Vol.45, No.6 June 2002

JMAJ

Japan Medical Association Journal

CONTENTS

Basic Policies of the Japan Medical Association

JMAJ 45(6): 227–230, 2002

Eitaka TSUBOI

President, Japan Medical Association

The following is a main part of the address of Dr. Eitaka Tsuboi, President of the Japan Medical Association, which was presented at the 106th General Assembly of the JMA House of Delegates that was held in Tokyo on April 2, 2002.

The Negative Reforms of the Medical Fee Payment System

The cutback revisions of the medical fee payment system that presently confront the nation stem from the uncompromising framework of ceilings that has been established as part of the expenditure controls enacted by Prime Minister Koizumi to restrict government bond issues to 30 trillion yen (240 billion US dollar). Subsequently, the estimated FY 2002 budget of 550 billion yen (4.4 billion US dollar) requested by the Ministry of Health, Labour and Welfare (MHLW) was reduced by 280 billion yen (2.24 billion US dollar) under the appellation of "structural reforms that leave no areas sacrosanct" or under the justification of "equal loss shared by three parties". The remaining 270 billion yen (2.16 billion US dollar) that was allocated for the budget has forced the ministry to face the difficult problem of covering increased costs within this amount. This reduced budget is unrealistic, and the 280 billion yen that was eliminated must be restored. Irrespective of the impoverished state of our national finances, the government's fallacious idea that a social security system which guarantees stable retirement for Japanese citizens can be established through financial control measures, leaves one apprehensive of the government's ability to formulate a permanent national policy.

Following the government's proposal to impose a framework of ceilings, the JMA repeatedly requested of the MHLW that the budget be expanded. But the government took no interest in reviewing the request and proceeded to establish the framework of ceilings with a no-questions-asked attitude. The intrinsic basis for this difficult to understand decision-making process is the market principles embraced by the Cabinet Office, and the influence of the former Ministry of Finance. Their despotic attitude, which ignores the fundamental essence of health care, has been very revealing. The top-down decision making process by which the ministry's proposed estimated budget was reduced by 280 billion yen was a point of contention between the JMA and the MHLW. The cutback revisions of the medical fee payment system based on a resource procurement approach emerged in detail during this process.

The Ministry of Finance immediately advocated the need to slash the margin to 5.8 percent and to cut back Chuikyo (Central Social Insurance Medical Council) payments by at least 4 percent. JMA opposed this move and advocated a deferment of increases in medical

fees in view of the current social conditions. At present, a 1.0 to 1.5 percent reduction in insurance payments has been fixed based on the findings of the drug price survey conducted by Chuikyo. Subsequently, the cutback revisions can no longer be avoided. Moreover, this was followed by a request from the Minister of Health, Labour and Welfare to enact financial procurement methods that included cutbacks in health care itself as well as reductions in drug prices, in order to supplement the budget for health costs which had been subject to a curtailment assessment. A three percent cutback was proposed. However, in order to provide adequate health care for the populace, the JMA advocated that it was vital to maintain the status quo and adamantly opposed any cutbacks in mainstream health care. But, finally, in accordance with the Prime Minister's wishes and the top-down decision-making process, Chairman Niwa, of the LDP Basic Health Issues Committee, submitted a proposal for a 2.8 percent cutback.

As a result of these debates, the bill to cut back overall health care by 1.4 percent was revised to 1.3 percent. Combined with the 1.4 percent decrease in drug prices and pharmaceutical materials, we were forced to agree to a total reduction of 2.7 percent. It was a bitter compromise for the JMA based on social impact considerations.

Medical Fee Payment System

The detailed task of revising financial resource allocations in long-term negotiations with the MHLW was started to minimize the risk of curtailments. However, when the actual revised proposal was submitted to the medical and health care sector, it evoked extremely strong repercussions when the gradual systematized reductions of follow-up consultation fees, especially in the field of orthopedics where earnings are estimated to be greatly reduced, the contradictory assessment of surgery fees and the number of surgery cases, and other issues were disclosed. These issues stemmed from a deriding government policy that completely ignored the fundamental essence of health care; and it outraged many who believe that expanding special medical care costs was tantamount to eradicating the national universal health insurance. I am also of the same opinion. Therefore, JMA will immediately begin the task of reversing these proposed revisions.

All of these policy issues have been included as specific measures in JMA's health care structural reform plan. It is nothing less than the high-handedness of bureaucratic politics that JMA's proposed allocations have been completely ignored. Presently, a segment of these allocations have been revised following our strong opposition; and the JMA will continue to push for early revisions of high-profile areas. However, the task of revising only certain specific areas will not improve the situation. Therefore, we have informed the director of the Health Insurance Bureau of the Ministry of Health, Labour and Welfare to submit a new revision proposal to the Chuikyo in 2002.

Council on Economic and Fiscal Policy and the Council for Regulatory Reform

The argument that would lead to the eventual collapse of the universal insurance system was also strongly debated. The Council on Economic and Fiscal Policy (Finance Minister Heizo Takenaka) set forth an overall framework of regulations to control medical costs and introduced a bureaucratic framework to manage the growing medical costs for the elderly. Such a move violates the discretionary authority of physicians and absolutely must not be allowed.

In addition to lobbying the MHLW, the JMA successfully achieved the complete withdrawal of the bill at the scene of medical care politics.

The bill to allow private corporations into the medical and health sector, the combined use of public and private medical insurance,

individual agreements between medical institutions and insurers and other initiatives submitted by the Council for Regulatory Reform (Nobuteru Ishihara, Minister of State for Regulatory Reform) were passed by the Cabinet without any consultation with the JMA. This bill is utterly unacceptable since it will directly contribute to the future collapse of Japan's universal health insurance system. The JMA strongly opposed this bill and much of its original content was withdrawn, however, we must maintain our vigilance as problems continue to surface in quick succession. As a mainstay of medical care, it is our duty to submit our proposals to the Koizumi Cabinet based on fair and just arguments and to stringently ensure that each reform is enacted from a free and unbiased perspective.

Public Relations Activities

To protect our outstanding universal health insurance system from market principle advocates who vaunt humiliating reform arguments that prioritize self-interests akin to profit-making corporations with little or no regard for national interests, all JMA members must unite sustained by high aspirations and a strong ethical perspective. In addition, we must inform the public of our views and together with their understanding and assistance, we must conjoin to ensure the continuity of the universal insurance system.

The public relations activities of the JMA has always addressed issues that were both internal and external to the association, but they have been inclined to be inadequate in accurately reflecting the prevailing social conditions. To rectify this situation, the JMA will pursue diverse, strategic public relations activities in conjunction with its regular PR activities. In other words, to pursue public relations from a two-way, bi-directional perspective rather than from one viewpoint, plans to establish an information and public relations center within the association are also under review. A specific example is the JMA's "Grand Design on Health Care (for 2016)" that has been distributed to the JMA members, and it is an addendum to the association's "Grand Design for Health Care for Year 2015" that was publicly announced some time ago. The center will be responsible for the timely distribution of information about JMA's policies to all members and to directly respond to the questions and comments from them. It will serve as an organ that will ensure that information is shared by all association members. In addition, it will also function as a channel of information for the general public and serve as a key station for an information network that the JMA has gradually developed.

Furthermore, this strategic approach will help to effectively delineate JMA's overall policies, clarify its position on different issues, and provide an accurate representation for both the general public and government officials. Of course, it will also serve as an efficient means of amassing member consensus.

Japan Medical Association Research Institute (JMARI)

To maintain JMA's unswerving policies on health care and to avoid being tossed about by the complex and bizarre health care policies of the current Cabinet; there is a need to consolidate the function of the JMARI. The previous executive board established a committee to review the future concept of the institute and based on their invaluable and key suggestions, the significance of the institute will be raised in keeping with its position as a think tank of an academic and professional organization.

JMA's Stance as an Academic Professional Organization

It is the duty of the JMA to accurately assess the bewildering pace of progress and development in medical science and technology and to oversee their practical application in regional

health care in response to the needs of the Japanese people. However, JMA's heretofore-academic activities alone no longer suffice as an adequate means of bridging advanced medicine and regional health care. Therefore, a project will be started to establish a systematic organization that will enable the entire range of medical science, from preventive to advanced medicine, to be widely applied throughout the nation.

There is a need to strengthen JMA's position as a national opinion leader in the consensus on difficult ethical issues that accompany stem cell research, the risks created by genetic manipulation, organ transplants, and many other issues where viewpoints must be actively expressed or JMA's position must be advocated.

In tandem with measures to improve the CME program for physicians, there is a need to build the foundations by which we can actively advocate our views on advanced clinical and medical technology within the international and domestic arenas.

Conclusion

As the president of the JMA, I have attempted to state my views on the various issues and activities that face us as I enter my fourth term. I would also like to clarify the three pillars that support the actions of the new executive board of the association. They are as follows.

(1) To focus our energies on CME as an academic and professional association, to endeavor greatly to elevate our standards as professionals, and to serve as the bridge between regional medical care and the rapid developments in medical science and technology
(2) To disseminate information to all members, thereby enabling the association to exhibit its strength as a united group of medical professionals and to shift from passive to active public relations activities
(3) To elevate medical care related political activities from a new perspective and secure JMA's standing as a policy-making organization

The next one to two years will be a crucial point in time that will determine whether medical care in Japan will retain its fundamental characteristics in the 21st century. I believe that the key to maintaining the world's best health and medical care system hinges on whether the JMA will be able to successfully produce a heightened public awareness of structural reforms.

As an opinion leader of Japan's health care policies, we must strive under the highest aspirations while ascertaining the foremost health care needs of the Japanese people. We must create a health and medical care system that will be an asset for future generations who will feel proud to be Japanese citizens. Thus, this is the time when not only JMA members, but also all Japanese physicians must overcome myriad difficulties and strive to fulfil our solemn mission.

Characteristics of Respiratory Diseases in Older People

JMAJ 45(6): 231–236, 2002

Hidetada SASAKI*, Mutsuo YAMAYA**, Takashi OHRUI**, Hiroshi KUBO**, Manabu EBIHARA** and Hiroyuki ARAI***

Professor, Lecturer**, and Assistant Professor****
Department of Geriatric and Respiratory Medicine,
Tohoku University School of Medicine

Abstract: Pneumonia among old people is the fourth leading cause of death, and its mortality has remained the same for the last 100 years despite development of antibiotics. We have elucidated the onset mechanism of pneumonia among old people and developed methods for its prevention. Its primary cause is considered to be cerebrovascular disorders in the basal ganglia, and absence of substance P causes sub-clinical aspiration, which in turn causes pneumonia. Prevention of pneumonia is now possible without the use of antibiotics by increasing substance P. As old people are immune-compromised by depressed state, measures against depression are important for preventing infections such as pneumonia and common cold. The older the patient is, the more intense the effect of gene appears. It was shown that elderly persons with L polymorphism of heme oxygenase (HO)-1 gene are more susceptible to pulmonary emphysema. Systemic examination of the elderly, particularly their physiological characteristic, is essential for treatment of elderly persons with respiratory diseases.

Key words: Silent cerebral infarction; Immune function; Polymorphism in gene; Depressed state

Introduction

For young people, treatment of a single affected organ cures a disease while in elderly people, one should always be conscious of the relation to the entire body even when treating, for instance, a single respiratory disease. This paper discusses systemic treatment of respiratory diseases that are characteristically seen in the elderly.

Cerebrovascular Disorders and Pneumonia

Pneumonia in young people is exogenous and is described as community-acquired pneumonia

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 7, 2001, pages 973–977).

Table 1 Effect of Oral Care on Incidence of Pneumonia and Mortality by Pneumonia

Groups	No. of patients	Age	Gender (F/M)	Previous ADL	Previous MMS	No. of febrile patients(%)	No. of pneumonia patients (%)	No. of deaths (%)
Received oral care	184	82.0±7.8	148/36	16.3±6.5	13.6±6.9	27** (15)	21* (11)	14** (7)
Did not receive oral care	182	82.1±7.5	145/37	16.2±6.7	13.9±6.9	54 (29)	34 (19)	30 (16)

*$p<0.05$, **$p<0.01$ (Reference 9)

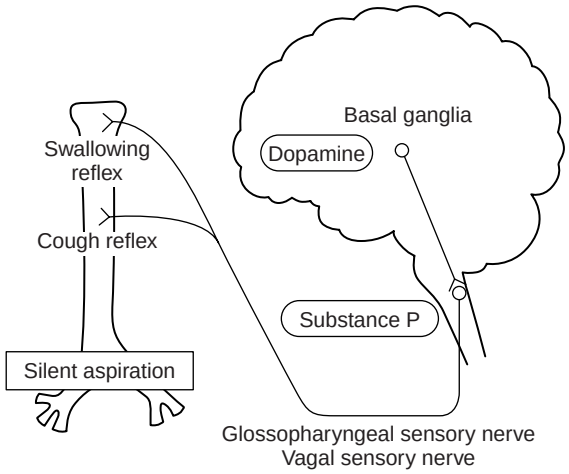


Fig. 1 Silent aspiration is caused by cerebrovascular disorder in the basal ganglia.
(Reference 4)

while that of old people is indigenous and nosocomial. Treatments against pneumonia in them are usually described based on the incidence of MRSA, etc. Since healthy subjects are not at all affected even when they are surrounded by MRSA, prevention of pneumonia in old people needs elucidation of their defense mechanism against infection and taking appropriate prevention. Old persons develop pneumonia by sub-clinical aspiration of bacteria in the oral cavity. Prevention of pneumonia in the elderly consists simply of preventing silent aspirations.

Silent aspiration occurs by impaired swallowing reflex[1] and cough reflex[2] (Fig. 1). These reflexes become impaired as a result of decreased reverse distribution of substance P that is synthesized at the cervical ganglion of the vagal sensory nerves.[3] Production of substance P is decreased by a decrease in dopamine production in the nigrostriatum.[4] Dopamine production is decreased by basal ganglion infarctions. In other words, cerebrovascular disorders are the underlying disease for repeated silent aspirations that lead to pneumonia in the final analysis.[5]

Identifying the causal bacteria and selecting antibiotics are not a positive method for prevention of pneumonia since pneumonia is recurrent and MRSA appears. Promoting increases of substance P and dopamine is necessary to prevent silent aspirations.

