administration could result in enhanced first stage initiation, and the continuced presence of parasites causing a chronic increase in cell turnover might act as a second stage, promoting stimulus to cholangiocarcinogenesis. Evidence is now accumulating that humans infected with OV have an elevated endogenous nitrosation. Srianujata et al., (1987) reported higher levels of nitrate and N-nitrosoproline in the urine of subjects infected with OV than in the uninfected subjects. Srivatanakul et al., (1991) confirmed this observation in a study in which dietary intake of nitrate and N-nitrosoproline were controlled. Recently a human study with controlled low nitrate diet showed that subjects with OV infection had increased amounts of saliva nitrite and urinary and plasma nitrate compared to uninfected controls (Haswel-Elkins et al., 1994). Ohshima et al. (1994) demonstrated increased nitrosamine and nitrate biosynthesis mediated by nitric oxide synthase induced in hamsters infected with OV; the enzyme was located in the macrophages, eosinophils and mast cells in the inflamed area surrounding parasite-containing bile ducts. Since excess nitric oxide and nitrosamine could be mutagenic (Wink et al., 1991;Nguyen et al., 1992) the findings suggest subjects infected with OV have an elevated risk of CCA in conbination with the above exposures. While effective treatment for OV is avialable by the use of a single dose of Praziquantel (Mairiang et al, 1993). Unfortunately, breaking the reinfection cycle has proved difficult in practice.

Genetic Alterations

The incidence and pattern of mutations of the *ras* oncogenes and the *p53* tumor suppressor gene have been shown to differ among different cancer types and even among the same cancer types with different etiological background. (Hollstein et al., 1991). Tada et al, (1992) reported a high incidence (67%) of *c-Ki-ras* gene mutation in CCA obtained from Japanese patients with no identified etiological factors. Tsuda et al. (1992) and Kiba et al. (1993) detected a marked contrast in the incidence of *c-Ki-ras* mutation in CCAs from Japanese and Thai. Point mutations of the *c-Ki-ras* gene were detected in 56% (5 of 9) and 58% (7 of 12) of Japanese cases but had a low incidence in Thai CCAs : 0% (0 of 12) and 8% (2 of 26). The pathogenic significance of point mutation of *c-Ki-ras* proto-oncogene in haman cancer is still unclear. Point mutations in the *Ki-ras* gene result in uncontrolled stimulation of ras-related functions caused by the altered p21 ras protein-related pathway being locked in the "on" position for signal transduction (Tahey and McCormick, 1987). Results suggest that point-mutation activation of the *c-Ki-ras* proto-oncogene may be involved in cholangiocarcinogenesis but most CCAs associated with OV infestation may follow an alternate genetic pathway. Interestingly, in hepatitis *c-Ki-ras* mutations were also infrequent or absent (Ohashi et al., 1995). However the incidence of *p53* mutation was almost equal in CCAs from Japanese and from Thai : 33% (4 of 12) in the former and 35% (9 of 26) in the latter. In all cases but one, the *p53* gene mutations were clustered within the evolutionarily conserved regions, especially in exons 5 and 7 ; the predominant form of the mutation was G : C to A : T transition at CpG sites in both sets of CCA, similar to that reported for colorectal cancers. These results indicate that *p53* gene mutations occur frequently in CCA irrespective of differences in etiology. This pattern of contrast in the incidence of *c-Ki-ras* mutation but a similar incidence of *p53* mutation was also reported in the cases of colon cancer with ulcerative colitis compared to sporadic cases (Burmer et al., 1990; Greenwald et al., 1992). Inactivation of *p53* due to missense mutations on interaction with oncogenic viral protein allows progression through the cell cycte without a physiological checkpoint, resulting in a selective growth advantage for cancer cells (Baker et al., 1990). Somatic *p53* mutation can be early or late events in the multistage carcinogenesis of many types of cancer (Harris and Hollstein, 1993). The *p53* mutation was frequently involved in the development of CCA in both Japanese

and Thai patients, suggesting that the intrahepatic bile duct might proceed to malignancy by some similar pathways, independently of fluke involvement.

Conclusion

A causal association between infection by OV and CCA is a multifactorial process. Fluke infection may not invoke all the required steps in multistep carcinogenesis. Host reactions to infection may contribute to tumor development by : (I) causing chronic infection and stimulating proliferation of blie duct epithelium (II) facilitating formation of genotoxic substances, including excess nitric oxide and nitrosamine at infection sites. Genetic studies imply that there are at least two distinct subtypes of CCA. Further studies examining the association between known specific point mutations and genotoxicants (in vivo amount) are warranted to aid our understanding of cholangiocarcinogenesis and certain cancers associated with chronic infection.

References

Baker, S.J., Markowitz, S., Fearon, E.R., Willson, J.K.V., and Vogelstein, B. (1900)Suppression of human colorectal carcinoma cell growth by wildtype p53. *Science*,**249**:912-915.

Bhamarapravati, N., Thamavit, W., and Vajrasthira, S. (1978) Liver changes in hamsters infected with a liver fluke of man, *Opisthorchis viverrini*. *Am. J. Trop.Med.Hyg.*, **27**:787-94.

Burmer, G.C., Levine, D.S., Kulander, B.G., Haggitt, R.C., Rubin, C.E., and Rabinovitich, P.S. (1990) *c-Ki-ras* Mutations in chronic ulcerative colitis and sporadic colon carcinoma. *Gastroenterol.*, **99**:416-420.

Flavell, D.J., and Lucas, S.B. (1982) Potentiation by the human liver fluke, *Opisthorchis viverrini*, of the carcinogenic action of N-nitrosodimethylamine upon the biliary epithelium of the hamster. *Br.J. Cancer*, **46**:985-989.

Greenwald, B.D., Harpaz, N., and Yin, J. (1992) Loss of heterozygosity affecting the *p53*, *Rb. and mcc/apc* tumor suppressor gene loci in dysplastic and cancerous ulcerative colitis. *Cancer Res.*, **52**:741-745.

Harris, C. C., and Hollstein, M. (1993) Clinical implications of the *p53* tumor-suppressor gene, *N. Engl. J. Med.*, **359**:1318-1327.

Haswell-Elkins, M.R., Satarug, S., Tsuda, M., Mairiang, E., Esumi, H., Sithithaworn, P., Mairiang, P., Saitoh, S., Yongvanit, P., and Elkins, D.B. (1994) Liver fluke infection and cholangiocarcinoma : model of endogenous nitric oxide and extragastric nitrosation in human carcinogenesis. *Mutat. Res.*, **305**:241-252.

Hollstein, M., Sidransky, D., Vogelstein, B., and Harris, C.C. (1991) *p53* mutations in human cancers. *Science*, **253**:49-53.

Hou, P.C. (1995) The pathology of *Clonorchis sinensis* infestation of the liver. J. *Pathol. Bacteriol.*, **70**:56-64.

Hou, P.C. (1956) The relationship between primary carcinoma of the liver and infestion with *Clonorchis sinensis J. Pathol. Bacteriol.*, **42**:239-246.

Jongsuksantigul, P., Chaeychomsri, W., Techamontrikul, P., Jeradit, P. and Suratavanit, P. (1992) Studies on prevalence and intensity of intestinal helminthiasis and opisthorchiasis in Thailand in 1991. (in Thai) *J trop. Med. Parasitol.*, **15**:80-85.

