

COMMENTARY

“One Step” for Cancer Prevention

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Introduction

I have been involved in cancer research for many years. When I think about what is most important in this field, I believe it must be “cancer prevention”. Unhappily, this area has not been always sufficiently valued either by researchers or by the general public. However, from a realistic perspective, cancer prevention is extremely important at both an individual and collective level. This fact, I believe, will eventually be understood by society and, consequently, more effective measures will be taken. In this paper, I will introduce my views on cancer prevention, along with a few experimental results.

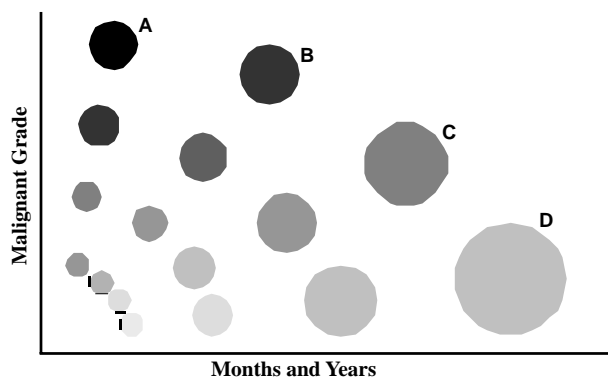
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Experimental Prevention of Malignant Progression

The purpose of cancer prevention is to prevent the development of cancer. However, even though we may accept that cancer development cannot be avoided as one grows older, if we can prevent malignant progression of cancer, this must be the second-best countermeasure for cancer.

Clinically speaking, malignant grades of cancer vary individually in the cancer development and its process (Chart 1). Some cancers turn malignant in a short time (A), while in other cases only a minute degree of malignancy may be detected after a long period of time (D). However, those cases (A, D) are perhaps 10% to 20% of all cancer cases. If these extremes were given too much emphasis, one might prematurely conclude that “cancer screening has no merits whatsoever” or “if I have cancer, I won’t do anything about it”. However, in most cases, cancer gradually turns malignant



Text-Figure 1. Sizes of Tumours and Malignant Grades (denoted by shading)

with passage of time (B, C). That is why early detection of cancer is recommended; it is not only because small size of cancer can be removed relatively easily by surgery, but also because, since malignant progression is not complete, the prognosis may turn out to be good. Therefore, it is always safe and best to detect cancer in its early stages, and treat early. The reality, however, is that there is never sufficient information as to how the individually different patterns of malignant progression of A, B, C, and D can be produced.

One intrinsic factor is that the inflammatory reaction to cancer cells can possibly be a cause of malignant progression. According to this theory, the reactive oxygen that is produced from white blood cells (Okada et al., 1992; 2006) and macrophages (Yamashina et al., 1986) scar the genes of cells, and this will act towards the onset, as well as malignant progression of cancer. Proof of this was provided by the following experiment. Pseudo cancer cells originally called regressors, which do not grow in normal isogenic animals, begin to proliferate and kill the host when white blood cells are added (Okada et al., 1992). However, when an anti-neutrophilic antibody is administered to those animals, malignant progression is prevented; the cells return to the original regressor state, so that malignant progression is controlled (Tazawa et al., 2003).

Such experiments need to be pursued further. In any case, it is necessary not just to prevent the onset of cancer, but rather it is important to broaden our perspective to preventing malignant progression of developed cancers as well.

Chemoprevention in Newborn Animals

It is said that cancer prevention should begin as early as possible. The same can be said of cancer chemoprevention.

For example, what kind of result can we obtain if chemopreventive agent is administered to a newborn baby instead of to a mature animal? It would be best if chemopreventive agent could be administered to a fetus in the pregnant mother. But that would come with technical restrictions. Thus, we assumed that a newborn infant (within 24 hours after birth) is an organic environment corresponding to the fetus, and gave the infant various chemopreventive materials to study cancer preventive effects on becoming adult.