A small amount of capsaicin in the oral cavity will produce a large amount of substance P, which in turn improves swallowing reflex. Use of ACE inhibitor (Tanatril®) inhibits the substance-P-decomposing-enzyme, raises the concentration as substance P remains undecomposed, and improves swallowing and cough reflexes.[6] Administration of ACE inhibitors for two years decreased the incidence of pneumonia to 1/3[7] while that of amantadine, which stimulates dopamine synthesis, for three years decreased the incidence to 1/5.[8]

Aspiration does not induce pneumonia if there are fewer oral bacteria. The incidence of pneumonia in the group receiving oral care for two years lowered by about 40% (Table 1). While the survival ratio of elderly pneumonia patients in welfare nursing homes is as low as 20% even under treatment by antibiotics, the

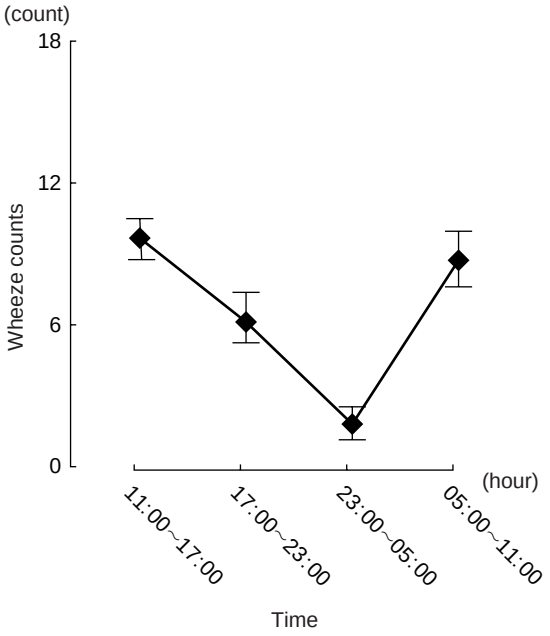


Fig. 2 Wheezing disappears during nocturnal sleep. (Reference 13)

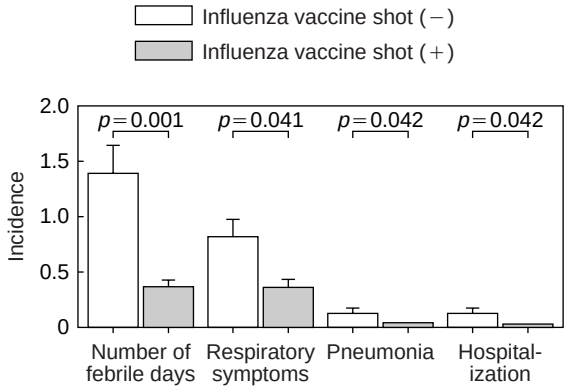


Fig. 3 Influenza vaccine shots to bed-ridden patients shortened durations of febrile days, respiratory conditions, pneumonia, and hospitalization. (Reference 16)

incidence of death by pneumonia decreased by almost half by oral care.[9] There are many phases in geriatric medicine where nursing care is superior to medical care.[10]

Sleep and Respiratory Diseases

The influence of sleep on respiratory diseases is evident in old people, but hardly observed among young people. Almost 50% of those aged 65 and older have cerebrovascular disorders, and swallowing[11] and cough reflexes[12] are suppressed at night when they are asleep, thus decreasing coughing. Silent aspirations therefore occur during nocturnal sleep and pneumonia develops. Mild sleeping pills administered to the elderly patients when they complain of insomnia do not create problems, but strong pills (which also inhibit dopamine production) lower the swallowing reflex and induce pneumonia.

Asthma attacks tend to occur at night and are therefore called nocturnal asthma. This is, however, based on reports by patients, nocturnal wheeze did disappear during sleep by examination actually conducted at night (Fig. 2). Thus, it transpires that there is no nocturnal asthma.[13] This may be attributable to the fact that the nerve control is lifted when the brain is asleep.

Immunity in the Elderly

It is not yet known how immunity changes with ageing. Immunity comprises cellular immunity represented by helper T_1 lymphocytes and humoral immunity represented by helper T_2 lymphocytes. In elderly people leading active life, both types of immunity remain unsuppressed. But in the bed-ridden elderly, cellular immunity is suppressed, making them more susceptible to pneumonia.[14] But their humoral immunity is not suppressed. Thus, a single dose of influenza vaccine raises influenza antibody titer in them as in young people,[15] and actually shortens the durations of febrile days, of poor respiratory tract conditions, of pneumonia, and of hospitalization (Fig. 3).

Since the antibody titer rises even in bed-bound patients, it was concluded that influenza vaccine should be administered.[16]

The Elderly and Genes

The incidence of genetic diseases rises among older people rather than in young people. Weak

Table 2 Polymorphologic Genes of Heme Oxygenase (HO)-1

Allele class	No. of emphysema patients (%)		Odds ratio (95% CI) versus allele			
	Without CPE (%) $n=200$	With CPE (%) $n=202$	All other classes	S	M	L
L	20 (10)	42 (21)	2.4 (1.3～4.1)[a]	2.9 (1.6～5.3)[b]	2.0 (1.1～3.6)[c]	1.0
M	88 (44)	93 (46)	1.1 (0.7～1.6)	1.5 (0.9～2.2)	1.0	
S	92 (46)	67 (33)	0.6 (0.4～0.9)[d]	1.0		

CPE: chronic pulmonary emphysema (Reference 17)
[a]$p<0.004$ [b]$p<0.001$ [c]$p<0.03$ [d]$p<0.02$

Table 3 Incidences of Cold Among Depressed and Not Depressed

Depressed state	Incidence of cold (%)		Odds ratio (95% CI)	p
	−	+		
Depressed (n=68)	21 (30.9)	47 (69.1)		
Not depressed (n=40)	5 (12.5)	35 (87.5)	3.3 (1.1～9.9)*	0.03

*adjusted by age and gender (Reference 19)

factors are largely amplified by ageing. Old people often develop pulmonary emphysema, and since smoking is an important environmental factor, young people are recommended not to smoke. However, as there are people who live to be hundred years old even when they do not quit smoking, people do not quite appreciate the importance of stopping to smoke.

Active enzymes generate by smoking, and polymorphism in heme oxygenase-1(HO) promotes dissipation of active enzymes. Polymorphism in HO-1 gene induces pulmonary emphysema by smoking if HO-1 is reduced.[17] Table 2 shows that those with class L alleles of HO-1 are more susceptible to pulmonary emphysema. This kind of gene analysis may be useful in persuading such people to stop smoking even when they are young.

Thus, a characteristic feature of geriatric diseases is that genetic anomalies become clear by ageing and are expressed as diseases such as pulmonary emphysema.

Depressive State and Respiratory Diseases

Confucius said 2300 years ago that "the spirit becomes stable with ageing". An extreme case of depressed state is manifested as suicide. The age of those committing suicide reaches a peak at 60, but suicide may be described as a disease of old people with its incidence per population increasing with advance in age. In 1999, 32,000 people committed suicide, a cause of death occupying the close-to-fifth 6th position.

When a person is depressed, glucose metabolism is suppressed in the limbic system.[18] Those who are depressed are more susceptible to common cold than others by three times[19] (Table 3). They are also more susceptible to cancer than smokers by five times, demonstrating the fact that mental depression affects systemic diseases including respiratory diseases. As indicated by the increased number of suicide with advanced in age, old people are more prone to depression, and depression induces systemic diseases, thus completing a vicious cycle.

What then can we do to decrease the incidence of depression among old people? According to researchers working on artificial intelligence, a brain that merely eats, walks, and urinates is a brain of the poorest quality. It eats, but instantly forgets that it ate. It walks like humans, but it urinates in the alcove of a drawing room. Thus, an inadequately functioning brain is acceptable if it can pass information to other functions of the brain. Those who need assistance in eating meals but can say "thank you" are superior.

Old people tend to think within their limited sphere, as they receive limited information. If they could share their abilities with others, especially young people, teach them to lead a better life, they would be regarded as good old people.

However, there must be lots of people who approach young people trying to be useful but who are not respected by young people. Old people should not expect returns from young people. Try to clean streets in front of your house as well as of your neighbors every morning. Young people may have little regard to this service, but would not speak ill of you. If you find a restaurant with few clients, you should visit it maybe once a week and order something light. The owner would notice your presence and may become friendly. When you see a long line of empty taxis waiting for customers in front of a station, you should take one maybe once a week and give the driver a chance to earn the fare instead of taking the customary free bus ride. If an airplane is empty with a few passengers and lots of cabin attendants, you should fly maybe once a year. Japanese airlines are now ready to welcome the elderly even when they are on wheel chairs. If there are lecture meetings, attend them by all means. This will please young people sponsoring the lecture.

Thus, all these things keep old people busy that they have no time to become depressed. Old people are not necessarily pressed for money. Their activities in the end benefit the young people. To stay at home always for fear of giving extra trouble to young people does not benefit them. As the years go by, the number of active old people increases. Longevity is an intensive result of accumulation of culture and the basis for respect by the entire world even if old people are living in modest houses.

Conclusion

Medical care for respiratory diseases of the elderly has just entered a new era as comprehensive medicine including mental activities has started.

REFERENCES

1) Ebihara, T., Sekizawa, K., Nakazawa, H. and Sasaki, H.: Capsaicin and swallowing reflex. *Lancet* 1995; 345: 1447.
2) Sekizawa, K., Ujiie, Y., Itabashi, S., Sasaki, H. and Takishima, T.: Lack of cough reflex in aspiration pneumonia. *Lancet* 1990; 335: 1228–1229.
3) Nakagawa, T., Ohrui, T., Sekizawa, K. and Sasaki, H.: Sputum substance P in aspiration pneumonia. *Lancet* 1995; 345: 1447.
4) Yamaya, M., Yanai, M., Ohrui, T., Arai, H. and Sasaki, H.: Progress in Geriatrics. Interventions to prevent pneumonia among older adults. *J Am Geriatr Soc* 2001; 49: 85–90.
5) Nakagawa, T., Sekizawa, K., Arai, H., Kikuchi, R., Manabe, K. and Sasaki, H.: High incidence of pneumonia in elderly patients with basal ganglia infarction. *Arch Intern Med* 1997; 157: 321–324.
6) Ishizuka, S., Yanai, M., Yamaya, M., Ohrui, T., Sekizawa, K. and Sasaki, H.: Cough syncope treated with imidapril in an elderly patient with dysphagia. *Chest* 2000; 118: 279.
7) Sekizawa, K., Matsui, T., Nakagawa, T., Nakayama, K. and Sasaki, H.: ACE inhibitor and pneumonia. *Lancet* 1998; 352: 1069.
8) Nakagawa, T., Wada, H., Sekizawa, K., Arai, H. and Sasaki, H.: Amantadine and pneumonia. *Lancet* 1999; 353: 1157.
9) Yoneyama, T., Yoshida, M., Matsui, T. and Sasaki, H.: Oral care and pneumonia. *Lancet* 1999; 354: 515.
10) Nakajoh, K., Nakagawa, T., Sekizawa, K., Matsui, T., Arai, H. and Sasaki, H.: Relation between incidence of pneumonia and protective reflexes in post-stroke patients with oral or tube feeding. *J Intern Med* 2000; 247: 39–42.
11) Pinto, A., Yanai, M., Nakagawa, T., Sekizawa, K. and Sasaki, H.: Swallowing reflex in the night. *Lancet* 1994; 344: 820–821.
12) Zheng, S., Yanai, M., Matsui, T., Sekizawa, K. and Sasaki, H.: Nocturnal cough in patients with sputum production. *Lancet* 1997; 350: 864–865.
13) Kanda, A., Yanai, M., Suzuki, T., Ohrui, T. and Sasaki, H.: Nocturnal wheeze in asthmatic patients. *Chest* 2000; 118: 278.
14) Fukushima, T., Nakayama, K., Monma, M.,

Sekizawa, K. and Sasaki, H.: Depression of T helper-1 and tuberculin responses in older bed-bound patients. *J Am Geriatr Soc* 1999; 47: 259–260.
15) Fukushima, T., Nakayama, K., Monma, M., Sekizawa, K. and Sasaki, H.: Influenza vaccination in bedridden patients. *Arch Intern Med* 1999; 159: 316–317.
16) Fukushima, T., Nakayama, K., Monma, M., Sekizawa, K. and Sasaki, H.: Benefits of influenza vaccination for bedridden patients. *Arch Intern Med* 1999; 159: 1258.
17) Yamada, N., Yamaya, M., Okinaga, S., Nakayama, K., Sekizawa, K., Shibahara, S. and Sasaki, H.: Microsatellite polymorphism in the heme oxygenase-1 gene promotor is associated with susceptibility to emphysema. *Am J Hum Genet* 2000; 66: 187–195.
18) Tashiro, M., Itoh, M., Sasaki, H. *et al.*: Reproducibility of pet brain mapping of cancer patients. *Psychooncology* 2000; 9: 157–163.
19) Shinkawa, M., Yanai, M., Yamaya, M., Matsui, T. and Sasaki, H.: Depressive state and common cold. *Lancet* 2000; 356: 942.
20) Nakagawa, T., Sekizawa, K., Nakajoh, K., Tanji, H., Arai, H. and Sasaki, H.: Silent cerebral infarction: a potential risk for pneumonia in the elderly. *J Intern Med* 2000; 247: 255–259.

Treatment and Management of Elderly Bronchial Asthma

JMAJ 45(6): 237–244, 2002

Noritaka HIGASHI and Kazuo AKIYAMA

Clinical Research Center for Allergy and Rheumatology, National Sagamihara Hospital

Abstract: There are certain characteristics of elderly bronchial asthma that are associated with aging, which must be considered during diagnosis and treatment. From the physiological viewpoint, a decrease in the forced expiratory volume per 1 sec (FEV1), an increase in the incidence of complications, such as chronic obstructive pulmonary disease and chronic heart failure, and a decrease in ventilatory response to hypoxemia must be considered. From the viewpoint of allergic reaction, the incidence of atopy-type asthma is not always low among elderly asthmatic patients, and their positive reaction to allergens is almost the same as that in young patients. In elderly asthmatic patients, obstruction of respiratory tracts tends to be severe, thus there is a high incidence of severe asthma. Because of the high incidence of death caused by asthma, introduction of inhaled steroids in the early stages for long-term control is important. Taking those characteristics in the elderly such as complications, drug interaction, and patients' drug compliance into consideration, the patients must be repeatedly educated, through which a partnership between doctors and patients needs to be established. This is a basic requirement for the treatment and management of bronchial asthma in elderly patients.

Key words: Elderly bronchial asthma; Chronic obstructive pulmonary disease; Drug interaction; Compliance

Introduction

Since the majority of our society will consist of elderly people in the very near future, patient-oriented treatment will be reexamined primarily to improve the quality of life (QOL) of the patients. In actual diagnosis and treatment of elderly bronchial asthma, many factors must be considered; not only decreases in physiological functions such as respiratory function, but also complications associated with chronic cardiopulmonary diseases, and drug metabolism and compliance. The purpose of this review is to clarify the characteristics of elderly bronchial asthma in order to properly diagnose it in the early stages and to treat the patients appropriately.

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 7, 2001, pages 988–992).

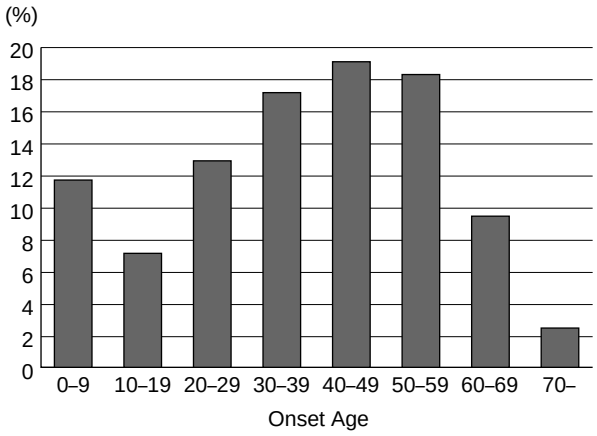


Fig. 1 The distribution of onset age in adult bronchial asthma in Japan
(quoted from Ref. 2))

Epidemiology

The incidence of elderly bronchial asthma is approximately 4 to 8% of individuals who are 65 years old or older.[1] With respect to the age of onset of the disease, Fig. 1 shows that the number of patients with adult-onset bronchial asthma is the highest for those in their onset age at 40's, whereas the incidence of onset of bronchial asthma among the elderly (60 years or older) is low at approximately 10% of the total asthmatic patients.[2] Tabe and Akiyama[3] reported that depending on the severity of bronchial asthma, mild cases account for 48.1%, moderate cases 38.2%, and severe cases 12.7% of adults. However, among elderly patients, the incidence of mild cases is low whereas the incidences of moderate and severe cases are high. Consequently, among the elderly (60 years or older), mild cases account for 37.7%, moderate cases 43.2%, and severe cases 13.9%.[3] It is believed that intractable asthma accounts for approximately 10% of adult-onset asthma and it is mostly observed among patients in their 60's and 70's. In Japan, due to less use of inhaled steroid, death due to asthma among the elderly remains high and tends to be frequently observed among males in their 50's to 70's.[4]

Pathophysiology

In elderly bronchial asthma, chronic airway inflammation is the main pathophysiological characteristic, the same as that in younger asthmatic patients.[5] However, it is important to note that elderly patients with bronchial asthma exhibit physiological changes and allergic characteristics associated with aging that result in the intractability of their asthma.