Kiba, T., Tsuda, H., Pairojkul, C., Inoue, S., Sugimura, T. and Hirohashi, S. (1993)Mutations of the *p53* tumor suppressor gene and the *ras* gene family in intrahepatic cholangiocellular carcinomas in Japan and Thailand. *Mol. Carcinog.*, **8**:312-318.

Kim, Y.L. (1984) Liver carcinoma and liver fluke infection. *Drug Res.*, **34**: 1121- 1126.

Kurashina, M., Kozuka, S., Nakasima, N., Hirabayasi, N. and Ito, M. (1988)Relationship of intrahepatic bile duct hyperplasia to cholangiocellular carcinoma. *Cancer* **61**:2469-2474.

Lee, J.H., Yang, H.M., Bak, U.B. and Rim, H.J. (1994) Promoting effect of *Chonorchis sinensis* infection on induction of cholangiocarcinoma during two-step carcinogenesis. *Korean J.Parasitol.*, **32**:13-18.

Mairiang, E., Haswell-Elkins, MR., Mairiang, P., Sithithaworn, P., and David B. (1993) Elkins. Reversal of biliary tract abnormalities associated with

Opisthorchis viverrini infection following praziquantel treatment. *Trans. R. Soc. Trop. Med. Hyg.* **87**:194.

Migasena, P., Reasuwan, W. and Changbumrung, S. (1980) The nitrates and nitrates and nitrites in local Thai preserved protein foods. *J. Med. Assoc. Thai.* **63**:500-505.

Mizumoto, R., Kawarada, Y. (1988) Diagnosis and treatment of cholangiocarcinoma and cystic adenocarcinoma of the liver. In : *Neoplasms of the Liver* (K. Okuda, and K. Ishak, eds.) pp.381-396, Springer. Verlag, Tokyo.

Nakanuma, Y., Terada, T., Tanaka, Y., Ohta, G. (1985) Are hepatolithiasis and cholangiocarcinoma aetiologically related? A morphological study of 12 cases of hepatolithiasis associated with cholangiocarcinoma. *Virchows Arch.* (A) **406**:45-58.

Nakanuma, Y., Sasaki, M., Terada, T. and Harada, T. (1994) Intrahepatic peribiliary glands of humans. II. Pathologic spectrum. *J. Gastroenterol. Hepatol.* **9**:80-86.

Nguyen, T., Brunson, D., Crespi, C.L., Penman, B.W., Wishnok, J.S., and Tannenbaum, S.R. (1992) DNA damage and mutation in human cells exposed to nitric oxide in vitro. *Proc. Natl. Acad. Sci. USA*, **89**:3030-3034.

Ohshima, H., Bandaletova, T.Y., Brouet, I., Bartsch, H., Kirby, G., Ogunbiyi, F., Vatanasapt, V. and Pipitgool, V. (1994) Incroased nitrosamine and nitrate biosynthesis mediated by nitric oxide synthase induced in hamster infected with liver fluke *(Opisthorchis viverrini). Carcinogenesis,* **15**:271-275.

Ohashi, K., Nakajima, Y., Kanehiro, H., Tsutsumi, M., Taki, J., Aomatsu, Y., Yoshimur, A., Ko, S., T., Yagura, K., Konishi, Y. and Nakano, H. (1995) Ki-ras Mutations and p53 protein expressions in intrahepatic cholangiocarcinomas : relation to gross tumor morphology. *Gastroenterology,* **109**:1612-1617.

Pairojkul, C., Sithithaworn, P., Sripa, B., Thamawit, W., Ito, N., Shirai, T. and Itoh, M. (1991) Risk. group for opisthorchiasis-associated cholangiocarcinoma : indicated by a study of worm burden related biliary pathology. *Kan Tan Sui* **22**:393-402.

Parkin, D.M., Srivatanaku, P., Khlat, M., Chenvidhya, D., Chotiwan, P., Insiripong, S., L'Abbe, K.A. and Wild, C.P. (1991) Liver cancer in Thailand : I.A case-control study of holangiocarcinoma. *Int. J. Cancer,* **48**:323-28.

Parkin, D.M., Ohshima, H., Srivatanakul, P. and Vatanaspt, V. (1993) Cholangiocarcinoma : epidemiology, mechanisms of carcinofenesis and prevention.*Cancer pidemiol. Biomarkers prev.*, **2**:537-544.

Riganti, M., Pungpak, S., Punpoowong, B., Bunnag, D. and Harinasuta, T. (1989) Human pathology of Opisthorchis viverrini infection : a comparison of adults and children *S.E. Asian J. trop. Med. public Health,* **20**:95-100.

Srianujata, S., Tonbuth, S., Bunyaratvej, S., Valyasevi, A., Promvanit, N. and Chaivatsagul, W. (1987) High urinary excretion of nitrate and N-nitrosoproline in opisthorchiasis subjects. In : Bartsch, H., O'Neill, I.K. and Schulte-Hermann, R., eds, *The Relevance of N-Nitroso Compounds in Human Cancer : Exposures and Mechanisms* (LARC Scientific blications No. 84), *Lyon, IARC*, pp. 544-546.

Shirai, T., Pairojkul, C., Ogawa, K., Naito, H., Tamavit, W., Bhudhisawat. W. and Ito,N. (1992) Histomorphological characteristics of cholangiocellular carcinomas in northeast Thailand, where a region infection with the liver fluke, *Opisthorchis viverrini* is endemic. *Acta Pathol Jpn*, **42(10)**:734-9.

Srivatanakul, P., Sontipong, S., Chotiwan, P. and Parkin, D.M. (1988) Liver cancer in Thailand:temporal and geographic variations. *J. Gastroenterol. Hepatol.*, **3**: 413- 420.

Srivatanakul, P., Ohshima, H., Khlat. M., Parkin. M., Sukarayodhin, S., Brouet, I. andBartsch, H. (1991) Endogenous nitrosamines and liver fluke as risk factors for cholangicarcinoma in Thailand. *In : Relevance to Human Cancer of N-Nitroso Compounds, Tobacco Smoke and Mycotoxins,* (I.K. O'Neill, J. Chen, . and H. Bartsch, eds.), pp. 88-94, IARC, Lyon.

Tada, M., Omata, M., and Ohto, M. (1992) High incidence or ras gene mutation in intrahepatic cholangiocarcinoma. *Cancer (Phila.)*, **69**:1115-1118.

Tahey, M. and McCormick, F. (1987) A cytoplasmic protein stimulates normal N-ras p21 GTPase, but does

not affect oncogenic mutants. *Science*, **238**:542-545.

Tansurat, P. (1971) Opisthorchiasis, *In : Pathology of Protozoal and Helminthic Diseases with Clinical Correlation* (P.A. Marcial-Rojas, ed.), pp. 536-545, Williams and Wilkins, Baltimore.

Tarada, T., Nakanuma, Y. and Ohta, G. (1987) Glandular elements around the intrahepatic bile ducts in man : Their morphology and distribution in normal livers. *Liver*, **7**:1-8.

Terada, T. and Nakanuma, Y. (1990) Pathological observations of intrahepatic peribiliary glands in 1,000 consecutive autopsy livers. II. A possible source of cholangiocarcinoma. *Hepathology;* **12**:92-7.