We kept the minimum dose of chemopreventive materials at birth within a range that indicated healthy growth of the infant and posed no impediment to its development. We then administered AOM (azoxymethane) to induce colorectal cancer and measured the number of ACF (Aberrant Crypt Foci), a precancerous lesion of colorectal cancer. The control was the AOM-induced ACF number in normal animals without administering chemoprevention materials at birth. An outline of the experiment is shown in Chart 2. By administering PSK, lactoferrin, sulindac, and curcumin at birth, the later emergence of ACF was controlled (Matsunaga et al., 2000; Kobayashi et al., 2000; 2002; Iijima et al., 2004). Particularly, the ACF inhibition effect of sulindac and PSK was stronger than that of other materials. This ACF-inhibition effect seemed stronger than in animal to which the same materials were administered for the first time after becoming adults. However, after administering these materials at birth, the same agents additionally administered in the adult tended to further reduce ACF numbers (particularly with sulindac and curcumin).

Our understanding of the mechanisms underlying such effects is still insufficient. Thymus-derived T-lymphocyte activation was found to be increased in animals to whom chemopreventive agents had been administered at birth and levels of glutathione S-transferase were also increased. As far as the database up to this point is concerned, there have been no reports on chemoprevention to a newborn for the purpose of cancer prevention. Thus, there is a need to investigate the extent of universality in this phenomenon,

Table 1. Effects of Agents on ACF Development

Agent		At Birth	When Adult	Both
PSK	Treatment	82 (14)	162 (13)	
	Control	176 (18)	168 (13)	
	Inhibition Rate	53.4%	3.6%	
Lactoferrin	Treatment	115 (72)	193 (48)	
	Control	198 (72)	218 (68)	
	Inhibition Rate	41.3%	11.5%	
Sulindac	Treatment	72 (42)	90 (47)	49 (23)
	Control	193 (96)	193 (96)	193 (96)
	Inhibition Rate	62.7%	53.4%	74.6%
Curcumin 1	Treatment	115 (22)	156 (72)	102 (38)
	Control	176 (96)	193 (96)	193 (96)
	Inhibition Rate	34.7%	19.2%	47.2%
Curcumin 2	Treatment	130 (23)	200 (31)	
	Control	196 (72)	218 (68)	
	Inhibition Rate	33.7%	8.3%	

Joint research with Matsunaga et al at the Kureha Chemical Research Lab

which includes clarifying its mechanism.

ABCD and the E Strategy

Discussions of human “lifestyle-related diseases” often draw attention to cardiovascular diseases, such as heart attacks, and cerebrovascular disease; in general, cancer tends to be forgotten. Is this because of our preconceived notion that cancer is complicated in its etiological mechanism and difficult to understand? And yet, cancer is the most common lifestyle-related disease. Using this opportunity, we should adopt a new approach for the prevention of cancer and cardiovascular diseases by gathering all of these as “lifestyle-related diseases”.

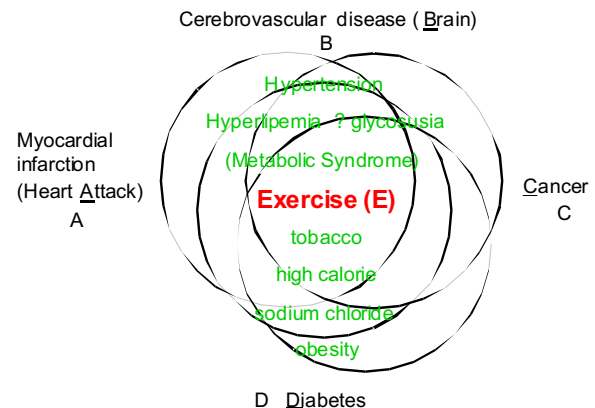
As lifestyle-related diseases, Heart Attack (A), Cerebrovascular Disease (Brain, B), Cancer (C), and Diabetes (D) share common causes as shown in Text-Figure 2. In other words, cancer prevention effects can positively influence other lifestyle-related diseases including cerebrovascular diseases. Conversely, if those lifestyle-related diseases can be prevented, that will have a positive effect on cancer prevention as well.