1. Physiological changes with aging

Aging and smoking are the main risk factors that influence pulmonary function. In the lungs of elderly patients, the airway space distal from the respiratory bronchiole to the alveolar duct and alveolus is dilated, causing age-related changes, such as an increase in residual volume and decrease in forced expiratory volume per 1 sec (FEV1) by 25 to 30 m*l*/year. In asthmatic patients, the decrease in FEV1 is larger compared to that of healthy controls (Fig. 2).[6] Furthermore, the amount of cigarettes smoked and sensibility to smoking are also causes of a decrease in FEV1,[7] which should also be considered in the treatment of chronic obstructive pulmonary diseases (COPD) including emphysema and chronic bronchitis. Indeed, the incidence of the complication of COPD in asthmatic patients 70 years or older is high; chronic bronchitis was observed in 16.3% and emphysema in 19.0%.[3] In addition, it was reported that unlike in the case of young asthmatic patients, smoking was an independent risk factor for the development of steroid-dependent asthma in the elderly.[8] Accordingly, education of elderly patients regarding the dangers of smoking must be thoroughly carried out not only to reverse the decrease in FEV1 so that it will be equivalent to that of nonsmokers by abstaining from smoking,[6] but also to eliminate factors that contributed to the exacerbation of asthma.

The next important point is that ventilatory response to carbon dioxide is not likely to be influenced by aging, whereas ventilatory response to hypoxia deteriorates with aging.[9]

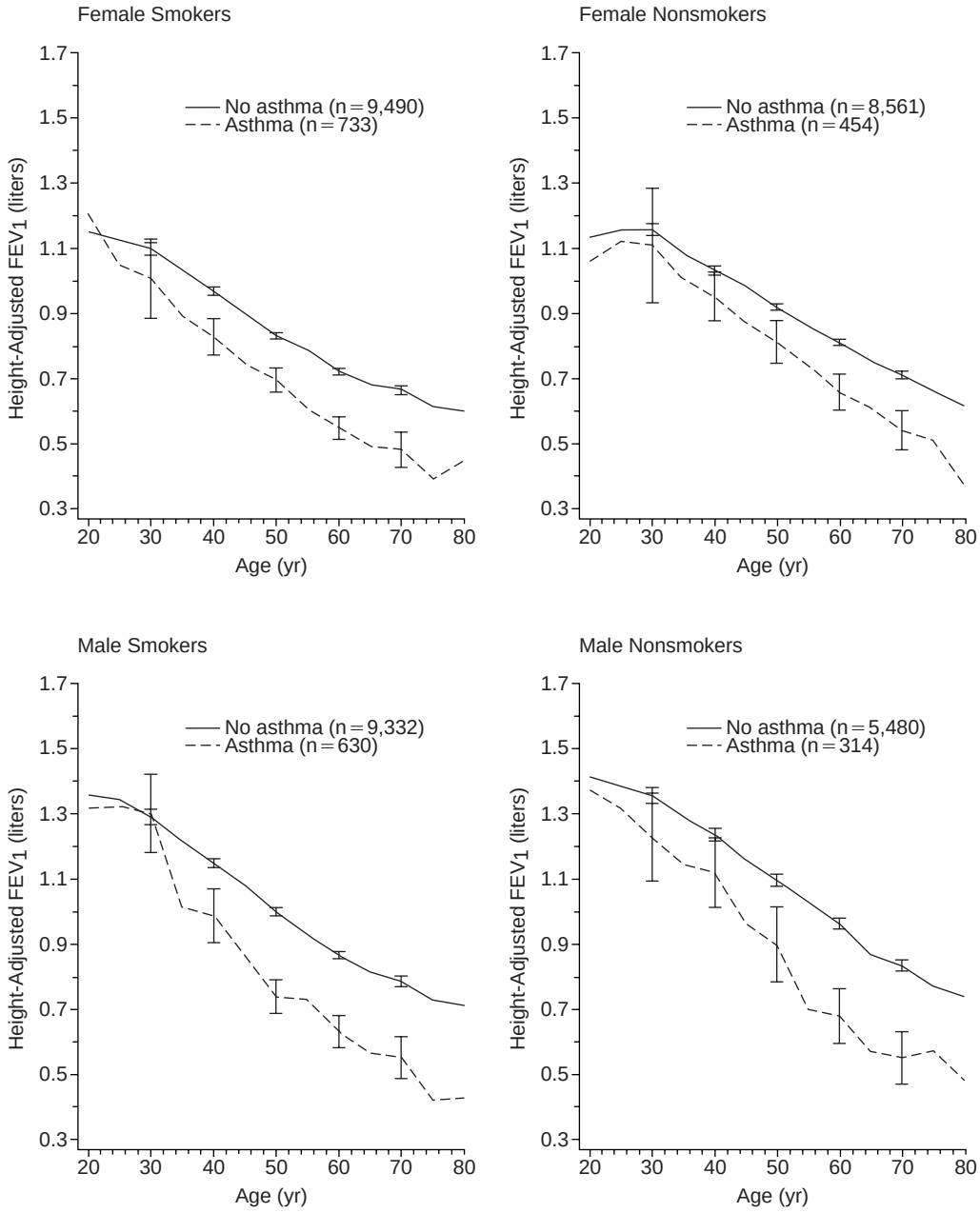


Fig. 2 Change with age in the height-adjusted forced expiratory volume in one second (FEV1) according to sex, smoking status, and the presence or absence of asthma (quoted from Ref. 6))

In particular, patients with senile depression and dementia lack subjective symptoms such as dyspnea, thereby requiring more attention. Ischemic heart disease and congestive heart failure due to arrhythmia, namely cardiac asthma, must always be considered in treating elderly asthmatic patients. In cases of complication of pulmonary tuberculosis sequelae, increased chest wall resistance due to thoracic deformity should be considered.

With deterioration of immunoprotective ability in elderly patients, chronic respiratory infec-

Table 1 Allergy Characteristics of Elderly Patients with Bronchial Asthma[14–18)]

1) Ability to produce IgE decreases with aging.[14,15)]
2) The total IgE level in the serum and RAST positivity rate decrease in the elderly.[16,17)]
3) With respect to age, the positivity rate for immediate intradermal skin reaction to major allergens, such as house dust, mites and Japanese cedar pollen, decreases with aging reaching 30% or less among patients in their 60's and 70's. On the other hand, the positivity rate for *Candida* ranges from 40% to 50%, and *Candida* is the allergen that elicits positive reaction at a highest rate among patients in their 50's or older (Fig. 3).[18)]
4) Positivity rate in the bronchial provocation test of patients with positive intradermal reaction to dust is 70% to 80% for age groups. Bronchial hypersensitivity and intradermal skin reaction to histamine are not influenced by aging.[18)]

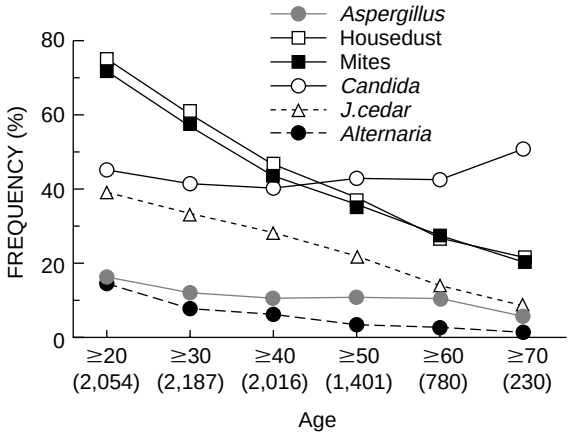


Fig. 3 Immediate intradermal skin reaction to major allergens at various ages[18)] (quoted from Ref. 18))
Horizontal axis indicates year.
Number in parentheses indicates the number of patients in a specific age group.

tion frequently makes treatment more difficult. Not only the efficacy but also the cost-benefit ratio of influenza vaccination of the elderly 65 years or older has been determined,[10)] through which safety of the vaccine has been empirically established. On the other hand, the efficacy of inhaled zanamivir, a potent and selective inhibitor of influenza A and B virus neuraminidase, for severe or intractable bronchial asthma or COPDs has not been confirmed. There was concern for the safety of patients using inhaled zanamivir because of adverse reactions such as bronchospasm. However, according to recent findings, inhaled zanamivir did not increase the incidence of harmful events.[11)] In addition, based on the report that inhaled zanamivir could prevent the development of influenza,[12)] it may be applicable as a preventative measure for patients at high risk of developing an infectious disease of the respiratory organ and for whom inoculation with the influenza vaccine is contraindicated, or as a preventative measure against deterioration of patients' conditions after exposure to influenza.

2. Characteristics of allergy associated with aging

The longer the duration of a disease, the more severe and irreversible the airway obstruction becomes, thus predisposing an individual to greater hypersensitivity; due to airway remodeling phenomena. Those are the reason that asthma in elderly patients tends to be chronic and intractable.[13)] Table 1 and Fig. 3 show characteristics of elderly patients with respect to IgE production in response to allergens, indicating that the incidence of atopy-type asthma decreases in elderly patients, whereas positive reaction to allergens is almost the same as that in young asthmatic patients.[14–18)] A study of the total IgE level in patients 60 years or older in our hospital revealed that the percentage of patients with high levels of total IgE, that is, 400 IU/m*l* or more, was 35.2%, which is almost the same as that in young patients with asthma (Fig. 4). As stated above, since COPD is often observed as a complication in elderly patients, it is often difficult to accurately determine the presence or absence of bronchial asthma. To confirm this, the following examinations should be performed: determination of whether or not bronchial hypersensitivity, airway reversibility by inhaled β-stimulants and the eosinophil ratio in sputum increased; these tests are clinically easily performed and effective.

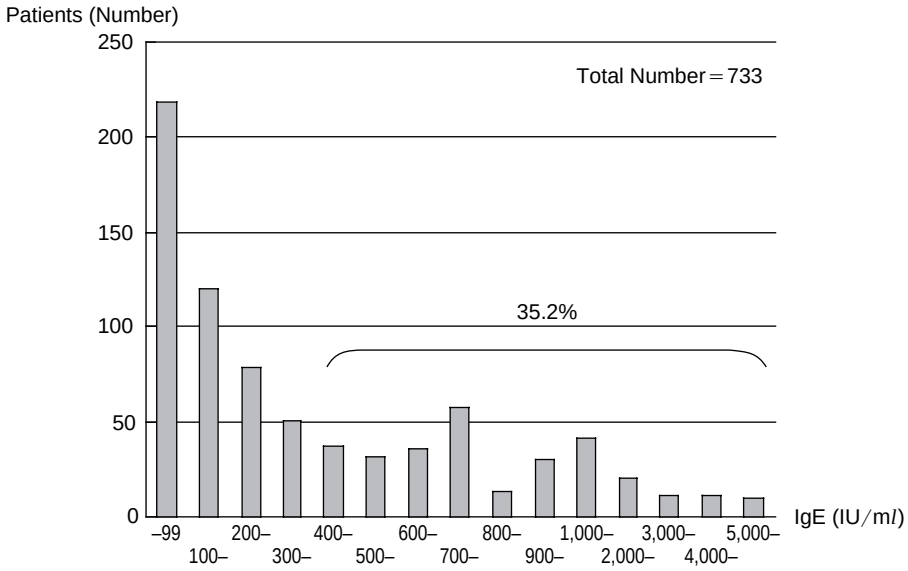


Fig. 4 Total IgE level (IU/m*l*) of elderly bronchial asthmatic patients (65 years or older) (National Sagamihara Hospital~1999)
Total IgE level, 400 IU/m*l* or more: 258/733 = 0.352.

Treatment and Management

Treatment of elderly bronchial asthma must not deviate from the principles of treatment stated in the guideline.[5] However, in general, with deterioration of physiological functions due to aging, drug concentrations in the plasma tend to increase and the degree of response to drugs increases, thereby adverse reactions are likely to develop. In addition, due to complication of multiple diseases, adverse reactions due to multiple-drug interactions sometimes develop. The actual state of drug treatment including compliance, which needs to be studied, is discussed below.

1. Steroid inhalation

In the guideline, inhalation of steroids is the main strategy for long-term control of asthma. To promote inhalation of beclomethasone dipropionate (BDP) using a metered dose inhaler (MDI), use of a spacer and repetitive inhalation need to be strongly recommended to the elderly patients. The frequency of inhaling fluticasone (Diskheller is used), using a dry powder inhaler (DPI), is twice daily. Moreover, DPI is easier for the patients to use, therefore, from the aspect of compliance, the use of fluticasone is advantageous. It is also frequently used recently due to its effect of inhibiting airway inflammation. On the other hand, to prevent regional adverse reactions such as hoarseness and oral candidiasis, patients need to be repeatedly educated; for example, they should be encouraged to gargle after inhalation. A recent report indicates that significant differences were observed in the improvement of pulmonary functions and bronchial hypersensitivity depending on the stage of asthma at which inhaled steroids were introduced. Based on this finding, early intervention with inhaled corticosteroid to prevent the development of airway remodeling is being tested.[19] Moreover, in elderly patients, osteoporosis and cataracts, which are complications occurring with high incidence, cannot be ignored. To determine the long-term efficacy of high doses of inhaled steroids, large-scale clinical trials were carried out in subjects that included the elderly. These trials provide evidence of a negative relationship

Table 2 Drugs that Influence Plasma Theophylline Concentration

1. Drugs that increase plasma theophylline concentration:	Cimetidine, mexiletine hydrochloride, amiodarone hydrochloride, enoxacin, pipemidic acid trihydrate, ciprofloxacin hydrochloride, norfloxacin, tosufloxacin tosilate, erythromycin, clarithromycin, roxithromycin, tiabendazole, ticlopidine hydrochloride, verapamil hydrochloride, diltiazem hydrochloride, fluvoxamine maleate, fluconazole, aciclovir, interferon, ipriflavone, cyclosporin, allopurinol and halothane
2. Drugs that decrease plasma theophylline concentration:	Riphampicin, phenobarbital, lansoprazole, ritonavir, phenytoin and carbamazepine

between total cumulative dose of inhaled corticosteroid and bone-mineral density; however, the risk of developing cataracts did not increase following the use of inhaled steroids.[20] According to latest findings, inhaled corticosteroids lead to a dose-related loss of hip bone-mineral density in premenopausal women.[21] Further studies are required in order to accumulate more relevant data.

2. β_2 stimulants

β_2 stimulants must be carefully administered because these are contraindicated for patients with hyperthyroidism, hypertension, chronic cardiac disease, and diabetes mellitus; further consideration is required in the case of elderly patients who develop complications at a high incidence. The American Thoracic Society (ATS)[22] encourages careful attention be paid to the occurrence of adverse reactions in elderly asthmatic patients, such as tremor, restlessness, palpitation, and tachycardia. On the other hand, it is reported that the affinity between catecholamine and β-adrenoreceptors decreases with aging,[23] whereas another report indicates a decrease in drug response that is proportional to the duration of the disease rather than age.[24] Recently, since the efficacy of increasing the dose of inhaled steroids has been limited and frequent use of short-acting inhaled β_2-stimulants causes the wearing-off phenomenon, regular use of inhaled steroids in combination with long-acting β_2 stimulants (salmeterol and formoterol) is recommended to control moderate and persistent chronic asthma in Europe and United States. It is reported that concomitant use of formoterol is effective to improve and avert acute deterioration of pulmonary functions for patients with intractable asthma and whose conditions were insufficiently controlled by merely inhaling steroids,[25] leading to an improvement of QOL.[26] Similar efficacy of concomitant use is expected in elderly patients.