Terada, T. and Nakanuma, Y. (1992) Pathological observations of intrahepatic peribiliary glands in 1,000 consecutive autopsy livers. IV. Hyperplasia of intramural and extramural glands. *Hum. Pathol* ; **23**:438-90.

Thamavit, W., Bhamarapravati, N., Sahaphong, S., Vajrashira, S. and Angsubhakorn, S. (1978) Effects of dimethylnitrosamine on induction of cholangiocarcinoma in *Opisthorchis viverrini*-infected Syrian golden hamsters. *Cancer Res.*, **38**:4634- 4639.

Thamavit, W., Kongkanuntn, R., Tiwawech, D. and Moore, M.A. (1987) Level of *Opisthorchis* infestation and carcinogen dose-dependence of cholangiocarcinoma induction in Syrian golden hamsters. *Virchows Arch.* [B], **54**:52-58.

Thamavit, W., Moore, M.A., Hiasa, Y. and Ito, N. 1988 Generation of high yields of Syrianhamsters cholangiocellular carcinomas and hepathocellular nodules by combined nitrite and aminopyrine administration and *Opisthorchis viverrini infection. Jap. J. Cancer Res.*, **79**: 909-916.

Tsuda, H., Satarug, S., Bhudhisawasdi, V., Kihana, T., Sugimura, T. and Hirohashi, (1992) Cholangiocarcinomas in Japanese and Thai patients : difference in etiology and incidence of point mutation of the c-Ki-*ras* proto-oncogene. *Mol. Carcinog.*, **6**:266-269.

Wink, D.A., Kasprzak, K.S., Maragos, C.M., Elespuru, R.K., Misara, M., Dunams, T.M., Cebula, T.A., Koch, W.H., Andrews, A.W., Allen, J.S. and Keefer, L.K. (1991) DNA deaminating ability and genotoxcity of nitric oxide and its progenitors. *Science*, **254**:1001-1003.

Vatanasapt, V., Tangvoraphonkchai, V., Titapant, V., Pipitgool, V., Viriyapap, D. andSriamporn, S. (1990) A high incidence of liver cancer in Khon Kaen Province, Thailand. *S.E. Asian J. trop. Med. public Health,* **21**:489-494.

Vatanasapt, V., Martin, N., Sriplung, H., Chindavijak, K., and Sontipong, S. (1993) *In: Cancer in Thailand 1988-1991* (D.M. Parkin, and J. Ferley, eds.), IARC, Lyon.

General Discussion

Date: October 8th(Sunday), 2000
15：20～16：50

Place: "Granship", Shizuoka City

—**MC** Now we would like to move on to the discussion. Dr. Yamaguchi, please proceed.

—**YAMAGUCHI** We may have 30 or 40 minutes for the general discussion in this session. Before the start of the general discussion, I will ask all participants for a record of this general discussion. This session will be recorded and some comments will be written down to serve as a record. Therefore, those participants who would like to make a comment should first state their name and then present their comment.

When we have recorded today's presentation, we will divide the discussion into three or four parts. In the first part, the discussion will focus on the presentation of Dr. Khuon from Cambodia who discussed the cancer control system and future plans of her country, and that of Dr. Yoo from Korea who demonstrated and discussed the future plans for breast cancer control in Korea. In the second part, we will focus on the two participants from Indonesia who explained about the very low incidence of stomach cancer in Indonesia. I believe this is the result of natural intervention as related to Indonesian lifestyle. In the third part of the discussion, we will discuss China studies, or Linxian studies, for esophageal cancer and typical chemo-preventive studies. This is a very new approach to cancer control. Finally, in the fourth part, we will discuss an issue that has become very important recently, namely infection and cancer; and these topics relating to infection and cancer are very important. In this part, a discussion will also be held regarding, ATL in Japan, liver fluke-associated, liver cancer in Thailand, and hepatitis virus-associated hepatocellular carcinoma in Mongolia. These three topics deal with the relationship between infection and cancer.

Since we do not have enough time, I would like to start now with a discussion of the systems of cancer control in various countries. First of all, I would like to call on Dr. Khuon. After hearing all of the presentations from different countries, do you have any comments or questions for other participants? You may also have some feelings about the future plans for your cancer control project in Cambodia.

—**KHUON** Thank you, Professor Chairman. It is very significant that I am able to attend this symposium. After listening to all the presentations and some recommendations from other participants during my presentation, I think that other countries such as Korea, China, Indonesia, Thailand, Japan, already have such a system, and especially one for cancer therapy. In my country, I think that in our future plan, we will have to reorganize the system and develop it into a system for cancer therapy. According to the comments from China, I think that, prior to developing a system for cancer therapy, we will have to conduct a cross-sectional survey to try to collect and determine all available information on cancer. In addition, I found that primary prevention is still very important for our national program, because our country is still a developing country, and that we should focus on primary prevention. These are my comments.

—**YAMAGUCHI** If any other participants have

some opinions, questions or comments, please raise your hand.

—**SANTOSO** Yes. I would like to suggest the collaboration in this case, because according to our experience, when we started to collaborate with different countries like Holland, we encouraged our people to mainly work as a cancer team. We then collaborated with Japan and other countries. We have been able to work at a more rapid pace as a result of this. In terms of cancer control, I think guidelines will become similar because WHO has already established standard guidelines and we will following those guidelines. However, in terms research, and I am referring not research in cancer control, but research on cancer itself, we have to have the possibility of conducting collaboration between at least two countries, and if necessary more than two countries in the form of international collaboration. Ideas for proceeding with research can be based on certain strategies as I call them. These strategies consist of two considerations. Firstly, there may be a common problem or common interest, such as a similar high incidence of a certain cancer in two countries. One example of this is liver cancer. We had similar problems with respect to the high incidence of liver cancer and its etiology in the beginning. Secondly, if there is a contrasting incidence, collaboration may help to answer some critical questions and benefit both countries. Naturally, there is actually even more benefit because in countries with a high incidence of a certain cancer, there is already more experience and more data. For example, with respect to gastric cancer, considerable research has been conducted in Japan and collaboration enables this research to be applied by the collaborating countries. Another example is the research being conducted on skin cancer. Skin cancer in Indonesia is the most common cancer among males according to our data and pathology findings from our 13 university. With respect to this, we have implemented a joint study with a group in Kobe and a group in Nagoya, and this project actually involves other universities and cancer centers. We intend to continue with this joint study while focusing on molecular epidemiology and related topics as I previously mentioned. We have also conducted a joint liver cancer project in the form of a GSPS program, for example. This has contributed to a more extensive knowledge of liver cancer. I think the Shizuoka forum provides an very good opportunity for discussing issues like this.

—**YAMAGUCHI** Thank you. Are there any other comments or questions?

