

# JMAJ

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### CONTENTS

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#### **Feature: Prevention and Early Detection for Cancer**

##### Carcinogenic Risk Factors

Hiroshi SAEKI and Keizo SUGIMACHI ... 245

##### Prophylaxis and Early Detection for Breast Cancer

Hiroki KOYAMA *et al.* ..... 250

##### Prevention and Early Detection of Colorectal Cancer

Toshio SAWADA ..... 255

#### **Progress in Basic Medicine**

##### Psychopathology of Social Withdrawal in Japan

Natsuko HIRASHIMA ..... 260

#### **Progress in Clinical Medicine**

##### The Status of Hepatitis Vaccines: Type A and Type B

Shiro IINO ..... 263

##### Central Retinal Vein Occlusion (CRVO)

—Visual Disorder in Patients of  
Middle and Advanced Age—

Ikuo TOBARI ..... 268

##### Distinction between Dementia and Memory Decline

Shunsaku HIRAI ..... 274

##### Depression Associated with Physical Illness

Koho MIYOSHI ..... 279

#### **Progress in Public Health**

##### Cancer Screening and Radiation

Takeshi IINUMA ..... 283

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## Notice

The Asian Medical Journal (AMJ) has changed its name to the Japan Medical Association Journal (JMAJ) from the April 2001 issue. The AMJ has been in publication for more than 40 years since its first issue. Its goal has been to promote medicine and health care mainly in Asia. Relevant articles were selected mainly from the Journal of the JMA and translated into English. It has been an academic journal containing the latest information in the field of medicine.

In conjunction with the change in the name, the journal's cover has been revised. The content of the JMAJ will continue to contain the latest information in medicine and health care in Japan, but it will be disseminated to medical-related organizations throughout the world, in addition to Asia. It will also contain information on JMA's activities and its stance on health care policies in Japan. Please note that the first issue of the JMAJ is volume number Vol. 44, No. 4 and the numbering continues consecutively from the previous AMJ issue. The ISSN 0004-461X will also continue to be the same. In addition, we are no longer accepting contributions to the AMJ or the JMAJ.

*JMAJ Editorial Office*

# Carcinogenic Risk Factors

JMAJ 44(6): 245-249, 2001

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**Abstract:** Carcinogenic risk factors can be roughly divided into environmental factors and genetic factors. Environmental carcinogenic factors include the following: ionized radiation, etc. as physical factors; benzo [ $\alpha$ ] pyrene contained in tobacco smoke, ethyl alcohol, etc. as chemical factors; and various viruses, etc. as biological factors. Meanwhile, abnormalities in DNA repair genes and cell cycle genes have been identified as genetic factors. Now that the mechanisms of carcinogenesis have been understood from a genetic standpoint, relationships between risk factors and carcinogenesis have also become comprehensible from the viewpoint of gene abnormalities. In the future, if "susceptibility to cancer" becomes predictable based on individual genetic information, living environment, etc., then individualized cancer prevention will be realized from a new point of view.

**Key words:** Environmental factors; Genetic factors; Cancer prevention

## Introduction

Cancer is a disease caused by gene abnormalities in any of the cells. However, clear individual difference exists in the "susceptibility to cancer," which is related to carcinogenic risk factors. Cancer prevention should become possible if risk factors can be avoided.

Rapid advances in recent cancer studies has made it possible to theorize on carcinogenic risk factors. Such risk factors can be roughly divided into environmental factors and genetic factors. It has long been known that the incidence of cancer differs according to the region, occupation, eating habits, and lifestyles. Such differences occur due to variations in carcinogens in the environment which induce mutations in some genes. Genetic factors, which

have been identified through studies on familial neoplastic diseases, are considered to be the state of susceptibility to cancer induced by the transmission of mutations in cancer-related genes.

In the present report, we review the carcinogenic risk factors that have been studied from various viewpoints.

## Environmental Factors

In the epidemiological studies conducted to date, various environmental factors have been shown to be carcinogenic risk factors. Among these, representative factors are listed in Table 1. These factors include those whose carcinogenic effects can be avoided by altering lifestyles such as a smoking habit, and can be said

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This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 3, 2001, pages 297-300).

Table 1 Known Environmental Carcinogenic Factors

Factor	Site of carcinogenesis
1. Physical factors	
Ionized radiation	Myelopoietic tissue, Lung, Thyroid gland
Ultraviolet	Skin
2. Chemical factors	
Benzo [ $\alpha$ ] pyrene: Smoking	Lung, Head and neck, Esophagus, Bladder
Heterocyclic amine: Overcooked meat and fish	Mammary gland, Large intestine
Ethyl alcohol: Drinking	Head and neck, Esophagus
Aflatoxin: <i>Aspergillus flavus</i>	Liver
Asbestos	Lung, Pleura
Cadmium	Prostate
3. Biological factors	
Hepatitis B virus, hepatitis C virus	Liver
HTLV-1 (human T-lymphotrophic virus type 1)	T cell lymphoma
Human papilloma virus	Uterine cervix, Esophagus

to be directly linked with cancer prevention. In addition, many gene abnormalities induced by such environmental factors have been discovered, and molecular targets of environmental factors are increasingly being clarified.

## 1. Physical factors

### 1) Ionized radiation

It is well known that ionized radiation may cause gene mutation or chromosome aberration. The results of an epidemiological survey of carcinogenesis in atomic bomb victims show increased incidence of leukemia, lung cancer, etc. in the population. With respect to the timing of carcinogenesis, while the incidence of leukemia was high between 5–20 years after the exposure to atomic-bomb radiation, that of lung cancer is still high even now, more than 50 years since the exposure. Applying the current theory that carcinogenesis is the result of the multi-stage carcinogenic process accelerated by the accumulation of mutations in cancer-related genes, to the above findings, it can be assumed that exposure to ionized radiation may trigger off any of the steps involved in multistage carcinogenesis.

### 2) Ultraviolet light

Ultraviolet light is an environmental factor that is closely associated with skin cancer. Al-

though the incidence of skin cancer is extremely low in Japan, it is frequently the most or second most prevalent cancer in Europe and America. Ultraviolet irradiation may modify DNA base pairs, resulting in the formation of pyrimidine dimers. Moreover, ultraviolet light contributes to the production of a reactive oxygen species, which directs cells toward carcinogenesis.

## 2. Chemical factors

### 1) Benzo [ $\alpha$ ] pyrene

Smoking is most clearly associated with the increased risk of cancer. Smoking-associated cancers include lung cancer, head and neck cancer such as laryngeal and pharyngeal cancers, esophageal cancer, bladder cancer, pancreatic cancer as well as uterine cervix cancer.

Lung cancer is exhibiting a decreasing tendency in Europe and America. However, in Japan, lung cancer is the most common cause of cancer death in males, and its incidence is expected to increase further in the future. This is attributable to a slower decrease in the smoking rate as compared with Europe and America. Concerning the carcinogenic substances in tobacco smoke, benzo [ $\alpha$ ] pyrene is thought to have great significance. It is known that benzo [ $\alpha$ ] pyrene may cause characteristic point mutation in the *p53* gene, a tumor sup-

Table 2 Genetic Carcinogenic Factors

Disease	Related tumors	Responsible gene	Function
Hereditary nonpolyposis colon cancer (HNPCC)	Colon cancer, Cancer of uterine body	I . DNA repair genes 1) <i>MLH1</i> , <i>MSH2</i> <i>MSH6</i> , <i>PMS1</i> <i>PMS2</i>	DNA mismatch repair
Xeroderma pigmentosum (XP)	Skin cancer	2) <i>XPA</i> , <i>XPB</i> <i>XPC</i> , <i>XPD</i> <i>XPF</i> , <i>XPG</i>	Nucleotide excision repair
Familial breast cancer	Breast cancer	3) <i>BRCA1</i> , <i>BRCA2</i>	Recombination repair (?)
Retinoblastoma	Retinoblastoma	II . Cell cycle genes 1) <i>Rb1</i>	Transcriptional control, Cell cycle control
Li-Fraumeni syndrome	Breast cancer, Soft tissue tumor, Brain tumor	2) <i>p53</i>	Transcriptional control, Cell cycle control
Familial melanoma	Melanoma	3) <i>p16</i>	Cell cycle control
Wilms tumor	Wilms tumor	4) <i>WT1</i>	Transcriptional control
von Hippel-Lindau disease	Angioblastoma, Renal cancer, Retinal angioma	5) <i>VHL</i>	Transcriptional control
Familial adenomatous polyposis (FAP)	Colon cancer	III. Genes responsible for tissue organization 1) <i>APC</i>	Membrane structure and signal transduction
Familial gastric cancer	Gastric cancer	2) <i>E-cadherin</i>	Cell adhesion
Neurofibromatosis type II	Acoustic neurinoma	3) <i>NF2</i>	Cell adhesion
Juvenile polyposis	Hamartoma	IV. Signal transduction genes 1) <i>PTEN</i> <i>SMAD4</i>	Phosphatase Signal transduction
Hereditary papillary renal cell carcinoma	Papillary renal cell carcinoma	2) <i>MET</i>	Receptor tyrosine kinase
Multiple endocrine neoplasia type II (MEN2)	Adrenal pheochromocytoma Medullary carcinoma of thyroid	3) <i>RET</i>	Receptor tyrosine kinase
Neurofibromatosis type I	Neurofibroma	4) <i>NF1</i>	Signal transduction

pressor gene,<sup>1)</sup> which is considered to be one of the mechanisms of carcinogenesis due to tobacco smoke.

2) Ethyl alcohol

Heavy drinking is also associated with the incidence of head and neck cancer as well as gastrointestinal cancer. With regard to esophageal cancer in particular, alcohol intake has been shown to trigger carcinogenesis cooperatively with tobacco smoke. The results of our studies have also shown that heavy drinking and smoking frequently leads to multiple cancers in the head and neck and in the esophagus.<sup>2)</sup> Furthermore, in patients with esophageal

cancer who consume a large amount of alcohol and tobacco, the incidence of *p53* gene abnormalities is 90% or higher,<sup>3)</sup> suggesting the possibility that the *p53* gene is the molecular target for the carcinogenesis of esophageal cancer due to drinking and smoking.

3) Heterocyclic amine

Heterocyclic amine is known to be a carcinogenic substance in overcooked meat and fish. In experiments using rats, the substance has been reported to induce both colon and prostate cancer in male animals, and breast cancer in female animals. In epidemiological surveys, intake of overcooked meat and fish is also said

to be associated with the occurrence of breast cancer and colon cancer.<sup>4,5)</sup>

### 3. Biological factors

Biological carcinogenic factors include various viruses. For example, chronic hepatitis and hepatic cirrhosis owing to persistent infection with hepatitis B virus or hepatitis C virus have been epidemiologically proven to be related to the occurrence of liver cancer. The hepatitis B virus is a DNA virus, and is known to incorporate its partially deleted DNA into genomes in the hepatocyte. On the other hand, the hepatitis C virus is an RNA virus, whose genes do not encode reverse transcriptase. Therefore, it does not incorporate its DNA into the hosts' genomes, and its contribution to carcinogenesis is unclear.

### Genetic Factors

Carcinogenesis is often sporadically observed, but sometimes concentrates in certain families. The causes of such familial neoplastic diseases were unknown for many years, however, in recent aggressive studies on cancer-related genes, the *Rb1* gene which is responsible for retinoblastoma was identified in 1986, and subsequently, a succession of genes responsible for hereditary neoplastic syndrome have been identified. As shown in Table 2, these genes include DNA repair genes, cell cycle genes, genes responsible for tissue organization, signal transduction genes, etc. Abnormalities of such genes also represent carcinogenic risk factors, and should be isolated from the above-mentioned environmental factors as genetic factors.

#### 1. DNA repair genes

##### 1) DNA mismatch repair

Hereditary nonpolyposis colon cancer (HNPCC) is a hereditary neoplastic disease which occurs in individuals with abnormalities in DNA mismatch repair genes.<sup>6,7)</sup> Normally, adenine and thymine or cytosine and guanine are paired by hydrogen bond and form DNA

double-helices. When a base is substituted by another inappropriate base which forms a mismatch with the other base during DNA replication, the base pair will be removed from the strand and the DNA strands will be repaired. This system is called the mismatch repair mechanism. In families affected by HNPCC, where gene mutations involved in the mismatch repair mechanism are transmitted from generation to generation, family members are known to be susceptible not only to colon cancer but also to cancer of the uterine body, pancreatic cancer, gastric cancer, etc.

##### 2) Nucleotide excision repair

Xeroderma pigmentosum (XP) is a recessive hereditary neoplastic disease, and is associated with the abnormalities in genes involved in the repair of DNA damage caused by ultraviolet light.<sup>8)</sup> Ultraviolet irradiation may modify DNA base pairs and cause the formation of pyrimidine dimers, but in the cells without the abnormality, such abnormality will be corrected through the nucleotide excision repair system. In the genes of patients with XP, abnormalities in some of the proteins involved in the nucleotide excision repair system are present, and pyrimidine dimers will not be excised, resulting in a susceptibility to skin cancer.

#### 2. Cell cycle genes

##### 1) *Rb1* gene

Retinoblastoma is a malignant neoplastic disease occurring in 1 in 15,000 individuals. Bilateral retinoblastoma is always considered to be hereditary. In 1986, the *Rb1* gene, which is responsible for the disease, was cloned,<sup>9)</sup> and it thus became apparent that the RB protein encoded by the gene plays an important role in cell cycle control.

##### 2) *p53* gene

In Li-Fraumeni syndrome various organs are affected, leading to the manifestation of breast cancer, soft tissue tumor, brain tumor, etc. The concept that the syndrome was caused by a single-gene abnormality was therefore questioned. However, in 1990, the disease was proven

to be an autosomal dominant hereditary disease associated with inherited mutation in the *p53* gene.<sup>10)</sup>

## Conclusion

As carcinogenic risk factors, environmental factors including benzo [ $\alpha$ ] pyrene contained in tobacco smoke and ethyl alcohol, as well as genetic factors including abnormalities in DNA repair genes and cell cycle genes have been identified. In addition, the mechanism of carcinogenesis has been understood from a genetic standpoint, the relationship between risk factors and carcinogenesis is beginning to be understood from the viewpoint of gene abnormalities. In the future, if "susceptibility to cancer" becomes predictable based on individual genetic information, living environments, etc., then cancer prevention from a new point of view, for example, individualized prophylaxis, as well as early diagnosis or treatment in light of individual risk factors, will be realized. Further studies in various areas including epidemiology and experimental medicine is anticipated.