3. Theophylline

Theophylline is widely used in Japan, but it is believed to be inferior to long-acting β_2 stimulants with respect to capability of mitigating nocturnal dyspnea and improving pulmonary functions.[27] Since theophylline has many interactions with other drugs and its effective and toxic concentrations are close, its concentration in plasma needs to be monitored. Table 2 shows a list of drugs which influence plasma theophylline concentration.[28] In addition, clearance of theophylline decreases in cases of severe liver damage and congestive heart failure. On the other hand, smoking decreases plasma theophylline concentration. These are clinically significant points.

4. Anticholinergic drugs

Anticholinergic drugs have a great bronchodilating property for central airways but less bronchodilating ability for peripheral airways, and the onset of its efficacy is slowly developed compared to inhaled β_2-stimulants. Rather, anticholinergics are effective for asthmatic patients complicated with mild to moderate pulmonary emphysema. The duration of effectivity is long

and its efficacy is not reduced by long-term use.[29] The amount of sputum and its viscosity are negligibly influenced by anticholinergic drugs; however, attention must be paid to the possible adverse reaction of ischuria in male patients with benign prostatic hyperplasia, which rarely occurs. The synergistic effect between a β_2 stimulant and an inhaled anticholinergic drug has been reported, based on which a MDI containing both types of drugs, Combivent, is used in United States.

Conclusions

The disease state and treatment of elderly bronchial asthma were outlined in this paper. The purpose of treatment in the clinical field is to prevent death from asthma and improve QOL. The necessity of administering appropriate treatment in the early stages is important to build an established partnership between physicians and patients, and is the same for both the young and elderly asthmatic patients.

REFERENCES

1) Kitch, B.T., Levy, B.D. and Fanta, C.H.: Late-onset asthma: epidermalogy, diagnosis and treatment. *Drugs Aging* 2000; 17: 385.
2) Akiyama, K.: Study of the characteristics of asthma based on epidemiological study of adult asthma. *Journal of Japan Thoracic Disease* 1994; 32: 200. (in Japanese)
3) Tabe, K. and Akiyama, K.: Incidence and disease type of bronchial asthma with aging. *Progress of Medical Science* 1991; 159: 539. (in Japanese)
4) Nakazawa, T. *et al.*: Epidemiology and clinical study of death due to bronchial asthma. *Clinical Study on Allergy* 1990; 10: 792. (in Japanese)
5) Research group of Health and Welfare Ministry on immunity and allergy: Supervised by Makino, S., Kosho, K. and Miyamoto, A.: Guideline on the prevention and management of asthma. *Kyowa-kikaku Report.* 1998, p. 32. (in Japanese)
6) Lange, P., Parner, J., Vestbo, J. *et al.*: A 15-year follow up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339: 1194.
7) Flecher, C. *et al.*: The natural history of chronic airflow obstruction. *BMJ* 1977; 1: 1645.
8) Ishioka, S., Terada, M., Haruta, Y. *et al.*: Multiple logistic regression analysis of risk factor for the development of steroid-dependent asthma in elderly: a comparison with younger asthmatic patients. *Respiration* 2001; 68: 35.
9) Nishimura, M. *et al.*: Longitudinal analysis of respiratory chemosensitivity in normal subjects. *Am Rev Respir Dis* 1991; 143: 1278.
10) Gross, P.A., Hermonogenes, A.W., Sacks, H.S. *et al.*: The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of literature. *Ann Intern Med* 1995; 123: 518.
11) Stepheson, J.: Study allays therapy concern, finds new flu drug safe for patients with asthma, COPD. *JAMA* 2000; 284: 3115.
12) Hyden, F.G., Gubareva, L.V., Monto, A.S. *et al.*: Inhaled zanamivir for prevention of influenza in families. Zanamivir Family Study Group. *N Engl J Med* 2000; 343: 1282.
13) Cassino, C., Berger, K.I., Goldring, R.M. *et al.*: Duration of asthma and physiologic outcomes in elderly nonsmokers. *Am J Respir Crit Care Med* 2000; 162: 1432.
14) Delespesse, G., De Maubeuge, J., Kennes, B. *et al.*: IgE-mediated hypersensitivity in aging. *Clinical Allergy* 1977; 7: 155.
15) Story, P.J., Roitman-Jonson, B., Walsh, G. *et al.*: Aging and immunoglobulin E level, immediate skin tests, and RAST. *J Allergy Clin Immunol* 1981; 68: 421.
16) Maeda, Y., Yasueda, H., Yui, Y. and Shinta, T.: IgE concentration in patients with asthma caused by indoor dust and mite, and influence of aging on tissue reactivity to histamine and acetylcholine from peripheral white cells. *Allergy* 1987; 36: 1037. (in Japanese)
17) Nogami, Y., Kishikawa, R. and Odajima, H.: Characteristics of bronchial asthma in the elderly. *Allergy* 1993; 42: 514. (in Japanese)
18) Akiyama, K., Maeda, Y., Tabe, K., Kaneko, T., Hayakawa, T., Hasegawa, M. *et al.*: Characteristics of bronchial asthma in the elderly from the viewpoint of their allergic reaction. *Allergy* 1994; 43: 9. (in Japanese)
19) Oliveri, D., Chetta, A., Del Donno, M. *et al.*: Effect of short-term treatment with low-dose fluticasone propionate on airway inflamma-

tion and remodeling in mild asthma. *Am J Respir Crit Care Med* 1997; 155: 1864.
20) Wong, C.A., Walsh, L.J., Smith, C.J., Wisniewski, A.F., Lewis, S.A. *et al.*: Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 2000; 355: 1399.
21) Israel, E., Tanyra, R., Banerjee. M.P.H. *et al.*: Effect of Inhaled glucocorticosteroids on bone density in premenopausal women. *N Engl J Med* 2001; 345: 941.
22) American Thoracic Society Official Statement: Standards of the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152: s77.
23) Connolly, M.J., Crowley, J.J., Nielson, C.P. *et al.*: Peripheral mononuclear β adrenoceptor and non-specific bronchial responsiveness to methacholine in young and elderly normal subjects in asthmatic patients. *Thorax* 1994; 49: 336.
24) Bellia, V. *et al.*: Effect of age upon airway obstruction and reversibility in adult patients with asthma. *Chest* 1998; 114: 1336.
25) Pawels, R.A., Loffdahl, C.G., Postma, D.S. *et al.*: Effect of inhaled formoterol and budesonide on excerbation of asthma. *N Engl J Med* 1997; 337: 1405.
26) Kemp, J.P., Cook, D.A., Incaudo, G.A. *et al.*: Salmeterol improves quality of life in patients with asthma requiring inhaled corticosteroids. *J Allergy Clin Immunol* 1998; 101: 188.
27) Wilson, A.J., Gibson, P.G. and Coughlan, J.: Long acting beta-agonists versus theophylline for maintenance treatment of asthma. *The Cochrane Database of Systematic Reviews* (ISBN 1 901868 05 2) 2001; 1: 00563.
28) Itabashi, S. and Sasaki, H.: Treatment with theophylline. *Allergy and Immunity* 2000; 7: 66. (in Japanese)
29) Bel, E.H., Zwinderman, A.H., Timmers, M.C. *et al.*: The protective effect of β_2-agonist excessive airway narrowing in response to bronchoconstruction stimuli in asthma and chronic obstructive lung disease. *Thorax* 1991; 46: 9.

Prophylaxis and Treatment for Influenza among the Elderly

JMAJ 45(6): 245–250, 2002

Hajime GOTO

Professor, The First Department of Internal Medicine,
Kyorin University School of Medicine

Abstract: The treatment for influenza has undergone drastic changes in the last two years. The important changes are summarized below: 1) Introduction of accurate, simple and quick diagnostic techniques, 2) Introduction of novel anti-influenza virus drugs, 3) Reevaluation of influenza vaccination as a prophylaxis. Outbreaks of influenza are a matter of particular concern for the elderly because the elderly form a high-risk group for influenza. According to the data obtained in the epidemic season between 1998 and 1999, over 90% of influenza-related deaths in Japan occurred among persons aged 65 and older. The present review summarizes prophylaxis and treatment for influenza in the elderly focusing on the following: the efficacy of the influenza vaccine, the efficacy of single dose influenza vaccines, and the properties of anti-influenza virus drugs including amantadine, oseltamivir, and zanamivir, and antimicrobial treatment for influenza.

Key words: Amantadine; Oseltamivir; Zanamivir; Influenza vaccine

Introduction

The news of the emergence of a new influenza virus (influenza A: H5N1) in Hong Kong swept through the world in May 1997.[1)] This event has completely changed the understanding of doctors for influenza.

Since this world-shaking event, influenza is no longer regarded as a type of common cold syndrome and the necessity to implement countermeasures on a national scale has been recognized.

Consequently, the clinical approaches applied to the diagnosis, treatment, and prevention of influenza have undergone drastic changes in the last two years.

The important changes are summarized as follows:

1) Introduction of accurate, simple and quick diagnostic techniques
2) Introduction of novel anti-influenza virus drugs
3) Reevaluation of influenza vaccination as a prophylaxis

A clear line had not been drawn between influenza and the common cold syndrome pro-

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 7, 2001, pages 1008–1012).

duced mainly by rhinovirus. However, in those years, the conception has changed. Influenza has come to be considered as an independent disease requiring immediate virological diagnosis and specific antiviral treatment, and this infection can be prevented by vaccination.

Why Has the Occurrence of Influenza among the Elderly Become an Issue?

The occurrence of influenza among the elderly has become an issue because they form a high-risk group for influenza.

In Japan, epidemiological surveys of influenza are generally confined to epidemics among school-age children and less information is available on epidemics among the elderly. Since the influenza pandemic of 1998–1999, a project of fixed point observation has been promoted and a system to investigate the actual conditions of influenza among the elderly has been established. However, so far, there is insufficient information available on influenza activity among this population and further effort is necessary to obtain more data.

In the US, which has a population approximately double that of Japan, influenza deaths exceed the predicted number by twenty to forty thousand during the epidemic season, and accordingly, the number of influenza-related deaths in Japan can be estimated at ten to twenty thousand. Special attention should be directed to the fact that most of these deaths occur among the elderly. Taniguchi *et al.*[2] assessed the data obtained between 1998 and 1999 and reported that over 90% of influenza-related deaths occurred among persons aged 65 and older in Japan. Thus, this population can be categorized as a high-risk group in Japan.

Countermeasures for Influenza Epidemics among the Elderly

1. Vaccination

(1) **Influenza vaccination in Japan**

In Japan, a system of group influenza vaccination for school-age children is adopted and this vaccination had been in practice for many years. Up to 1987, the number of vials of vaccines used annually per 1,000 population exceeded 200, indicating that the quantity of influenza vaccine used in Japan was consistently more than double that used in the US.[3]

In subsequent years, however, doubts had been expressed over the efficacy of the influenza vaccine and since the revision of the Preventive Vaccination Law in 1994, the vaccination has been administered on a voluntary basis. At the time of this revision, no recommendation was made to encourage elderly individuals to receive influenza vaccination, which resulted in a significant reduction of influenza vaccination rates.

On the other hand, the efficacy of the influenza vaccine has been considered as established in foreign countries and many medical care providers have endeavored to introduce a practical method to improve influenza vaccination rates. So, nowadays, significant differences exist in the number of vials of vaccines used annually per 1,000 population in Japan and foreign countries.[4] The statistics obtained are as follows: US (239), Canada (150), France (119), UK (102), and Japan (8).

(2) **Is the influenza vaccine effective?**

In 1973, Sugiura *et al.*[5] conducted a comparative study using tetanus toxoid as a control to evaluate the efficacy of influenza vaccine at the Institute of Public Health, Japan. According to their results, the vaccine provided 80% protection against influenza virus A and 43% protection against influenza virus B. In 1997, Sugaya *et al.*[6] conducted a controlled study on infants and reported that the vaccine was effective in preventing influenza virus A in 67.5% and in preventing influenza virus B in 43.7%.

These figures do not directly indicate the effective rates of the influenza vaccine, and do not therefore mean that 67.5% of those who underwent the vaccination were free from infection. They indicate that, of those who did not receive the vaccination who suffered the infec-

tion, 67.5% could have been free from the infection if they had undergone the vaccination.

The effective rate of the vaccine can be calculated by the following formula:

> Effective rate of vaccine (%) = {1 − (morbidity among the vaccinated/morbidity among the unvaccinated)} × 100

The results obtained in the above controlled studies are considered to demonstrate the effectiveness of the influenza vaccine among infants and normal adults.

Among cases of influenza in the elderly, the following points require consideration:

a. Does the vaccine provide a similar rate of protection among the elderly as among younger adults?
b. If the vaccine fails to prevent the occurrence of infection, does it contribute to the amelioration of influenza symptoms?
c. Does the vaccine prevent the development of influenza complications, especially pneumonia?
d. Does vaccination contribute to a reduction in influenza-related deaths?

The problem lies in the fact that insufficient data has been accumulated giving answers to these questions, and more data will be needed before the clinical implications of influenza vaccination for the elderly can be clarified.

(3) **Is one dose of the influenza vaccine sufficiently effective in preventing the infection?**

As mentioned above, the influenza vaccination was first introduced as group immunization for school-age children in Japan and two doses have routinely been indicated for all individuals including school-age children and adults. In foreign countries including the US, one dose has routinely been indicated and the efficacy of this immunization technique has been evaluated.

In this situation, doctors have evaluated the effectiveness of single dose vaccinations in Japan. Horie *et al.* measured the elevation of serum antibody levels after one and two doses for comparative study. They observed no difference in the elevation of serum antibody levels between the one dose group and two dose group. They divided the subjects into two groups according to their ages and recognized no significant difference in the elevation of serum antibody levels between those aged 40 and above and those under 40.

The Council for Public Health, the Ministry of Health and Welfare, Japan, considered these scientific data and finally concluded, on October 18, 2000, that a single dose of the influenza vaccine was to be indicated for elderly individuals aged 65 and over. Accordingly, one dose will be routinely indicated, at least among the elderly, in Japan.

2. Amantadine

The target-site of amantadine is the M2 protein which has the functions of an ion channel and virus uncoating. Amantadine shows antiviral effects by affecting this ion channel and inhibiting virus uncoating. This drug has been used as an anti-Parkinson agent in Japan, although it is widely used as an effective anti-influenza virus drug in foreign countries, including the US. Amantadine is ineffective for influenza B because the M2 protein exists only in influenza virus A.

Influenza viruses are regarded as a group of viruses with certain mutations (quasispecies), and amantadine resistant viruses are detected with a frequency of $1/10^4$. In the course of antiviral treatment, resistant strains are selected and increases in accordance with the duration of treatment. Therefore, the recommended duration of amantadine treatment is less than five days.

When amantadine is given orally in a dose of 50 mg, its peak blood level is 0.12 μg/m*l*, and it has a comparatively long half-life of 12.3 hours. The usual dosage is 50 mg per dose, twice daily. Influenza viruses proliferate rapidly and the viral amount reaches its peak within two days of infection. Accordingly, the beneficial effects of amantadine can not be obtained if 24–48 hours have passed before the administration. Thus, the fundamental problem of treating influenza patients with amantadine is the timing of

its administration. A person may catch a cold and decide to rest at home for a few days; if the symptoms persist it may lead him/her to consult his/her physician. Amantadine therapy is not indicated for this type of patient, as it is too late for such patients to start this antiviral treatment. It is necessary for physicians to educate the public so that they can have correct knowledge about antiviral treatment for influenza.

Amantadine is approved both as a drug to treat influenza and as a drug to prevent influenza. For preventive purposes, amantadine can be administered by the following two methods.

1) Consecutive administration following influenza vaccination for two weeks till the elevation of the antibody titer
2) Prolonged consecutive administration to persons who are unable to undergo vaccination because of, for example, anaphylactic hypersensitivity to (chicken) eggs

Adverse reactions of amantadine include digestive symptoms such as anorexia and nausea, and psychiatric symptoms such as insomnia, easy fatigability and depression.

3. Neuraminidase inhibitors

(1) Oseltamivir

Oseltamivir displays its antiviral activity by inhibiting the neuraminidase of the influenza virus. It is a synthesized antiviral agent, which has been designed in a completely novel manner.

