

„Pathologist’s advice on How to combat cancer“ series

Part 1: Cancer is not a horrifying disease

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

“Isn't cancer inherited?” “I'm worried because we have a family history of cancer.” “Is cancer a lifestyle-related disease?” “Can we prevent cancer by changing our lifestyle?” These are questions that I as a physician, MD and PhD, commonly encounter. The first two beliefs have little supporting evidence and are not considered to be true for adult cancer. The latter two can be answered in the affirmative. This comment will change your “common sense” with a great surprise, won't you?

Generally speaking, cancer is commonly considered a horrifying disease. However, this is not necessarily true; many adult cancers can be prevented. If it can be detected early, complete recovery is possible through early treatment by conventional modern medicine in the almost all cancers with exceptions of lung cancer as well as pancreas cancer.

The length of the latency period of cancer is closely associated with diet and lifestyle

In many cases, adult cancers grow to a visible size after a long latency period of 10 or more years. Believe it or not, the length of the latency period may be made shorter or longer, and this is closely associated with the individual's lifestyle, such as diet and lifestyle habits, as well as with the physical characteristics of the individual. This means that in the extreme case, the latency period may be extended semi-permanently over your expected life long by self discipline.

Once cancer becomes a visible size, its growth apparently becomes sharply accelerated. The cancer then spreads to other areas of the body, causing a troublesome state known as metastasis, so-called advanced cancer. Compared to its long latency period, it only takes a couple of years for the cancer to reach its terminal stage. This situation itself makes us cancer as a horrifying disease.

The association between latency period and diet/lifestyle has become evident through medical research in the past ten years. So, if you are mature-aged and currently cancer-free, thinking that your cancer is in its latency period would make you cherish your body forever, and you would take care of yourself to seek ways to prevent cancer if it is possible at all. Being just over 60 years old myself, I am right in the midst of the cancer-prone age, but I am eager to practice better lifestyle and cooking better recipe and habits, and I am actively trying to recognize how to prevent cancer.

Strategies against cancer that emphasize the relationship between the mind and body

Certain constituents of food, especially plant nutrients (fruit and vegetables), will be discussed in details later. They have extremely potent protective effects against cancer. The primary objective of this column is to raise your awareness of these foods.

There aren't many foods that you need to abstain from, as long as you eat them in moderation. Almost all foods or habits are “dos”. Unfortunately, refraining from “cigarette” smoking is “not-dos” and is of the foremost importance. Difference of the term between cigarette and tobacco will be discussed in the later chapter.

In unfortunate cases where cancer is found in progressed stages, new treatment options can be considered in addition to the conventional options, such as surgery, chemotherapy and radiation. The possibilities of cancer immunotherapy and complementary and alternative medicine (CAM) are currently being studied extensively. I believe that strategies against cancer should be directed at the individual as a whole, and at the individual's entire lifestyle, with an emphasis on the

relationship between the mind and body. Medical professionals must supply evidence-based and neutral information available at the level of state of art to every patient or client. Also, they must provide various healing ways with a motto of never-give-up fit for each individual as much as possible, so-called tailor-made medicine. To do this, the second objective of this column is to discuss the concepts and clinical applications of supplementing modern medicine and creating an integrated form of medicine.

Doubts about modern medicine during 29 years of hospital work experience and over 700 cases of clinical autopsy

Looking back to a couple of decades ago, I used to believe that it was common sense to treat for cancer using surgery, radiation therapy, or chemotherapy. That was when I was completely immersed in conventional modern medicine, and working as a pathologist as well as a clinical immunologist at a general hospital in Tokyo.

During the 29 years of my work at the hospital where I experienced over 700 cases of clinical autopsy of patients who passed away despite undergoing treatments, I often pondered over whether or not the cancer treatments provided for these patients were in fact effective.

Also, at that time, I was ignorantly unaware of the deeper meaning of words such as “cancer-prone age,” “lifestyle-related disease,” and “adult disease.” Embedded within all these words is the concept of a latency period. Recently, some have suggested the use of the concept of “Mi-Byou” or “expecting-disease” used in Chinese medicine in place of latency period.

Collecting scientifically accurate information from varied sources, conducting comparative analysis, and providing clear explanations

People are easily manipulated by information that surrounds them. Even physicians are no exception; we easily find ourselves buried within medicine, our area of specialization. It is a painstaking task even for physicians to break free from the barrier of our specialization by recognizing that a doctor is first and foremost one individual, and to collect accurate scientific information from a broad range of sources.

It is a most difficult task to find universal ideas in the modern media that have been hiding among overflowing information. There seems to be little available information on strategies against cancer that is gathered with a sense of purpose, that extends beyond one's field of expertise, and that is compared, analyzed, and explained in comprehensive language.

I hope that this column will serve as a source of disseminating such information. Using my experience in pathology and immunology based upon modern medicine and physiology, I will be analyzing the advantages and disadvantages of modern medicine, and thinking of ways to choose supplement and/or conventional modern medicine. I then hope to effectively translate this information into detailed guidance for cancer prevention not only for non-professionals but also for the medical professionals. I would very much appreciate it if you could provide comments and criticisms on my health advice so that I would be able to incorporate them into the upcoming articles.

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Part 2: Contemporary medicine has become an integrated part of our lives

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

If you catch a cold or get appendicitis, you probably would not think that you would die from it. Indeed, antibiotics or surgery can easily cure these diseases, and nowadays people take this for granted. Similarly, if you become pregnant, you would not think that you would die during childbirth. Instead, you will be filled with joy when your baby is born in perfectly good health, thanks to the help of hospital staff or midwives. Contemporary medicine has really become an integrated part of our lives.

Let us look back on the state of medical care about fifty years ago, for example, around the period after World War II. Antibiotics were not readily available, and technologies for anesthesia, sterilization, and disinfection were still underdeveloped. Back in those times, people were constantly faced with the possibility of death from bacterial infections such as tuberculosis.

This also included deaths from childbirth (due to puerperal fever). Considering these circumstances, the fear of diseases that people had in the past is probably incomparable to the fear people have today. During those times, the average life span of Japanese men and women was around 50 years. Who could have imagined that only five decades later, the average life span would increase to around 80 years?

In the past, before vaccination and antibiotics were discovered, many children passed away before they reached the age of majority (which is 20 years of age in Japan). This is why the coming of age celebration was significant.