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# Prophylaxis and Early Detection for Breast Cancer

JMAJ 44(6): 250–254, 2001

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**Abstract:** Breast cancer is steadily increasing in number in Japan due to less child bearing, less breast-feeding, and more westernization of life style than ever. Cancer registration in Osaka reported the incidence of breast cancer in 1996 to 1998 to be 41.1/100,000, four-times higher than the value in 1966–1968. Avoiding overweight, animal fat intake and mental stresses is a basic and easy measure for prevention of breast cancer. A unique study performed in Japan shows that daily intake of 10 or more cups of green tea inhibits development of breast cancer. A large-scale study by National Surgical Adjuvant Breast and Bowel Project (NSABP) revealed that 5-year tamoxifen administration to high-risk women decreased the incidence of breast cancer to 1/2 of the value for control women. Early diagnosis of breast cancer is most effectively achieved by fine needle aspiration cytology if the tumor is palpable with joint work with capable cytologists. More recently, stereo-tactic biopsy devices are available for non-palpable lesions. Mammography is more frequently used in mass screening system though its essential merit is yet to be investigated.

**Key words:** Increased incidence of breast cancer;  
Breast cancer prevention by drugs;  
Cytological and histological examinations;  
Breast cancer mass screening

## Introduction

The steady increase in number of breast cancer patients in Japan is attributed to increased calorie intake, particularly that through animal fats. The advance of women in society due to

changes in social structure is also a notable cause for the increase. This paper analyses the increase of breast cancer and discusses the present situation and future prospect for the method of primary prevention and early diagnosis as secondary prevention.

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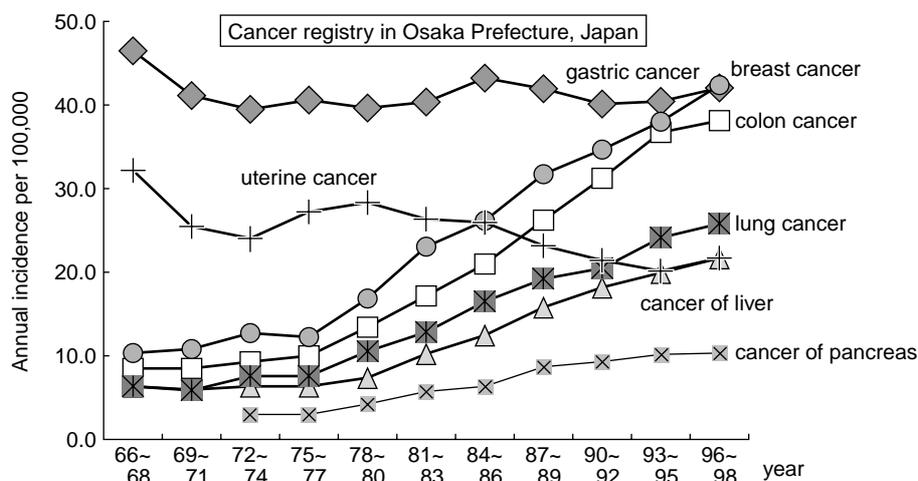


Fig. 1 Annual changes in the incidence of cancer (women)

## Prevention of Breast Cancer

Fig. 1 shows the incidence of cancers in women in cancer-registry of Osaka Prefecture, Japan (the incidence of cancer per year per 100,000 population). It is clear from the figure that the incidence of breast cancer has increased by approximately four times during these 30 years (1966–1998) from 10.5 to 41.9. Such a tendency is observed worldwide, especially in developing countries, indicating the correlation between economic development and increased incidence of breast cancer.

When contemplating prevention of breast cancer, one merely has to consider the causes for its increase in recent years. Obesity is an important high risk factor for breast cancer as well as for cardiovascular diseases and colon cancer. Obesity control by proper diet and physical exercises is important for improving overall health as well as for breast cancer prevention. The incidence of breast cancer is higher in women who have had less childbirth, who are older at the first childbirth, and whose period of breast-feeding is shorter. This means that effective breast cancer prevention can be achieved if the conditions reverse to these are met. However, it is not appropriate to recommend them as preventive measures because of

various individual views about life and social conditions.

The Gail model<sup>1)</sup> proposes to comprehensively examine these risk factors and projects individualized probabilities of developing breast cancer. If the risk calculated by this method is high, it is necessary to take some concrete countermeasures.

The breast cancer preventive effect of polyphenol in green tea was recently reported. According to Fujiki,<sup>2)</sup> daily intake of 10 or more cups of green tea delays the onset of breast cancer or restrains its recurrences.

A large-scale research (P-1 study) on prevention of breast cancer with drugs was conducted by National Surgical Adjuvant Breast and Bowel Project (NSABP).<sup>3)</sup> This study randomized 13,388 women who were identified high risk for breast cancer by using the Gail model including the family history of breast cancer and the past history of mastopathy, into two groups; a group administered tamoxifen and a group given placebo for five years. It revealed that 5-year tamoxifen administration decreased the incidence of breast cancer to 1/2 of the value for control women (Fig. 2). The cost of tamoxifen administration for such preventive purpose, however, is not covered by the health insurance scheme in Japan.

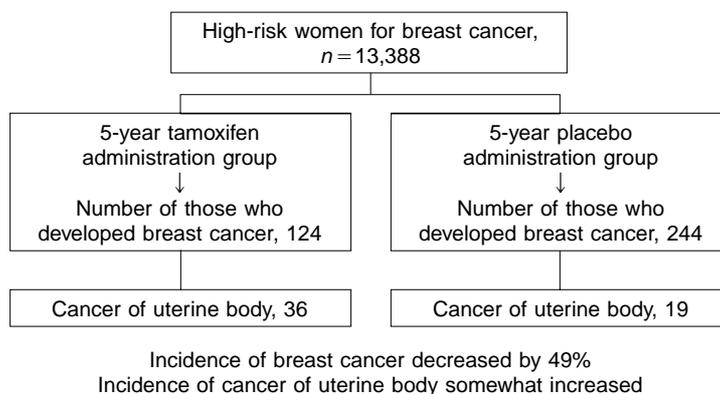


Fig. 2 Result of P-1 study by NSABP

Table 1 Result of Fine Needle Aspiration Cytology (Osaka Prefecture Adult Disease Center)

Pathological diagnosis	Year	No. of cases	Positive(%)	Suspectie(%)	Negative(%)	Indeterminable
Breast cancer	1965–1989	1,113	915 (82.2)	53 ( 4.8)	95 ( 8.5)	50
	1995	133	118 (88.7)	10 ( 7.5)	3 ( 2.3)	2
	1996	140	125 (89.3)	7 ( 5.0)	5 ( 3.6)	3
	1999	229	207 (90.4)	6 ( 2.6)	8 ( 3.5)	8
Benign lesion	1965–1989	827	41 ( 5)	50 ( 6.0)	641 (77.5)	95
	1995	54	0 ( 0)	3 ( 5.6)	45 (83.3)	6
	1996	57	0 ( 0)	9 (15.8)	44 (77.2)	4
	1999	74	1 ( 1.4)	4 ( 5.4)	65 (87.8)	4

Recent studies on families with high incidence of breast cancer identified BRCA 1 (17q) and BRCA 2 (13q) genes.<sup>4)</sup> They are considered to be the breast cancer controlling genes, and the probability of developing breast cancer in women with mutations of these genes is said to be 50–70%. These people are recommended to undergo frequent screenings and receive prophylaxis administration. There is, however, less number of Japanese people with these gene abnormalities.

## Early Detection of Breast Cancer

### 1. Palpation and diagnostic imaging

Since breast cancer develops in the organ located close to the body surface, patients themselves can easily palpate and detect it. However, a considerable skill is required to

establish diagnosis of breast cancer only by palpation. About 2/3 of outpatients requesting mammary examination do not have tumor and their main complaint is the tenderness in the mammary gland. Although such pain is usually caused by mastopathy, it is occasionally complicated by cancer, requiring careful palpation.

When tumor is suspected by palpation, the patient is given mammography or ultrasonography. Since those younger than 30 have ample mammary parenchyma, imaging of tumor by mammography is difficult. In such cases, ultrasonography is conducted first. In those older than 50, on the other hand, mammography is quite effective. Even when the tumor is non-palpable, if fine calciferous deposit is observed, this leads to the definite diagnosis of breast cancer, because the finding is quite unique to breast cancer.

Table 2 Merits and Demerits of Various Diagnostic Methods for Breast Cancer

Classification	Palpation	Mammography	Ultrasonography	Fine-needle aspiration cytology
Nature of lesion				
Large tumor	○	○	○	○
Small tumor	△	△	△	○
Non-palpable	×	△ (calcareous deposit)	×	×
Age				
Young (hard breast)	△	×-△	△	○
Older (soft breast)	○	○	○	○
Pathological type				
Diffuse type (papillary adenocarcinoma)	×	△	×	△
Localized type (medullar carcinoma of breast)	○	△	△	○
Infiltrating type (scirrhous carcinoma)	△	○	○	△

○ Highly useful    △ Moderately useful    × Not so useful

## 2. Cytological and histological examinations

Palpation and mammography, palpation and ultrasonography, or combination of these three techniques establishes the diagnosis of 80% of breast cancer. If it is still not possible to establish the diagnosis, fine needle aspiration cytology is performed. It is particularly effective for small size tumors as well as for confirming the benign nature of tumor. Table 1 shows annual changes in diagnoses established by needle aspiration cytology at the institute where the authors work. The institute uses needle aspiration cytology for establishing the diagnosis, and the Class V result is deemed as confirming the diagnosis of breast cancer. The problem arises when false positive diagnosis is made for pathologically benign lesions. Due to our continuing efforts to improve cytodagnosis, the number is approximating zero. Table 2 shows the characteristics, merits, and demerits of various diagnostic methods.

When cancer is suspected by diagnostic imaging but not confirmed by needle aspiration diagnosis, surgical biopsy is indicated. Of the two types of biopsies, incisional and excisional, excision is usually performed. When performing a biopsy, the patient should be offered sufficient information that an appropriate sur-

gery (mastectomy or lumpectomy) will be performed if the tumor is found to be malignant and obtain her consent in advance.

Core biopsy<sup>5)</sup> or vacuum-assisted biopsy device<sup>6)</sup> is often relied on in recent years instead of surgical biopsy. This technique consists of taking tissue samples of the size enabling histological examination by inserting a considerably thick needle of 12 to 14 gage into the lesion, and is expected to replace surgical biopsy. Presently, partial resection of the mammary gland (lumpectomy) is the mainstay of breast cancer operation, therefore a measure that obtains firm diagnosis with smaller invasion is being welcomed.

When the tumor is not palpable by palpation of the mammary gland, ultrasonography or mammography may detect a lesion. A cystic lesion, one type of mastopathy, may be clearly depicted by ultrasonography, enabling fine needle aspiration, core biopsy or vacuum-assisted biopsy guided by ultrasonography. When microcalcification deposits are observed by mammography, stereotactic imaging is performed to decide coordinates for the lesion, and cytological or histological samples are sampled. Alternatively, a hook wire may be inserted into the lesion and surgical biopsy

performed along the wire to establish the diagnosis.

### 3. Significance of breast cancer mass screening

Significance of mass screening of breast and other cancers is often discussed regarding its effectiveness or ineffectiveness. Since about 10 years previously, breast cancer mass screening has been performed mainly by palpation, combined by ultrasonography or mammography. The screening by Osaka Prefecture Government in which the authors participate, the subjects are limited to women over 35. The result for 1996–1998 screenings consisted of about 8% of 2,148,788 women over 35 undergoing screening, about 0.2% of those screened being found with breast cancer, and about 35% of the breast cancer being early stage cancer. The report<sup>7)</sup> on data from Japan and abroad suggests the screening combined with mammography is more effective, promoting the mass screening system for breast cancer.

### Conclusion

The advance of women into society in recent years is expected to increase the incidence of breast cancer due to less number of childbirth, higher nutrition intake, and increased stresses. Although it is still difficult to secure preven-

tion, the techniques for early detection are certainly making progress, enabling patient-friendly treatments such as lumpectomy.

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# Prevention and Early Detection of Colorectal Cancer

JMAJ 44(6): 255–259, 2001

Toshio SAWADA

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**Abstract:** Chemoprevention and early detection are key to reducing the mortality rates in patients with colorectal cancer. Epidemiological studies have demonstrated the major role of diet in the etiology of colorectal cancer. In the carcinogenesis of colorectal cancer, a high fat, low residue diet is causative, whilst a low-fat, high residue diet is protective. Epidemiological studies had documented a 40–50% reduction in the risk of developing colorectal cancer in individuals taking NSAIDs as aspirin, which are inhibitors of cyclooxygenase. These data strongly suggest that the inhibition of COX-2 is chemopreventive. However, epidemiological and experimental studies pertaining to vitamins, antioxidants, fiber, and calcium supplementation have led to some discrepancies. Randomized trials have revealed that screening with fecal occult blood tests facilitates a 15–25% reduction in the mortality from colorectal cancer. Whilst the National Polyp Study has reported that removal of colorectal adenomas (over 5 mm in diameter) contributes to a 76–90% reduction in the mortality rates of the disease. These results also support the hypothesis of the adenoma-carcinoma sequence in the carcinogenesis of colorectal cancer.

**Key words:** Primary prevention; Secondary prevention; Early diagnosis; Early-stage colorectal cancer

## Introduction

The control of factors involved in the occurrence and progression of colorectal cancer is important for the prevention (primary prevention) of the cancer, and for early diagnosis (secondary prevention), and mass screening has considerable significance. We report the currently available results of chemoprevention and data on the efficacy of colorectal cancer mass screening.