After proliferation in the cells, influenza viruses are released from the infected cells. In the process of acceleration of the infection, sialic acid is to be incised by neuraminidase and influenza viruses are to be released from infected cells. Oseltamivir, which is similar in structure to sialic acid, blocks the activity of neuraminidase and finally inhibits the release of viruses from the infected cells. Because neuraminidase exists both in influenza virus A and in influenza virus B, oseltamivir is effective for influenza caused by these two viruses.

During the period between 1997 and 1998, a clinical trial was conducted in the US to evaluate the efficacy of oseltamivir as a treatment for influenza.[8] Regarding the morbid period as one of the main endpoints, oseltamivir showed a significant reduction in morbid period when administered orally in a dose of 75 mg twice daily (placebo administration group 124.2 hours vs. oseltamivir administration group 93.9 hours).

In 1998, the use of oseltamivir as a prophylactic drug was evaluated in the US.[9] When oseltamivir was orally administered in a dose of 75 mg once a day, the incidence of influenza was 25/519 in the placebo administration group and 6/520 in the oseltamivir administration group. Thus, oseltamivir provided protection against influenza at the significantly high rate of 76%.

Oseltamivir is effective both in treating influenza and in preventing the disease but its beneficial effects are considered to be shown more significantly in patients with influenza virus A than in those with influenza virus B.

The frequency of oseltamivir resistant strains was lower than that of amantadine resistant strains. The infectivity of oseltamivir resistant strains is definitely lower than that of original strains because the resistant strains possess weaker activity of neuraminidase.

The advantages of oseltamivir are summarized as follows:

a. Effective both for influenza virus A and for influenza virus B
b. Lower frequency of resistant strains
c. Reduction of infectivity of resistant strains

Like amantadine, oseltamivir shows minimum therapeutic effects unless the administration is started within 24 to 48 hours. This disadvantage remains as the most important issue to be resolved in the future.

Oseltamivir has been approved in fourteen countries including the US, Canada and Switzerland. In Japan, it was approved in February 2001.

(2) Zanamivir

Like oseltamivir, zanamivir is a neuraminidase inhibitor.[10] The antiviral activity of zanamivir *in vitro* is as strong as that of oseltamivir. Zanamivir is inhaled through the respiratory tract using a special inhaler. This inhaler is the

same as that used for fluticasone treatment.

It was approved in February 2001.

As in the case of amantadine, these neuraminidase inhibitors are considered to be effective for the influenza viruses which possess new assortment of hemagglutinines and neuraminidases, they therefore play important roles in treating and preventing such new influenza viruses.

4. Antimicrobial treatment

The complication of bacterial pneumonia and resulting death are serious problems among elderly patients with influenza. The impairment of the epithelium of the respiratory tract due to influenza facilitates the development of pneumonia. The major causative bacteria include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*.

Consideration of the risks of complicated bacterial pneumonia is indispensable in treating elderly patients with influenza. Although antimicrobial treatment is not necessarily indicated in younger adult patients, the use of antimicrobials agents is recommended in older adult patients.

The following antimicrobials are available:

(1) β-lactam: Since β-lactamase producing bacteria such as *Haemophilus influenzae* and *Staphylococcus aureus* are frequently detected, the β-lactamase inhibitor containing penicillins or cefems are to be selected.

(2) Macrolides: The existence of macrolide resistant strains of *Streptococcus pneumoniae* and *Staphylococcus aureus* and insufficient antimicrobial effects on *Haemophilus influenzae* are pointed out as disadvantages, therefore available macrolides are limited.

(3) New quinolones: Since the antimicrobial effects on *Streptococcus pneumoniae* present a problem, so-called respiratory quinolones including sparfloxacin, which are effective for *Streptococcus pneumoniae*, are to be selected.

Conclusion

Remarkable improvements have been made in the clinical treatment for influenza during the last two years and this marked progress has caused clinicians to change their recognition of this disease.

An influenza epidemic immediately causes large numbers of patients to visit clinics within a short period of time, and respiratory internists can not manage all patients when an influenza outbreak occurs like a storm. In this situation, all physicians regardless of their specialist field, are expected to have an up-to-date knowledge of the treatments available for influenza and of the modalities involved.

REFERENCES

1) Claas, E.C., Osterhaus, A.D., van Beek, R. *et al.*: Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. *Lancet* 1998; 351: 472–477.
2) Taniguchi, S. and Shindo, N.: Excessive deaths following epidemics of influenza. *Information on the Detection of Pathogenic Microorganisms* 1999; 20: 293–294. (in Japanese)
3) Hirota, Y., Fedson, D.S. and Kaji, M.: Japan lagging in influenza jabs. *Nature* 1996; 380: 18.
4) Hirota, Y. and Kaji, M.: Issues related to influenza vaccine. *Sogorinsho* 1997; 46: 2665–2671. (in Japanese)
5) Sugiura, A., Yanagawa, H., Enomoto, C. *et al.*: A field trial for evaluation of the prophylactic effect of influenza vaccine containing inactivated A2/Hong Kong and B influenza viruses, *J Infect Dis* 1970; 122: 472–478.
6) Sugaya, N., Nerome, K., Ishida, M. *et al.*: Efficacy of inactivated vaccine in preventing antigenically drifted influenza type A and well-matched type B. *JAMA* 1994; 272: 1122–1126.
7) Horie, M., Sugaya, N., Mitamura, K. *et al.*: Effectiveness of one dose of inactivated influenza vaccine in adults. *J Jap Assoc Infect Dis* 1998; 72: 482–486. (in Japanese)
8) Treanor, J.J., Hayden, F.G., Vrooman, P.S. *et al.*: Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza. A randomised controlled trial. *JAMA*

2000; 283: 1016–1024.
9) Hayden, F.G., Atmar, R.L., Schilling, M. *et al.*: Use of the oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med* 1999; 341: 1336–1343.
10) The MIST Study Group: Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. *Lancet* 1998; 352: 1877–1881.

Treatment of Community-Acquired Pneumonia in the Elderly

JMAJ 45(6): 251–257, 2002

Toshiharu MATSUSHIMA

Professor, Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School

Abstract: Pathogenic organisms responsible for pneumonia in the elderly and the younger population are not drastically different, though subtle differences exist such as a higher frequency of pneumococci and a lower frequency of mycoplasma among elder patients. Similarly, while the elderly tend to show mild symptoms and laboratory data, no major differences are observed between the two groups. Although same antimicrobial drugs can be applied to both groups, the elderly are more prone to exhibit adverse drug reactions due to differences in pharmacokinetics. Since underlying renal hypofunction is observed among the elderly, in particular, limited dosages or drug administration at prolonged intervals are required. Incidence of and mortality due to pneumonia increase with accelerating speed as individuals age. As the saying goes, "pneumonia may well be called the friend of the aged." From now forward, different approaches to management may be needed for the elderly by studying differences in pneumonia between the elderly and the younger population, focusing on symptoms, physical and laboratory findings, diagnostic methods, treatment, and prevention measures. At a minimum, pneumonia among the elderly needs to be further studied.

Key words: The elderly; Pneumonia; Antibiotic chemotherapy; Guidelines

Introduction

Pneumonia is a major disease with high incidence and mortality rates. Since it frequently occurs among the elderly, Osler said that "pneumonia may well be called the friend of the aged."[1)]

This paper demonstrates how age factors are managed in guidelines, what differences in causative bacteria, symptoms, findings, and treatment exist between the elderly and non-elderly populations, and what methods should be taken in the treatment of pneumonia in the elderly.

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 7, 2001, pages 1013–1017).

Table 1 Physician Treatment and Mortality Rates for Pneumonia Patients by Age Group

Age groups	Total	15～19	20～24	25～34	35～44	45～54	55～64	65～69	70～74	75～79	80～84	85 and above
Physician treatment rate (per 100,000)	19	5	4	8	7	7	17	30	56	85	126	206
Mortality rate (per 100,000)	64.1	0.6	0.8	1.1	2.5	7.6	29.1	59.9	134.8	335.3	802.9	2,209.4

Source: Reference 10)

How Age Factors Are Considered in Guidelines for the Management of Pneumonia from Various Countries

Guidelines for the management of pneumonia were introduced in many devolved countries including the U.S. and European countries in the 1990s. The most well-known document in Japan is the Guidelines for Community-Acquired Pneumonia published by the American Thoracic Society (ATS) in 1993.[2)]

The ATS guidelines are very concise and classify pneumonia patients into four different groups on the basis of age, comorbid illness, and disease condition. Group 1 includes outpatients 60 years of age or younger and without comorbid illnesses, and Group 2 includes outpatients over 60 or with comorbid illnesses. The age factor is taken into account in these categories. Also, as one of the risk factors that increases mortality, complicates the clinical course, and provides a criterion to recommend hospitalization, the age of 65 and above is used. The guidelines also mention that clinical features of pneumonia among the elderly may be atypical or silent, the clinical course may be prolonged, and the mortality rate may be high.

Approximately seven years have already passed since the first publication of the guidelines, and revisions are being considered. One of the changes under review is the use of the age factor (60 years of age) as a criterion for susceptibility to acquiring penicillin resistant pneumococci, rather than as a reference point for the stratification of pneumonia patients.[3)]

The Guidelines published by the Infectious Disease Society of America (IDSA) in 1998[4)] are more complicated but more scientific than the ATS guidelines. In the IDSA guidelines, points are assigned to patient's prognosis and need for hospitalization on the basis of age, sex, comorbid conditions, physical findings, and laboratory findings. In this system, the number of points derived from subtracting 50 from the patient's age is added (ten points are deducted in the case of women).

The Guidelines issued in Germany in 1998[5)] characterize Group 1 as patients 65 years of age or younger with mild pneumonia and no risk factors. The consensus guidelines (1998) issued by the Respiratory Society and the Chemotherapy Society in Spain[6)] define the elderly simply as a group of people who are more susceptible to bacterial pneumonia and drug-resistant pneumococcal infection.

According to the guidelines published by the Japanese Respiratory Society in March 2000,[7)] in terms of the classification of severity of pneumonia, those 65 and above who have difficulties in visiting a hospital as an outpatient are placed in one class higher category.

In these guidelines mentioned above, pneumonia among the elderly is not considered as a special disease.

Incidence of Pneumonia Among the Elderly

Although the annual incidence rate of pneu-

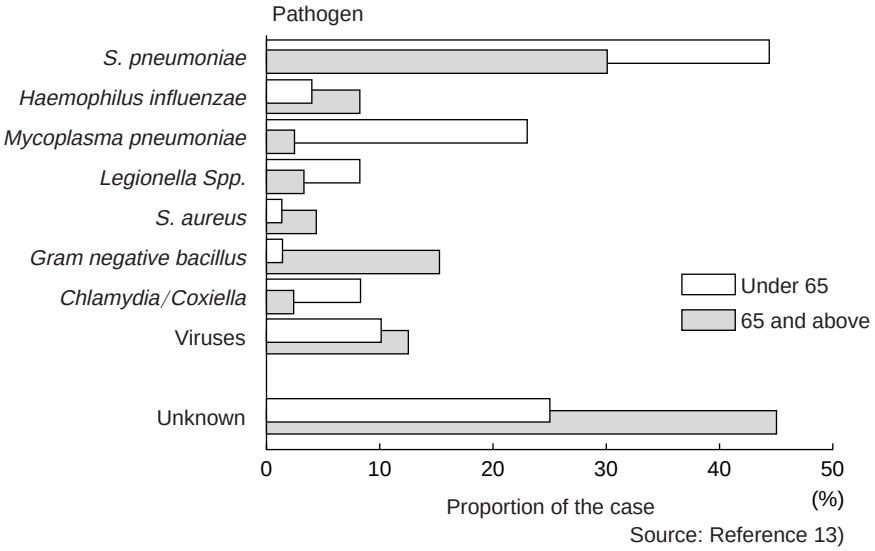


Fig. 1 Microbial causes of community-acquired pneumonia. A comparison of those younger than 65 years of age with those older than 65 years

monia is 12 per 1,000,[8] the figure is reported to go up to 34 among patients 65 and above.[9] In terms of patient statistics in Japan, as indicated by the figures in Table 1 which were excerpted from "Kokumin Eisei no doukou (Trends in National Public Health in Japan)," both the physician treatment rate and the mortality rate show an abrupt and accelerating increase among pneumonia patients over 65. It can be stated that pneumonia is a disease of the elderly rather than a disease frequently observed among them.

Pathogenic Microbes for Pneumonia Among the Elderly

Pathogenic microbes for pneumonia may differ between the elderly and the younger population. Mycoplasma pneumonia is found overwhelmingly among the younger population, but rarely seen among the elderly. Bacterial pneumonia, on the other hand, is a kind of pneumonia frequently observed among the elderly. Chlamydia pneumonia has been reported to be much more common among the elderly than the younger population.[11] However, chlamydia pneumonia has also been reported to be frequently seen in the younger population, and the disease, including mixed infection with bacterial pneumonia, needs to be further examined.

Figure 1 shows comparisons of pathogenic microbes for pneumonia between the elderly and the younger population.[13] Overall, no major differences seem to exist regarding pathogenic microbes, and there are at least no critical differences.

Symptoms and Findings of Pneumonia Among the Elderly

Since the contrast between the elderly and the younger population can be ascribed to the difference in abilities of the infected host to fend off infections, differences in symptoms and findings are presumed to exist, which draws the most attention.

Table 2 shows the comparisons of symptoms and findings in community-acquired respiratory infections between the elderly and adults complied by Suga.[14] Although the elderly with community-acquired respiratory infections are likely to exhibit mild symptoms, atypical physical

Table 2 Comparisons of Clinical Features of Community-acquired Respiratory Infections between the Elderly and Adults

	The elderly	Adults
Onset of the disease	Slow	Abrupt
Symptoms		
Fever	Mild	Present
Chest pain	Mild	Severe if inflammation reaches the pleura
Cough	Slight, or no	Cough with Purulent sputum
Dyspnea	Common	Not common
Consciousness Disturbance	Frequent	Rare
Physical findings		
Chest	Atypical	Typical
General	Significant	Mild
Laboratory findings		
Inflammatory reactions	Mild	Significant
Hypoproteinemia	In some cases	No
Renal Disturbance	In some cases	No
Chest X-ray	Atypical finding	Typical shadow
(Bacterial pneumonia)	Interstitial or persistent shadows in some cases	Consolidation
Outcome	Intractable	Good response

Source: Reference 14)

findings, and mild laboratory findings, their disease is resistant to treatment and is often intractable. On the other hand, the diseases develop abruptly in adults with severe symptoms and severe abnormal laboratory findings, but they respond well to treatment. While these are classical examples that are generally observed, not all cases present such trends, and that is what makes clinical medicine complicated.

In a period of five years between April 1985 and March 1990, the author and colleagues experienced 406 cases of pneumonia at Kawasaki Medical School, Kawasaki Hospital, Okayama, Japan. Fifty-seven cases were found among patients aged 80 and above, and 51 cases among patients under 50 years of age. Table 3 shows the comparisons of their cardinal symptoms (at most up to the top three chief complaints) and laboratory findings.

Although chest pain and bloody sputum seem to be more common among the younger population, and disturbed consciousness, dehydration, loss of appetite, and general malaise among the elderly, no obvious differences are seen in cardinal symptoms of pneumonia such as fever, cough, and sputum.

In view of laboratory findings, no obvious differences are observed in variables important in pneumonia patients including body temperature (fever), white blood cell count (WBC) in peripheral blood, and C-reactive protein (CRP). Differences exist in serum protein and a tuberculin skin test, though it is unknown if they are the result of or basis of pneumonia.

One of the characteristics of pneumonia among the elderly that is frequently noted is that they do not often run a fever. However, despite normothermia at the first consultation or hospital admission, all of the above-mentioned pneumonia patients, except those in shock, showed body temperatures of 37 °C or greater when a careful thermometry was performed after admission.