—**TAJIMA** My name is Tajima from the Aichi Cancer Center, Japan. Today's conference is very meaningful because it provides us with the opportunity to come together and discuss cancer issues affecting the Pacific region. I think Pan-Pacific and Asian countries have some common factors. And of course we also have independent factors. So in terms of epidemiological studies, we should clarify those common factors and independent factors, and then exchange information. In addition, we are somewhat different from European countries; and we share some common life-styles based on Oriental culture. I therefore think that collaboration between countries of the Pan-Pacific and Asian countries is very important. We therefore need continue such meetings to mutually information exchange. With respect to prevention strategies in particular, we can share information on methodology and strategies. For example, in Cambodia, we heard from Dr. Mony that the mass media is very powerful. For this reason, the repeated providing of information by television and radio is very effective. This is probably true not only in Cambodia, but also in Japan, and these communication tools should be used. These strategies in Japan are presently quite poor, however. I would now like to take this opportunity to introduce a program that we have established in the Asian Pacific organization relating to cancer

prevention. We have already published four books and we hope to continue to publish a journal that will include reviews as well as original papers for mutual exchange. This deals with subjects such as epidemiological studies and prevention strategies. We need to continue with mutual exchange of information not only with respect to general areas, but also through annual conferences. We can also take up the challenge of conducting collaboration in the conducting of studies. For example, we are very much interested in the low incidence rate and low risk of gastric cancer that are very high in Japan, Korea, and China. We would like to collaborate in conducting studies to determine why the risk in other countries is so low. It is therefore my hope that other countries will join the Asian Pacific Organization of Cancer Prevention. Next month, we will be holding the first conference of APOCP. I would like to request your collaboration because it is desirable that this organization be comprised of all Asian countries.

—**YAMAGUCHI** Thank you. Dr. Yoo, do you have any comments about breast cancer control in Korea or other countries?

—**YOO** In fact, breast cancer itself is not that serious a problem in my country and in other Asian countries except for Japan, although I am not sure of the reason for this. In my country, however, it does not present a serious problem. From the standpoint of an epidemiologist, in my country, we should put emphasis on not only common and serious diseases like stomach cancer and liver cancer, but also on new emerging diseases that have the potential to present serious problems such as breast cancer and other types of cancer. In a sense, this would enable us to find more effective ways to modify the trends of future cancer incidence or cancer mortality in the early stages by considering the experiences of other countries like Western countries as well as other countries in the Asian region. This is a very good opportunity to share our experiences and findings regarding cancer epidemiology, including preventive strategies.

—**YAMAGUCHI** I also think that Japan, Korea, and many other Asian countries are implementing very good preventive measures for breast cancer and prostate cancer in our lifestyle unconsciously. The mortality rate for these cancers in Asian countries is very low when compared to Western countries. An important issue is to continue with these lifestyles for preventing prostate and breast cancer may be very important. Even though these breast cancer may not be that serious in Korea at present, it is still very important to examine what types of lifestyles should be promoted to decrease the incidence of this cancer and other cancers related to lifestyle. From this viewpoint, I think your study is very important. Are there any other comments about this issue?

—**ITO** My name is Dr. Ito of Shizuoka General Hospital. I would like to add some comments on the problem of breast cancer. In Japan, there is an NGO network of patients with breast cancer. This is a special group comprised of patients for patients with breast cancer. This group provides considerable support to the actual patients and also gives various announcements for prevention, annual check-ups and so on. I would therefore like to recommend such a non-government patient network in each country. It is very helpful for doctors as well.

—**SUKARDJA** In implementing cancer control, including control of breast cancer, the first problem to be overcome is determining the magnitude of the problem in society. This problem mostly has to do not with factors within hospitals, but rather outside hospitals in society. If a patient does not come to the hospital, we are unable to find out about that patient. In order to solve this problem, we establish cancer societies who go out into society and provide the public with information about cancer. According to my own dissertation,

the early detection of breast cancer through public cancer education only was found to be very high and significant after seven years of intensive public education. We therefore should have hospitals without walls in the same manner as university facilities without walls. This involves going out into society to provide important information, and one important factor behind this is how to communicate with members of the general public. We as physicians have the means for doing this as a result of our contact with the public. We therefore have the opportunity to talk with people about cancer. However, this can also be a problem. Namely, we should not talk with patients using sophisticated media, but rather simply talk in an effort to try to persuade the patient to come to the hospital. That is all that is required. Later on, once patients have understood the problem, they will then actually come to the hospital on their own.

—**YAMAGUCHI** Do you have any problems with contacting certain people?

—**SUKARDJA** Yes, but this is something that has to be done because this is a comprehensive cancer control program involving prominent organizations and prominent members of society. We start out by going directly to members of the general public and then continue with prominent people in society. This is the method that we employ.

—**YAMAGUCHI** I understand. I would like to now move onto a similar problem, namely the low incidence of stomach cancer in Indonesia.

—**SUKARDJA** Because the incidence of stomach cancer is very low, we do not consider to present that much of a problem. However, we carefully examine for cervical cancer, breast cancer and skin cancer because of their high incidences, and other cancers may be added in the future. We know at this time that not all cancers can be prevented, only some cancers.

— **YAMAGUCHI** Investigations of the low incidence of stomach cancer may in the form of a research project rather than a public project. Do you have any comments about the low incidence of stomach cancer in Indonesia? We had a very good discussion after your talk. Do you now have other comments on the low incidence of gastric cancer in Indonesia.

—**SUKARDJA** For the general public, we have been informing people about dietary habits. What dietary habits are followed, however, we encourage them not to eat too much preserved foods or prepared foods, and eat more fiber. We urge them not to change to a Western diet because those dietary habits are different from ours. The Western diet consists of high levels of protein and low levels of carbohydrates. We consume high levels of carbohydrates and low levels of protein. We provide education to the general public through what we refer to as women's organizations which are active throughout our country with additional assistance from WHO.

—**YAMAGUCHI** Based on your presentation, the incidences of other cancers in Indonesia are also rather low when compared to other countries. It is therefore likely that the incidences of breast cancer and prostate cancer are also rather low when compared to Western countries. Your lifestyle may therefore be the best means for cancer control at this time.

—**SUKARDJA** In addition, various forms of protection may also be effective.

—**ITO** I'd like to ask Dr. Santoso for some comments. Do you have any idea or speculation on the role of herbal spices. Are herbal spices consumed in large amounts in your country for the prevention of gastric cancer? What do you think?

—**SANTOSO** This subject should be studied practically, because, for example, there are some

differences with the spices you use in Japanese food. For example, when you use ginger, you directly eat the ginger in its entirety. We, however, grind many foods and make them into a powder. We only use this ground powder and do not eat it raw. We like to use only the aroma of the ingredients in our cooking. Direct consumption of raw ginger is not preferred because it is irritating. When I am in Japan, I eat the raw ginger, but only because others are eating it. This may be related to the observance of chronic irritation to the mucosa of the stomach and so forth. In addition, we naturally do not eat raw seafood or raw fish. When you eat shrimp, you eat the entire shrimp. We do not do that. We remove the shell. It is one of our habits to do this. Thus, there are some differences in dietary habits. I would like to propose a systematic study on this topic. For example, when a joint study was conducted on skin cancer, it was shown that the sun results in a higher risk for skin cancer. We are willing to apply systematic studies by epidemiological methods. It just so happens that this has already been proposed in a paper by Professor Ono for conducting a behavioral study, although this study relates to epidemiological methodology. We will probably be able to accomplish this by working together with the Indonesian Cancer Society because we have to get many people involved. These is also an example from studying abroad in the United States involving the use of a sun protecting agent and its protective behavior. Thus, we are able to design better studies through collaboration. With respect to the low incidence of cancer, we have had the experience of establishing a multi-center structure. This is because when only working in Jakarta or Surabaya, we are able to obtain no more than a small number of cases. However, by establishing a multi-center structure, it is possible to acquire more data. As I previously showed you, we were able to collect data on 105 patients over the course of 15 years in Jakarta. If we adopt a multi-center organization in your country, however, we can achieve a better study design. I am also interested in attempting to conduct a cohort study which are currently being deployed in Japan and perhaps you have already experienced. I would like to do this to learn about cohorts because I am unsure as to what is meant by a true cohort study. This type of study has not been conducted in our country. Now, I think we are able to propose such a study with collaboration, and that now is the time to proceed with that collaboration.