The birth of modern medicine in the mid 19th century

Modern medicine was the forefather of contemporary medicine, which is now integrated with our lives. How did modern medicine and modern medical care arise? Modern medicine developed in the mid 19th century in Europe. It was a period when doctors were not as skilled and "magician-like doctors" were providing medical care. This was the time when evidence-based medicine began to emerge in Germany (Berlin) and France (Paris).

By today's standards, the facilities available to doctors in the 19th century would be considered dangerously unprotected against infection. Those doctors dissected the bodies of patients who had passed away, seeking to understand the origins of diseases and the cause of death of the patients. The doctors in Paris matched the macroscopic observations (observations that were visible to the eye) made for each of the patients at the bedside with those made in the autopsy room, and recorded details of each case.

In Berlin, the light microscope ("microscope") was adopted as a new tool in pathological autopsy, and doctors sought to understand diseases at the cellular level. The observations using microscopes required another room in addition to the hospital room and autopsy room: the research laboratory. These approaches in Berlin laid the foundations of contemporary medicine (laboratory medicine). In any case, we must not forget to acknowledge the many doctors and researchers who dedicated their lives to academic study.

The tar in tobacco cigarettes causes skin cancer in animal experiments

German medicine during the latter half of the 19th century had an incredible driving force. One of the leaders behind it was Rudolf Ludwig Karl Virchow. Rudolf Virchow scientifically established the concept that "every cell originates from another existing cell like it" (omnis cellula e cellula) and founded the discipline of "cytopathology". Virchow was a revolutionary figure in both political

and academic arenas. It is not an overstatement to say that our present understanding of concepts such as cancer and inflammation was established based on the research achievements of Rudolf Virchow and other German scientists.

Rudolf Virchow sought to understand disease as a body's response to stimuli. A Japanese scientist by the name of Katsusaburo Yamagiwa followed this approach in his research. Katsusaburo Yamagiwa and his assistant Kouichi Ichikawa continuously stimulated the ears of rabbits with coal tar. After several years, their work bore fruit.

They were the first in the world to produce skin cancer under experimental conditions and their work was highly appraised. Coal tar contained not only stimulants, but also countless carcinogenic substances. These substances were the same as those found in tobacco tar, and scientists in the United States later conducted experiments using tobacco tar on rabbits' ears and similarly produced skin cancer under experimental conditions.

Mastering the use of the microscope leads to the discovery of antibiotics

The work of Heinrich Hermann Robert Koch led to the development of the discipline of bacteriology. This was during a time when diseases were primarily caused by bacteria. For a while, the study of infectious diseases became the central focus among other disciplines in medicine. During that period, intellectuals from around the world gathered in Germany to study medicine. Researchers from the United States were among them. Prominent intellectuals from Japan, including Shibasaburo Kitasato and Kiyoshi Shiga, went to study in Germany and contributed to research in bacteriology.

As mentioned earlier, pathology is characterized by mastering the use of the microscope. The approach of enlarging by a thousand times objects that could not be seen by the naked eye, and examining the forms of diseases and bacteria in this manner, was in fact a revolutionary movement.

This was the origin from which bacteriology and almost all other academic disciplines in medicine developed, which later led to contemporary medicine being established as a field of science.

World War I ended in 1918 with German defeat. As a result, the center of medicine started shifting from Germany to the USA, together with a shift in the center of the world economy to the USA and England, a trend that has remained unchanged since then. Such changes led to the discovery of antibiotics, a revolutionary treatment for bacterial infections.

The judgment of the skilled pathologist determines the fate of the patient

If we likened contemporary medicine and medical care to a tree, diseases can be likened to the roots and trunk of the tree. The wealth of information accumulated from microscope studies in the past 150 years is crucial for an accurate diagnosis of diseases. This can then lead to the treatment of diseases, which can be likened to the various branches and leaves of the tree.

For example, the diagnosis of cancer is made by skilled pathologists in university hospitals or municipal hospitals. (*) A doctor specializing in surgery may provide surgical treatment, such as removing stomach cancer or colon cancer tumors. Alternatively, a doctor specializing in internal medicine may use a thin, needle-like device to take a biopsy sample, such a sample from the liver or kidney. The tumor cells and biopsy samples receive treatment that allows them to be examined under a microscope. Here, the judgment of the pathologist determines the fate of the patient.

Some pathology tests are urgent and performed during surgery (intraoperative evaluation). In such cases, the surgeon requests a pathology test on a small sample from the patient's body during surgery, and the sample is examined under a microscope. Microscopic examinations of these samples may be necessary in order to confirm the extent of the spread of cancer and judge

the appropriate surgical resection; for example, in a patient with stomach cancer, surgeons can use microscopic evaluation to determine whether the stomach can be partially retained or whether it should be completely removed.

In such cases, the pathologist acts as the headquarters for planning the surgery. If you have had surgery before, I would like to remind you of the pathology team, who were vigorously working—even more so than the surgeon—while you were sleeping under anesthesia. The pathology team is the "unsung hero" that works behind the scenes; medical care relies upon teamwork.

Reconsidering "magic-like" traditional medicine, which was formerly the target of criticism by proponents of modern medicine

Another important area in pathology is pathological autopsy. The purpose of pathological autopsy is to reveal the cause of death, to identify the state of disease, and to evaluate the effects of treatment, from a perspective that is different to the patient's doctor in charge, in unfortunate cases where patients pass away in hospital. Pathological autopsy is unprofitable work considering the present state of affairs in medical care. However, I believe that this is the minimum requirement for objectively evaluating modern medicine. Even though pathological autopsy is not profitable, it is done for purposes of inspection and improvement of a hospital's medical care, as this reflects the hospital's philosophy and moral standards.

Before I finish this chapter, I would like to mention that certain elements of "magic-like" traditional medicine, which were formerly the target of criticism by proponents of modern medicine, are being reconsidered today. Despite many infectious diseases being conquered using antibiotics, some diseases remain difficult to cure, such as cancer and chronic diseases. These are diseases that cannot be cured suddenly. These are known as lifestyle-related diseases. It is being increasingly acknowledged that changing one's lifestyle, improving the content of one's diet, and experiencing the natural power of healing, are also important treatment methods.

There is a need for a system of medicine that integrates contemporary medicine with complementary and alternative medicine, and a need for a patient-focused treatment that is individually customized for each patient. The message I wish to get across to patients is that they should think of themselves as the key players in their treatment.

(*) Contemporary medicine is considered to be based on evidence, and is known as evidence-based medicine. Therefore, both the diagnosis of a patient's illnesses and the selected treatments should be based on evidence. Patients have the right to receive this evidence, i.e., their medical records, as an official document. The medical service provider has an obligation to disclose information to patients. Pathology test reports are official documents containing personal information of the patient, and they belong to the patient. Therefore, pathology reports are very important documents, not only for applications for cancer insurance, but also for seeking a second opinion.