## Primary Prevention

### 1. Initiation and promotion

It has been assumed that colorectal cancer is caused by the accumulation of multiple genetic alterations (multi-stage carcinogenesis). The details of the process have not been uncovered, however, it is known that the initiators (carcinogen and mutagens) change normal cells into mutant cells, and that the promoters (tumor promoting agent) induce the proliferation and

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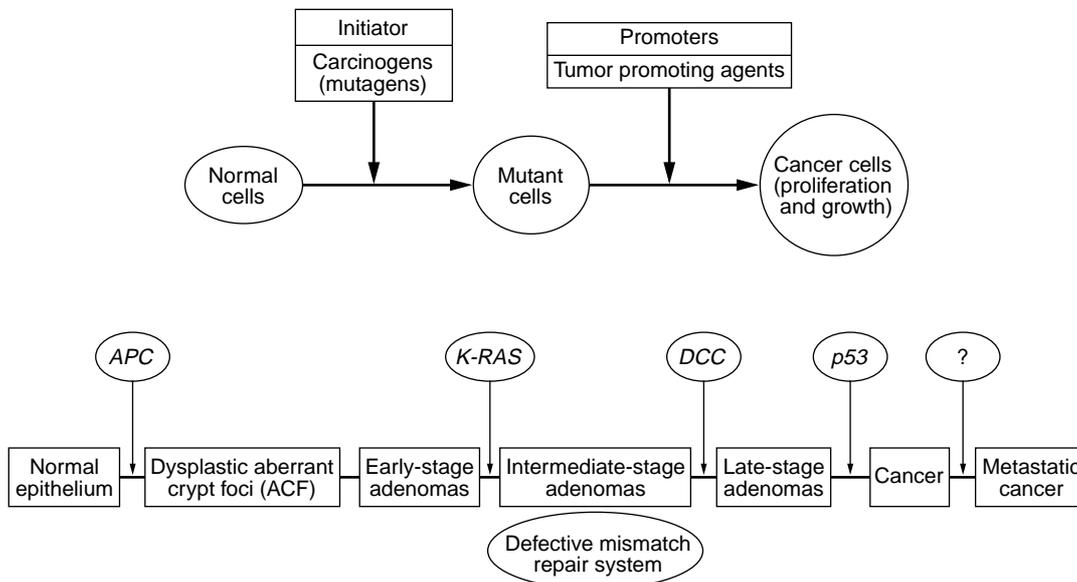


Fig. 1 Multistage carcinogenesis model with the initiation and promotion stages (Kinzer, K.W. and Vogelstein, B.: *Cell* 1996; 87: 159–170)

growth of the mutant cells (cancer cells) (Fig. 1).

## 2. Primary prevention of carcinogenesis

Primary prevention is defined as the attempt to decrease the incidence of colorectal cancer by removing the above factors (initiators and promoters), and is the most important strategy for cancer eradication.

The initiation of carcinogenesis (the stage at which genes in normal cells are damaged by chemical substances, etc.) is considered to occur in the age range from the twenties to the early thirties. Conversely, eliminating environmental factors that may contribute to genetic damage and the active consumption of foods containing antioxidative substances, which prevent genes from being damaged, are considered to be essential until this age. In order to prevent the initiation of carcinogenesis, i.e., to “prevent cancer from putting forth buds,” cancer prevention should be started in the teenage years.

Factors or substances affecting the initiation of carcinogenesis include lifestyle (smoking, excessive fat intake, obesity, lack of exercise,<sup>1</sup> food additives, etc.), and living environments (various chemical substances, air pollution, endo-

crine disrupting substances, etc.).

Following the initiation of carcinogenesis, accumulated gene mutations cause carcinogenic promotion. At this stage, cancer can be prevented by “nipping cancer in the bud.” For example, green tea (catechin), red wine (polyphenol) and the pigment in oranges ( $\beta$ -cryptoxanthin) have been reported to decrease the incidence of cancer. These substances are thought to retard the progression of carcinogenesis instead of inhibiting the carcinogenesis itself.

Some foods promote carcinogenesis and others inhibit it. With regard to the carcinogenesis of colorectal cancer, it has long been understood that a high-fat, low-residue diet is causative, while a low-fat, high-residue diet is protective.<sup>2</sup> In addition to the above-mentioned factors, it is known that bile acid, alcohol, and estrogen promote colorectal carcinogenesis, while dietary fiber, vegetables rich in beta-carotene, vitamins C, D, and E, beta-carotene<sup>3</sup> as well as NSAIDs (nonsteroidal antiinflammatory drugs)<sup>4</sup> inhibit it. Both the rectum and the colon are parts of the large intestine, but they are thought to differ in terms of the envi-

Table 1 Effective Substances for Primary Prevention

Mechanism of action	Substance
Antioxidative activity	Selenium (Se), Vitamin C, Vitamin E, Disulfiram (drug for the symptomatic treatment of alcoholism)
Free radical scavenging	Vitamin C, Vitamin E, SOD
Intestinal flora balancing	Fiber-rich diet (biscuits containing 30% wheat bran), Tetracycline, Erythromycin (antibiotics)
Antiinflammatory effect	Indomethacin
Bile-acid toxicity inhibition	Calcium
Arachidonic acid metabolism	Fish-derived fatty acid (EPA), Perillaol ( $\omega$ -3 polyunsaturated fatty acid), $\beta$ -carotene, Chlorophyll
Tumor immunity protection	E amino caproic acid
Polyamine synthesis	$\alpha$ -difluoromethyl
Carcinogen metabolism	Ornithine $\beta$ -glucuronidase

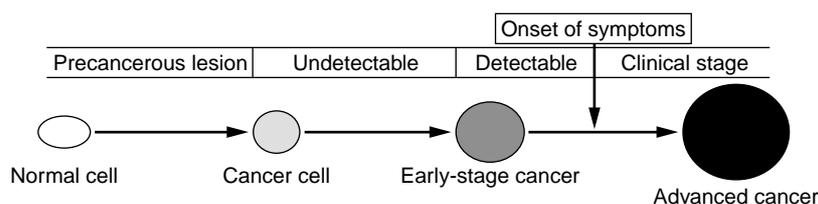


Fig. 2 Progression from carcinogenesis to early-stage cancer and to advanced cancer

ronmental factors that contribute to their carcinogenesis. In the past, the region most prone to cancer in the large intestine in Japan was the rectum with few exceptions, but in recent years this region is increasingly located in the colon, especially in the sigmoid colon. Concerning the risk factors of rectal cancer, it has been reported that excessive alcohol intake and positive family history are associated with a 4-fold increase in risk, and that black tea, vegetables, and seaweed are linked to 50% decrease in the risk. On the other hand, with respect to the risk factors for colon cancer, it has been reported that excessive alcohol intake<sup>5)</sup> and positive family history are related to an increase of some 2–3 times, that black tea and fruits are associated with a 2–3 fold increase in the risk, and that coffee, smoking, and green

tea are linked to decreased risk. Among the substances which have been reported to exert an effect on “primary prevention,” antioxidative substances, free radical scavengers, intestinal flora balancers, antiinflammatory substances, bile-acid toxicity inhibiting substances, substances involved in the arachidonate cascade, tumor immunity protectors, etc. are considered to exhibit efficacy (Table 1).

## Secondary Prevention

### 1. Significance of mass screening

Although all cancers including colorectal cancer become difficult to eradicate once they have invaded deeper tissues or have metastasized, most early-stage cancers can be cured completely, and it is possible to eradicate 98%

of early-stage colorectal cancers. In addition, unlike gastric cancers, which are linked to poor prognosis if they have already progressed to the later stages, about 80% of colorectal cancers, even when advanced, can be surgically resected and cured completely if they have not metastasized.

Cancers detected through mass screening examinations are often in the earlier stages, and are curable even if they are relatively advanced. It takes considerable time for tumors to grow into visible masses (with diameters of 1 cm), and the growth rate is not steady (Fig. 2). In order to detect smaller tumors (early-stage cancers), advances in diagnostic techniques by imaging or endoscopy are crucial. Whilst visible tumors were previously thought to be about 1 cm in diameter, it is currently possible to detect colorectal cancers measuring about 3–5 mm in diameter.

## 2. Methods and efficacy of mass screening for colorectal cancer

Currently, various immunological fecal occult blood tests utilizing human hemoglobin-specific antibodies (including reversed passive hemagglutination [RPHA] technique) are used as the mass screening methods of colorectal cancer. In a case-control study, it was reported that when compared with groups of subjects who did not undergo mass screening, the relative risk for mortality due to colorectal cancer in the group of subjects who underwent mass screening was 0.36.<sup>6)</sup> Therefore since 1992, mass screening using 2-day immunological fecal occult blood testing has been incorporated into the third program of health care services for the elderly in Japan. However, in 1998, since mass cancer screening services were considered to be well established in this country, the screening was subsequently excluded from health care services for the elderly.

The rate of positive results (rate of identification of individuals who need to undergo detailed examination) in the 2-day immunological fecal occult blood testing is about 5–6%,

and among individuals who get positive results in mass screening, about 70–80% undergo a detailed examination (currently, total colonoscopy is adopted), although this rate varies regionally. The incidence of detection of colorectal cancer is 0.1–0.3%, and 60–70% of the detected cancers are in the earlier stages.

## 3. Lowering effects of colonoscopic polypectomy on the incidence of colorectal cancer

In the National Polyp Study<sup>7)</sup> conducted by Winawer *et al.*, it was reported that the relative risks of colorectal cancer in patients who underwent colonoscopic polypectomy, as compared to comparators, were 0.10 (0.03–0.24) in the cases at the Mayo Clinic, 0.12 (0.04–0.27) in the cases at St. Mark's Hospital, and 0.24 (0.08–0.56) in the cases in the SEER Program (Surveillance, Epidemiology, and End Results). Given the rate of risk decrease in subjects who underwent colonoscopic polypectomy, it can be said that at least 50% or more (possibly 76–90%) of colorectal cancers originally develop as adenomatous polyps and undergo malignant transformation.

In a multicenter study conducted by Saito's team (belonging to the team council of the Ministry of Health, Labor and Welfare), the incidence of colorectal cancer in the groups of subjects who underwent colonoscopic polypectomy was compared with that in the subjects who did not undergo this examination. The incidence rates in the former group and the latter group were 0.7% and 1.0%, respectively, at 5 years after the polypectomy, and 2.2% and 5.2%, respectively, at 10 years, suggesting that the incidence of colorectal cancer is significantly decreased in subjects who undergo polypectomy.<sup>8)</sup>

Further, in a multicenter study performed by Murakami *et al.*,<sup>9)</sup> the risk of colorectal cancer in subjects with colorectal polyps and the decreasing effects of colonoscopic polypectomy on the incidence of colorectal cancer were also evaluated, demonstrating that during the

observation period of 9.8–11.8 years on average, 5-year cumulative incidence rates of colorectal cancer were 0.3% in Group N (the group of subjects who did not develop colon polyp), 1.1% in the group of subjects who underwent polypectomy, and 2.3% in the group of subjects who did not undergo polypectomy. This suggested that the incidence of colorectal cancer was significantly higher in the subjects with colorectal polyps and in those subjects who did not undergo polypectomy as compared with that in those subjects undergoing polypectomy. In this study, Murakami *et al.* also assessed the 5-year cumulative incidence rates of colorectal cancer by stratifying the subjects by polyp size (length of major axis), thereby ascertaining that the incidence rates were 0.4% in the <5-mm stratum, 1.7% in the 5–9-mm stratum, and 12.9% in the  $\geq 10$ -mm stratum, leading to the conclusion that polypectomy is not indicated for patients with polyps with diameters of 5 mm or less because the 5-year cumulative incidence rate of colorectal cancer in such patients is low.

## Conclusion

Colonoscopic polypectomy has been shown to inhibit the occurrence of colorectal cancer and to lower the mortality rate due to the cancer. In other words, the “malignant transformation of adenomas” has been indirectly proven and the prevention of adenomas is therefore considered to be significant for the prevention of colorectal cancer; progress in studies on NSAIDs, COX2, etc. is expected. In addition, early detection, diagnosis, and treatment of colorectal adenomas and cancers should be conducted through mass screening utilizing the immunological fecal occult blood test. At present, however, it is considered that only adenomas with a diameter of 6 mm or more should be resected.

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# Psychopathology of Social Withdrawal in Japan

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**Abstract:** Active challenges to social withdrawal among young people have recently been implemented in Japan against the following background: 1) The number of cases of social withdrawal among young people has reportedly increased to some hundreds of thousands; and 2) As there are few clinical studies in the US and Europe, it is necessary to compile our own clinical experience to produce useful findings. The term “social withdrawal” is not a diagnosis, but means both a “phenomenon” of social withdrawal and a “pathology” of introverted withdrawal. Patients with social withdrawal can be further classified into a “secondary withdrawal group” due to some psychiatric disorders and a “primary withdrawal group” characterized by withdrawal itself (Kinugasa, 1998). As a young patient with primary withdrawal rarely visits a psychiatrist for help, his or her family members should assist with patience.

**Key words:** Social withdrawal; Psychopathology; Japan; Adolescence; Young adult

## Introduction

Two academic journals, *Rinsho Seishin Igaku*<sup>1–3)</sup> and *Seishin Bunseki Kenkyu*<sup>4–6)</sup> had articles featuring social withdrawal in the past two years. As this indicates, there has recently been an active response to the challenge of social withdrawal among young people in Japan against the background of an increase in the phenomenon.<sup>7)</sup> There are reported to be some hundreds of thousands of young people with this condition.<sup>8)</sup> As there are few clinical studies focusing on social withdrawal in the US and Europe, it is necessary to compile clinical

experience in Japan in order to obtain useful findings.<sup>4)</sup> The present report addresses the challenges to clinical pioneers by reviewing the psychopathology of social withdrawal among young people at the present time.

### 1. “Phenomenon” and “pathology” of social withdrawal

The term “social withdrawal” is not a diagnosis for a specific psychiatric disorder. Withdrawal means both the phenomenon of social withdrawal and the pathology of introverted withdrawal. The former refers to the condition of staying in one’s own house to avoid relation-

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ships with others including family members. The latter means pathology due to some psychiatric disorders or personality of introversion. Quite a few people with potential introversion seem to be socially adapted. Patients with withdrawal are classified into a "secondary withdrawal group" due to psychiatric disorders, and a "primary withdrawal group" characterized by withdrawal itself.<sup>9)</sup>

## 2. Secondary withdrawal

Secondary withdrawal includes cases of a patient staying in his or her own house due to abulia and autism caused by schizophrenia. A patient with depression tends to withdraw, complaining of trouble in meeting with or talking to others in the period of serious depression. A patient with eating disorders, especially bulimia nervosa often withdraws to avoid the eyes of others, or disclosure of his or her figure when weight has been gained contrary to expectations. Due to the fear of a panic attack, patients with panic disorder tend to stay indoors to avoid places where there is no possibility of help in case of panic (such as trains and overcrowded streets). In this case, panic attack means "sudden development of symptoms including palpitations, dyspnea, and derealization with strong anxiety".