—**CHAWALIT** May I respond to Professor Ito's question? Based on our experience, a large amount of chili peppers are consumed in Thailand. In some cases, this can lead to acute gastritis. However, we have not found a correlation between persons who eat large amounts of chili peppers and chronic gastritis. Moreover, we found a correlation between consumption of chili peppers and the occurrence of esophageal cancer in addition to the possibility of chronic gastritis. We found that in those persons who consume large amounts of chili peppers, certain ingredients in the peppers can cause defibrilation. Thus, the evidence of venothrombosis is low in Asia as compared with Latin America.

—**TAJIMA** My impressions are that although we have very useful and very, very important information, one problem is that there are insufficient and immature standards for comparison. In Indonesia, for example, I think that the incidence of stomach cancer is probably very low compared to Japan, China and Korea. However, we want to know more about nutritional conditions because this evidence is very important to us. We therefore need more reliable evidence. For this reason, we should share standard ideas and standardized methodology. We have now started studies in three countries sponsored by the Japanese Ministry of Education, namely China, Japan and Korea. To begin with, we are now conducting standardization of a nutritional survey. This is because if we want to compare some differences, we need to standardize the survey.

This will then allow us to compare the incidence of cancer as well. We therefore need more standardization in the Pan-Pacific region. We can then discuss more and very, very useful information that becomes available along with protective factors that are found. To achieve this, however, we need more adequate studies.

—**YAMAGUCHI** Researchers want to know more and more. Dr. Tajima mentioned research funding. For this purpose, I believe that the most important thing is the subject matter. The first step is to learn from other countries what is important. We may now have a key for this in that our country has a high incidence of stomach cancer and yours has a very low incidence. Special topics like these are also very important for funding, at least based on what I perceive at this point in time. Since we do not have much time, I would like to move on to Dr. Qiao. Linxian nutritional studies are very important and clearly defined studies. This may be the first opportunity for us to hear about their follow-up studies today. This is very interesting for me. Do you have any comments Linxian studies at this time?

—**QIAO** Yes, I do. I am You-Lin Qiao from the Chinese Academy of Medical Sciences in China. To begin with, I would like to say that I really appreciate this conference because it provides an opportunity for direct dialogue between Asian countries. And just as Dr. Yamaguchi pointed out in the speech, these 13 Asian countries are responsible for publishing nearly half of the papers in the world. I therefore think that if we are able to resolve cancer issues, we will be contributing to the wellbeing of people everywhere throughout the world. Among our Chinese studies, because the time limit, I was asked only give a presentation about the Linxian cancer studies. We are also conducting lung cancer studies among teenage minors and have cerebral cohorts. In total, we have three cohorts. I would like to take this opportunity to open up these studies to our neighboring countries and encourage you to collaborate with China. If we are willing to collaborate with the United States, we should have no reason not to collaborate with our neighboring countries. With respect to our cohorts, as I mentioned to Dr. Tajima and during the meetings, when we set our cohorts, we also collect biological samples. Just for our Linxian study, we started our nutrition intervention trial with 33,000 subjects. Although nearly 10,000 of these subjects have died, since we have already obtained biological samples, we are able to easily design case studies for the purpose of investigating genetic and environmental exposure interactions. As one example of this, we have combined very good designs in our tests. These do not only relate to subjects involving cancer. We also have the same cohort among teenage minors, enabling us to conduct studies on lung cancer and cerebral cancer. This concludes my comments.

—**YAMAGUCHI** Are there any other comments? I'd like to move on to the last three speakers. They presented the relationship between infections and cancer. Since many participants on the floor did not have the opportunity to ask questions, I would like to call on Dr. Oku and other researchers who may have some question about this subject.

—**OKU** My name is Dr. Oku from the University of Shizuoka. I have one question for Dr. Qiao, if I may. Although this is quite interesting data and perhaps others have asked the same question, what do you feel are the most important nutrients, minerals or vitamins for protecting against cancer? If you have any insights into this, I would be grateful. Naturally, I assume that various combinations of these are also important.

—**QIAO** According to our data, we think that the most important nutrient is selenium followed by Alpha-tocopherol, riboflavin and fluorine. These are the four micronutrients that we have proposed for the next round of intervention studies.

—**OKU** You mentioned that the difference between the placebo and treatment became obvious after five years' follow-up. What is the reason for this? What I mean is that, since there were no differences in the nutrients for five years, why would the difference become obvious after five years? What do you think is the reason behind this?

—**QIAO** I think this is a very complicated question. As you know, an intervention trial is not exactly a treatment trial. When treatment is being provided, you give medicine to the patient and you can observe changes very quickly. In the case of nutritional supplementation, however, there is no specific dose. What is more, this is not treatment per say. The nutrition provided is administered to help them strengthen their bodies. Thus, it is not expected to observe results in a short period of time. Although this is our explanation of this, if you look at other studies, during the intervention time a washout period is provided to wash out the initial effects. After this period, follow-up is continued after which is possible to observe the true effects. When you are looking at a particular study, even though there may be differences between certain years, this may not be reliable due to intervention. As I showed in the data during my presentation, we examined certain age groups. We found that if intervention was started at a younger age, the benefits are greater. In contrast, if intervention is started at a later age, the effects are not that significant.

—**SUZUKI** I am Dr. Suzuki of the University of Shizuoka, School of Pharmaceutical Science. I would be pleased if I had the opportunity to ask a question of Dr. Chawalit Pairojkul. It was said that in northeastern Thailand, you have many patients with cholangiocarcinoma or liver fluke. This is reported to be caused by a parasite that thrives in river fish. When people eat the fish and the parasite enters their bodies, the parasite either migrates through the entire body or only in the liver. What is the molecular mechanism behind the reason for the parasite remaining in the liver?

—**CHAWALIT** The liver fluke (O.V.) usually resides in the intrahepatic bile ducts, gall bladder, extrahepatic bile duct and occasionally in the pancreatic duct. They never migration outside the biliary passages. When the infective stage (metacercaria cyst) excysts in the duodenum, the young flukes directly creep to the bile duct via the ampulla of Vater and establish chronic infestation mostly at the large intrahepatic bile ducts.They keep remaining in the biliary trees, because they eat bile and bile constituents. Young flukes can survive 1-2 weeks in the bile media had been reported.

—**SUZUKI** I suppose there is some form of association with molecules in the parasite or involvement of the parasite surface with regard to these parasites staying in the liver cells or other components of the liver. Do you have some ideas about this?

—**CHAWALIT** Recently our colleques reported that localisation of parasite antigens and inflammatory responses in experimental opisthorchiasis, and that relationship between parasite-specific antibody responses and intensity of Opisthorchis viverrini infection in hamsters. In these reports, they demonstrated that fluke-specific antigens in fluke, biliary epithelium and inflammatory cells around the bile ducts. The parasite specific antibody responses also can detected in serum. These findings strongly support the role of fluke-associated antigens and local parasite-specific inmune responses in the pathogenesis of opithorchiasis.