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Part 3: The introduction of antibiotics rapidly extends life expectancy

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

Until the end of World War II in 1945, the average life expectancy of humankind remained largely unchanged at around 50 years.

Since then, life expectancy improved rapidly owing to the discovery and widespread use of antibiotics (such as penicillin) and anti-tuberculosis agents, and today, a life span is considered to be 80 years in developed countries. A gain of 30 years in average life expectancy within a time frame of 50 years is a revolutionary achievement in the history of humankind. However, due to aging populations, cancer has become a major cause of mortality in developed countries, and its treatment has become a serious issue.

In the United States, cancer treatment centers were established one after another during the 1940s to 1950s. The National Cancer Institute on the east coast of the United States and the Memorial Sloan-Kettering Cancer Center in New York are famous institutes for cancer treatment and research.

Back in those days, the principal treatment for cancer was surgical treatment, and radiation therapy was used additionally as required. There was much hope that anti-cancer agents would be just as potent in cancer as were antibiotics in infectious diseases. Treatment methods superior to both the surgical knife and radiation were sought. Of course, that was a time when techniques in surgical anesthesia and radiation equipment were far more inferior compared to what we have today.

Development of anti-cancer agents begins in the 1950s, led by the National Cancer Institute

The discovery that a poison gas called mustard gas was effective in malignant lymphomas originated from hints gained from clinical observations of exposed soldiers in World War I. That discovery was made in the 1920s. Although several agents were effective, at least for a temporary period, such agents were primarily targeted for leukemia or malignant lymphomas. It was already known at the time that these agents would have little effect in tumor-forming cancers that occur in adults, such as stomach cancer and colorectal cancer.

These agents also caused strong adverse effects. The research and development for new substances began in the 1950s, and was led by the US National Cancer Institute. Tens of thousands of different chemical substances were searched through, and narrowed down to those with development potential. Taxol, currently used as an anti-cancer agent, is one of the key products resulting from the anti-cancer drug development initiative in the US. Enormous federal funds and human resources were invested for its development.

Unfortunately, however, there are no anti-cancer drugs at present that are as revolutionary and superior in their action as antibiotics. People are waiting for extremely effective anti-cancer drugs that have no adverse effects. It may be necessary here to explain how anti-cancer drugs work, as well as outline some of the characteristics of cancer.

Anti-cancer drugs destroy DNA or nuclear substances of rapidly-growing cells

Cancer in adults is very different from cancer in children. In children, leukemia, malignant lymphomas, cancer of the retina, and brain cancer are common cancers. In adults, cancer typically forms tumors in organs such as the stomach, colon, lung, mammary gland, prostate gland, and uterus (these are also known as “solid cancers” as it occurs in solid organs).

Adult cancers grow slowly. Anti-cancer agents attempt to destroy DNA and nuclear substances of rapidly growing cells. If anti-cancer agents enter a person's body within which cancer cells are growing slowly, healthy cells will be destroyed first, resulting in noticeable adverse effects.

Most cancers in adults grow slowly, so anti-cancer agents cause greater damage to healthy cells than to cancer cells. New drugs are currently being developed to overcome this problem, including drugs with molecular targets that selectively destroy substances on the cell surface associated with the growth of various cancers, and vascular targeting agents that disrupt the blood flow to tumor cells and starve them of nutrients.

The development of the "dream anti-cancer drug" is still a long way to go

Scientists still have not found an apparent "cancer mark" that distinguishes between cancer cells and healthy cells, which would enable cancer cells to be attacked like a patriot-missile attack. We often hear about the serious adverse effects of new anti-cancer drugs on the news. Unfortunately, it is still a long way to go before the development of the "dream anti-cancer drug."

Given the current situation, the ideal medical care would be one in which the patient, the patient's family and the medical team are united as one in a relationship of trust (and sharing the same viewpoint), with the cancer patient at the center of the team. Ideally, explanations about the cancer and the limitations of anti-cancer agents and their adverse effects will be accurately explained to the patient, so that the patient can understand his or her own circumstances. Furthermore, it is necessary for both the doctor and patient to actively participate in discussions on the difference in prognosis resulting from the use or non-use of chemotherapy, and in discussions on other possible treatments.

When considering treatment options, it is important to consider complementary and alternative medicines, and not only limit one's options to modern medicine. Why? It is because modern medicine is not perfect. And, if medical care aims to provide a comprehensive treatment for each person as a whole, we would need to return to the origins of Hippocrates. I plan to return to this point again in a later article.

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Part 4: Conquering externally-caused diseases, but fighting internally caused diseases

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

Today, most diseases that are identified as having external causes such as bacteria and viruses can be largely controlled. However, internally-caused diseases, or “disease from within,” such as lifestyle-related diseases, allergies, and autoimmune diseases (which are all closely related to body constitution) have started to afflict humans. In fact, adulthood cancer belongs to the category of lifestyle-related diseases. The idea of cancer as a lifestyle-related disease might come as a complete surprise to many people.

Cancer is a lifestyle-related disease because its prevention is linked to the concept of protecting the human body as a whole, which is what I aim to do in my medical practice. In simplified terms, cancer is a DNA-related disease. Cancer develops when a parent cell divides into two daughter cells, which divides into four cells, eight cells, and so on, dividing limitlessly. In other words, cancer originates from DNA defects in a parent cell.

Defects in chromosomal DNA accumulate over a decade or more, resulting in cancer

A pathologist makes the diagnosis of cancer by examining cell samples under a microscope. The appearance of the cells change, and this indicates the various stages of the cells, ranging from normal to cancerous stages. The earlier stages are sometimes referred to as atypical cells or pre-cancerous change. That is to say, cancer cells do not develop suddenly. All diseases have a latency period, and likewise, many adulthood cancers have a latency period that is ten or more years long.

What happens during this latency period? Minor damages occur daily to the DNA of cells in various parts of the body. The body has a mechanism that tries to repair these damages. However, if too many damages accumulate in the DNA, and if they cause defects in genes that regulate cell division or cell death, cells gradually become abnormal.