Years ago, when Japan was cornered in World War II, the ABCD Alliance was created. With the axes of America (A), Britain (B), China (C) and the Dutch (D), their economic blockade was designed to make it impossible for Japan to be economically self-reliant. Although my A, B, C, and D in this context are not related to politics, one can say that causal factors for lifestyle-related diseases (A, B, C, D) can be considered “health-blockade factors” as well. There is one thing that can protect against these lifestyle-related diseases: Exercise (E). If I may be permitted to use a Japanese pun, this Exercise (E) is the only “ii (good in Japanese)” element that can stand in the way of the A, B, C, and D lifestyle-related diseases.

Public Health Against Cancer

Background for the Introduction of Public Health Programs

From historical data, we can see that a country’s approach toward public health influences the disease pattern of that country. Tuberculosis, called Japan’s national disease, is one



Text-Figure 2. Prevention of Lifestyle-related Diseases

example. Today it is believed that the reason for reduced TB deaths was the emergence of streptomycin, which prevented the spread of tubercle bacilli through secondary infection. Yet, streptomycin cannot be the only reason for this. Another possible major reason is the improvement of the living environment in the postwar years (especially the fact that the intake of highly nutritious foods became possible, helping the body's resistance to recover).

The decrease in stomach cancer can be seen not only in decreased mortality rates but also in the drop in incidences. The latter can be explained by improved diet (e.g. decreased sodium intake). The drop in uterine cancer can also be attributed to preventive effects such as improvements in the living environment, such as bathing facilities at home.

In the United States, the drop in the incidence of lung cancer corresponds to the decrease in smoking rates; thus the drop in colorectal cancer is also considered a result of dietary improvement.

From the above facts, I can confidently assert that the cancer preventive effect from improving living environments has a greater impact than advancement of cancer treatment (by surgery, radiation and chemotherapy). It's true that once cancer occurs, a person has no choice but to resort to treatment at hospital. Nonetheless, the involvement of our daily living environment is crucial in the process of human cancer prevention. This is the reason we place such importance upon public health campaigns against cancer. Speaking of prevention, in recent years, there has been active research on aggressive cancer chemoprevention by drugs. Expectations concerning chemoprevention against cancer are already high; specifically, they are observed in the cancer preventive effects on breast cancer by tamoxifen, and on colorectal cancer by CoQ10 inhibition.

Of course, I have the highest regard for academic advances in cancer chemoprevention and expect further progress in the future. Yet, if asked to promise that success in chemoprevention will be more than in improvement of living environment, frankly, I cannot easily do so. I believe that we should expect to see preventive effects to cancer by prioritizing behavioral prevention of improving daily life style and that secondarily we should also expect active chemoprevention as a complementary method in individual organs (or their precancerous lesions).

Reason for Choosing Sri Lanka for Public Health Programs

It is only logical to implement a public health campaign against cancer in our local area. In fact, several public health campaigns against lifestyle-related diseases including cancer have been carried out in Japan. I have also done something similar to these. However, it is also true that experience forced me to face the limitations of one person after leaving college. Fortunately, I happened to have relations and ties with another Asian country, Sri Lanka, which I found appropriate as a model country for cancer prevention. Thus, I decided to carry out studies.

There were several reasons for selecting Sri Lanka. First, just as in advanced nations, Sri Lanka, a developing country,

has an overwhelmingly number of lifestyle-related diseases. Second, its medical level is relatively high and its life expectancy is above 70 years, the highest among Southeast Asian or neighboring nations. Third, one direct and personal reason is that I visited Sri Lanka in 1998 and became interested in its culture --- the smiling, mild-mannered, and rich culture of the Sri Lankan people. Although the living standard is low, Sri Lankan children have a twinkle in their eyes. So, this was one big motivation for me to get involved in this country.

Since the Sri Lankan government has a socialist system, the government pays all medical expenses, there is no individual burden of medical cost. This is a major factor for the exhaustion of its national economy. On top of that, if the cost of the ongoing military campaign against the Liberation Tigers of Tamil Eelam (LTTE), active in the northwestern part of Sri Lanka, is added, there are numerous grim factors in its economic outlook.

Target for the Activities

In Sri Lanka, oral cavity cancer caused by the habit of betel chewing tobacco accounts for a high percentage of deaths. Oral cavity cancer patients have difficulty taking meals; it is quite an unfortunate cancer in terms of appearance as well. Thus, we decided to conduct a prevention campaign against oral cavity cancer there. As part of this campaign, Professor Itsuo Chiba of the Health Science University of Hokkaido created campaign posters with the text in both Sinhali and Tamil saying, "Chewing tobacco causes oral cavity cancer; Let's stop it", and widely distributed them to those concerned (Text-Figure 3).