—**SUZUKI** Thank you very much.

—**YAMAGUCHI** In autopsy cases, has the fluke been found only in the liver, or has it been found in other organs such as the lung?

—**CHAWALIT** In autopsy we found the flukes (O.V.) in the lumen of bile ducts and gall bladder. The majority of flukes were found in the large intrahepatic bile ducts near the hepatic hilum. We never found the fluke (O.V.) outside the lumer of biliary trees except in pancrecatic duct.

However in the patient with advance cholangiocarcinoma, which tumor invading lung and forming bilio-bronchial fistula, flukes or fluke ova in reflux bile can find contamination in sputum. In my presentation I mention about another fluke (Fasciola) this giant liver fluke is the fluke of cattle, man is an accidental host. The infective stage is attached with water plant.

When the larvae excyst in the duodenum, they directly penetrate the duodenal wall and take transperitoneal migration to the liver. At the liver they penetrate the capsule and liver perenchyma in order to find the bile ducts. This giant fluke stay in the lumen of human bile ducts for a short periord because it too narrow. They leave the bile ducts and end up as parasitic abscesses in liver parenchyma or parasitic pseudoturmor intraperitoneum.

—**YAMAGUCHI** Is there any other parasite associated with cancer ?

—**QIAO** Yes, I do. In my cervical cancer project, we found 22 percent of the HPV infections among our cohort. This is another study that I think we need to take a look at either by examining the HPV interaction between genetic factors, vaccine studies and others.

—**CHAWALIT** There is another parasite, referred to as a shizosome, that is usually found in Egypt. This parasite resides in the venous plexus of the urinary bladder, and can cause infection of the urinary bladder. The cancer is usually a chromacellular carcinoma, and does not involve tanfiginal cells. This blood fluke remains high up in the digestive tract, and are present in the colon or liver. There are few that are associated with colon cancer. Evidence of a direct association in an IARC review is still not convincing. In the case of shizosome mensona in Egypt, however, there is very strong evidence that there is an association with cancer. In addition, I think that espaola is another organism that is associated with gastric cancer.

—**SANTOSO** In Indonesia, we actually have an endemic area of the cystozoma mansoni on Surabesi Island. Until now however, we have not studied this organism in relation to cancer development, which is known in Egypt, for example, or bladder cancer. Also related to infection, I can tell you that we have a very high incidence of nasopharyngeal cancer. For example, in our own hospital in Jakarta, there are 100 to 115 new cases a year of nasopharyngeal carcinoma and what is interesting for us is that they are not confined to Chinese as reported in the literature.

This indicates some incorrect ideas about this cancer. Among the patients with nasopharyngeal cancer, about 50% are native Indonesians. We naturally want to determine if there are genetic differences. There has recently been a new publication regarding EBV DNA present in cervical cancer. I heard about this just before I left. As part of a collaboration, Professor Kenzo Takada tested some DNA samples from Indonesia which I happened to work with that had cervical cancer. We found positive cases for EBV LMV 2A. These findings are considered to be interesting. Although we did not initially expect these DNA samples to be positive, they turned out to actually be positive.

—**ITO** With respect to schistosomiasis in liver cancer, in Japan, the Yamanashi University group reported that there was no significant difference between a schistosomiasis positive group and a negative group in terms of incidence of hepatocellular carcinoma. Almost all of the patients with schistosomiasis and hepatocellular carcinoma later proved to have hepatitis C.

—**TAJIMA** I would like to make a general comment. In Asian countries, infectious agents are one of the

most important factors for cancer. I think infections and cancer constitute a very good model for studying carcinogenicity, because the cause is very clear and preventable. However, only selected people have cancer, which indicates that genetic background may be very important. For example, EBV exhibits worldwide distribution. EBV demonstrates an infection rate of 95 percent, but only in Africa, Papua New Guinea, and in China, it develops the malignancy. Thus, it is very, very risky but only to selected groups of people. This would probably provide a very useful hint in studying carcinogenicity as well as environmental factors, genetic factors and immune response. Thus, I think not only viruses but also parasites and other agents are very important in Asian countries. I think that 10-15 percent of the cancers found in Asian countries are caused by infectious agents.

—**CHAWALIT** Dr. Tajima, I am Dr. Chawalit from Thailand. With respect to nasopharyngeal cancer, a vaccine has already been tried for EB virus in 1989, I believe. What are your plans for the disease involving T cells? Do you intend to prepare a vaccine? If not, how are you going to control it?

—**TAJIMA** I do not think we need a vaccine now. We can eradicate it by controlling the transmission. A critical issue for us now is that we have more than one million carriers of HTLV-1 in Japan. Moreover, every year we have 1,000 new cases and they are very critical because there is no effective treatment. Thus, the major factor is how to control the progression of the disease.

—**CHAWALIT** What I meant to say is that, because it is a retrovirus, vaccine may be able to be applied.

—**TAJIMA** Vaccines are not available, but we can control viral transmission. This will also probably allow us to prevent the disease in the same manner as HIV.

—**CHAWALIT** Another organism mentioned by Dr. Yamaguchi is the papilloma virus associated with cancer of the cervix.

—**ITO** When considering infection-associated cancers in Asian countries and other parts of the world, I would like to stress the crucial role of the concept of global precaution or standard precaution for any infection. Although this is very important for the entire population of your country, in order to implement this, a social foundation must be properly established. Thus, this is a problem to be dealt with by government officials.

—**YAMAGUCHI** I agree with you, because although certain parts of Asia may contain fluke-derived liver cancers. Similar diseases may be found in countries such as Cambodia or Laos that are nearby, even though they may not have been found yet. Thus, global control is very important. It appears that the time is up. I am sure that we all have enjoyed these interesting discussions. Later, we will have an additional opportunity to discuss these subjects at the party to be held 30 minutes from now. I would like to call on Dr. Tominaga to say a few words regarding today's opportunity.

—**MC** Dr. Yamaguchi, Dr. Tominaga, Dr. Ito, and all of the speakers, thank you very much.

Chairpersons

Chairperson

Ken Yamaguchi

Deputy Director, National Cancer Center Research Institute; and Staff Physician, TheDepartment of Internal Medicine, National Cancer Center Hospital, Japan

Born in:	1950	
Education:	1974	M.D., Keio University School of Medicine, Tokyo, Japan
	1981	D.Med.Sci., University of Tokyo, Faculty of Medicine, Japan
Past Records:	1974-1975	Research Fellow, The Department of Pathology, Keio University School of Medicine; Visiting Fellow, Endocrinology Division, National Cancer Center Research Institute, Japan
	1976	Research Fellow, Endocrinology Division, National Cancer Center Research Institute
	1976-present	Staff Physician, The Department of Internal Medicine, National Cancer Center Hospital, Japan
	1983	Section Head, Endocrinology Division, National Cancer Center Research Institute, Japan
	1983-1986	Visiting Lecturer, Kitasato University School of Medicine, Japan
	1986	Chief, Endocrinology Division, National Cancer Center Research Institute, Japan
	1987-present	Chief, Growth Factor Division, National Cancer Center Research Institute, Japan
	1995 -present	Visiting Lecturer, Thohoku University School of Medicine, Japan
	1999 -present	Deputy Director, National Cancer Center Research Institute, Japan
	1999 -present	Special Advisor to the Imperial Household