For example, if a person has a job that involves being exposed to the sun for long periods, precancerous changes develop in their skin cells, and these slowly develop into cancer. Ultraviolet rays in sunlight damage the DNA of skin cells. When cells are destroyed by UV, a fatty acid called arachidonic acid, an inflammation-causing substance that originally exists in the cell membrane, causes inflammation. White blood cells appear at the sites of inflammation and produce “bad” oxygen species (reactive oxygen species), which not only kills bacteria and other pathogens, but also begins to damage the DNA of the body’s own cells. Similar series of events are occurring all the time, in all parts of the body. The development of cancer signifies that such events had been continuously occurring for a decade or more.

Considering how cancers in adults develop after a long latency period, it should come as no surprise if the number of cancer patients increases as the population ages. People who are aged 50 years old and above are generally considered more “cancer-prone.” Is this an accurate conclusion? Thorough research suggests that this conclusion may not be necessarily true.

Stomach cancer and cervical cancers are tending to decline

Looking at adulthood cancers as a whole, mortality rates have continued to rise in recent years. In fact, one in three people die from cancer in Japan. However, a closer examination of the different adulthood cancers reveals that while the mortality rates of some cancers are continuing to rise, certain cancers have declining or stagnant mortality rates. Thus, it would be inaccurate to conclude that death rates of all cancers are rising.

Among the cancers on the decline, stomach cancer in the elderly has shown the largest decline. Both the mortality rate and incidence of stomach cancer have been declining worldwide. During the first half of the 20th century, the most common cause of death from cancer for American men was stomach cancer. In response, the US National Cancer Institute's main research focus in the 1940s was the eradication of stomach cancer. Cancer death rates naturally declined in the United States, and the rate of this decline has been particularly prominent after the 1960s.

During the 1960s, Japan, Chile, and Finland were among countries with a high stomach cancer mortality rate. However, mortality rates started declining after the 1960s, particularly in Finland. Although Japanese people were previously thought to have some genetic predisposition to developing stomach cancer, no genes associated with stomach cancer have been found in the Japanese to date.

The dissemination of screening programs for cancer is considered to be one of the contributing factors in the reduction of stomach cancer mortality. However, stomach cancer mortality also tended to decline in countries in which cancer screening programs were not commonplace. Diet is also considered as a contributing factor. Topics such as food preservatives, chronic gastritis caused by pyloric bacteria, restrictions in salt intake, intake of fresh vegetables, and vitamin C have received much attention. Much information on stomach cancer has been accumulated to date, and it is perhaps not an overstatement to say that medical professionals now have almost all the knowledge required to eradicate stomach cancer in the elderly.

Cervical cancer is the second fastest declining cancer after stomach cancer. Cervical cancer is triggered by chronic inflammation of vagina caused by viral infection or sexual intercourse. The decline in cervical cancer mortality has been mediated by screening programs, sex and hygiene education, and by habits such as keeping the vagina clean.

Searching for factors that trigger the onset of cancer and devising preventive measures

Though lung cancer mortality has been increasing in many countries around the world, including Japan, it has tended to decrease in men in the USA and UK. It is interesting to note that lung cancer is not a cancer that has been feared throughout history. Up until the beginning of the 20th century, when tobacco cigarettes began to be mass produced and sold, lung cancer was a very rare type of cancer. Following the period in which shredded tobacco was popular came the period of cigarette smoking, which rapidly increased tobacco tar inhalation and triggered an increase in the incidence of lung cancer. Anti-smoking campaigns in the USA and UK have been reducing lung cancer mortality in men. However, mortality is still tending to rise in women. The male smoking rate in the USA is approximately 25% while Japan's male smoking rate still lingers at around 50%.

Colon cancer, breast cancer, and prostate cancer are among cancers whose incidences have been rising. These cancers have been strongly associated with the increase in consumption of Western-style foods. In fact, we have already come to understand many of the causes of adulthood cancer through a careful study of these cancers. The causes can be directly linked to people's lifestyles, in areas such as diet and daily habits.

Analysis of these causes will allow us to devise preventive measures against cancer. As the saying goes, know thy self, and know thy enemy; if we can achieve this, we may be able to extend the latency period of cancer limitlessly, which practically means that we will no longer have cancer. An ounce of prevention is worth a pound of cure; it is imperative that we find measures to prevent this lifestyle-related disease.

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Part 5: Colorectal cancer rises as our diet becomes westernized

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

Let us focus on colorectal cancer as we examine some of the defense strategies we can employ against cancer. I have chosen colorectal cancer because it is most intimately linked with food. Colorectal cancer (a cancer of the large intestine) is truly a lifestyle-related disease; the incidence of colorectal cancer has risen in both men and women in Japan as our diets became more westernized.

Furthermore, new medical evidence has given us clues on how to prevent colorectal cancer. That is, the chances of developing colorectal cancer can be reduced by maintaining a healthy large intestine using medications that reduce inflammation.

The large intestine extends upwards from the lower-right side of the abdomen to the upper abdominal area, traverses to the left side, descends to the lower left side of the abdomen, and ends at the anus. The total length of the large intestine is about 1.5 meters. Water in food matter is gradually absorbed while it moves through the large intestine, and the food residues are accumulated and solidified in the lower left side of the abdomen, particularly in the rectum. That is why you can sometimes feel the accumulated food matter in the lower left area when you feel your abdomen. On the right side of the abdomen and in the upper abdominal area, food matter is still in a liquid or semi-solid form. This food matter is gradually pushed towards the lower left area by the muscular movements of the large intestine.

Cancer prevention: Preventing epithelial cells from becoming cancerous

The food matter in the large intestine is called feces in simplistic terms, but the amount of fat or protein it contains varies greatly depending on which portion of the large intestine the food matter is moving through. The passage time of the food matter and its effect on the large intestine has been a subject of interest.

When a colonoscope is used to look inside the large intestine, a soft mucous membrane lining the internal wall can be seen, and the large intestine looks like a pink tube. When the wall of the pink tube is magnified using a microscope, one can see fine, deep folds that are tightly organized. It is due to these folds that the large intestine can have an immense area of contact with the contents that pass through it. The surface of these folds of the mucous membrane is covered with an epithelial layer, which contains a row of tube-like projections. The epithelial cells absorb nutrients and water, and secrete digestive enzymes and mucus that facilitate the movement of the intestinal contents.

These epithelial cells, which are in direct contact with the intestinal contents, can become cancerous. To prevent cancer, we must prevent epithelial cells from becoming cancerous. Certain things we eat can cause these epithelial cells to become cancerous, while other foods are gentle and soothe the epithelial cells.