As these examples suggest, despite the fact that there are certain severity patterns in symptoms and findings of pneumonia among the

Table 3 Differences in Symptoms and Laboratory Findings of Pneumonia between the Elderly and the Younger Population

A. Main symptoms

	Fever/chills	Cough	Sputum	Bloody sputum	Dyspnea/wheezing	Chest pain	Other pains	Disturbed consciousness/shock	Malaise	Loss of appetite, dehydration, digestive disorders
80 years old and above (57 cases)	40	34	27	0	10	1	1	4	3	7
Under 50 years old (51 cases)	45	35	17	6	3	10	2	0	1	1
Total (108 cases)	85	69	54	6	13	11	3	4	4	8

B. Laboratory findings

	WBC	CRP (+)	Body temperature (°C)	Serum protein (g/dl)	Tuberculin skin test		
					+	−	Not performed
80 years old and above (57 cases)	3,600 to 34,000 (average: 10,240)	0 to 6 (average: 4.51)	35.0 to 39.3 (average: 37.4)	4.9 to 8.6 (average: 6.49)	6	23	26
Under 50 years old (51 cases)	4,000 to 28,100 (average: 12,169)	0.5 to 6 (average: 4.64)	35.3 to 39.8 (average: 37.8)	5.9 to 8.8 (average: 7.09)	8	16	22

Table 4 Precautions for Antibacterial Chemotherapy Among the Elderly

A.

1. Management of and awareness against polymicrobial infection
2. Confirm the presence and management of comorbid conditions and complications.
3. Recognition of organs hypofunction (particularly renal). Careful dosage and administration intervals
4. Teach how to take oral drugs appropriately (do not forget and do not take over).
5. Monitoring of adverse drug reactions

Source: Reference 15)

B.

1. The elderly may have underlying renal hypofunction.
2. In drugs excreted by the kidney, the time (T 1/2) half-life is prolonged, and the area under the curve (AUC) increases.
3. May have different absorption properties in each oral drug
4. The rate of urinary excretion is lower in the elderly than in healthy adults.
5. In intravenous administration, the dosage and administration intervals must be considered.

Source: Reference 16)

elderly, no definitive differences exist between the elderly and the younger population. Furthermore, since there are individual differences among pneumonia patients, the regular treatment approach should be applied even to the elderly.

Table 5 How to Use Antimicrobial Drugs in Patients with Renal Dysfunction

The dosage should be administered regularly.	Macrolides Clindamycin Doxycycline Minocycline
The dosage should be adjusted in patients with moderate to severe renal dysfunction*[1].	β-lactams New quinolones (ofloxacin) Lincomycin New macrolides
The dosage should be strictly controlled according to the level of renal function*[2].	Aminoglycosides Glycopeptides

*[1] β-lactam drugs and new quinolone drugs (except sparfloxacin) should only be administered at 1/2 to 3/4 of a regular dosage to patients with moderate (creatinine clearance [Ccr]: 20 to 5 m*l*/min) to severe (Ccr: less than 20 m*l*/min) renal dysfunction, or they should be administered at prolonged intervals (every 12 to 24 hours) twice as long as the regular interval.

*[2] Aminoglycoside drugs require a careful selection of usage. There are three different methods of usage: (1) After the first administration at a regular dosage, half the dosage is administered every half-time as a maintenance dose; (2) A regular dosage is administered at an interval twice or three times longer than the half-time; and (3) The dosage is adjusted (reduced) and administered at the interval equal to that of patients with no renal dysfunction.

Source: Reference 15)

Treatment of Pneumonia Among the Elderly

The most important treatment of pneumonia is antibiotic chemotherapy. Although there are no specific choice regarding the selection of drugs according to pathogenic bacteria, careful attention should be given to administration and dosage. Table 4 lists precautions in introducing antibiotic therapy on elderly pneumonia patients.[15,16] They are well summarized and provide sufficient information.

Of these precautions, the most important point to notice is underlying renal dysfunction in the elderly. Table 5 shows the dosage and administration for using antibacterial agents in such a case.[15] Treatment should be planned on the basis of this table.

As the therapies other than chemotherapy, managements of dehydration, diet, or body temperature are needed. Also, expectoration of bronchial secretion are required to subside pneumonia.

Conclusion

There are no critical differences in pneumonia between the elderly and the younger population, and just slight differences are present in various aspects. As stated earlier, pneumonia is a disease overwhelmingly found among the elderly and is regarded as "the friend of the aged." This suggests that pneumonia among the elderly should be considered a common, standard disease.

Our thinking patterns need to be changed so as to consider pneumonia in the elderly as the standard and to study further comparisons of pneumonia between the elderly and the younger population. I believe that guidelines on the treatment of pneumonia should be developed mainly for the elderly.

REFERENCES

1) Esposito, A.L.: Bacterial pneumonia in the elderly. ed. Pennington, J.E., In *Respiratory Infec-*

tions: Diagnosis and Management. 2nd ed., Raven Press, NY, 1989; 207–220.
2) Niederman, M.S. *et al.*: Guidelines for the initial management of adults with community-acquired pneumonia: Diagnosis, assessment of severity and initial microbial therapy. *Am Rev Respir Dis* 1993; 148: 1418–1426.
3) Campbell, Jr. C.D. *et al.*: Commentary on the 1993 American Thoracic Society guidelines for the treatment of community-acquired pneumonia. *Chest* 1999; 115: 14s–18s.
4) Bartlett, J.G. *et al.*: Community-acquired pneumonia in adults: guidelines for management. *Clin Infect Dis* 1998; 26: 811–838.
5) Schaberg, T. *et al.*: Deutsche gesellshaft fur pneumologie. Empfehlungen zur therapie der ambulant erworbenen pneumonie. *Pneumologie* 1998; 52: 450–462.
6) Dorca, J.: Guidelines for community-acquired pneumonia in Spain: another perspective. *Clin Pulm Med* 2000; 7(1): 1–8.
7) Organizing Committee of the Japanese Respiratory Society for the guidelines on pneumonia: *Basic perspectives for the management of community-acquired pneumonia in adults.* The Japanese Respiratory Society, Tokyo, 2000. (in Japanese)
8) Bartlett, J.G. and Mundy, L.M.: Community-acquired pneumonia. *N Engl J Med* 1995; 333: 1618–1624.
9) Dean, N.C. *et al.*: Frequency of subspecialty physician care for elderly patients with community-acquired pneumonia. *Chest* 2000; 117: 393–397.
10) Health and Welfare Statistics Association: *Kokumin eisei no doukou* (National public health trends in Japan), *Kousei no shihyo (Public health indicators)* 1997; 44(9): 416–466. (in Japanese).
11) Grayston, J.T.: *Chlamydia pneumoniae,* strain TWAR pneumonia. *Annu Rev Med* 1992; 43: 317–323.
12) Bernstein, J.M.: Treatment of community-acquired pneumonia IDSA guidelines. *Chest* 1999; 115: 9s–13s.
13) Torres, A. *et al.*: Community-acquired pneumonia in the elderly. *Semin Respir Infect* 1999; 14(2): 173–183.
14) Suga, M.: Differential diagnosis in symptoms and laboratory findings of respiratory infections. *Nichinai kaishi (Journal of the Japanese Society of Internal Medicine)* 1998; 87(2): 223–229. (in Japanese)
15) Ueda, Y. *et al.*: *Modern antimicrobial drug therapy for clinicians.* Life science, Tokyo, 1994; 83–90. (in Japanese)
16) Yamamoto, T. and Suzuki, K.: Attentions in antibacterial drug therapy among the elderly. In *Antibacterial drug therapy* (ed. Shimada, J. *et al.*), Kobundo, Tokyo, 1992; 225–234. (in Japanese)

Current Imaging Diagnosis of the Breast Tumors

JMAJ 45(6): 258–264, 2002

Tokiko ENDO

Director of the Department of Radiology, National Nagoya Hospital

Abstract: Breast masses include the tumors or lesions detected by diagnostic imaging as well as those detected by inspection and palpation. In Japan, we make a definite diagnosis, and select appropriate treatment using mammography, ultrasonography, CT or MRI to detect the lesions. Mammography will soon be the leading technique for detecting breast cancer because of the progress that has been made in imaging devices, imaging techniques, and interpretation techniques. Currently, mammography training programs have been launched to popularize the interpretation technique using common technical terms and categorization, imaging techniques, and the techniques for maintaining the precision of devices. Evaluation of the imaging has started to be performed for each institution. Devices for ultrasonography are being improved, and diagnostic criteria are being reviewed. Ultrasonography, which has been used to determine whether lesions are benign or malignant, can be used for suspected diagnosis of breast disease from the aspect of histology, and additional methods for definite diagnosis such as ABC and core needle biopsy are also available. Furthermore, diagnostic imaging of intraductal proliferative lesions and non-invasive breast cancer can be performed without difficulty. Once a patient is diagnosed with breast cancer, she should undergo contrast-enhanced MRM or CT to determine appropriate treatment. The three-dimensional reconstruction image is sufficiently objective to demonstrate the lesion and can be used to obtain informed consent from the patient.

Key words: Mammography; Ultrasonography of the breast; MR mammography; CT mammography

Introduction

In the past, the mammary gland was mainly examined by inspection and palpation and the palpable mass led the patient to consult her doctor. Progress in diagnostic imaging, however, has enabled the visualization of various types of breast lesions such as those detected by inspection and palpation and those only detectable by imaging. The minimization of the

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 11, 2001, pages 1701–1705).

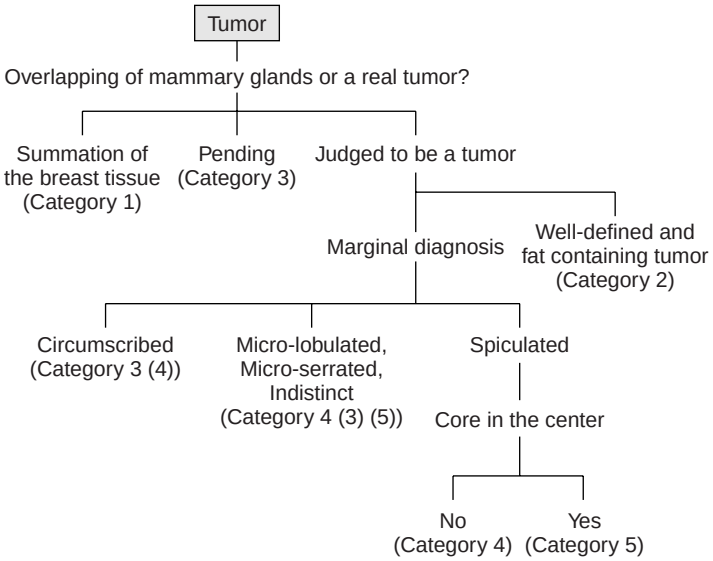


Fig. 1 Diagnostic imaging of masses by mammography (quoted from "Mammography Guidelines")

rapidly increasing number of deaths from breast cancer is largely dependent on the development of techniques to discover the abnormality necessarily resulting in tumor.[1] In view of future technological developments, the author will discuss the present conditions of diagnostic imaging of the mammary gland.

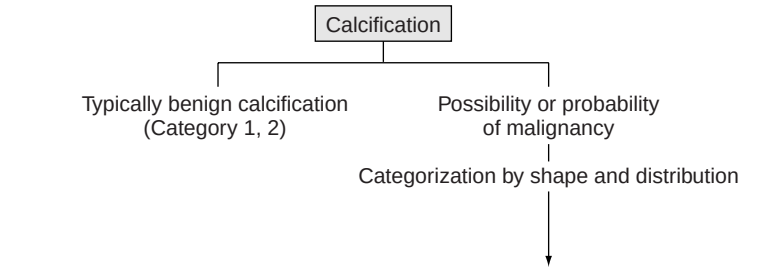
Mammography, ultrasonography, MRI, and CT have been widely used in the diagnostic imaging of diseases of the breast. Furthermore, RI has been used to study sentinel lymph nodes. In this paper the current conditions of diagnostic imaging of the breast are described.

Mammography

The imaging devices and techniques and the interpretation used for mammography are changing considerably. The essential change in mammography is the change in imaging target from the breast to the mammary gland. Conventional mammography covered the nipple and skin, while current mammography covers only mammary gland tissues, which facilitates the detection of abnormalities in the mammary gland. Although the reliability of diagnostic imaging by mammography has been remarkably improved, more clinicians recognize the importance of the maintenance of precision of specifically improved devices.

All the devices used for diagnostic imaging are to meet the mammography guidelines established by the Japan Radiological Society.[2] As a beam receiving system, the screen/film system is required to have high levels of sensitivity and contrast. The observation of the inside of the mammary gland in a small dose can only be achieved when these conditions are satisfied. The films for mammography, which are completely different from the films used in other fields, require strict maintenance of precision in their development.[3]

Compared with conventional standard radiography, which comprises medial-lateral imaging and craniocaudal imaging, the current standard radiography, comprising medial-lateral oblique imaging and craniocaudal imaging visualizes the inside of the breast more extensively. Mammography should not simply be defined as an X-ray examination requiring compression of the breast. Mammography should provide clinicians with sufficient information about the inside of the mammary gland. For this purpose, the mammary glands are to be spread so that overlap-



Distribution \ Shape	Small round	Amorphous	Pleomorphic	Fine linear, fine linear branching
Diffuse Regional	Category 2	Category 2	Category 3	Category 5
Clustered	Category 3	Category 3	Category 4	Category 5
Linear Segmental	Category 3 or 4	Category 4	Category 5	Category 5

Fig. 2 Diagnostic imaging of calcification by mammography (quoted from "Mammography Guidelines")

ping can be minimized. Only highly-trained and experienced technicians are allowed to perform mammography. The Ministry of Health, Labor and Welfare, which is considering the introduction of mammography into the screening of breast cancer in Japan, is insisting on the importance of device maintenance and the necessity for excellent imaging techniques.[4)]

The techniques for interpreting mammograms have been changed and the propositions mentioned in the mammography guidelines have been widely accepted through training seminars. The addition of other findings focusing on the structure of the mammary gland to the conventional mammographic findings of breast cancer, such as tumors and calcification, has been proposed. An interpretation technique for screening has been proposed for the diagnostic process consisting of the definition of individual findings and diagnosis using the definition and the diagnostic tree. This method is widely used in clinical treatment and is regarded as an important property to be shared among all clinicians.

Tumor is classified according to its shape, border, margin, and density (Fig. 1). Calcification is categorized into benign calcification and calcification requiring the differentiation between benignancy and malignancy. The latter type of calcification is subcategorized according to shape and distribution (Fig. 2). Regarding other findings, the degrees of benignancy and malignancy are categorized according to the structural irregularity of the lesions (Table 1). In clinical treatment, the results obtained by categorization and those obtained by pathological and histological examinations are used to make a definite diagnosis.

Table 1 Categorization of Mammogram

Category N:	Not assessable
Category 1:	Negative
Category 2:	Benign
Category 3:	Benign, but malignancy can't be ruled out
Category 4:	Suspicious abnormality
Category 5:	Suggestive malignancy

In order to minimize the number of breast cancer deaths, mammography was introduced into the screening of breast cancer. Because appropriate maintenance of devices, accurate interpretation and effective management of the system are indispensable for implementation

of precision screening, the academic associations which are engaged in screening breast cancer (Japanese Association of Breast Cancer Screening, Japan Breast Cancer Society, Japan Radiological Society, Japanese Society of Radiological Technology, Japan Society of Obstetrics and Gynecology including Japan Association of Obstetricians and Gynecologists for Maternal Protection, Japanese Association of Radiological Physicist) have established a central committee for the assurance of precision in mammography. The central committee organized a subcommittee covering education and training to promote the improvement of imaging and interpretation techniques. The subcommittee sponsored several training programs and its activities have been highly acclaimed. Institutional image evaluation boards have been established and have been conducting their practical activities since April 2001.[5)]

With the recent progress in digital technology, new devices for mammography have been developed and improvements made in the techniques of digital mammography. Furthermore, computer assisted diagnostic devices for evaluation of mammograms are also now available.[6)] The precision of digital mammography should be as high as that of conventional mammography using screen/film system. The introduction of digital mammography has been welcomed because of its usefulness. This new technique, however, is faced with various problems including image quality and cost-effectiveness. Further improvement of digital mammography is eagerly anticipated ahead of its practical introduction.