Patients with serious anthropophobia are sometimes kept at home to avoid relationships with others, resulting from a feeling of guilt for giving an unpleasant impression to others because of their own perceptions and physical defects. According to Nakamura *et al.*, however, an increasing number of patients without serious symptoms tend to avoid relationships with others.<sup>3)</sup> The clinical features include vague feelings of personal stress or oppression, strong fear of others and self-uncertainty, and sometimes depression and inertia.

## 3. Primary withdrawal

Anthropophobia characterized by avoidance and withdrawal reported by Nakamura *et al.* can be classified as primary withdrawal because

the withdrawal itself is a major symptom.

Studies of primary withdrawal among the young in Japan date back to a study on "withdrawal neurosis" by Kasahara in the 1970s, originating from "student apathy" noticed in university students.<sup>10)</sup> The author proposed a new concept of neurosis characterized by inertia and partial retreat (social withdrawal). He described this type of neurotic as one who "does not ask for other's help. Some of them do not visit a hospital even though their family members do". This is exactly the condition that can be seen in the withdrawal of young people at the present time. In most cases, since the patient rarely visits the hospital voluntarily, the persistent support of family members is essential to making them appear.<sup>2,6,9)</sup>

In primary withdrawal at the present time, almost all patients are male<sup>8)</sup> and their clinical features often include personal stress, a sense of futility, inertia, and self-incompleteness.<sup>9)</sup> Some are struggling against withdrawal, while others are rather satisfied with it.<sup>9)</sup> They tend to underestimate themselves, and sometimes be impulsive. Behavior in some suggests the presence of trauma.<sup>4)</sup> They are often classified into schizoid personality disorder, avoidant personality, and narcissistic personality disorder<sup>5,6)</sup> specified in "DSV-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition."<sup>11)</sup>

Kondo<sup>6)</sup> listed the following features of their families from his longtime experience: 1) Because parents tend to be anxious and keep up appearances, the patient comes to rationalize or deny the problem, leading to delayed responses and prolonged withdrawal; 2) Family members are too cautious to go into the internal feelings of each other; 3) The parent of the same sex also tends to withdraw; 4) There is little parental identification with the patient's subjective experiences.

## Conclusion

Local mental health welfare centers and

medical institutions have been implementing various measures against social withdrawal. It is expected that a deeper understanding of social withdrawal will be obtained based on these clinical practices.

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# The Status of Hepatitis Vaccines: Type A and Type B

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**Abstract:** The existence of five types of hepatitis viruses has been established until now, namely, hepatitis viruses A, B, C, D, and E. Among these, hepatitis viruses A, B, and C are of particular relevance in Japan. While vaccines are available against hepatitis A and B, none has as yet become available for hepatitis C. Both hepatitis A and B vaccines have satisfactory efficacy and minimal side effects. In particular, they are of great value in the prophylaxis of health care professionals against hepatitis A and B. The status of the hepatitis A and B vaccines is reported in this paper.

**Key words:** Hepatitis A vaccine; Hepatitis B vaccine

## Hepatitis A Vaccine

### 1. Epidemiological background and the need for a vaccine

Hepatitis A virus (HAV) is transmitted by the fecal-oral route, through ingestion of contaminated drinking water or food, and proliferates mainly in the liver. The virus reaches the gastrointestinal tract via the bile, and is excreted in the feces, which then serves as a new source of infection.

Infection with the hepatitis A virus may occur in a sporadic fashion, in a small population (including intrafamily occurrence), or as a mass outbreak. The source of infection is usually untraceable in sporadic cases. Infection in a small population is often caused by contamination of food by the feces of patients with latent hepatitis who excrete HAV. To prevent such

contamination, it is necessary for people who handle foodstuffs, such as cooks, to acquire the habit of routine and thorough hand washing. Mass outbreaks are often caused by contamination of drinking water or shellfishes (shellfishes concentrate HAV in their bodies, and were the cause of infection spreading among 200,000–300,000 people in Shanghai in 1987), or contamination of food in large food manufacturing companies, (contamination of strawberries in USA in 1997).

As a general prophylactic measure, it is important to avoid taking foods and drinks served under unheated conditions in HAV endemic regions (almost all countries excluding Japan, Scandinavia, and North America). However, it may not be realistic to specify the foods that must be avoided in high-prevalence areas.

It has been said that globally, hepatitis A

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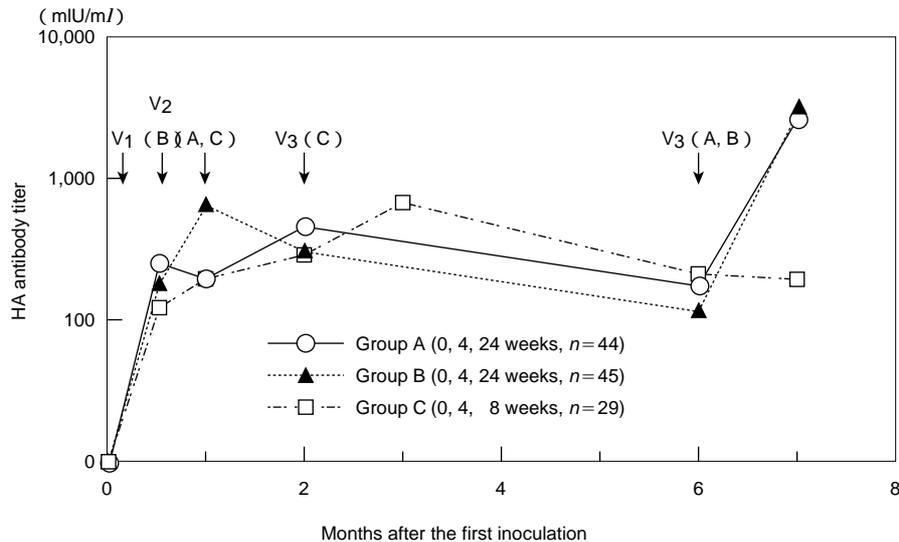


Fig. 1 Comparison of inoculation schedules in a phase-II clinical study (intramuscular 0.5  $\mu$ g)

Two inoculations yielded HA antibody positivity in all the vaccinated individuals. The antibody positivity after two inoculations carried out 2–4 weeks apart lasted for more than 6 months.

outbreaks occur every 6–7 years. In Japan, outbreaks occurred in 1983 and 1990. Although an outbreak was expected in the year 1997, the annual incidence of hepatitis A has been decreasing steadily since the year 1990. In addition, there has been no conspicuous increase in the number of new patients diagnosed between the months of January and May, a pattern which was consistently noted in the previous years. The number of people infected with hepatitis A virus in previous years was estimated to be approximately 10,000 to 50,000 per year, but currently, the corresponding number runs into only several thousands. However, one cause for concern is the observation that the HA antibody prevalence curve is shifting steadily toward the elderly age group year by year, with a rapidly increasing susceptible population under the age of 50 years.<sup>1)</sup> Therefore, it is possible that once the spread of infection begins, a large epidemic outbreak may occur. Furthermore, Japanese people run the risk of becoming infected with the virus when they visit areas with high prevalence of hepatitis A.

The incidence of hepatitis A in Japanese

people plotted by age shows a bimodal distribution, with two peaks at the age of 10 years and in the age range of 30 to 50 years. This suggests that intrafamily infection is dominant. This is also related to the fact that the duration of viremia, and thus the duration of viral shedding, is considerably longer than formerly expected, and that excretion of HAV continues even after the patient is cured of hepatitis. It would appear that this prolonged HAV excretion is responsible for maintaining HAV among humans.

## 2. Practical aspects of the HA vaccine<sup>2-5)</sup>

HA vaccine is a formalin-inactivated vaccine made from a strain of HAV attenuated in tissue culture. In Japan, the vaccine is a freeze-dried preparation different from, and superior to other foreign products, in that they contain no preservatives and adjuvants (immunopotentiators).

A phase-I clinical trial was begun in 1988, followed subsequently by phase II and phase III trials. The HA vaccine was finally approved for use in October 1994. The results of all the trials were similar, both in terms of the efficacy

and in terms of the side effects of the vaccine.

The HA antibody titer is considered to be maintained above the minimum protective level (10 mIU/mL) for more than 6 months when the vaccine is administered twice at the dose of 0.5  $\mu$ g, at 0 and 2 or 4 weeks; protective titers have also been reported to be maintained almost throughout life when a third dose is administered in addition after 6 months. Fig. 1 shows a comparison of the antibody titers induced by three different inoculation schedules examined in a phase-II study. In this study, antibody production appeared to be easily induced by the vaccine, since most of the 1,500 subjects enrolled in the study became HA antibody-positive after the first inoculation, and all of the subjects became positive after the second inoculation. Antibody induction showed a slight gender-related difference, but scarcely any age-related difference. As to adverse reactions, pain, redness, and swelling at the injection site occurred in about 10% of the subjects, and general malaise and slight fever in about 3%.

### 3. Vaccination targets

Vaccination against hepatitis A is ideally recommended for all persons in the general population, because it has scarcely any side effects, the antibody is easily induced and protective titers are well maintained, and several people continue to excrete HAV for long periods of time after they become infected. On a more practical level, the major candidates for vaccination include people traveling overseas to work, tourists on long vacations, persons in the vicinity of a source of intrafamily infection or a mass outbreak, cooks and food handlers, health care professionals, including nursing personnel, homosexuals (there are records of mass infection in this group both in Japan and overseas), and patients with advanced hepatic disease (who run the risk of developing hepatic failure).

Intramuscular injection of commercially available immunoglobulins has also been employed for prophylaxis against hepatitis A. However,

since there are wide variations in the HA antibody content among preparations, it is impossible to predict the effective duration of the protection offered. Furthermore, since these are blood products, they should preferably be replaced by vaccines.

## Hepatitis B Vaccine

### 1. Epidemiological background and the need for a vaccine

Hepatitis B virus (HBV) infection is transmitted by the following routes: 1) mother-to-child transmission; 2) sexual transmission; 3) infection via blood or blood products; 4) infection from injuries with instruments contaminated by the blood of patients with the infection.

In the case of mother-to-child transmission, almost 100% of the children born to mothers positive for the HBe antigen are infected with the virus, and 85% become HBV carriers. This is the major source of HBV carriers in Japan. On the other hand, about 10% of children born to HBe antigen-negative mothers are infected with the virus; while these children rarely become carriers of the virus, they often develop fulminant hepatitis within 2–3 months after birth. Specific prophylactic measures against mother-to-child transmission of the infection will be described later. Since the program for preventing mother-to-child transmission of hepatitis B virus began in 1986, only 300–400 children per year have become carriers (0.05% of all infants born), which corresponds to only 1/10 of the number of carriers introduced into the population per year before the project began.<sup>6)</sup> Fulminant hepatitis among neonates has also become extremely rare.<sup>7)</sup>

Most cases of acute hepatitis B develop as a result of sexual transmission of the virus. Testing of the specific partner usually reveals that the person is an HBe antigen-positive HBV carrier. The incidence of acute hepatitis B exhibits a peak in people in their 20s, and varies in relation to the incidence of other sexually trans-

mitted diseases; there is a temporary decrease in the incidence after HIV has presented itself on the scene, and variations in the incidence became apparent within 3 months after HIV infection was first announced. Vaccination with the HB vaccine is extremely effective for preventing hepatitis B, but it is difficult to practice such prevention under the current circumstances.

Infection via blood or blood products has become extremely rare after the introduction of screening for the HBs antigen (1972) and HBc antibody (1989). Furthermore, performance of the nucleic acid test (NAT) on all blood materials has almost completely eliminated transmission of the disease by this route.

Transmission of infection via injury with instruments contaminated by blood from HBV carriers was relatively common when boiled syringes were used in medical practice. It has been estimated that the frequency of this form of transmission of the infection has decreased sharply since the 1970s, when disposable syringes began to be used routinely. However, this mode of transmission of the infection is still prevalent among health care personnel.

## 2. Practical aspects of the HB vaccine

The most fundamental prophylactic measure against the spread of HBV infection is to increase the awareness in the general population that all body fluids, e.g., blood, can serve as a source of infection. When there is the possibility (high risk) that HBV infection may have occurred, passive prophylaxis using hepatitis B immunoglobulin (HBIG) (high-titer HBs antibody-containing immunoglobulin) in emergencies, or vaccination with HB vaccine in less urgent cases, are indicated. In particular, hepatitis B vaccination should be carried out in health care personnel, a high-risk population for HBV infection, especially those in the younger age groups, in whom antibody production is more strongly enhanced.

Although subcutaneous, intramuscular and intracutaneous routes are available for vaccination, the subcutaneous route is considered to

be inferior to the intramuscular route.<sup>8)</sup> Intracutaneous inoculation yields a seroconversion rate comparable to that following intramuscular inoculation, even when the dose inoculated is only 1/5 of the intramuscular dose. However, the increase in antibody titer after intracutaneous inoculation is slightly less dramatic than that after intramuscular inoculation.

The standard vaccination schedule in Japan against hepatitis B consists of three inoculations at 0, 1, and 6 months. For the prevention of mother-to-child transmission, the vaccination is administered thrice, at 2, 3, and 5 months of age. It may be noteworthy that, usually, the third inoculation yields a better antibody response when it is carried out later than 6 months and within 12 months after the second inoculation, as long as there is no threat of fresh infection. However, it still remains to be precisely established as to how long after the second dose the third inoculation must be carried out. A third inoculation is, however, definitely recommended even if the timing of administration of the first and second doses of the vaccine is uncertain. Four inoculations at 0, 1, 2, and 12 months are also used overseas. Although this method is useful for rapid induction of the antibody, the third inoculation is not effective at yielding an increase in antibody titer in the long run. Where there is urgent need for antibody induction, e.g., in the prevention of mother-to-child transmission or in medical contamination accidents, inoculation thrice at 0, 1, and 3 months is practiced. It has been reported that early seroconversion can be achieved by administration of the vaccine thrice at shorter intervals, i.e., 1-week intervals.