The immune system of the intestine is the driving force behind the power of natural healing

The contents of the large intestine are not entirely food material. The large intestine is originally inhabited by an enormous amount and variety of intestinal bacteria. Maintaining a good balance of intestinal bacteria is important for maintaining a healthy body. Even though intestinal bacteria are lost together with food matter during the excretion of feces, their population grows back again through multiplying, forming unique bacterial colonies inside the intestines. These intestinal bacteria are first acquired at birth, during the baby’s passage through the mother’s birth canal.

When you are thinking about the relationship between the intestinal contents and the wall of the large intestine, it is important that you give enough thought to not only the food, but also the bacteria, in the intestines. The wall of the intestines has immune functions, which function like a breakwater that protects the coast, and this is called the intestinal immune system.

The presence of intestinal bacteria helps to regularly maintain the entire body's immune functions. In other words, we can think of the intestinal immune system as the driving force behind the power of natural healing. Three factors comprised of the intestinal mucous membrane, the intestinal contents, and the intestinal bacteria, interact in complex ways to trigger not only colorectal cancer and inflammatory diseases of the intestines (such as ulcerative colitis and Crohn's disease), but also many other diseases that affect different parts of the body.

The relationship between dietary fiber and colorectal cancer

As I have mentioned in my previous articles, cancers have a latency period. The latency period of colorectal cancer is at least 10 years, and close to 20 years, before the cancer becomes visible to the eye. About 50 years have passed since the mid-1950s, which was when the economic situation improved in Japan, and people started incorporating Western foods into their diets. The incidence of colorectal cancer started rising approximately 20 years later, suggesting that during this time, this lifestyle-related disease was in its latency period. Colorectal cancer is an adulthood cancer. Aside from a rare inherited disease called familial adenomatous polyposis, which can lead to colorectal cancer, I have never heard of a single case of colorectal cancer in children.

You have probably heard of the term "polyp." A polyp is a growth that projects from a mucous membrane that has a "head" portion, somewhat resembling the cap of a mushroom. The epithelial cells of the "head" portion can often progress to cancer, so polyps are removed during colonoscopy, or in some cases a small sample of the polyp is removed for pathological testing (biopsy). Colorectal cancer can either progress from a polyp or from a lesion that originally forms as a shallow depression.

As I have mentioned earlier, it is the role of the pathologist to examine such areas under a microscope and to determine whether or not they are cancerous. Cancer is not confirmed based on endoscopic examinations and X-rays. The diagnosis always involves a pathological examination of the tissue as well as a pathology report, which is an official documentation of the findings. If a pathological examination is conducted when you have an endoscopic examination, I recommend that you ask the medical institution to give you the pathology report for your personal record so that you can seek a second opinion based on this report.

The causes of colorectal cancer lie in the Western pattern diet

The development of colorectal cancer is not equally common across the full length of the large intestine. In the Japanese population, about three quarters of all cases of colorectal cancer are found around the lower left part of the abdomen. It is often concentrated in the rectum. This trend is generally the same in other countries, though in developed countries, cancer has also been found to develop in other areas of the large intestine. This general trend suggests that the long period of contact between the solidified contents and mucous membrane of the rectum increases the likelihood of developing cancer.

The fact that cancer occurs in other areas of the large intestine in developed countries may suggest that foods in Western pattern diets contain more factors that cause cancer. Red meats such as beef and pork, burnt portion of those meats, the fat in dairy products and bile that tries to break down the fat, and metabolites produced by intestinal bacteria are considered to be possible sources of carcinogens. These foods and substances are therefore thought to be intricately linked to the onset of colorectal cancer.

A relationship between dietary fiber and colorectal cancer was first reported in an investigation conducted by a British surgeon named Dr. Denis Burkitt, in South Africa. In the local people who consumed potatoes and other root crops as a staple food and who could not consume meat, virtually no cases of colorectal cancer, intestinal polyps, diverticulosis, or gallstones were found- however, these diseases were common in England. This finding suggests that certain foods, particularly foods that are rich in dietary fiber, may be preventing those diseases.

Predisposition to colorectal cancer (Risks)

The reality is that colorectal cancer is often discovered too late in clinical practice. The reason for this is because there are few symptoms that we can notice ourselves (subjective symptoms). In many cases, the cancer is already in advanced stages when people experience subjective symptoms such as diarrhea or constipation. However, since colorectal cancer develops slowly, if there are no abnormalities found after a careful endoscopic examination it is not necessary to take the test annually as part of your regular medical check-up.

A thorough check-up every few years is sufficient for starting treatment, if necessary. The fecal occult blood test, which tests for traces of blood in the stool, can be easily done and is effective to an extent. However, it is not adequate for detecting early stage cancers. This brings up an important point: How do we detect colorectal cancer early? Firstly, we must realize whether or not we are prone to getting colorectal cancer.

There are several characteristics that make a person more prone to developing colorectal cancer (risk factors). These include: having a family member with colorectal cancer; a predilection for beef, pork, dairy products and eggs; disliking fruit and vegetables; and being a smoker. If any of these apply to you, I recommend that you have a colonoscopy once you reach the age of 50, even if you do not have any subjective symptoms. According to some studies, a small percentage of such people (who have the above characteristics) would have developed cancer by this age. Naturally, those people who are at low risk often have the opposite characteristics as those listed above. Nevertheless, even those at low risk should undertake a thorough endoscopic examination, to have their own peace of mind.

Chronic inflammation promotes cancer

Recent studies have shown that regular users of analgesics such as aspirin are less likely to get cancer in general, including colorectal cancer; this finding has been attracting some attention. Aspirin, however, has several side effects, so please do not immediately follow this practice after reading my article. Drugs that are better suited for this purpose have been developed, and the use of such drugs to reduce inflammation as well as to prevent cancer has been studied. Aspirin has an effect of reducing inflammation and relieving pain. It is believed that aspirin also exerts these effects on the mucous membrane inside the large intestine. The chance of developing colorectal cancer increases when the large intestine is inflamed for a long period of time (chronic inflammation) as a result of diseases such as ulcerative colitis and Crohn's disease.

Chronic inflammation is a key factor in the progression of cancer. There are many things we can do to alter the contents of our intestine and make the mucous membrane healthy. Yoghurt made from soybean, calcium, sources of dietary fiber such as boiled vegetables and vegetable salad, and probiotics (which have been popular recently) are some of the foods that are currently in the spotlight. Biobran, which has shown diverse effects including anti-inflammatory effects, is another health food that is anticipated to not only assist in the treatment of colorectal cancer, but is also effective in the prevention of cancer relapse.