Initially, we also planned to conduct an experiment on



Text-Figure 3. Poster Message "If you don't stop this habit you will end up in a coffin"

chemoprevention (especially by introducing curcumin-chewing gum) on people with precancerous lesions of oral cavity. However, we noticed something unexpected. When giving out chewing gum to those people, we had advised them to stop chewing tobacco. But regardless of the use of curcumin-chewing gum, by simply not chewing tobacco, Dr Chiba noticed precancerous lesion had a tendency to disappear naturally. In other words, simply by ceasing to chew tobacco, the prevention of oral cavity cancer is possible. Needless to say, this fact had a major impact on our thinking.

The campaign was conducted with this progression. It seemed that the Sri Lankan government had long been telling them to do the same. The effect of our campaign was not necessarily as we had hoped. Allow me to introduce a typical conversation over this issue between a Japanese doctor and a Sri Lankan doctor at that time:

Japanese Doctor: Since the habit of chewing tobacco definitely causes oral cavity cancer, they must stop this habit.

Sri Lankan Doctor: Chewing tobacco is a traditional Sri Lankan custom; it's part of our everyday life. People cannot easily stop it - it's almost like a 2000-year old religion.

Japanese Doctor: Yet, what's bad is bad. Of all types of cancer, mouth cavity cancer is a particularly miserable type.

Sri Lankan Doctor: I understand well what you're saying, but in reality, it's not easy to kick this habit. I understand that smoking rates in Japan haven't dropped easily; I think it is harder to quit the habit of chewing tobacco here in Sri Lanka than to quit smoking in Japan.

As one can imagine from the above conversation, we realized how difficult it is to educate and enlighten adults about quitting chewing tobacco.

How We Can Appeal to Children - Utilization of the Mass Media

We cannot continue to expect adults to do efficiently what they will not agree to do. Thus, we decided to switch our prevention campaign target from adults to elementary, middle, and high school children (Text-Figure 4). Not that we passively switched our policy because adults did not change. Rather, it was because we remembered the historical fact that the success in improving lifestyles in the United States began in elementary school classrooms. “Healthy People 2000”, a lifestyle improvement movement undertaken in America, began under the leadership of Senator George McGovern. The focus of this was on education against lifestyle-related diseases such as cancer, and selected subjects among upper-grade elementary-school students at several schools in the nation. The plan emphasized no smoking (aimed at preventing juvenile delinquency, rather than disease prevention), blood pressure checks, and cholesterol-level measurement, plans seemed



Text-Figure 4. Targets for Disease Prevention Education

to be most found impossible to conduct with elementary schoolers. Although schoolteachers fiercely objected to those plans initially, they became persuaded by the enormous research funding that supported McGovern's strong enthusiasm, which resulted in an educational movement with the unanimous support of schools.

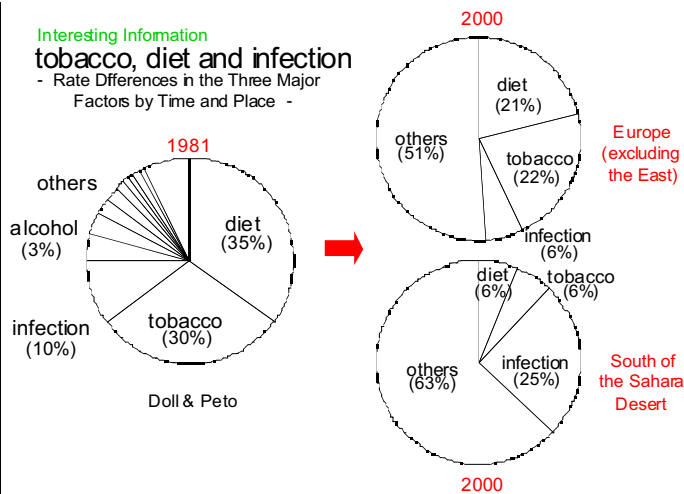
Children who received this kind of education went home and began to indirectly affect their parents. This eventually became a citizens' movement in local communities, and with the understanding of the mass media, a climate of lifestyle improvement went on to spread throughout the entire nation. As a result, drops in age-adjusted mortality and in incidence could be observed in the cases of heart attack, cerebrovascular disease, lung cancer, and colorectal cancer. This was indeed a successful case of mass-media strategy for improvement of lifestyles. Therefore, I began to think that this success model in the United States might be applied to Sri Lanka.