In Japan, vaccination for the prevention of mother-to-child transmission is, as a rule, begun at 2 months after birth, since it has been reported that a delayed start yields better results in neonates who exhibit weak immune responses, considering the relatively low potency of the plasma-derived vaccine that was used at the time that the project for preventing the transmission of the infection was initiated.

Now that recombinant vaccines with higher potency are available, the first inoculation immediately after birth, as in countries overseas, may be a feasible option.

### 3. Side effects of the HB vaccine

As side effects, transient slight fever, muscle aches, local changes, or general malaise were seen in about 10% of the inoculated individuals for several days after the inoculation. Eruptions due to yeast allergy may occur very rarely as a prominent adverse reaction, which has been confirmed by re-administration and other tests. Summed data on the side effects in a large number of vaccinated individuals have been reported by McMahon *et al.*<sup>9)</sup>

### Conclusion

Currently, vaccines for hepatitis A and B are commercially available. Both are highly effective and have minimal side effects.

Although the incidence of hepatitis A has been decreasing in recent years, it is difficult to predict when a mass outbreak might occur. Groups which are candidates for HA vaccine inoculation include health care personnel, cooks and food handlers, homosexuals, persons traveling overseas, etc.

On the other hand, HB vaccine should be administered to health care personnel, especially those in the younger age groups in whom stronger induction of antibody is likely. Meticulous prevention of mother-to-child transmission must be continued for 2 to 3 decades to completely eliminate HBV infection in Japan. In addition, acute hepatitis B should be addressed as a

sexually transmitted infection.

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# Central Retinal Vein Occlusion (CRVO) —Visual Disorder in Patients of Middle and Advanced Age—

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**Abstract:** Patients with central retinal vein occlusion (CRVO) have retinal hemorrhages in all four retinal quadrants around the posterior pole, with a markedly dilated and tortuous venous system. CRVO frequently develops in patients at 60–69 years of age, and approximately 90% of the incidence is noted in patients at 50 years of age or older. It usually occurs in one eye, but occasionally in both eyes if patients have an increased blood-viscosity condition, including hypervolemia and hyperlipemia. CRVO is generally associated with systemic complications, including hypertension and arteriosclerosis. Younger patients with CRVO principally caused by inflammation and blood disease often have favorable prognosis because their vision is improved by treating underlying diseases and using drug therapy. In nonischemic CRVO that develops in patients at 50–69 years of age, who had a specific level of vision at the onset of the disease, the prognosis varies according to whether arteriolar sclerosis is present, and to the duration of retina circulation time. In the absence of arteriolar sclerosis and delayed retina circulation time, visual acuity can be improved in most cases. In ischemic CRVO, which occurs in patients at 60–79 years of age who have poor vision at the onset of the disease, the condition is usually associated with arteriolar sclerosis and delayed retina circulation time, and thus the visual acuity is rarely improved. Laser photocoagulation is used to prevent the development of neovascular glaucoma.

**Key words:** Central retinal vein occlusion; Retina circulation time;  
Retinal arteriolar sclerosis; Laser photocoagulation

## Introduction

The incidence of central retinal vein occlusion (CRVO) is not high, but it is frequently

associated with poor prognosis. Therefore, although CRVO is easy to diagnose, subsequent treatment is somewhat problematic. We describe our clinical findings, clinical types of

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the disease, and therapeutic procedures.

### Clinical Characteristics

CRVO is associated with hemorrhages over all four retinal quadrants, and a markedly dilated and tortuous venous system. It commonly occurs in patients at 60–69 years of age, and those at 50 years of age or older account for 90% of all patients with CRVO, with a slightly higher proportion of males. CRVO in younger patients is induced by inflammation, including optic disk angitis and retinal angitis. The disease usually involves one eye, but occasionally both eyes in patients with hyperlipemia, and hypervolemia with increased blood viscosity. The systemic complications observed in CRVO include hypertension, diabetes mellitus, cardiovascular disease, and cerebrovascular disease.

The typical fundusoscopic appearance is hemorrhages in all quadrants with the optic disk in the center, involving the superficial and middle layers of the retina. A markedly dilated and tortuous venous system, and edema of the retina and optic disk are observed. The early-stage appearance of the disease principally consists of a dilated and tortuous venous system with only slight retinal hemorrhage but no edema. In advanced-stage CRVO, marked retinal hemorrhage and edema are present, which are occasionally associated with soft exudates, and vascular occlusion in the periphery of the optic disk. Findings in end-stage CRVO include vitreous hemorrhage caused by retinal and optic disk neovascularization, traction retinal detachment, angle and iris neovascularization, and occasionally, neovascular glaucoma.

### Clinical Types

CRVO is classified into two groups according to impending or complete occlusion, venous stasis retinopathy or hemorrhagic retinopathy, and nonischemic or ischemic characteristics, respectively.

The difference between impending and com-

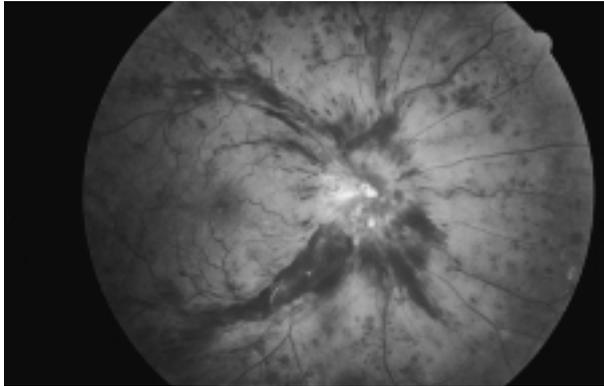
plete occlusion is based on the time after onset. Impending occlusion frequently advances to complete occlusion. Patients with CRVO due to inflammatory disease and blood disease are under the condition of impending occlusion, but the treatment of the causative diseases can sometimes lead to cure within several months.

Hayreh<sup>1)</sup> conducted an experiment in monkeys, and discovered that occlusion of only the central retinal vein caused no hemorrhage but that transient occlusion of both the central retinal vein and artery resulted in hemorrhage in the fundus. Therefore, Hayreh considered that there are two types of CRVO, i.e., venous stasis retinopathy with central retinal vein occlusion without circulatory disorder of the central retinal artery, and hemorrhagic retinopathy with central retinal vein occlusion and circulatory disorder of the central retinal artery, which are induced by different mechanisms of pathogenesis, and whose fundusoscopic findings, complications, and prognosis of visual acuity differ from each other.

In clinical practice, however, we have encountered patients whose fundusoscopic findings are of venous stasis retinopathy but associated with the complications usually seen in hemorrhagic retinopathy, suggestive of an intermediate type. Inomata<sup>2)</sup> considered that if the ophthalmic artery and vein, proximal to the optic nerve, are occluded in monkeys, central retinal artery occlusion must occur, and indicated that the above classification is inconsistent with the pathogenesis of CRVO.

Although CRVO is classified as a nonischemic and ischemic disease on the basis of visual acuity, fundusoscopic findings, fluorescent fundus angiographic findings, and electroretinogram (ERG), there is an intermediate type,<sup>2)</sup> and differences in neovascularization were seen according to the severity of ischemia. Some nonischemic diseases develop into ischemic disease.<sup>3)</sup> The classification into two types poses clinical issues, and it appears to be inappropriate from the standpoint of treatment.

In retinal hemorrhage in CRVO, whether



a: Retinal hemorrhage in surrounding of the optic disk and along retinal vessels, with relatively mild macular edema, hemorrhage, and no arteriolar sclerosis.  
Visual acuity: 0.8



b: Visual acuity after 7-month drug treatment: 1.2

Fig. 1 48-year-old male—right eye—nonischemic CRVO

ischemic or nonischemic, not only central retinal vein with occlusion and narrowing but central retinal artery with circulatory disorder are involved. The narrowing of the lumen due to arteriolar sclerosis reduces the blood flow into the eye, and this is considered to have an effect on the prognosis of CRVO. The reduced intraretinal blood flow due to arteriolar sclerosis causes retinal ischemia, impeded blood flow, and occlusion of the capillaries, leading to fusion of the occluded areas making more extensive vascular occlusion to establish typical ischemic CRVO.

Most ischemic CRVO are associated with arteriolar sclerosis, and CRVO with marked arteriolar sclerosis is associated with delayed retina circulation time. Patients with a retina circulation time of 20 seconds or longer are considered to have poor prognosis.

Younger CRVO patients without associated arteriolar sclerosis, and patients with ischemic CRVO who have no underlying diseases such as hypertension or arteriosclerosis have no or slightly delayed retina circulation time, and most have favorable prognosis of visual acuity, which could be improved by drug therapy alone.

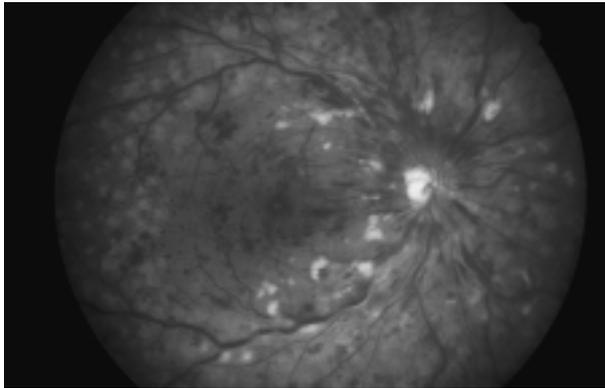
The prognosis for elderly patients with CRVO frequently with associated arterioscle-

rosis is poor. Extremely reduced intraocular blood flow induces occlusion of the cilioretinal artery, which then causes severe edema and opacity over the optic disk and the macula retinae, leading to very poor prognosis of CRVO.

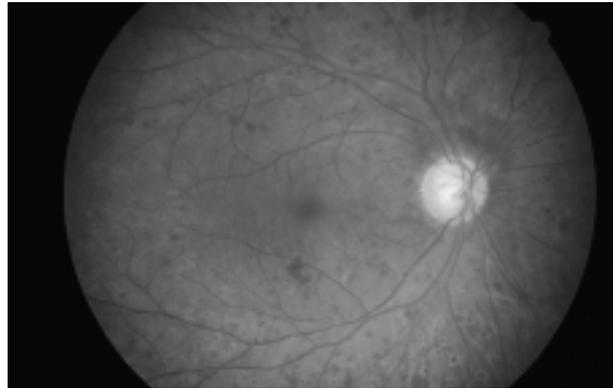
## Clinical Types and Prognosis of Visual Acuity

### 1. Early-onset CRVO

90% of CRVO develops in patients at 50 years of age or older. However, CRVO due to inflammation and blood disease frequently occurs in patients under 50 years of age. In the absence of hypertension and arteriosclerosis, visual acuity can often be improved by the treatment of the underlying disease and medication for CRVO, generally resulting in favorable prognosis. At the time of onset of CRVO, patients usually have good vision, and fundoscopic findings show a dilated and tortuous venous system but only slight retinal hemorrhage with no or slight macular edema. Fluorescent fundus angiography showed no delay in retina circulation time, no leakage of fluorescent dye from blood vessels, and no abnormality in parafoveal capillaries. The impending occlusion type of the disease with minimal retinal hemorrhage can occasionally be cured



a: Marked retinal hemorrhage, soft exudates in the surroundings of the optic disk and along arterial and venous vessels. Visual acuity: 0.08



b: Visual acuity after 5-month laser photocoagulation: 0.1. Hemorrhage, exudates absorbed, and optic disk atrophy

Fig. 2 68-year-old male—right eye—ischemic CRVO

without further progression.

## 2. Nonischemic CRVO (Fig. 1)

The visual acuity and age of patients varies widely at the onset of the disease. Visual acuity ranges from 0.2 to 1.0 at onset, varying according to the degree of macular hemorrhage and edema. The disease can occur in younger patients but commonly occurs in patients at 50–69 years of age. Funduscopy findings in nonischemic CRVO show a markedly dilated and tortuous venous system, and retinal hemorrhages in all four retinal quadrants around the posterior pole, but relatively mild macular edema and hemorrhage. The optic disk frequently has redness and swelling with hemorrhagic involvement of the periphery. Arteriolar sclerosis is rarely observed and mild if present. Fluorescent fundus angiography revealed slightly delayed venous perfusion, slight leakage of fluorescent dye from the capillaries, and no vascular occlusion.

If patients maintain their visual acuity despite relatively severe hemorrhage, they are treated with aggressive drug therapy. Basically, thrombolytic therapy, vascular-reinforcing agent, anti-inflammatory enzyme drug, and vitamin C are administered, and antiplatelet agent and anticoagulant are added where necessary. If macu-

lar edema is present, acetazolamide and steroids are used, and if the visual acuity declines to 0.2–0.3, laser photocoagulation should be performed immediately to absorb edema and hemorrhage and thereby to prevent cystoid macular edema. Laser photocoagulation is sometimes useful to prevent macular dysfunction, and progress to ischemic CRVO.

The clinical findings of CRVO which are expected to cure or restore the vision include relatively well maintained vision, only slight leakage of fluorescent dye from the blood vessels, absence or mild arteriolar sclerosis, and early bypass formation.<sup>4)</sup> If patients are of advanced age, and have marked arteriolar sclerosis, marked delayed retina circulation time, marked fluorescence-dye leakage at the macula retinae, even a combination of drug therapy and laser photocoagulation results in poor outcomes.<sup>4)</sup> Therefore, when many unfavorable prognostic factors are present, laser photocoagulation is used at an early stage in combination with drug therapy. In patients with many favorable prognostic factors, CRVO can be treated by drug therapy alone. A grid pattern of laser photocoagulation performed after the establishment of cystoid macular edema is not sufficiently effective to improve the vision, although edema may be improved.

Therapeutic approaches to treat diffuse macular edema due to CRVO include drug therapy, laser photocoagulation, compressed oxygen therapy, and vitrectomy. In drug therapy, carbonic anhydrase inhibitor is used, and in laser photocoagulation, a grid pattern of laser photocoagulation is used. However, although these approaches are useful for some forms of nonischemic CRVO, they are not efficacious for ischemic CRVO. Compressed oxygen therapy has never been useful in elderly patients, patients with poor visual acuity at the onset of the disease, or patients with ischemic CRVO.<sup>5)</sup> Surgical resection of the vitrectomy together with the internal limiting membrane of retina improves edema in most cases but visual acuity is only improved in a few cases.<sup>6)</sup>

### 3. Ischemic CRVO (Fig. 2)

If patients develop ischemic CRVO at 60–79 years of age, with a visual acuity of approximately 0.1 at the onset of the disease, marked retinal hemorrhage in all four retinal quadrants around the posterior pole, a markedly dilated and tortuous venous system, and occasionally soft exudates in the surroundings of the optic disk and along arterial and venous vessels, the visual acuity generally remains poor. In such cases, marked arteriolar sclerosis, macular hemorrhage immediately after the onset of the disease, and progressive edema are seen. Fluorescent fundus angiography reveals delayed retina circulation time and extravascular leakage of fluoresce dye. In patients with markedly delayed retina circulation time, the disease advances rapidly, resulting in poor outcomes.