The concept of coexisting with cancer rather than eradicating cancer

In contemporary medicine, treatment with anticancer agents is the first choice treatment or the only available treatment for advanced colorectal cancer. However, the treatment effect of

anticancer agents on colorectal cancer varies greatly depending on each individual patient because of the difference in characteristics of the individual's cancer, such as the ways in which it spreads, or the speed of its growth. Therefore, we cannot expect anticancer agents to have the same clear-cut effect as antibiotics. Anticancer agents also cause serious adverse effects. In other words, there are infinitely many ways to select an appropriate treatment method for each person.

Many new treatment methods have been developing in recent years. These include immunotherapy, endovascular therapy, hyperthermia, and cocktail treatment using herbal medicine or Chinese medicine. In cases where there are no treatments that are particularly effective for that patient, I believe it is a matter of gradually finding treatments that have at least a slight effect, and adding such treatments to the patient's treatment regimen, step by step. During this process, it is important to shift our focus away from eradicating cancer; rather, we should focus on slowing down the speed of cancer progression by even a little bit, or on coexisting with cancer. First and foremost, this requires the patient and the treatment provider to have a tremendous level of trust in their relationship. I believe that by following through with a selected treatment and not giving up, patients can expect a longer survival period.

Finally, let me touch upon the greatest mystery in medicine pertaining to cancer of the digestive tract. As we have discussed, the large intestine is vulnerable to cancer. The mystery is that, in adults, cancer never affects the small intestine, which is about three times longer than the length of the large intestine. Many hypotheses for this phenomenon have been put forth, but no compelling medical evidence has been found. It remains a medical mystery of the 21st century. If we can find out why cancer does not develop in the small intestine, I believe it would give us clues as to how colorectal cancer can be prevented-don't you think? In the next article, we will examine some of the defense strategies we can employ against stomach cancer.

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„Pathologist’s advice on How to combat cancer“ series

Part 6: Prevention of Stomach Cancer through environmental factors

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

Introduction

We are all hoping that the 21st century will be an age of building a society that enjoys healthy longevity. Japan has the longest average life expectancy in the world, ahead of developed countries in Europe and America. However, the critical issue is that a long life is not necessarily a long life in good health. If you ask me what I think are vital for maintaining our bodies into old age, I would definitely say a healthy brain, ability to move (motor functions), and healthy teeth. The maintenance of these functions is probably our biggest challenge.

To enjoy longevity, it is necessary to prevent lifestyle-related diseases such as cancer. From a contemporary view, cancers of the digestive system, such as stomach cancer and colorectal cancer, and cancers of the lung, breast, prostate, and pancreas, etc., can all be considered as lifestyle-related diseases. We have come to understand that these cancers are intimately associated with our lifestyle habits such as smoking and dietary patterns, rather than with family history or heredity.

I've mentioned that we must maintain a healthy brain; this involves improving blood circulation in the brain. More specifically, it involves extensive learning and playing, being proactive, adopting challenges, and enriching one's life without adding stress. We are now in an age where the relationship between the body and mind are being reconsidered. The primary prevention(*) of lifestyle-related diseases is the best way to preserve a healthy body, and this in turn helps to create a healthy mind.

For instance, dementia associated with circulatory disorders such as high blood pressure or diabetes, and Alzheimer's disease, which is associated with nerve cell abnormalities, have already been labeled as lifestyle-related diseases; and there has been an increasing number of research reports on how improving dietary patterns can prevent these diseases.

Next, let us discuss motor function. If you have a problem with motor function, for example, a persistent, dull ache in the lower back or joints, it will have a direct effect on the range of daily activities you can carry out and on your mood. Furthermore, if you develop osteoporosis, it will have a serious effect on your ability to maintain your back in good condition, due to postural problems; and if you have a hip fracture (femoral head fracture), it will significantly limit the range of daily activities you can carry out.

In other words, these problems will significantly reduce our QOL (quality of life), a term we often hear these days. Improving dietary and lifestyle patterns has been shown to have the most beneficial effect on the maintenance of motor function.

Finally, the third point, the maintenance of good teeth and oral health, is important for the maintenance of a healthy body and mind. In Yasuo Kagawa's book from the Iwanami shinsho series titled "Seikatsu sh?kanby? o fusegu (Preventing Lifestyle-related Diseases)"(1) there is a reference to a set of health guidelines called "Kenko Nippon 21 (Healthy Japan 21)." When examining these guidelines, it is apparent that a large proportion of them are on dental health.

In summary, objectives such as reducing tooth decay in infants, lowering the prevalence of periodontitis in prime-age adults, and keeping as many natural teeth as possible into old age, are described in detail. To achieve these objectives, the authorities mention that the proportion of children who have received topical fluoride treatment before the age of three will be increased.

"Healthy People" movements

Long-term national plans related to health have been put together by governments in countries such as Japan, the United States and Canada. Particularly large in scale are Healthy People 2000 and Healthy People 2010 in the United States. The fundamental purposes of these campaigns are to encourage people to quit smoking, and to improve people's dietary and lifestyle patterns. Scientists point out that smoking and dietary patterns are risk factors in 70 to 80 percent of cancers that occur in adults. Other major risk factors for cancer include viral infections, radiation, UV, and chemicals. In other words, most cancers in adults occur due to environmental factors--family history and heredity rarely have any influence on the risk of developing cancer. This is why primary prevention of adulthood cancers is possible.

In the United States, health campaigns are being conducted based on these scientific facts. These national campaigns have been carried out in partnership with grassroots organizations. One of their major achievements is the anti-smoking campaign that has taken root. Despite this achievement, the smoking rate still lingers around 25%. There are concerns that this is still very far from the target of reducing the smoking rate to 12% by 2010. This being said, the important thing is that we can see evidence that the anti-smoking campaign and information on the dangerous health effects of smoking have infiltrated our society in various ways. For example, it is prohibited to advertise tobacco products in the mass media such as the TV and radio, auto racing, and public facilities. The dangers of second hand smoke have become widely accepted, and smoking areas of hospitals and public buildings are now strictly isolated.

For example, in McMaster University (located in the outskirts of Toronto) where I used to work, smokers were to always smoke outdoors no matter how cold it was outside. As Canada is a bilingual country, the cigarette boxes sold in Canada have warnings (about the harmful effect of cigarettes) printed on the front- and back- sides of the box in both English and French. Printed using half of the space on both the front and back of the cigarette box are color images of diseases, for example, an endoscopic image of a bronchi in lung cancer, an image of a heart during a heart attack, or an image of a stroke. The purpose is to draw consumers' attention to the harmful effects of smoking on health.