Ultrasonography

The devices for ultrasonography have been improved and remarkable advances made in diagnostic imaging by means of ultrasound. In addition to the information provided by brightness-mode (B-mode) images, blood flow information obtained by color Doppler method is used for diagnostic imaging. The high frequency probe for surface organ is indispensable in the examination of breast disease. Diagnosis of the breast disease can not be made by the expanded application of the abdominal probe.

The Diagnostic Criteria for Breast Lesions,[7)] which was established by the Japan Society of Ultrasonics in Medicine in 1987, has contributed toward differentiating the mass lesion between benign and malignant. In recent years, ultrasonography has been indicated for the diagnosis of histological type, diagnosis of intraductal spreading of the lesion and diagnosis of non-mass forming lesions. In order to deal with the recent conditions, the Japan Society of Ultrasonics in Medicine organized a subcommittee to promote the establishment of the diagnostic criteria of diseases of the mammary gland as a part of the committee for establishing a glossary and diagnostic criteria. This subcommittee is reviewing the current situation in order to establish a diagnostic criteria which can satisfy clinical needs. The draft of the diagnostic criteria is stated for presentation within 2001 and its practical introduction is expected.

Histological type is determined by evaluating the shape, echo pattern of the border, internal echo pattern, and degree of ultrasonic attenuation (by posterior echo intensity) and identifying the constitutive tissues or substances of the tumor.[8)] Ultrasonic attenuation is less remarkable within moist cysts, mucus, and cell components, and posterior echo is enhanced in extreme cases. Ultrasonic attenuation associated with a acoustic shadow is recognized within the fibrous tissues of scirrhous carcinoma. Generally, the combination of these echo patterns is observed in tumors and histological diagnosis can therefore be made by interpreting the details of each echo pattern. Echograms provide reliable information which can not be obtained by mammography.

Additional information such as blood flow information provided by the color Doppler method and contrast ultrasonography other than B-mode imaging has contributed to improvements in the accuracy of histological diagnosis.

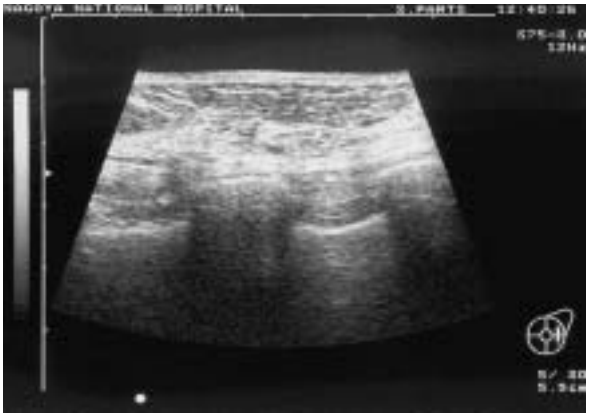


Fig 3 Echogram of non-invasive ductal carcinoma
A segment characterized by slightly smaller and less echogenic change is observed.

These new techniques are gradually being introduced into clinical treatment.

The success of breast-conserving treatment depends on the imaging diagnosis of the intraductal components of the breast cancer. Recently developed devices can visualize the minimum dilatation of the duct and tumor and/or microcalcification in the duct. Such technological progress enables visualization and identification of the cancerous components in the duct and non-mass forming breast cancer[9] (Fig. 3). Ultrasonography provides new simple approaches to cytology or core biopsy of disease of the mammary gland which forms no palpable tumors and accordingly plays an important role in the examination of the mammary gland.

MRI and CT

Currently breast-conserving surgery is adopted as a routine surgical treatment for breast cancer. The cancerous lesion should be accurately, clearly, and stereoscopically visualized so that the lesion can be thoroughly resected. For this purpose, MRI and CT have been introduced into practical treatment as the most effective examinations.

The machines used for MRI and CT are expensive diagnostic apparatus. When we examine the breast by MRI, we have to prepare a phased-array coil for the breast. Considering the time necessary for examination by means of nuclear magnetic resonance, its introduction into routine screening is not recommended. Generally, MRI is indicated for patients who have already been diagnosed with breast cancer, and includes those women who are to undergo breast conserving surgery or those whose requests for breast-conserving surgery are likely to be rejected. MRI is used in these cases only to clarify the affected area.[10] As an exception, screening by MRI is indicated for patients who have received an implant insertion because examinations other than MRI are usually ineffective in these cases. In Japan, implant insertion is not common. MRI will be widely introduced into screening tests for detection of local recurrence and metachronal multiple lesions as a result of the popularization of breast-conserving treatment and breast reconstruction surgery.

In MRI, a contrast medium is used to conduct dynamic studies and differentiation between benignancy and malignancy is made according to the chronological and spatial imaging patterns. Furthermore, the diagnostic imaging of the spread of malignant lesions is also performed. Although the type of manipulation varies according to the apparatus used for MRI, an example is given below by way of explaining the practical technique.

A scan is conducted prior to imaging. Contrast medium (Gd-DTPA 0.1 mm Mol/kg) is injected intravenously and scans are performed repeatedly 2, 4, and 8 minutes after intravenous injection. Generally, the malignant lesion is stained in the early scan image and ring enhancement is characteristic of serious degeneration including scirrhous carcinoma. Blush in a benign lesion is gradually enhanced and the inside of the lesion is stained in a relatively uniform manner. The septal wall of fibroadenoma is occasionally visualized. The lesion within the lactiferous duct is visualized as a funicular struc-

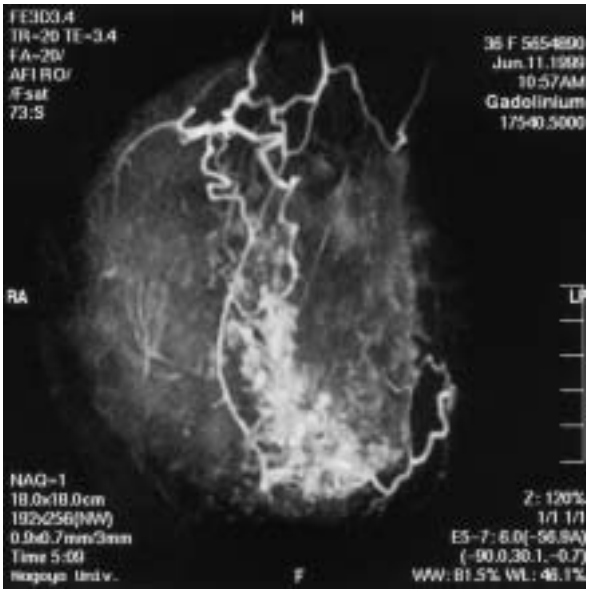


Fig 4 Diagnostic imaging of the spread of breast cancer by MRI

All the lobes affected by the extended non-infiltrating cancer are clearly stained.

ture starting from the primary tumor, while multiple lesions are visualized as nodules, which are separate from the primary tumor (Fig. 4). Depending on the histological subtypes of the components within the lactiferous duct, relatively small malignant lesions are not necessarily visualized. MRI is not always effective for making a differential diagnosis of mastopathy.

The theory of three-dimensional visual information obtained by MRI can be directly applied to CT. The effectiveness and usefulness of MRI are virtually identical to those of CT.[11] Compared with MRI, CT is less expensive and more widely used in clinical treatment, as it can be completed within a short period of time. Some surgeons may request the implementation of breast-conserving treatment although hospitals are not equipped with the apparatus to perform MRI. In these cases, the introduction of CT is recommended because CT can provide similar information to that supplied by MRI. Thanks to the recent development of multidetector-Row CT (MD-CT), we can obtain more accurate and detailed three-dimensional images.

Below is an example of a currently adopted technique. Nonionizing contrast medium (90 m*l*) is injected at the rate of 1.5 m*l*/sec. Seventy to 100 seconds later, an area ranging in size from 9 to 11 cm is scanned while the patient holds her breath under the following conditions: beam amplitude 3 mm and table rate 3 mm/0.8–1 sec. Image reconstruction is conducted at intervals of 1.5 mm to display the three-dimensional image of the lesion. (The rate of injection of contrast medium and the time required for scanning are individually determined by the facility performing the technique. They are also affected by the types of apparatus used for CT scan.)

In the images obtained by these techniques, the spread of disease is stereoscopically visualized and multiple lesions or disseminated lesions are clearly detected without difficulty. Because these techniques provide surgeons and patients with convincing visual information, the images can be used to explain the pathological conditions to the patients and to obtain their informed consent for surgery.

Conclusion

This paper explains the current conditions of diagnostic imaging for detection of disease of the mammary gland including mammography, ultrasonography, MRI, and CT. Diagnostic imaging is useful for detecting both palpable tumors and non-mass forming lesions. It is used to determine the appropriateness of breast conserving treatment and is applied to various examinations including screening, cytology, and biopsy for detection of non-palpable non-mass forming lesions.

REFERENCES

1) Endo, T. and Kuroishi, T.: Epidemiology and screening. *Clinical Radiology* 2000; 45: 1245–1254. (in Japanese)
2) Japan Radiological Society, Japanese Society of Radiological Technology, ed.: *Mammo-*

graphy Guidelines, Igakushoin, Tokyo, 1999. (in Japanese)
3) Japanese Society of Radiological Technology: *Manual for Maintenance of Precision of Breast Imaging*. 1999. (in Japanese)
4) Ouchi, N. ed.: *Handbook for Screening of Breast Cancer by Mammography: Manual for Maintenance of Precision*. Nippon Ijishimpo Publishing Co., Ltd., Tokyo, 2000. (in Japanese)
5) Morimoto, T. *et al.*: Roles of the committee for the maintenance of precision of screening by mammography. *Journal of Japanese Association of Breast Cancer Screening* 2000; 9: 25–30. (in Japanese)
6) Fujita, H.: Current conditions and problems of computer assisted diagnostic (CAD) system used in mammography. *Clinical Treatment for Breast Cancer* 2000; 15: 635–646. (in Japanese)
7) The Committee for the Establishment of Diagnostic Criteria for Ultrasonics in Medicine, the Japan Society of Ultrasonics in Medicine: Diagnostic criteria for breast ultrasonic tomography. *Ultrasonic Medicine* 1989; 16: 106–107. (in Japanese)
8) Ueno, E. *et al.*: Classification and diagnostic criteria in breast echography. *Ultrasonic Medicine* 1986; 13: 19–31.
9) Tsunoda, H.: Selection of treatment for breast cancer: roles of ultrasonography. *Clinical Radiology* 1999; 44: 565–571. (in Japanese)
10) Kawashima, H. *et al.*: MRI. *Clinical Radiology* 2000; 45: 1300–1314. (in Japanese)
11) Uematsu, T. *et al.*: Diagnostic imaging of infiltration of breast cancer in the lactiferous duct and multiple cancerous lesions by helical CT. *Journal of Japan Radiological Society* 1997; 57: 85–88. (in Japanese)

Molecular Diagnosis for Breast Cancer

JMAJ 45(6): 265–270, 2002

Takemitsu NAGAHATA, Natsuki KOSAKA, Masashi SHIMIZU, and Mitsuru EMI

Department of Molecular Biology, Institute of Gerontology, Nippon Medical School

Abstract: Within the past few years a number of genes whose mutated forms are associated with a high risk of breast cancer have been identified, including *BRCA1*, *BRCA2*, *c-myc*, *erbB2*, and *p53.* The identification of these genes, together with rapid advances in techniques for molecular genetic analysis, should improve the diagnosis and therapy of this group of diseases. Allelic losses at other specific loci in breast tumors also may serve as prognostic factors. This article reviews the genetic basis of hereditary and sporadic breast cancers and discusses the clinical application of new molecular knowledge with regard to diagnostic testing, surveillance, and prognostic diagnosis for women with hereditary predispositions or who are at high risk for recurrence of breast cancer.

Key words: Breast neoplasms; Oncogenes; Tumor suppressor genes; Loss of heterozygosity

Introduction

It is now widely accepted that cancer is a complex disease that results from the accumulation of numerous genetic aberrations within the tissue in question. The isolation of two breast cancer-susceptibility genes, *BRCA1* and *BRCA2*, has opened the door to early detection and pre-emptive treatment of familial breast cancers. Furthermore, because over-expression of another gene, *erbB2*, is highly correlated with shortened disease-free survival and with overall survival of node-positive patients, a bioengineered product called Herceptin may be indicated for the treatment of patients with metastatic breast tumors that over-express the *erbB2* product, HER-2 protein. Other highly specific cancer therapies based on results of molecular diagnoses will be available in the near future. In this article we review recent findings, including some from our own research, that have revealed some underlying genetic mechanisms of breast cancer.

Familial Breast Cancer

A family history of breast cancer has long been recognized as an important risk factor, contributing as it does to about 10% of all breast cancer cases. *BRCA1* and *BRCA2* have been identified already as tumor suppressor genes associated with familial breast cancer.

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 125, No. 11, 2001, pages 1731–1734).

1. *BRCA1* and *BRCA2*

In 1990 Hall *et al.*[1] performed linkage analyses of pedigrees exhibiting a high incidence of breast cancer, and found linkage between polymorphic DNA markers in region 17q21 of the long arm of chromosome 17 and early-onset breast cancer. They assumed the existence of a familial breast cancer susceptible gene in this region, naming it *BRCA1*, and in 1994 Miki *et al.*[2] identified the gene itself. Then, by conducting shotgun linkage analyses of pedigrees with familial tendencies to breast cancer that did not show linkage to *BRCA1*, Wooster *et al.*[3] localized *BRCA2*, another breast-cancer susceptibility gene, to an interval of approximately 6 cM in region 13q12–13 on the long arm of chromosome 13; in 1995 they succeeded in identifying the gene in the same manner as *BRCA1* had been, that is, by localizing parts of *BRCA2* using detailed linkage analysis and positional cloning techniques. Both *BRCA1* and *BRCA2* encode potential tumor-suppressing proteins. Murine embryos carrying a *BRCA1* null mutation are developmentally retarded and hypersensitive to gamma-irradiation, suggesting a failure in DNA damage repair.[4] Both genes are large; each spans approximately 80 kb of genomic DNA, and both have extremely large central exons encoding >50% of the protein. Both proteins are large as well: 1863 and 3418 amino acids respectively. BRCA1 protein and BRCA2 protein maintain genomic stability through their involvement in homologous recombination and in repair of transcription-coupled and double-strand breaks.

2. Genetic diagnosis before onset

Germline mutations in *BRCA1* or *BRCA2* together account for only 15–20% of breast cancers known to cluster in families and less than 5% of breast cancer overall in the US and Western Europe. However, mutations in these two genes are assumed to be actually responsible for up to 45% of familial breast cancers in Western countries. Germline mutations in *BRCA1* are observed in 1–2% of all patients with breast cancer in Japan.[5] Both *BRCA1* and *BRCA2* are transmitted through autosomal dominant inheritance. The onset of breast cancer tends to occur at younger ages, and more often with concomitant onset of ovarian cancer, in pedigrees that transmit alterations in the *BRCA1* gene than in pedigrees that do not carry mutations in *BRCA1*.