Sclerosis of the optic artery and the central retinal artery reduces intraocular blood flow, and induces a large number of soft exudates in the periphery of the optic disk, where vascular occlusion begins, leading to neovascularization at the angle and iris. Markedly decreased intraocular blood flow induces occlusion of retinal capillaries, resulting in the occurrence of severe yellowish hard exudates over the posterior pole of eyeball. The prognosis is

extremely poor.

There is no definitive therapy, which is particularly effective in the treatment of the disease. CRVO is resistant to drug therapy, laser photocoagulation, compressed oxygen therapy, and surgical resection of the vitrectomy. Therefore, we perform panretinal laser photocoagulation over hemorrhage, and use adjuvant drug therapy with vascular reinforcement agent, antiinflammatory enzyme agent, vitamin C, and antiplatelet agent to prevent commonly occurring angle and iris neovascularization, vitreous hemorrhage, and neovascular glaucoma.

Electrophysiological investigation of CRVO is frequently conducted, and diminution of b wave, decreased b/a ratio, prolonged peak latency of b wave have been reported. Decreased b/a ratio is observed in ischemic CRVO, and patients with markedly decreased b/a ratio are observed to develop neovascular glaucoma.<sup>7)</sup>

Retinal circulatory disorder due to CRVO induces retinal ischemia, and induces retinal nerve tissue disorder of bipolar cells and amacrine cells, leading to deterioration of vision. Damage to the vascular wall, and vascular occlusion due to insufficient oxygen supply to retinal capillaries can cause damage to parafoveal capillaries, and is the major cause of visual deterioration.

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# Distinction between Dementia and Memory Decline

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**Abstract:** Although memory decline or memory impairment is a core symptom of dementia, simple memory decline accompanied by no other cognitive impairments is called amnesia, which should be distinguished from dementia. Memory impairment accompanied by disturbance of higher cerebral functions and performance is diagnosed as dementia. Amnesia can be observed even in normal elderly people, which is called benign senescent amnesia. Benign senescent amnesia should be differentiated from Alzheimer's disease in its early stage. A patient with benign senescent amnesia loses only a part of episodic memory to an insignificant degree, and has the ability of orientation, judgement, and abstract thinking. A patient with Alzheimer's disease also has a memory impairment. In this case, however, it is usually accompanied by disorientation, especially temporal disorientation, and often by delusions of having things stolen even in its early stage. It is also difficult for a patient with Alzheimer's disease to reproduce a 3-dimensional drawing even if drawing a 2-dimensional reproduction is possible. This provides a means to review the differentiation between benign senescent amnesia and Alzheimer's disease in its early stage.

**Key words:** Dementia; Amnesia; Alzheimer's disease;  
Benign senescent amnesia

## Introduction

This paper discusses the distinction between dementia and memory decline. As memory impairment is a major symptom of dementia, some readers may wonder what the title means. First of all, this title requires some explanation since it could be misunderstood.

Needless to say, memory impairment is a

core symptom of dementia. However, memory impairment accompanied by no other cognitive impairments is called amnesia, from which dementia should be distinguished. Accordingly, the "distinction between dementia and memory decline" can be paraphrased in medical terms as the "differentiation between dementia and amnesia". This is the first topic of discussion.

Secondly, cases requiring differential diag-

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Table 1 Items Common to All Types of Dementia in DSM-IV

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- A. Development of various cognitive impairments (both of the following items 1 and 2)
    - 1. Memory Disturbance (inability to retain new information, or to recall previously learned material)  
Deficits are in long- and short-term memory.
    - 2. In addition, one or more of the following cognitive disturbances should be present.
      - (a) aphasia (language disturbance)
      - (b) apraxia (impaired motor abilities despite intact motor pathways)
      - (c) agnosia (inability to identify objects or to recognize objects despite intact sensory pathways)
      - (d) disturbances in executive functioning (i.e., planning, organizing, sequencing, abstracting)
  - B. The cognitive impairments above (1 and 2) result in significant reduction of social and occupational functions and represent a significant decline from the previous functioning level.
  - C. The cognitive impairments above develop not only in the process of delirium.
  - D. The cognitive impairments above cannot be explained by diseases of the first axis. (e.g., depression, schizophrenia etc.)
- 

nosis between amnesia and dementia are reviewed. Common amnesia accompanied by no other cognitive impairments includes physiological memory decline in normal elderly people, which is called benign senescent amnesia (BSA). The most important dementia that should be differentiated from BSA is Alzheimer's disease in the early stage. Accordingly, BSA and Alzheimer's disease in the early stage are reviewed as the most important examples of conditions that require differentiation between dementia and amnesia. This is the second topic of discussion.

### Differences between Amnesia and Dementia

First of all, differences between amnesia and dementia will be explained. As already mentioned, memory impairment is a core symptom of dementia. But, a memory impairment with no other cognitive impairments is called amnesia from which dementia is differentiated. In other words, memory impairment is a necessary but not sufficient feature of dementia. Then, what kinds of symptoms are required for the diagnosis of dementia?

One of the most common diagnostic standards for dementia used in Japan is DSM, established by the American Psychiatric Association. This globally popular diagnostic stan-

dard is now in its fourth edition, DSM-IV.<sup>1)</sup> The previous edition, DSM-III-R specifies one of the following symptoms as a diagnostic standard for dementia; impairment of judgement and abstract thinking, impairment of higher cerebral functions such as aphasia, apraxia, and agnosia, or personality changes in addition to short-term and long-term memory impairments. DSM-IV does not specify a diagnostic standard for dementia itself, but indicates diagnostic standards for each type of dementia such as Alzheimer's disease and vascular dementia. Therefore, items common to all appear to be a diagnostic standard for dementia (Table 1).

The common items are impairment of higher cerebral functions such as aphasia, apraxia, and agnosia or performance disability in addition to short-term and long-term memory impairments. Performance ability defined as an ability to plan, organize, order, or prescind is considered to include judgement and abstract thinking specified in DSM-III-R, and to be interpreted as a more comprehensive function. Therefore, it can be said that only personality changes among items in DSM-III-R were excluded from DSM-IV. In addition, diagnostic standards specify that dementia can be diagnosed only when the reduction in these abilities is significant enough to prevent previous occupational and social activities even in the absence of delirium, and the reduction is not

caused by depression or schizophrenia.

They are almost the same as those of DSM-III-R in which "impaired consciousness" replaced "delirium", and "disorders caused by organic but not functional impairment of the brain", replaced "disorders not be caused by depression or schizophrenia." The reason why DSM-IV uses examples such as depression and schizophrenia instead of "functional causes" is that dementia is not caused only by significant organic factors but also by other factors such as drugs or hypothyroidism. Some pathology, such as hysteria, in addition to depression and schizophrenia should be differentiated from dementia.

Accordingly, memory impairment accompanied by no impairment of higher cerebral functions or performance should be recognized as amnesia, but not dementia. Amnesia develops from psychogenic causes, drugs, cerebrovascular disorders localized in the hippocampus and others. Amnesia can be temporary and curable, or persistent leading to dementia. Mild amnesia often seen in normal elderly people is called BSA.

Next, the distinction between BSA and Alzheimer's disease in the early stage is reviewed.

### **Differentiation between Benign Senescent Amnesia and Alzheimer's Disease in Its Early Stage**

BSA means conditions often observed in the normal elderly such as "leaving things behind" and "inability to immediately recall a person's name." Many people over a certain age seem to be aware of what is called "slip of memory." As Alzheimer's disease slowly develops along with aging, many of the elderly suspect that "slip of memory" is an early warning sign of Alzheimer's disease. In fact, it is often necessary to differentiate Alzheimer's disease in its early stage from BSA. What are the differences between them?

First, the detail and degree of memory impairment differ significantly between BSA

and Alzheimer's disease. First of all, while a person with BSA loses memory of only a part of events, a patient with Alzheimer's disease loses all memory of them. For example, when a person forgets in the evening what was eaten for breakfast, it can be caused by BSA. But when someone does not know whether they ate or not, they are likely to be suffering from dementia.

The characteristics of memory impairment are therefore detailed. In memory impairment caused by Alzheimer's disease, disturbance of delayed recall is the first and most significant symptom. It is different from memory decline in BSA. A test for delayed recall is included in the Revised Hasegawa's Dementia Scale (HDS-R),<sup>2)</sup> which is often used in screening tests for dementia. In this test, test subjects are asked to repeat the words "cherry", "cat", and "train" immediately after the examiner says them. Test subjects are asked to recite these 3 words again after questions asking them to calculate "100 minus 7" and "recite 3-digit or 4-digit figures backwards". The latter question is a test of delayed recall. Not only the normal elderly, but also patients with Alzheimer's disease in its early stage can repeat those words immediately after an examiner says them. With an interval of 2 other questions, however, it is easy to recall them for the normal elderly but not for patients with Alzheimer's disease. Delayed recall requiring memory recall after more than a few minutes is feasible in Alzheimer's disease.

Memory impairment is described next. Memory is divided into short-term and long-term types (it should be noted that these terms are used differently depending on the individual). Short-term memory, or immediate memory, is lost within a minute without repetition. A test asking for the immediate repetition of 3 words is a test of immediate memory. Long-term memory is further divided into recent memory sustained by the minute, hour, and day, and remote memory that is sustained for a longer period. Delayed recall is concerned with the

Table 2 Differentiation between Aging-related Memory Decline (Benign Senescent Amnesia) and Alzheimer's Disease

	Benign senescent amnesia	Alzheimer's disease
Features of memory impairment	Partial disturbance of episodic memory or word amnesia	Disturbance of memory in general (first-delayed recall)
Orientation	With no disorientation	With disorientation (first-temporal disorientation)
Other intellectual disorders	No disturbance of judgement or abstract thinking	Reduction of all intellectual capabilities
Progression	Not progressive	Progressive
Insight	Aware of memory decline	Unaware of memory decline
Degree	Mild and not affecting daily life	Affecting daily life

shortest of these. Disturbance of delayed recall can be observed even in amnesia, but not significantly in BSA. As it is disturbed in the early stage of Alzheimer's disease, it is helpful in identifying the differentiation.

Disturbance of recent memory is followed by disturbance of remote memory both in amnesia and dementia. While only a part of recent memory is disturbed to a degree that it does not affect social life in BSA, significant disturbance of recent memory is followed by disturbance of remote memory in Alzheimer's disease. Although differences between them are significant in later stage, it should be noted that only delayed recall can be disturbed in Alzheimer's disease in its early stage.

Memory can be divided into declarative memory and procedural memory depending on its features. Procedural memory is automatic memory that remains not only in amnesia, but also in dementia most of the time. Declarative memory can further be divided into episodic memory and semantic memory. Episodic memory is memory of a personal history type with temporal and spatial contexts, for example, "I remember something." Semantic memory is memory of knowledge, for example "I know something," such as the number of days in a year. While episodic memory is the first to be lost both in amnesia and dementia, only a part

of episodic memory is disturbed in BSA.

The second important difference between BSA and Alzheimer's disease is that disorientation is not observed in BSA, but it is in Alzheimer's disease. Alzheimer's disease is characterized by the early disturbance of temporal orientation. A patient with Alzheimer's disease in its early stage who maintains normal spatial and personal orientation sometimes does not know the current date or day of the week. When encountering an acquaintance, inability to recall the name is not personal disorientation, but a simple partial memory disorder. It is often observed in BSA. However, inability not only to recall the name but also to recognize who the person is, is personal disorientation, which is observed in the middle stage of Alzheimer's disease.

The third difference is that a person with BSA has insight, but a patient with Alzheimer's disease has no insight even in its early stage. Therefore, while an elderly outpatient complaining of memory loss is likely to be suffering from BSA or depression, one with less concern but is accompanied by family members or colleagues who are concerned about their memory loss is likely to be suffering from Alzheimer's disease. These differences are described in Table 2.

When it is difficult to differentiate dementia

Table 3 Working Characteristics for the Early Detection of Alzheimer's Disease

Features of dementia	Disturbance of delayed recall, temporal disorientation, disturbance of the reproduction of 3-dimensional drawings
Accompanying mental disorders	Delusions of persecution (delusions of having things stolen)
Imaging	Findings in PET and SPECT (impairment of cerebral metabolism and circulation in the temporal lobe, parietal lobe and/or posterior cingular gyrus)
Diagnostic markers	Tau in cerebrospinal fluid ↑, A $\beta$ 1-42/43 ↓, or a combination of the two

and amnesia after a review based on these points, it is important to observe the patient at a different time or different day, or to observe the progress over time. If the symptoms alter during the day, disturbance of consciousness or depression can be suspected. While memory decline does not progress over a period of a few months in BSA, the above-mentioned characteristics become significant in Alzheimer's disease.

Other accompanying mental symptoms in Alzheimer's disease such as paranoid judgement are helpful in making the differentiation. A patient with BSA searches for what has been lost, but a patient with Alzheimer's disease suspects that it is concealed or stolen based on paranoid judgement. When a person often suspects that things have been stolen, Alzheimer's disease in the early stage should be considered even if no symptoms other than "slip of memory" are observed. Additionally, it is difficult for a patient with Alzheimer's disease even in its early stage to draw 3-dimensional reproductions even though 2-dimensional reproductions can be drawn. This is also helpful in differentiating these two conditions.

In addition to these clinical symptoms, CT

and MRI, especially functional imaging such as SPECT and PET are helpful in differentiation. Furthermore, a diagnostic marker using cerebrospinal fluid has been developed (Table 3).

## Conclusion

This paper discusses differences between amnesia and dementia, and the differentiation between BSA and Alzheimer's disease in its early stage as common and important examples. Medicines for Alzheimer's disease have been developed and early diagnosis and treatment has become more important. It is hoped that this explanation will contribute to early and correct diagnosis.