It is interesting to note that, although fine textbooks on public health education are published in Japan, there have been few signs that educators strive to specifically implement the recommendations of those textbooks. How is it in Sri Lanka? This country is passionate about education, yet does not have public health education textbooks like those in Japan. It is easy to imagine how harsh its educational environment is from the fact that there is a shortage of chalkboards in classrooms which are essential for the school education.

Despite this, we are both hopeful and convinced that an education of “Make haste slowly” to impressionable children in Sri Lanka will bring great success. From this standpoint, since 1998, the Sapporo Cancer Seminar Foundation staff has continued to introduce health education to the elementary schools of Sri Lanka. Fortunately, it was decided, as of July of 2006, that we would receive the cooperation of JICA grassroots projects. Currently, we are planning to raise the level of health awareness by selecting four schools from Southern Province of Sri Lanka, by enlightening teachers, by holding teacher-student study groups and workshops that include parents, and by publishing newsletters. The details of those outcomes will eventually be reported.

Reconsideration of the Doll and Peto Theories

Interesting Information
tobacco, diet and infection
 - Rate Differences in the Three Major Factors by Time and Place -



Text-Figure 5. Risk Factors for Cancer (IARC 2000)

In 1981, a famous diagram of carcinogenetic environments was presented by Drs Doll and Peto of England. Diet (35%), smoking (30%) and infection (10%) accounted for 75% (3/4) of all carcinogenetic factors. These estimations were later largely confirmed in follow-up studies by several researchers, and have been utilized as solid data by many people. I used to think those rates of carcinogenetic factors would remain unchanged forever. However, according to 2000 data released by the International Agency for Cancer Research (IARC), at least in Western Europe, the rates of diet, smoking, and infection dropped to 21%, 22%, and 6%, respectively; the total rate also dropped to 49% (Text-Figure 5). It was hard to believe; I thought for a moment this was some kind of mistake.

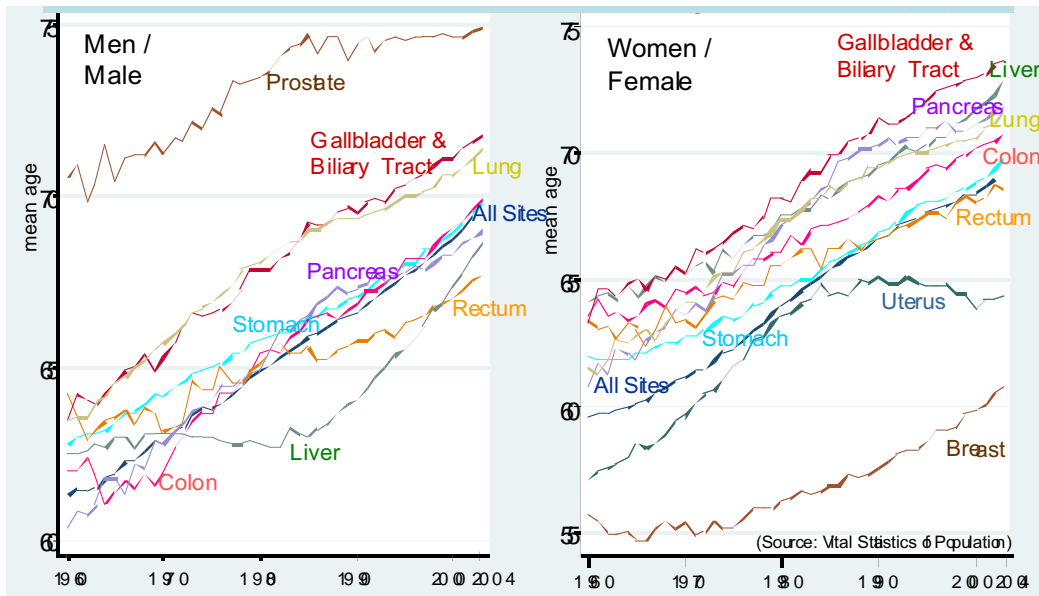
Yet, if considered very carefully, those changes were simply part of a natural progression. The three environmental factors were properly acknowledged and, consequently, many people decided to watch their diet and refrain from