On the other hand, there is also a lot of support for people who want to quit smoking. For example, nicotine gum and nicotine patches can be purchased without a doctor's prescription. Another available option is the nicotine nasal spray, which is sprayed onto the mucous membrane of the nose. There are also other measures in place, such as imposing higher cigarette tax rates, and higher retail prices for cigarettes. Recently, a reporter from CNN news announced that the price of a box of cigarettes in New York city has now risen to 7 dollars. In Japan, various aspects of tobacco have a string of serious problems related to the economy, politics and social welfare.

Lung cancer is the leading cause of cancer-related deaths in Japan. Considering this, Japan should follow Europe and America's example. Although stomach cancer used to be the leading cause of cancer-related deaths in Japan, the death rate from stomach cancer is currently appearing to be on the decline. So far, no studies have found the genes of Japanese people to be particularly vulnerable to stomach cancer.

Stomach cancer

In countries worldwide, death rates from stomach cancer are tending to decline, while death rates from lung cancer are tending to be on the rise. A similar trend has been observed in Japan. There is some interesting data on why stomach cancer is tending to decline. Stomach cancer used to be at the top of the list of cancer-related deaths in the United States as well, but that was more than half a century ago. Since then, stomach cancer death rates of Western countries have declined rapidly in a period of about 30 years, as you can see in the table below. The decline in death rates was particularly prominent in Finland, and in Chile (not included in the table).

During this time, Japan's stomach cancer death rates continued to rise before it gradually started showing a tendency to decline. From 1993 onwards, stomach cancer became second on the list of cancer death rates among Japanese males; lung cancer moved to the top of the list, and it is continuing to rise today. Japan's stomach cancer death rate and prevalence are still high relative to the rest of the world. The generally high prevalence of stomach cancer among populations in Japan and Southeast Asia may be suggestive of similarities in the type of food eaten, or the type of ingredients used in food consumed in these countries.

[Table] Declining trends of age-adjusted death rates (per 100,000 population) for stomach cancer in the 1950s and 1970s

	1950-1952	1977-1979	Percentage of decline
Finland	109	29	-73.4
Switzerland	56	16	-71.4
Norway	61	19	-68.9
United States	27	9	-66.7
Canada	35	14	-60.0
West Germany	66	27	-59.1
Czechoslovakia	75	42	-44.0
Japan	130	73	-43.8
Italy	62	35	-43.5

Source: Epidemiol Rev 1986 (Modified)(2)

The decline in stomach cancer death rates in the United States happened at almost the same time as the rapid spread of the electric refrigerator in the 1960s. The refrigerator helped keep food fresh. A historical analysis of American diets reveals that the consumption of fresh fruit and vegetables started rising from the 1950s.

In Japan, fresh vegetables became a familiar sight when artificial fertilizers became the common type of fertilizer used for growing vegetables. Researchers have indicated that Vitamin C and vitamin A found in fresh fruit and vegetables are particularly effective for the prevention of stomach cancer. They have also pointed out a relationship between excessive salt intake and the risk of stomach cancer. Salt was used to preserve food in the past, but it is believed that advances in refrigeration and freezing technology changed the methods of food preservation, and as a result, reduced people's intake of salty foods.

In Europe and America, there was a sharp fall in the intake of nitrates, which was commonly used to process hams, sausages, and bacon. Although the reduction in salt intake has been partly attributed to campaigns held for the prevention of high blood pressure, the reduction in salt intake was largely due to the technological advances in food storage that led to the reduction in the amount of salt used in foods such as processed meats (like those mentioned earlier), pickled vegetables, and salted fish.

Around the time when the death rate for stomach cancer declined in the United States, fluoridation of public water supplies became widely implemented. This could simply be a coincidence. In fact, the fluoridation of public water supplies is still a controversial issue in North America. The diffusion rate of fluoridated drinking water in the 1990s is thought to be 65% in the USA and 35% in Canada. On the US surgeon general's website is a document that recommends the diffusion of fluoridated drinking water.

However, there are also papers on the damaging effects of fluoridated drinking water on health. Determining whether fluoridation is beneficial or detrimental to health is indeed a difficult task. For example, in a recent study involving animals, the animals in the fluoridated water group showed changes in brain cells that resembled that of human Alzheimer's disease(3). How are fluoridation and stomach cancer related? Exploring this question leads us to consider tooth decay and periodontitis.

Countries with a low stomach cancer death rate are distributed in East Africa, in areas north of Lake Victoria. Uganda and Sudan have particularly low stomach cancer mortality rates. In these countries, people use well water as drinking water. Topographically, the region is covered in volcanic ash, and is rich in fluorine compounds. According to the report by the World Health Organization (WHO), the ratio of people with dental carries is remarkably low in local residents of this region, particularly in children. The health of teeth is not only has an intimate relationship with drinking water rich in fluorine compounds, but also with a low intake of sugar. Some people in this region have mottled enamel due to dental fluorosis, a condition caused by excessive fluoride.

Nitric acid compounds

Potential substances involved in causing stomach cancer (carcinogens) include nitrosamide compounds, which include nitrosamines and nitrosoureas. These substances are thought to be produced by bacteria in the mouth and stomach using materials derived from food. The bacteria in the mouth use nitric acid and nitrates as materials to produce nitrogen compounds. It is believed that, within the acidic environment of the stomach, these nitrogen compounds react with food-derived amino acid derivatives and produce trace amounts of nitrosamide compounds.

The stomach is a sac-like digestive organ that secretes hydrochloric acid, which has bactericidal effect, creating a unique environment that is highly acidic. Vitamin C in the blood is secreted into this environment. Animal experiments have shown that salt reduces the effect of hydrochloric acid, making the stomach environment more prone to the development of stomach cancer. The stomach secretes a proteolytic enzyme called pepsin, which breaks down protein. This enzyme digests food and breaks them down into amino acids and polypeptides that contain nitrogen.

When the stomach acid becomes more neutral, bacteria that produce nitric acid begin to multiply. In the highlands of Colombia, South America, there are high incidences of stomach cancer. It has been reported that when people drink well water, the nitrate in the well water increases the amount of nitric acid and nitrate in gastric juice. If the acidity in the stomach is weak, bacteria in the stomach produce nitric acid. After eating, it takes about one hour at least for the pH of the stomach to fall back down to pH 3 or below. We can therefore say that the defense mechanism of the stomach is weakened after meals.