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# Depression Associated with Physical Illness

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**Abstract:** Depression often accompanies a medical condition. It may also happen that the presence of a chronic disease changes the social situation of a patient, who then responds to the change by developing depression. Among the various systemic diseases, endocrine diseases, viral infections, collagen disease, pancreatic cancer, vitamin B<sub>12</sub> deficiency, and folic acid deficiency are particularly likely to cause depression. Drugs, including interferon, methyl dopa, and steroids, may also be the cause of depression. The depression seen in organic brain disease (secondary depression) includes depression in convalescence from disturbance of consciousness caused by head trauma or encephalitis, poststroke depression, and depression in Alzheimer's disease, Parkinson's disease, or other neurodegenerative diseases. The symptoms of depression associated with a medical condition are basically the same as those in endogenous depression, including depressed mood, sadness, diminished mental activity, and impatience. However, depression associated with chronic organic brain disorders is characterized by the predominant symptoms of diminished intellectual capacity, apathetic tendency, lability of mood, retardation in thinking and speech, and flat affect, whereas depressive mood, insomnia, anorexia, low self-esteem, obsessive-compulsive symptoms, and suicidal ideation are mild.

**Key words:** Secondary depression; Symptomatic depression; Poststroke depression; Depression in Parkinson's disease

## Introduction

Mental disorders associated with physical illness are characterized by the symptoms of disturbance of consciousness, disturbance of affect and volition, personality disorder, and dementia. In particular, affective symptoms often accompany physical illness, and depression is most frequent among them. Depression associated with a medical condition can be classified as reactive or psychogenic depression in-

duced by changes in the social situation of the patient or depression directly caused by the medical condition (somatogenic depression). Somatogenic depression is further divided into organic depression due to cerebral disorder and depression associated with systemic disease.

Depression resulting from organic brain disorder (organic depression) has frequently been called secondary depression (or secondary mood disorder) in recent years. This is because the involvement of "organic factors" from the

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viewpoint of biology of the brain has been speculated even in endogenous mental disorders, making the meaning of "organic" somewhat imprecise and unclear.<sup>1,2)</sup> Secondary depression is regarded as a mental condition that has a particular pattern and is produced by various causes, including physical illness and neurologic disease.<sup>3)</sup>

## Clinical Picture of Depression Associated with a Medical Condition

### 1. Depression as an adjustment disorder

Depression may occur as a result of adjustment disorder (DSM-IV)<sup>4)</sup> in response to stress caused by a medical condition. Beset by changes in the social situation resulting from chronic or severe physical illness, the patient finds difficulty adapting and develops depression. Although this type of depression is triggered by a medical condition, it is not a direct consequence of that condition.

### 2. Symptomatic depression

Mental disorders that accompany systemic disease are called symptomatic psychoses. Although disturbance of consciousness is commonly the main symptom in symptomatic mental disorders, the manifestation of affective symptoms, particularly depression, is not rare. Systemic diseases liable to induce depression include endocrine diseases such as hyper- and hypothyroidism, hyper- and hypoparathyroidism, hyper- and hypoadrenocorticism, hypoglycemia, Cushing's syndrome, and Addison's disease. In endocrine diseases, symptoms of emotion and volition, rather than intellectual disturbance or dementia, are predominant. Further, depression is likely to occur in patients with viral infection, systemic lupus erythematosus, HIV infection, pancreatic cancer, vitamin B<sub>12</sub> deficiency, or folic acid deficiency. Cytokines manifested in systemic diseases are considered to be a cause of depression.<sup>5)</sup>

Drugs are another notable cause of depres-

sion. The use of interferon, reserpine, methyl-dopa, or steroids often induces depression.

### 3. Secondary depression

#### 1) Depression in the recovery stage from disturbance of consciousness

When recovering from disturbance of consciousness caused by head trauma, encephalitis, or other central nervous system disorders, the patient may suffer from lability of mood, irritability, memory disturbance, hallucination or delusion, or depression, for several weeks or months. There are various patterns in the manifestation of these symptoms, with a high frequency of affective symptoms. These patterns include depressive mood combined with amnesic symptoms; marked anxiety and delusion; irritability and impaired social functioning; excessive or inappropriate guilt under depressive mood; inflated self-esteem and grandiosity associated with manic mood; hallucination, and delusion.<sup>6)</sup> It is not uncommon for very mild disturbance of consciousness to underlie depression in organic brain disorder.

#### 2) Depression in neurologic disease

##### a. Depression in cerebral circulatory disorder

In chronic cerebral vascular insufficiency, affective symptoms such as affective incontinence, depression, euphoria, short temper, irritability, and affective flattening may occur. In particular, depressive mood accompanied by impatience and affective incontinence are often seen.

It is also common for depression to occur after stroke (poststroke depression). Poststroke depression sometimes becomes persistent. Retardation in thinking and behavior is prominent. It has been reported that lesions in the left frontal lobe or basal ganglia are apt to cause depression, with the tendency that the more frontal the lesion, the severer the symptoms.<sup>7)</sup> On the other hand, some researchers consider lesions on the right side more important. Thus, the relation between the manifestation of affective symptoms and the site of the lesion remains controversial. In addition, there

is the view that asymptomatic cerebral infarction serves as the cause of depression.<sup>8)</sup>

#### **b. Depression in Alzheimer's disease**

It is frequent for affective symptoms such as depressive mood, decreased spontaneity, affective lability, sadness, affective flattening, and anxiety/impatience to occur as prodromal symptoms of dementia in the early stage of Alzheimer's disease. In these cases, anxiety, depressive mood, behavioral retardation, and inactivity are common, whereas feelings of guilt, suicidal ideation, and secondary delusion are rare.<sup>9)</sup>

#### **c. Depression in Parkinson's disease**

Patients with Parkinson's disease are sometimes misdiagnosed as having depression because of their impassive facial expression and motor retardation. However, beyond these features, depressive state with self-awareness of depressive experience are often seen. This type of depression is attributable to disorders of the dopaminergic projection system in the frontal region, and is considered to be directly related to Parkinson's disease itself.

Depression is a common psychiatric disorder in Parkinson's disease. Mean frequency of the recently reported studies was 40% and the range was 25–70%.<sup>10)</sup> Although depressive symptoms occur at the onset of the disease in most cases, depressive mood may occur in some cases as a prodromal symptom preceding neurologic symptoms. Depression is occasionally more prominent in the early stage of disease (Yahr's stages I and II).<sup>11)</sup> Symptoms are similar to those of endogenous depression. More specifically, depressive mood, loss of interest, feeling of hopelessness, loss of energy, psychomotor retardation, and diminished ability to think or concentrate may occur. The patient also may exhibit irritability, pessimistic view of the future, impatience, sadness, and suicidal ideation.

Conspicuous features of patients' symptoms are considered to be decreased feelings of guilt, self-reproach, and sense of loss, as well as a low incidence of delusion and hallucination, low suicide rate, and lack of diurnal variation. The

occurrence of anxiety/fretfulness, suicidal ideation, and hypochondriacal tendency is not frequent. Although the patient's depressive symptoms can be relieved by antiparkinson drug therapy alone, MAO inhibitors or serotonin reuptake inhibitors may also be used.

#### **d. Depression in other neurologic diseases**

Neurodegenerative diseases such as Huntington's disease, progressive supranuclear palsy, fronto-temporal lobe dementia, neurosyphilis, toxic diseases, pellagra, folic acid deficiency, and Wernicke's encephalopathy may be complicated by depression.

### **Diagnostic Criteria for Depression Associated with Physical Illness**

Accurate diagnosis of depression associated with physical illness is extremely important in view of its direct linkage to subsequent treatment. A diagnosis of secondary depression is made when the following criteria are met.

- (1) The depression is difficult to explain by other mental disorders (e.g., adjustment disorder accompanied by depressive mood manifesting as a response to stress from a general medical condition).
- (2) The patient's physical disease is well known to cause depression. Such diseases include endocrine diseases, metabolic diseases, Parkinson's disease, Alzheimer's disease, and cerebrovascular disorders.
- (3) A close temporal relationship exists between the physical disease and the onset of depression.
- (4) Clinical features characteristic of secondary mood disorder are present. In cases of depression as a secondary mood disorder, it is reported that depressive mood, insomnia, anorexia, low self-esteem, obsessive-compulsive symptoms, and suicidal ideation are mild, whereas acquired intellectual impairment, impaired sensorium, self-neglect, lability of mood, hostility, violent behavior, slowed speech and thought, lack of insight, eccentricity, thought process dis-

organization, developmental intellectual deficit, and flat affect are prominent.<sup>12)</sup>

- (5) Systemic disease or cerebral nervous disease is evident upon physical examination and laboratory testing.
- (6) The patient has no history of primary affective disorder.

## Conclusion

Organic depression, or secondary depression, includes depression common in the recovery stage from disturbance of consciousness, depression directly related to the essence of the disease such as that seen in Parkinson's disease, depression as a prodromal symptom seen in the early stage of Alzheimer's disease, and depression in cerebral circulatory disorders (e.g., poststroke depression). The clinical characteristics of these types of depression have been described.

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# Cancer Screening and Radiation

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**Abstract:** Government-sponsored cancer screenings in Japan are of the largest scale in the world. Screening is conducted for cancers of the stomach, uterine, lung, breast, and colon. As primary screening for the stomach, breast, and lung cancers, radiation particularly X-ray, is used. This paper discusses first the need to strike a balance between risks and benefits of life saving for those undergoing screening by use of radiation for medical purposes, and then calculates the risk and benefit of breast cancer screening by mammography and lung cancer screening by spiral CT. It is assumed that the former is performed once every two years with the dose of 3mSv whereas the latter is done annually with the dose of 9mSv. It was found that the benefits exceeded the risks for women over 30 in the former, and for men over 40 and women over 45 in the latter, thus justifying the mass cancer screening. In the future, the quality assurance of radiation dose is essential.

**Key words:** Cancer screening; Radiation; Risk-benefit analysis; Quality assurance; Mammography; Lung screening CT

## Introduction

Cancer screenings conducted in Japan are of the largest scale in the world. Up to 1998, mass screenings for five types of cancers, viz. gastric cancer, uterine cancer, lung cancer, breast cancer, and colon cancer, were conducted under the Health and Medical Services Law for the Aged. Radiation plays a major role, particularly in screening by image diagnosis. Radiography is used for gastric cancer, chest X-ray for lung cancer, and mammography for breast cancer since 2000. There is a marked trend for using lung screening CT (LSCT) in primary screening, which is another form of radiography.

Because of the inherent risk of irradiation, quantitative comparison with medical benefit is absolutely necessary. This paper discusses the basic principle of radiation for cancer screening and its future prospect.

## Concept of Radiation Exposure for Medical Purposes

There are three types of exposures; (1) occupational exposure, (2) public exposure, and (3) medical exposure. Radiation exposure in cancer screening falls under the category of medical exposure. The major difference between medical exposure and other types of exposure

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is that the subjects directly receive the benefit and risk of exposure. This is the reason why no limits are set on the dose. In other words, if the medical benefit is deemed to exceed the risk of exposure, there is imposed no limit on the dose.

A typical example is the radiation therapy, in which case massive doses are administered with the knowledge that certain degree of radiation injury may be inflicted. The patient takes the risk in expectation of the benefit of cure. Naturally, every effort is made to achieve cure with the lowest possible dose.

On the other hand, radiographic diagnosis does not use massive doses such as that for therapeutic purposes, but the expected medical benefit of diagnosis and risk of radiation exposure should be compared and the result should be presented quantitatively.

Low dose risk of diagnostic purpose is called stochastic effect and mainly consists of death by cancer induced by radiation. Theoretically, comparison is made of life saving by screening and death as a possible risk of irradiation.

Exposure in clinical medicine occurs in patients who visit the medical institution with some form of complaints, and in this case the benefit is expected to be quite large compared to the risk. This paper addresses, however, the mass screening for healthy population where most people are unlikely to get benefit. It therefore becomes necessary to analyze quantitatively for the subject population in radiographic primary screening in health examinations including those for cancer.

The risk-benefit analysis in mammography and LSCT, the two methods currently drawing attention of the medical world, is discussed.

### Risk-benefit Analysis in Cancer Screening

As a great many healthy subjects undergo cancer screening, the risk (side effects) of primary screening to which every subject is exposed may give large effects to the group as a whole even if it is anticipated to be slight for the indi-

viduals. Radiography in primary screening is considered, and I should like to state first that a similar consideration is warranted in screenings other than the radiographic one.

The author has already established a numerical model for cancer screening by expressing the benefit as person-years saved (number of persons saved  $\times$  life expectancy) and the risk as the reduced life expectancy in person-years due to death. Its outline is discussed here, but the details are to be found in the references.<sup>1,2)</sup>

The benefit of cancer screening is assumed for two groups matched by sex and age; one group which undergoes cancer screening every year (the screened group) and the other group which undergoes no screening (the outpatient group). The difference in benefits (number of persons saved per year) expected of the two groups is sought and the result set as the net number of lives saved per year. The final equation derived from the model is shown below.

$$\begin{aligned} \text{The number of life saved (N)} = & \\ & \text{number of groups (P)} \times \text{incidence (D)} \times \\ & \text{screening sensitivity (Fs)} \times \text{rate of those} \\ & \text{undergoing secondary screening (S)} \times \\ & \text{sensitivity of detailed examination (Fd)} \\ & \times [\text{the survival rate of the screened} \\ & \text{group (Ws)} - \text{the survival rate of the} \\ & \text{outpatient group (Wo)}] \dots\dots\dots (1) \end{aligned}$$

$$\begin{aligned} \text{The number of life saved} \times \text{year (NT)} = & \\ & \text{number of life saved (N)} \times \text{average life} \\ & \text{expectancy (T)} \dots\dots\dots (2) \end{aligned}$$

The equations (1) and (2) are general formulas and are applicable to all cancer screenings. Each variable should be examined separately for the cancer screening being reviewed. Concrete discussion follows.