smoking. Anti-infection measures have also been actively implemented. As a result, the total sum of the three big factors has decreased by 26% in the last 20 years. One question remains, however: what is the breakdown of “the rest” (51%)? “The rest” has increased to 51% from 25%. It may include newly discovered carcinogenic factors such as asbestos. It may also imply that we must focus more on genetic factors of the host and unknown carcinogenic factors that accompany ageing as life expectancy continues to lengthen. Meanwhile, according to IARC data, in South Africa (south of the Sahara Desert), the same rates of diet, smoking, and infection are 6%, 6%, and 25% respectively, making the total 37%. Although infection is understandably high, it makes one wonder why “the rest” is so high at 63%.

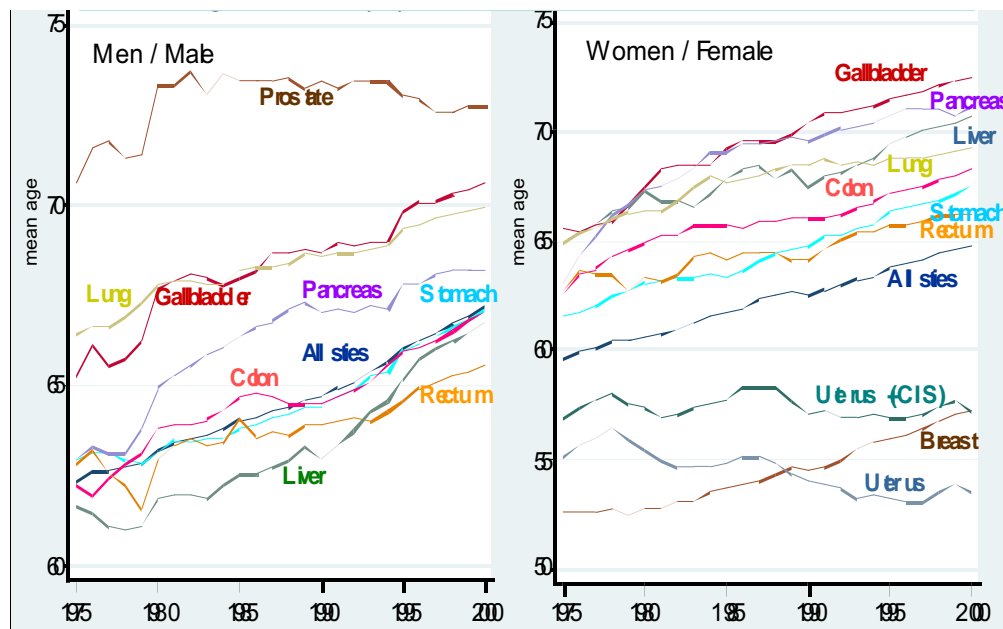
In the past, cancer prevention was relatively easy as long as carcinogenic factors were clear. Nowadays, carcinogenic factors relatively unknown to us have grown, while the familiar factors have declined. What kind of approaches do we need to adopt in the future? Once again, we realize the depth of cancer prevention measures.

Age at Death from Cancer

Cancer treatment outcomes are often told by mortality (or cancer survival rate). The current five-year cancer survival rate is 50% or greater; cancer treatment has come a long way. However, Japan’s age-adjusted cancer mortality at all sites shows little change in men, though women’s mortality has decreased slightly. If this is the case, mortality-wise, one cannot say our national cancer treatment outcomes have improved. How about age of death from cancer? For this research, we received the cooperation of Drs Tomotaka Sobue and Tomomi Marugame of the National Cancer Center in Tokyo. We learned that the age of dying from cancer became considerably older after 1960 (Text-Figure 6). In the last 40 years, the age at death at all sites has become



Text-Figure 6. Change in Age at Death from Different Cancers in Japan During the period 1960-2001



Text-Figure 7. Change in Age at Onset of Different Cancers in Japan During the Period 1975-2000

approximately 10 years later both in men and women. By organ, there are cases in which a conspicuous extension was added to the age at death (i.e. liver cancer) while others have not (prostate, uterus).