Co-chairperson

Suketami Tominaga

Director, Aichi Cancer Center Research Institute, Japan

Born in:	1937	
Education:	1962	M.D.from Osaka University Medical School, Osaka, Japan
	1967	Dr.MSc from Osaka University Medical School, Osaka, Japan
	1970	M.P.H.from Johns Hopkins University, School of Hygiene and Public Health
	1981	Finished the Master Course of Literature Department,Rissho University
Past Records:	1968-1969	Research Associate, University of Maryland, School of Medicine
	1969-1972	Assistant Professor, University of Maryland, School of Medicine
	1972-1973	Associate Professor, University of Maryland, School of Medicine
	1974-1977	Medical Officer, Ministry of Health and Welfare, Environment Agency
	1977-1985	Chief, Division of Epidemiology, Aichi Cancer Center Research Institute
	1985-1990	Vice Director, Aichi Cancer Center Research Institute
	1990-present	Director, Aichi Cancer Center Research Institute
	1994-present	Chairman, Epidemiology and Prevention Program of UICC

Co-chairperson

Kazuki Ito

Chief, Department of Hepato-Gastroenterology and Interventional Radiology, Shizuoka General Hospital, Japan

Born in:	1950	
Education:	1977	M.D.Shinshu University School of Medicine
Past Records:	1977-1979	Clinical and Research Fellow in Endocrinology and Geriatrics, Shinshu University School of Medicine, Matsumoto, Japan
	1979-1982	Senior Resident in Internal Medicine and Radiology, Tenri Hospital, Tenri, Japan
	1982-1989	Medical Staff in Hepato-Gastroenterology, Shizuoka General Hospital, Shizuoka, Japan
	1989-present	Chief, Department of Hepate-Gastroenterology and Interventional Radiology Shizuoka General Hospital, Shizuoka, Japan

Steering Committee of Asian Cancer Conference in Shizuoka,2000

Chairperson

Ken Yamaguchi	Deputy Director, National Cancer Center Research Institute

Co-Chairperson

Suketami Tominaga	Director, Aichi Cancer Center Research Institute
Kazuki Ito	Chief, Department of Hepato-Gastroenterology and Interventional Radiology, Shizuoka General Hospital

Office for Establishment of Cancer Center

Members

Mituaki Furuhashi	Director General
Kozo Nagaoka	Managing Director
Yoshiro Osuga	Director
Sunao Tamai	Technical Councilor
Togo Suzuki	Technical Councilor
Hideki Kuroki	Assistant Director
Satoe Koda	Assistant Director
Toshiro Fukazawa	Assistant Director
Toshio Ema	Assistant Director
Masahiro Akimaru	Assistant Director
Mitsuhisa Kozakura	Chief Staff
Yoichi Ikeya	Chief Staff
Osamu Furusawa	Chief Staff
Kazuo Fujiwara	Chief Staff
Kazuya Yamawaki	Chief Staff
Kiyoko Tsuruta	Chief Staff
Masumi Kaneiwa	Chief Staff
Miho Mochizuki	Sub-Chief Staff
Tetsuya Uematsu	Staff
Mutsumi Tsuchiya	Technical Staff
Ikuyo Watanabe	Technical Staff

Secretariat of Asian Cancer Conference in Shizuoka, 2000

Toshihiro Yasuda	Director, Shizuoka Research Institute(SRI)
Tetsuo Seki	Senior Reseacher, Shizuoka Research Institute(SRI)
Satoko Kageyama	Researcher, Shizuoka Research Institute(SRI)
Kanako Urushibata	Staff, Shizuoka Research Institute(SRI)

Overview of Shizuoka Cancer Center

SHIZUOKA CANCER CENTER

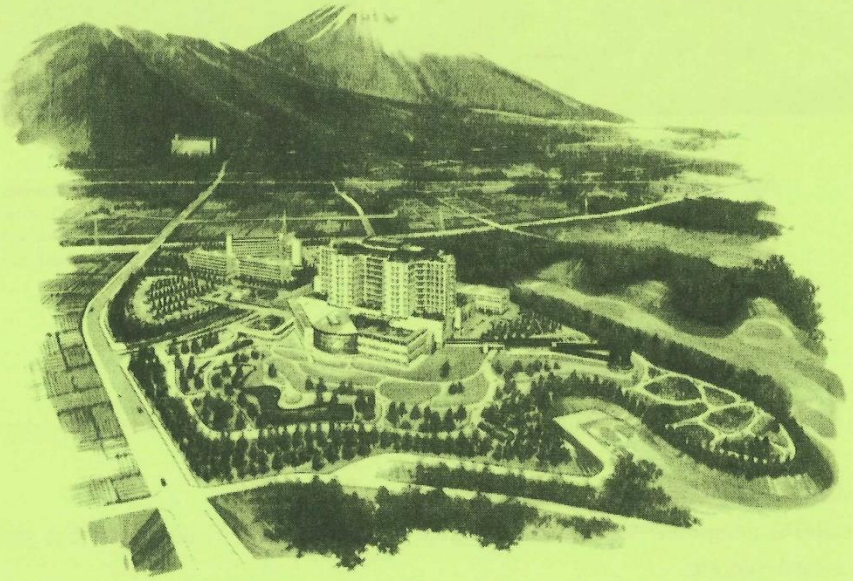
DESCRIPTION OF THE PROJECT

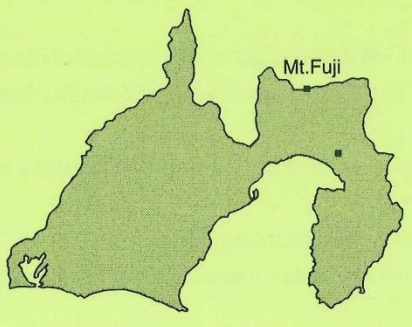
Today, cancer is the primary cause of death in Shizuoka Prefecture, and the number of cancer patients is expected to increase steadily in the future.
To help deal with this dreadful disease, Shizuoka Prefecture is in the process of establishing one of the most advanced cancer centers in Japan. Shizuoka strives for the best cancer care based on the fol1owing principles:

1) Realization of appropriate medical care of cancer with the most advanced technology
2) Promotion of patient-oriented care
3) Creation of a core center of cancer information networks and other countermeasures

Opening Schedule of the Hospital 2002
(Research sections will be formulated within three years after opening of the hospital)
Project Cost 48 billion yen (excluding medical equipment, etc.)

Expected View of the Hospital





Project site
Nagaizumi Town,
Sunto County,
Shizuoka Prefecture

Transportation
from JR Mishima Station
approx. 5km
Tomei Highway,Numazu IC
approx. 6km

FACILITIES

Proton beam treatment center
To conduct proton beam treatment, which is the most advanced cancer cure method in the world

Wards
About half of the 615 beds will be in single rooms for privacy and amenities of patients
To be arranged and designed for efficient care system by a medical team composed of doctors, nurses, pharmacists, etc.