The author reported another model regarding the risk of radiation exposure,<sup>3)</sup> and the conclusive equation is given below.

$$\begin{aligned} \text{Reduced life expectancy in person-years (S)} & \\ = & [\text{bone marrow dose (Eb)} \times \text{rate of} \\ & \text{leukemia induction (Rb)} \times \text{reduced life} \\ & \text{expectancy by leukemia } (\Delta\text{Mb}) + \text{dose to} \\ & \text{other site (Ek)} \times \text{rate of cancer induction} \\ & \text{at the other site (Rk)} \times \text{reduced life} \end{aligned}$$

Table 1 Incidence of Breast Cancer and Life Expectancy (1994)

Age	Women	
	Incidence (D) (person/10 <sup>5</sup> person-year)	Mean life expectancy (T) (years)
30–34	13.5	53.65
35–39	36.6	48.77
40–44	74.3	43.91
45–49	94.7	39.12
50–54	89.5	34.43
55–59	73.1	29.82
60–64	78.2	25.31
65–69	82.5	20.94
70–74	75.2	16.76
75–79	70.1	12.88

Table 2 Benefit-risk Ratio of Mammography Screening (biennial)

Age	Benefit/risk (3mSv) (NT/S)	Benefit/risk (1.5 mSv) (NT/S)
30–34	4.72	9.42
35–39	14.3	28.5
40–44	33.9	67.7
45–49	52.3	104
50–54	61.6	123
55–59	66.3	136
60–64	101	202
65–69	173	345
70–74	331	662
75–79	1,240	2,480

expectancy by cancer ( $\Delta Mk$ )]/coefficient of low dose effect (d) . . . . . (3)

The equation (3) calculates using the terms for leukemia induced by irradiation to the bone marrow and for cancer at other sites. The reason is because the pattern of leukemia induction is different from other cancers. This equation is also general, and the numerical values to be substituted with variables in cancer screening differ. It should be noted that the equations (2) and (3) can be directly compared because the values are expressed by the same unit of person-year.

**1. Screening by mammography**

The values used in (1) and (2) in mammo-

graphy screening are discussed. In this case, the results of once-in-two-year screening were used according to the guidelines of the Japanese Association of Breast Cancer Screening.

$$P = 100,000 \quad F_s = 89.0\% \quad S = 94.0\%$$

$$F_d = 95.8\% \quad W_s = 89.2\% \quad W_o = 81.5\%$$

These values are the means of values obtained from a questionnaire survey by the Breast Cancer Screening Study Group (leader; Dr. Ouchi). Since the incidence D and the average life expectancy T are largely dependent on age, they are shown in Table 1. D was multiplied by 1.8 considering that the screening is conducted once in two years. When these values are substituted in the equations (1) and (2), the number of life-years saved (NT) is obtained.

The risk is also calculated by substituting the values in the equation (3). In the case of mammography, only the breasts are irradiated and therefore the term for leukemia of the equation (3) becomes 0. The other site is also the breasts, and the equation (3) therefore becomes simple.

$$\begin{aligned} &\text{Reduced life expectancy in person-years (S)} \\ &= [\text{dose irradiated to the mammary} \\ &\text{gland (E}_k\text{)} \times \text{rate of breast cancer} \\ &\text{induction (R}_k\text{)} \times \text{reduced life expectancy} \\ &\text{by cancer (}\Delta\text{M}_k\text{)}] / \text{coefficient of low dose} \\ &\text{effect (d)} \dots\dots\dots (4) \end{aligned}$$

Since the dose to the mammary gland is one-directional (mediolateral oblique; MLO) under the guideline, the maximum dose is 3 mSv and the mean value 1.5 mSv as indicated by the Quality Assurance Committee of the Japanese Association of Breast Cancer Screening.

$$E_k = 3.0 \text{ or } 1.5 \text{ mSv}$$

Sv means Sievert, unit of radiation dose.

As for R<sub>k</sub>, the coefficient of the additive model proposed by the United Nations Scientific Committee (1988) is used.

$$R_k = 4.3 \times 10^{-3} \text{ person/Sv}$$

Since the reduced life expectancy by cancer ( $\Delta\text{M}_k$ ) is the function of the average life expectancy, it varies by age. For details of the equation, the reference<sup>3)</sup> should be studied.

Finally, d is assumed to be 2.0.

From these equations, NT and S were sought and the results are shown in Table 2. As NT and S are represented by the same person-year, NT/S (ratio of benefit/risk) is obtained.

When the value is greater than 1.0, the benefit is greater than the risk. While the risk of irradiation is greater when the subject is younger and decreases rapidly as the subject grows older, the benefit does not decrease even when the subject is quite old, indicating that NT/S is smaller in younger subjects and greater in older subjects. The most critical age is 30 years old when the dose is 3 mSv, but NT/S is above 1.0 that is 4.72. In subjects older than 50 as defined by the guideline, the benefit largely exceeds the risk as 3 mSv is 62 times and 1.5 mSv is 123

Table 3 Incidence of Lung Cancer and Life Expectancy

Age	Incidence of lung cancer (person/10 <sup>5</sup> person-year)		Mean life expectancy (years)	
	Men	Women	Men	Women
40-44	10.2	4.5	37.96	43.91
45-49	16.7	7.7	33.28	39.12
50-54	32.7	17.4	28.75	34.43
55-59	65.2	20.2	24.41	29.82
60-64	134.9	37.8	20.28	25.31
65-69	261.4	56.1	16.48	20.94
70-74	353.7	90.3	12.97	16.76
75-79	460.0	115.6	9.81	12.88
80-84	553.3	131.1	7.13	9.47

Lung cancer incidence in 1992 (Cancer statistics—1997, Foundation for Promotion of Cancer Researches)  
Mean life expectancy in 1995 (Trend in population, Population Statistics 1997, Institute of Population Problems)

times more. We may declare that there is no problem whatsoever. The above mentioned reference<sup>1)</sup> discusses the details for interested readers.

## 2. Lung cancer screening with LSCT

Lung cancer screening with CT is now discussed.<sup>2)</sup> Although this method is not officially recognized as mammography screening, it is being studied as an alternative for the currently prevailing indirect X-ray. The values to be substituted in the equations (1) and (2) are shown below.

$$\begin{aligned} P &= 100,000 & F_s &= 90\% & S &= 85\% \\ F_d &= 95\% & W_s &= 75\% & W_o &= 15\% \end{aligned}$$

The basis for these values are explained. The use of LSCT has only recently been started and measurement of the variables is not necessarily accurate. But assumption is possible. Since P is 100,000, F<sub>s</sub> is 90% because it is assumed to be more accurate than 70-80% of the indirect X-ray screening, S is 85% which is the value obtained in the current lung cancer screening, F<sub>d</sub> is 95% because it is considered quite high, and W<sub>s</sub> which is the survival rate of the screened group detected by LSCT is 75%. This is based on the result obtained by multiplying the frequency of detection by the disease

Table 4 Benefit/Risk of LSCT (ratio of prolonged life expectancy)

Age	Benefit/risk (NT/S)(50mA)		Benefit/risk (NT/S)(25 mA)	
	Men	Women	Men	Women
40-44	3.3	0.87	6.6	1.8
45-49	6.6	1.8	13.1	3.5
50-54	16.4	4.9	32.7	9.9
55-59	45.1	7.5	84.3	15.0
60-64	174	20.0	347	40.1
65-69	453	48.7	907	97.3
70-74	1,020	147	2,040	295
75-79	2,770	340	5,460	683
80-84	12,290	873	24,600	1,745

stage and the 5-year survival ratio for each stage published by Anti-Lung Cancer Association (ALCA).<sup>4)</sup> Lastly,  $W_o$ , the survival ratio of the outpatient group, was set at 15% which is considered to be reasonable. Table 3 shows the lung cancer incidence  $D$  and the average life expectancy  $T$  since these differ according to sex and age. When these are substituted into the equations (1) and (2), the life saved per person per year (NT) is obtained.

Risk calculation is now conducted. In the case of LSCT, the bone marrow and lung for men and the bone marrow, lung and mammary gland for women are irradiated, requiring two separate equations for men and women.

$$\begin{aligned} \text{(Men) } S = & [\text{bone marrow dose (Eb)} \times \text{leukemia induction rate (Rb)} \\ & \times \text{reduced life expectancy by leukemia} \\ & (\Delta Mb) + \text{lung dose (Ek)} \times \text{lung cancer} \\ & \text{induction ratio (Rk)} \times \text{reduced life} \\ & \text{expectancy by cancer } (\Delta Mk)] / \text{low dose} \\ & \text{effect coefficient (d)} \dots\dots\dots (5) \end{aligned}$$

$$\begin{aligned} \text{(Women) } S = & [\text{bone marrow dose (Eb)} \times \\ & \text{leukemia induction rate (Rb)} \times \\ & \text{reduced life expectancy by leukemia} \\ & (\Delta Mb) + (\text{lung dose (Ek1)} \times \text{lung cancer} \\ & \text{induction ratio (Rk1)} + \text{mammary gland} \\ & \text{dose (Ekb)} \times \text{breast cancer induction} \\ & \text{ratio (Rkb)}) \times \text{reduced life expectancy} \\ & \text{by cancer } (\Delta Mk)] / \text{low dose effect} \\ & \text{coefficient (d)} \dots\dots\dots (6) \end{aligned}$$

The values substituted in these equations were obtained by measurement with CT-WR 950R (Hitachi Medico) carried on LSCT vehicle.<sup>5)</sup> The conditions are the same as the ordinary screening: tube voltage, 120 kV; tube current, 50 mA; slice thickness, 10 mm; X-ray tube rotating speed, 2 sec; and table translation speed, 10 mm/sec. Following results were obtained.

$$\begin{aligned} E_b &= 2.65 \text{ mSv} & E_{k1} &= 8.7 \text{ mSv} \\ E_{kb} &= 9.42 \text{ mSv} \end{aligned}$$

As some institutions use 25 mA, which is 50% of the tube current, 50% doses at these three sites were also calculated. As for the cancer induction rate, the following values were used as in the above mentioned case of breast cancer based on the United Nations Scientific Committee.

$$\begin{aligned} R_b &= 9.3 \times 10^{-3} & R_{k1} &= 5.9 \times 10^{-3} \\ R_{kb} &= 4.3 \times 10^{-3} \end{aligned}$$

$\Delta Mb$  and  $\Delta Mk$  = the same as those for breast cancer mentioned above. Lastly, the low dose effect coefficient,  $d = 2.0$ .

These values were substituted in the equations (5) and (6), and  $S$  for men and women were obtained in respect of the tube currents 50 mA and 25 mA.

NT and  $S$  calculated from the above equations were used to obtain the benefit risk ratio (NT/S) similarly to the breast cancer screening. The result is shown in Table 4. For LSCT, calculations for men and women were done at

5-year intervals from the age 40 upward. When the tube current is 50 mA, the least NT/S is 0.87 that is smaller than 1.0 for women in their 40s, indicating that the risk is greater at this age. In the case of men, the risk is 3.3 for 40-year olds, indicating that the benefit becomes rapidly greater than the risk for both men and women with advance in age. The characteristics of lung cancer screening is that NT/S of men is much greater than that of women. This is because the lung cancer incidence among men is higher than that among women. If the current is 25 mA, the value becomes 1.8 even for women in their 40s, allowing screening. The author personally thinks that LCST is allowable for both men and women over 50 even with the current of 50 mA. If the image quality presents no problem, 25 mA would increase safety.

I would like to touch upon the benefit-risk analysis of lung cancer screening, which is currently being conducted by indirect X-ray. Firstly, the author believes that screening with indirect X-ray is not so effective. Although the benefit (NT) for the current screening is small, the dose of chest indirect X-ray is quite small compared to LSCT and therefore NT/S is greater, and it is greater than 1.0 for men and women even in their 40s. It is thus allowable from the point of risk-benefit analysis, but as will be discussed below, screening should be evaluated not only in respect of the benefit-risk analysis but also of the cost-benefit analysis.<sup>2)</sup>

The dose of 50 mA of LSCT is only 1/3 to 1/5 of the dose of spiral CT currently in clinical use. Researches on dose reduction are expected to proceed by investigating its relation with image quality.

### Future Prospect

Lastly, the relation between cancer screening and radiation are discussed for the 21st century. In the near future, radiography as a tool for primary screening tests will continue to be important. As discussed in respect of mammography and LSCT, its weight is expected to

increase. The essential issue is the quality assurance of irradiation. In screening, the dose should be controlled more strictly than in clinical medicine because the subjects are healthy. This corresponds to optimization as advocated by International Commission on Radiological Protection (ICRP). In other words, the dose should be minimized while maintaining the image quality required for diagnosis. Moreover, a quality assurance system to precisely monitor the doses should be established. Regrettably, we do not have a system for dose quality control for nationwide cancer screening in Japan.

The Quality Assurance Committee on Mammography mentioned above is about to establish the national system of quality assurance. It is hoped that such move will spread to the entire screening systems relying on radiation. The United States Federal Government has enacted the mammography quality standard act (MQSA) to control not only the dose quality but also the standards for personnels such as radiologists, radiographers, and medical physicists. The institutions not meeting the standards are not allowed to conduct screening. They are quite vigorous. The Japanese Ministry of Health, Labor and Welfare should also try to establish the quality assurance system adapted to Japan by expending money and advices.

As a medical physicist, the author is concerned about little interests in cancer screening shown by Japanese radiologists. The role played by American College of Radiology (ACR) is far greater than that of their counterparts in Japan. While Japan conducts health screenings of the largest scale in the world, it is mostly the internist who reads images of the stomach or lung cancers, and it is the surgeon who plays a bigger role in diagnosing by mammography. Revolutionizing the awareness of leaders in the academic society of radiology is warranted.

There are possibilities for primary screening with better cost-effective performance without relying on radiation, requiring replacement of radiography by such a new methodology. Natu-

rally, evaluation by EBM (evidence-based medicine) should be conducted first.

Lastly, it is emphasized that the benefit-risk analysis is applicable to all tests used in primary screening. For instance, it is advocated that the endoscopy should replace X-ray for the stomach cancer screening. In such a case, the benefit-risk analysis should be performed. According to our study, the risk is greater for endoscopy.<sup>6)</sup>

### Conclusion

When relying on radiography in primary screening for cancer, quantitative comparison of risks of exposure and benefits accrued as a result of screening should be made, and it should be demonstrated that the benefits exceed the risks. That is the benefit-risk analysis. This paper discussed mammography for breast cancer and LSCT for lung cancer screenings and demonstrated that benefits largely exceeded risks for subjects who are older than certain ages. Establishing a system of quality assurance for exposures on a nation-wide level is essential.

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