In conclusion, advances in cancer treatment outcomes may not be reflected in mortality, but they are clearly observed in the delaying effect on age at death. Humans all eventually die of a certain cause. Still, a 10-year extension of life must be considered quite precious. Thus, I believe more attention should be given to “age at death”.

Age at Onset of Cancer

Preventive effects on cancer should be indicated by age-adjusted incidence. In fact, cancer incidence in the United States is said to be on the decline. Japan’s cancer incidence, however, has been more or less the same. At least, there has been no trend of declining incidence. What about examining it by the age of onset? According to the data (Text-Figure 7), which we commissioned from Dr. Sobue of the National Cancer Center and were compiled by Dr. Marugame, the age of all-site cancer onset has been extended approximately five years in both men and women in the 25-year period from 1975. Although the age of onset varies depending on organ, the age of contracting cancer clearly has been delayed in general.

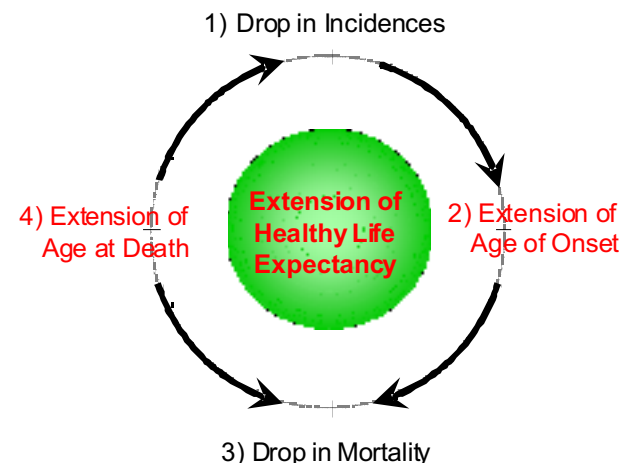
However, since the delay effect had already begun prior to the 1990s, when people became stricter about improving their lifestyles, we may not be able to assert with total confidence that this was “a result of cancer prevention campaign” contributed by the improvement of lifestyles such as smoking, diet, and infection. It will require a careful discussion. In any case, extension of the age of cancer onset does influence the extension of the age at death, which is a clear-cut advancement for the countermeasures against

cancer. The general public should be aware of this as well.

Goals of Cancer Medical Care - In Place of a Summary

It would be great if cancer treatment outcomes were always marked by a decline in mortality. Still, in the case if a drop in mortality is not observed, efforts in cancer medical care are not rewarded is not true. That is because a delay of the age at death alone is a valuable, successful result. Similarly, cancer prevention effects would be better if they were shown to cause a decline in incidence; but that is not necessarily so. Yet, even in this case, if we can delay the age of cancer onset five or ten years or even longer (a delay of age of onset), this too can be valued as a successful result of cancer prevention.

Because of advances in cancer medical care, we tend to indicate everything by mortality, incidence, or other “rates”.



Text-Figure 8. Goals of Cancer Prevention Measures

When those numbers are not satisfactory, people may think that the efforts to conquer cancer in medical care are not rewarding enough. But, as I mentioned above, those results are satisfactory. In other words, those efforts to beat cancer are clearly reflected when any cancer-related “age” is delayed.

At any rate, as shown in Text-Figure 8, the goals of cancer medical care should be viewed as a whole; they should be compiled in one set of the decline in incidence, the extension of age of onset, the decline in mortality, and the extension of the age at death. Furthermore, one ideal goal of cancer medical care is not only to achieve quantitative improvements represented by rates and extension of age, but to aim for qualitative improvements such as “healthy life expectancy”. When these two components, quantity and quality, are put together, we can claim for the first time that our goals have been realized.

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