Outpatient sectiom
To be composed of different centers for different organic ysytems, which will be distinctively designed so that patients can easily distinguish which directicns they should follow

Hospice care center
To alleviate pain and other symptoms so that patients can get the most out of life

Tomei Highway

Staff apartment

Research laboratories
To promote research in the support of advanced cancer care and to contribute to development of local medical industries

Parking
capacity : about 1,000 cars

Garden
To create"garden hospital" atmosphere surrounded with greenery and flowers

SCC'S GOALS FOR MEDICAL CARE

With skilled staff and state-of-the-art equipment, Shizuoka Cancer Center will realize highly advanced care for cancer.

SCC will provide all services from preventive medicine to follow-up care.

SCC will establish integrated care systems capable not only of direct cancer care but also of care for complications, mental care, etc.

SCC will be equipped with full rehabilitation therapy facilities, which will serve for the patient's prompt reintegration into society.

SCC will be fully concerned to establish proper "informed consent" system (sufficient explanation of disease and cure methods to be applied to the patients to get their understanding and agreement) and notification of cancer to the patients.

SCC will pursue patient-centered care system, such as shortening of waiting time for examinations and treatments, weekend services, etc.

SCC will support cancer care at patient's home, with cooperation of other local medical facilities.

SCC will establish the latest information system, which will be utilized for further improvement of medical care and for more efficient and effective hospital operation.

Proton Therapy Facility

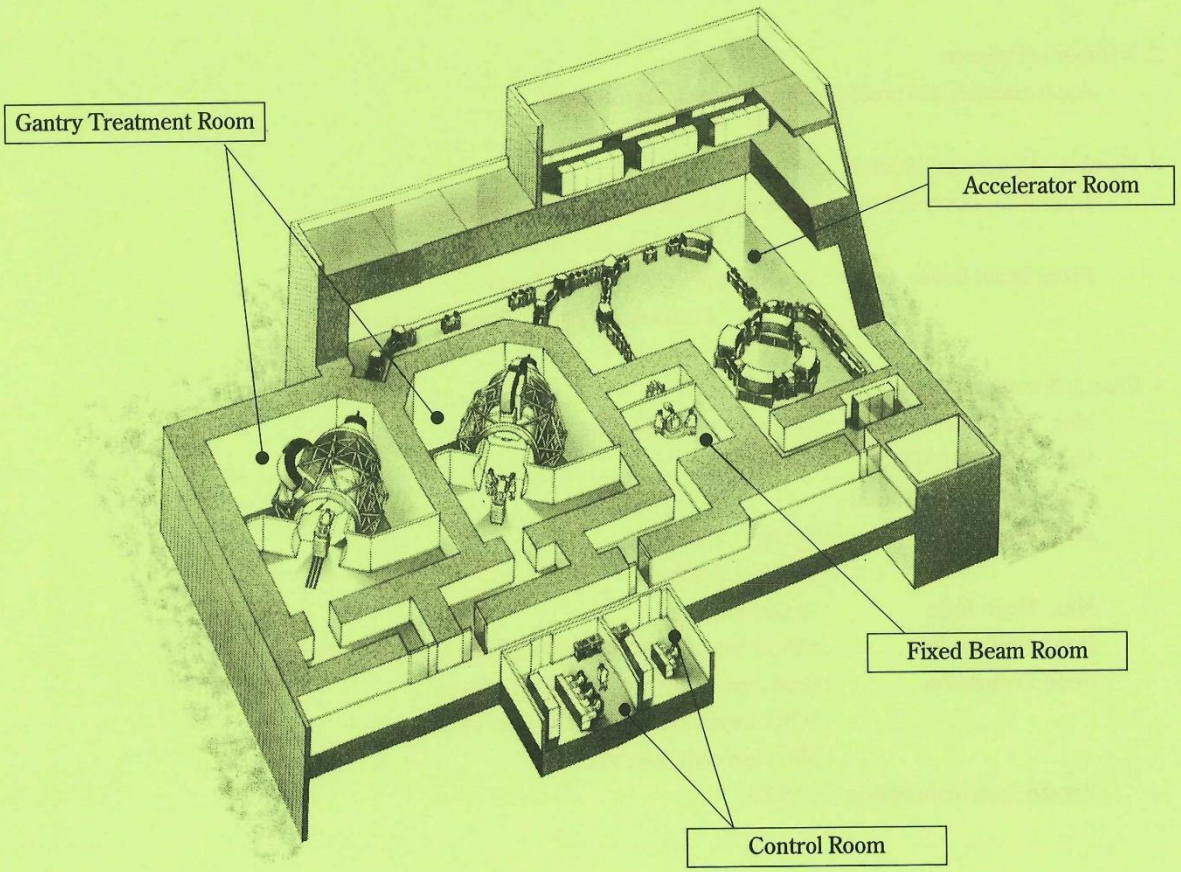
Overview

To proton therapy facility is currently under construction at the Shizuoka Cancer Center by Shizuoka Prefecture, scheduled to open in the year 2002. The facility includes an accelerator room for providing a proton beam, treatment rooms for delivering the beam to patients, and other supporting rooms.

Specifications of the Equipment

Beam Species : Proton
Beam Energy : 70-235MeV, reachable up to 25cm deep into the human body.
Accelerator : Synchrotron.
Treatment Rooms : ● Isocentric Gantry Rooms, capable of delivering the beam from 360 degrees and around a patient.
: ● Fixed Beam Room.

An Artist's View of the Facility



Detailed Design of the Proton Therapy Facility At Shizuoka Cancer Center

1. Criteria to Select Patients

Both of the following fundamental and practical criteria will be applied.

(1) Fundamental Criterion

One of the following conditions:

a) An improved tumor control rate is expected with the local dose escalation.

b) A prolonged lifetime or an improvement in quality of life is expected with the local lesion amelioration.

c) The lesion is located close to a critical organ for which risk of serious functional disorder due to the irradiation is high.

(2) Practical Criterion

All of the following conditions:

a) The location and outline of the tumor can be easily defined with the imaging diagnosis technique.

b) The physiologic movement of the tumor is within a range allowed by the beam delivery technology

c) There exists a benefit from the dose concentration.

2. Number of Patients

Approximately 400 proton patients per year are assumed.

3. Number of Treatment Rooms

Isocentric Gantry Room	: 2 rooms, approx. 320 patients / year (combined) Identical beam delivery system each room.
Fixed Beam Room	: 1 room, approx. 80 patients / year Primarily for the head and neck treatment.

4. Clinical Specification

Max. Range in Patient	: >25 cm, water equivalent
Max. Width of SOBP (Spread-Out Bragg Peak)	: >10 cm
Max. Field Size	: Gantry ϕ 20cm
	: Fixed ϕ 10cm
Max. Dose Rate	: >2 Gy/min
Dose Uniformity	: $\pm$2% or better, laterally and longitudinally (design goal)
Field Formation	: Beam spreading with a wobbler system.
	: SOBP formation with a ridge filter system.
	: Multi-leaf collimator available.
Breath Synchronization	: Capable.

Proceedings of Asian Cancer Conference in Shizuoka, 2000

Issue in March, 2001

Editorial Office Asian Cancer Conference in Shizuoka Secretariat
Shizuoka Research Institute
9-18 Ohte-machi, Shizuoka City, 420-0853
TEL 054-221-2323
FAX 054-221-2853

Issue Shizuoka Pref./Shizuoka Asian Cancer Conference Steering Committee

Print place Takayama print company

We will change the missing page.

Asian Cancer Conference
in
Shizuoka,2000