The discovery of the breast cancer-susceptibility genes has defined carriers of mutations in *BRCA1* and *BRCA2* as a high-risk group before onset, and management guidelines are now available for women who carry germline mutations of either gene. Pre-emptive approaches based on these guidelines appear to reduce the risk of breast and ovarian cancer by at least 60% and 90%, respectively.[6] Because both *BRCA1* and *BRCA2* are large genes, however, with no specific "hot spots" of mutation, searching for mutations in individual cases involves considerable expense and time. Hacia *et al.*[7] have designed high-density arrays consisting of over 96,600 oligonucleotides, each 20 nucleotides long, to screen for a wide range of heterozygous mutations within the 3.45 kilobases constituting exon 11 of *BRCA1*. Such DNA chip-based assays may represent a valuable new technology for high-throughput, cost-efficient detection of other genetic alterations as well.

Sporadic Breast Cancer

Cancerous solid tumors generally result from the accumulation of mutations in numerous genes. Genes that are involved in the development and progression of tumors can be divided into three major categories: oncogenes, tumor-suppressor genes, and mismatch-repair genes.

1. Amplification of oncogenes

Oncogenes encode products that facilitate cell growth, but they are termed proto-oncogenes in normal DNA. Once the oncogene has been activated by point mutation or gene amplifications, an affected cell may produce unusually large amounts of the normal gene product (or

an aberrant protein). This transforms the cell into a cancer cell that looks very different from its former self.

(1) ***C-myc* amplification**

The *c-myc* gene, located at 8p24.3, encodes a nuclear transcription factor that is involved in gene expression. To clarify the clinical significance of *c-myc* amplification, Deming *et al.*[8] conducted 29 studies in which the weighted average frequency of *c-myc* amplification in breast tumors was 15.7%. Amplification was significantly associated with risk of relapse and death. Harada *et al.*[9] reported that *c-myc* was amplified in 28% of the 279 breast cancers they examined in Japan. Amplification of *c-myc* is relatively common in breast cancers, where it correlates with poor prognoses, e.g. inflammatory carcinoma, progression of postmenopausal tumors, or metastasis to lymph nodes. However, the relationship between *c-myc* amplification and breast-cancer progression or the extent of malignancy remains to be fully clarified.

(2) ***ErbB2* amplification**

ErbB2 was cloned by virtue of its homology to the avian erythroblastosis virus oncogene (*v-erbB*). *ErbB2* is located at 17q22.1 and its product (known as HER-2, human epidermal growth factor receptor 2) is a receptor-type tyrosine kinase found on the surface of cells; when functioning normally, it is a key component for regulating cell growth. However, when the HER-2 protein is over-expressed, extra HER-2 receptors may be produced. This situation increases cell growth and reproduction, often resulting in more aggressive breast-cancer cells. Harada *et al.*[8] reported that *erbB2* amplification had occurred in 19% of 457 breast-cancers they examined in Japan. Clear relationships exist between *erbB2* positivity and the lack of steroid receptors, the ductal invasive and *in situ* histological subtypes of mammary tumors, worse histological and nuclear grades, aneuploidy, and a high rate of proliferation.[10] An available laboratory test for amplification of *erbB2* in breast cancers is useful for prognostication and for guidance of post-operative therapy. Herceptin/Trastuzumab, a monoclonal antibody against HER-2 protein engineered through biotechnology, can be prescribed for women with advanced (metastatic) breast cancer whose tumors over-express the HER-2 protein.

2. Tumor suppressor genes

The genes in this category normally control cell proliferation or differentiation. Mutations that inactivate one or more or these genes lead to abnormal cell growth.

(1) ***p53* and breast cancer**

p53, located at 17p13.1, was the first gene identified as a mutant in human tumors. Its normal protein product participates in regulation of the cell cycle and in apoptosis. Mutations of *p53* have occurred in 17–40% of sporadic breast cancers examined,[11] and most of them are missense mutations concentrated in a core region that encodes the sequence-specific DNA-binding. Mutant forms of p53 protein interfere with the growth-suppressing effects of wild-type p53, indicating that the gene product is actually a tumor suppressor (dominant negative). Many investigators have examined mutations of *p53* in detail and have correlated them with the prognosis and with the sensitivity to anti-tumor drugs. A statistically significant association has been noted between *p53* mutations that occur in conserved domains, and poor prognosis. As *p53* mutations are found most frequently in advanced breast cancers, it appears that aberrant p53 is involved in the progression stages of such tumors.

(2) **LOH and breast cancer**

A high frequency of somatically occurring losses of heterozygosity (LOH) at specific chromosomal sites in tumor cells usually suggests that one or more tumor suppressor genes should be present in those regions. Isolation of the *APC*, *RB*, and *WT1* genes on the basis of LOH analyses has supported this premise. LOH is also common in sporadic breast cancers. A pioneering study on breast-cancer allelotypes was conducted by Sato *et al.*[12] who searched for LOH on the short and long arms of all autosomal chro-

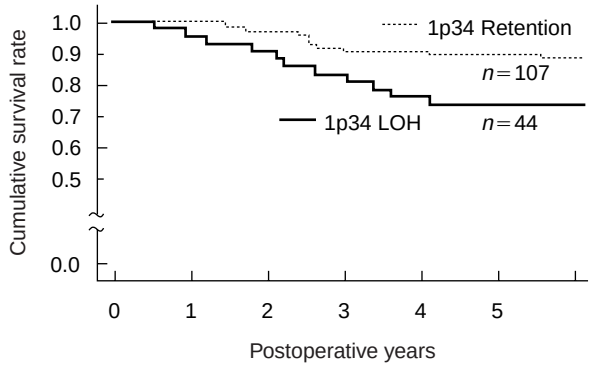


Fig. 1 Kaplan-Meier curves of overall postoperative survival for patients whose tumors retained both alleles (dotted line) or had lost one allele (LOH, solid line) of a marker at 1p34.[13]

mosomes in breast cancers from 79 women. The results indicated high frequencies of deletions on the short arm of chromosome 3 (46%), the long arm of chromosome 13 (25%), the long arm of chromosome 16 (51%), and the short arm of chromosome 17 (58%), suggesting the existence of tumor suppressor genes in those regions whose loss is associated with the onset and development of breast cancer. Correlations found among common chromosomal deletions and clinicopathological factors suggest that some chromosomal alterations are specific for different aspects of development and progression of breast cancer, e.g. differentiation of tumor cells, progression *in situ*, metastasis to lymph nodes, and hormonal dependency.

Molecular Diagnosis for Postoperative Prognosis

1. LOH for prognosis of breast cancers

We have investigated and reported the significance of LOH as a prognostic factor in breast cancers.[13] To examine whether specific allelic losses might correlate with postoperative survival, in a 5-year prospective follow-up we tested tumors from a cohort of 264 breast-cancer patients for allelic losses of 18 microsatellite markers representing either a known tumor suppressor gene or a region where genetic alterations are frequent in breast tumors. Patients whose tumors had lost an allele at 1p34, 13q12, 17p13.3, or 17q21.1 sustained significantly higher risks of postoperative mortality than those whose tumors retained both alleles at those loci at the time of initial surgery. Figure 1 shows our analysis of postoperative survival with regard to LOH status at 1p34. Kaplan-Meier analysis of overall survival revealed that postoperative mortality risk was increased in patients whose tumors showed LOH at this locus, compared with patients whose tumors retained both alleles (log-rank test, $p = 0.0047$). We conclude that allelic losses at these four loci can serve as negative prognostic indicators to guide postoperative management of patients.

2. Postoperative prognosis and LOH in node-negative breast cancer

Although the prognosis for patients whose breast cancers have not metastasized to lymph nodes (node-negative breast cancer) is better than that for patients with metastasis, about 10% of node-negative patients in Japan experience relapse within 10 years of initial surgery. With this discrepancy in mind we examined tumors from a cohort of 228 node-negative breast cancer patients for allelic losses at 18 microsatellite loci representing either known tumor suppressor genes or regions where breast cancers frequently exhibit allelic losses.[14] We followed the patients clinically for 5 years or until death. Patients whose tumors had lost an allele at 1p34–36 bore significantly higher risks of postoperative recurrence than those whose tumors retained both alleles in that region. The 5-year recurrence rate was 15% among patients with losses versus 2% among patients with retention (Fig. 2). Multivariate analysis demonstrated that allelic loss at 1p34–36 was an independent postoperative predictor of shorter disease-free survival (hazard ratio, 5.8; $p = 0.0117$). Thus, allelic loss at 1p34–36 in a tumor may have the potential of serving as a negative prognostic indicator to guide postoperative management of many breast cancer patients, especially as a

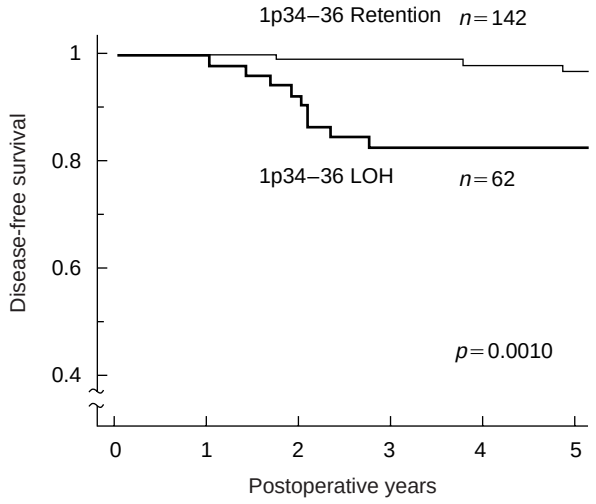


Fig. 2 Kaplan-Meier curves of disease-free postoperative survival for patients whose tumors retained both alleles (thin line) or had lost one allele (LOH, thick line) of a marker at 1p34–36.[14]

means of selecting the women who will benefit most from adjuvant chemotherapy and/or endocrine therapy.

3. Clinical application of genetic diagnosis for postoperative prognosis in breast cancer

As mentioned above, the postoperative recurrence rate among patients with breast cancer whose tumors had lost one allele at 1p34–36 was statistically greater than among patients whose tumors had retained both alleles. On the basis of these findings, we are now attempting to provide genetic diagnosis for LOH at the 1p34–36 locus in clinical settings. Samples from tumors and peripheral blood of breast-cancer patients undergoing surgery are transported from hospitals in Nagano and the Cancer Institute in Tokyo to our laboratory, where we analyze the tumor DNAs for LOH. The analyses are completed within a week and reports are returned to doctors in less than two weeks. We expect that the results of 1p34–36 LOH diagnosis, combined with St. Gallen's guideline and/or histopathological diagnosis, will assist postoperative therapeutic planning for high-risk breast-cancer patients.

Conclusion

Genes that are known to be implicated in sporadic and familial breast cancers, and the significance of molecular diagnosis for those genes, have been reviewed in this article. In western countries, where breast cancer is the most common cancer among women, prophylactic mastectomy or administration of antiestrogen are occasionally undertaken for prevention of breast cancer in high-risk individuals. Although prophylactic mastectomy seems to be associated with considerable reduction in the risk of breast cancer, such aggressive intervention is not the general rule in Japan where both morbidity and mortality are relatively low. However, postoperative molecular diagnosis is valuable for Japanese patients, to guide decisions regarding aggressive adjuvant therapy in malignant cases. It is also helpful for avoiding excessive administration of anticancer drugs in cases where prognosis is better. New technologies growing out of the Genome Project are contributing to the development of diagnostic methods that should allow even more rapid and accurate diagnosis. Even so, the protection of privacy for individual patients presents an ethical problem, and we recognize also the potential emotional consequences to a patient regarding genetic diagnosis. Therefore, it is necessary to develop appropriate policies for release of genetic information.

Acknowledgements

We thank Dr. M. Yoshimoto, Dr. T. Tada, Dr. G. Sakamoto, Dr. F. Akiyama, and Dr. F. Kasumi (Department of Surgery and Pathology, Cancer Institute) for their cooperation in our studies examining LOH and postoperative prognosis, and Dr. Y. Nakamura (Institute of Medical Science, University of Tokyo) for valuable advice.

REFERENCES

1) Hall, J.M., Lee, M.K., Newman, B., Morrow, J.E., Anderson, L.A., Huey, B. and King, M.C.: Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 1990; 250(4988): 1684–1689.
2) Miki, Y., Swensen, J., Shattuck-Eidens, D., Futreal, P.A., Harshman, K., Tavtigian, S., Liu, Q., Cochran, C., Bennett, L.M., Ding, W. *et al.*: A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. *Science* 1994; 266(5182): 66-71.
3) Wooster, R., Bignell, G., Lancaster, J. *et al.*: Identification of the breast cancer susceptibility gene *BRCA2*. *Nature* 1995; 378(6559): 789–792.
4) Shen, S.X., Weaver, Z., Xu. X., Li, C., Weinstein, M., Chen, L., Guan, X.Y., Ried, T. and Deng, C.X.: A targeted disruption of the murine *BRCA1* gene causes gamma-irradiation hypersensitivity and genetic instability. *Oncogene* 1998; 17(24): 3115–3124.
5) Emi, M., Matsushima, M., Katagiri, T., Yoshimoto, M., Kasumi, F., Yokota, T., Nakata, T., Miki, Y. and Nakamura, Y.: Multiplex mutation screening of the *BRCA1* gene in 1,000 Japanese breast cancers. *Jpn J Cancer Res* 1998; 89(1): 12–16.
6) Eisen, A., Rebbeck, T.R., Wood, W.C. and Weber, B.L.: Prophylactic surgery in women with a hereditary predisposition to breast and ovarian cancer. *J Clin Oncol* 2000; 18(9): 1980–1995.
7) Hacia, J.G., Brody, L.C., Chee, M.S., Fodor, S.P. and Collins, F.S.: Detection of heterozygous mutations in *BRCA1* using high density oligonucleotide arrays and two-colour fluorescence analysis. *Nat Genet* 1996; 14(4): 441–447.
8) Deming, S.L., Nass, S.J., Dickson, R.B. and Trock, B.J.: *C-myc* amplification in breast cancer: A meta-analysis of its occurrence and prognostic relevance. *Br J Cancer* 2000; 83(12): 1688–1695.
9) Harada, Y., Katagiri, T., Ito, I., Akiyama, F., Sakamoto, G., Kasumi, F., Nakamura, Y. and Emi, M.: Genetic studies of 457 breast cancers: Clinicopathologic parameters compared with genetic alterations. *Cancer* 1994; 74(8): 2281–2286.
10) Revillion, F., Bonneterre, J. and Peyrat, J.P.: ERBB2 oncogene in human breast cancer and its clinical significance. *Eur J Cancer* 1998; 34(6): 791–808.
11) Coles, C., Condie, A., Chetty, U., Steel, C.M., Evans, H.J. and Prosser, J.: *p53* mutations in breast cancer. *Cancer Res* 1992; 52(19): 5291–5298.
12) Sato, T., Tanigami, A., Yamakawa, K., Akiyama, F., Kasumi, F., Sakamoto, G. and Nakamura, Y.: Allelotype of breast cancer: Cumulative allele losses promote tumor progression in primary breast cancer. *Cancer Res* 1990; 50(22): 7184–7189.
13) Emi, M., Yoshimoto, M., Sato, T., Matsumoto, S., Utada, Y., Ito, I., Minobe, K., Iwase, T., Katagiri, T., Bando, K., Akiyama, F., Harada, Y., Fukino, K., Sakamoto, G., Matsushima, M., Iida, A., Tada, T., Saito, H., Miki, Y., Kasumi, F. and Nakamura, Y.: Allelic loss at 1p34, 13q12, 17p13.3, and 17q21.1 correlates with poor postoperative prognosis in breast cancer. *Genes Chromosomes Cancer* 1999; 26(2): 134–141.
14) Utada, Y., Emi, M., Yoshimoto, M., Kasumi, F., Akiyama, F., Sakamoto, G., Haga, S., Kajiwara, T. and Nakamura, Y.: Allelic loss at 1p34–36 predicts poor prognosis in node-negative breast cancer. *Clin Cancer Res* 2000; 6(8): 3193–3198.