Nitrate is secreted in the saliva (salivary nitrate), and some of it is converted by the bacteria in the mouth into nitric acid. Juices from vegetables such as spinach and celery contain a lot of nitrates. When these vegetable juices are consumed, the nitrate is absorbed into the body. Following absorption, the amount of nitric acid and nitrate secreted in saliva is known to increase to about ten times the normal amount. In poor dental and oral hygiene conditions, salivary nitrate is often converted to nitric acid by bacteria in the oral cavity. In surveys conducted in Holland, the UK, and the US, an intimate relationship was found between the risk of stomach cancer and tooth loss or poor oral hygiene. However, surveys in Japan yielded contradictory results.

One study investigated the relationship between stomach cancer mortality rate and the dietary intake of food-derived nitrate compounds (which contain nitrogen)(4). The study shows that in various countries there is a positive correlation between stomach cancer mortality rates and nitric acid intake. Japan had the highest intake of nitrate among other countries in 1983, which was when the study was published. This nitric acid is derived from vegetables that contain a lot of nitrates.

Although Europeans and Americans consume a high volume of fresh vegetables, their intake of nitrates is low. It is possible that nitrates were contained in larger volumes in some varieties of vegetables and preserved vegetables that the Japanese commonly consumed, and nitrates may also have been added to food as a food preservative in Japan. There may have been differences in the amount of nitrates in drinking water among the regions as well. From what has been observed, the dietary patterns of Europeans and Americans (which include fresh beef and pork and fresh vegetables) have been reducing the prevalence of stomach cancer, but have been increasing the risks for other types of cancers. There is a limit to the accountability of the hypothesis that nitrosamide compounds cause stomach cancer. This hypothesis alone cannot fully explain why stomach cancer is so common in the Japanese.

Helicobacter Pylori

There have been many studies on Caucasians in North America that have found that a type of bacteria called *Helicobacter pylori* was closely associated to the onset of stomach cancer. There are few Caucasians who have antibodies against *Helicobacter pylori*, and stomach cancer is known to occur frequently in those who have these antibodies. In contrast, most Japanese adults have antibodies to *Helicobacter pylori*, but they do not necessarily develop stomach cancer.

Certain conditions make people more prone to stomach cancer, for example, atrophic gastritis(*), and intestinal metaplasia(*). Factors that trigger atrophic gastritis include the intake of foods that are high in salt. People who eat a lot of fresh fruit and vegetables, or take vitamin C, tend to be less likely to develop atrophic gastritis. In Japan, the number of people with atrophic gastritis increases with age. In people with atrophic gastritis, the secretion of gastric acid is reduced, which means that the previously mentioned defense system through hydrochloric acid is reduced, making it easier for *Helicobacter pylori* to multiply.

In the case of Japanese immigrants to the United States, stomach cancer prevalence rates were still high even if a person was aged 20 at the time of immigration, but the prevalence fell in second-generation immigrants. From this, we can predict that the stomach environment is already determined by what people have been eating before the age of 20. In other words, eating a lot of foods that are high in salt, and eating little fresh fruit and vegetables can possibly create a favorable foundation for the development of atrophic gastritis.

As a result of this foundation, it is believed that the stomach's exposure to the nitric-acid-based carcinogens is increased, leading it towards cancer. However, there is no medical evidence showing a direct involvement of *Helicobacter pylori* in the onset of stomach cancer. A stomach environment that allows *Helicobacter pylori* to multiply makes the stomach prone to stomach ulcers and stomach cancer.

These foods and supplements are currently known to have some effect in preventing stomach cancer: vegetables (listed earlier), fruit, vitamin C, vitamin A, vitamin E, calcium, and green tea. Whether or not green tea has an effect on the prevention of stomach cancer is still a controversial issue. As green tea has a bactericidal effect on bacteria in the oral cavity, there is a hypothesis that taking your time to fully savor the green tea in your mouth before swallowing may help reduce the amount of nitrate inside the stomach. Therefore, when considering the preventive effect of green tea on stomach cancer it is important that we not only consider the amount of green tea that is consumed, but also its temperature, and the ways in which it is consumed.

Risk factors of stomach cancer include foods that are high in salt content, such as salted dry fish and smoked fish, and diets that are high in carbohydrates and low in protein. Processed meats and the nitrate content of water may also be cause for concern. Epidemiological studies show that salty foods consumed while a person is still growing can change the stomach's internal environment into the "Japanese-type," i.e., the type that is more prone to stomach cancer. It is important to take salt in moderation because the mucous membrane that protects the stomach (gastric mucosa) is very likely to get damaged by chemical reactions of salt.

Conclusions

In this article, we have examined stomach cancer prevention from the perspectives of food and oral hygiene. The salivary gland, oral cavity, teeth, and stomach are intimately associated with each other through the food that we eat, secretions, and resident bacteria. This organic interplay is affected by environmental factors such as food and smoking.

Early detection and early treatment of stomach cancer due to the spread of screening undoubtedly reduced the stomach cancer mortality rate. However, based on various survey results, researchers have pointed out that the factors discussed so far in this article had an even greater effect on the reduction in mortality rate. I believe that knowing what needs to be improved will give us more confidence that we can prevent stomach cancer.

(*)

Primary prevention:

Primary prevention avoids the development of diseases, such as cancer and other lifestyle-related diseases, through improvements in dietary and lifestyle patterns. In this definition, "diseases" refers to chronic diseases, and does not include acute infections and external wounds. Secondary prevention is aimed at early detection of the abovementioned diseases and early treatment. Tertiary prevention reduces the progression (deterioration) of an already established disease or prevents its relapse, and once the disease is in a stable condition, the aim of tertiary prevention is to restore as much function as possible through rehabilitation and other therapies.

Atrophic gastritis:

The glands in the stomach are of three types: cardiac glands, fundic glands, and pyloric glands (in order from the beginning to end of the stomach). Atrophic gastritis is characterized by atrophy of the stomach glands, particularly the pyloric glands, which occurs due to chronic inflammation. Atrophy may extend to the fundic glands, and the secretion of hydrochloric acid and pepsin is reduced when the condition becomes serious. In this condition, a microscopic finding called intestinal metaplasia can be observed. The cells of the gastric mucosa change to resemble the epithelial cells in the small intestine, and this cellular transformation is called metaplasia.

Intestinal metaplasia:

Intestinal metaplasia is a common condition in atrophic gastritis, in which the gastric mucosa transforms into small-intestine mucosa (as explained above). These cells may cause gastric erosion, or regenerate to compensate for the erosion. Inflammation occurs at sites of gastric erosion, and white blood cells produce oxygen radicals to kill bacteria and other pathogens, but in that process it also damages the DNA in its own epithelial cells. The repetition of this process in chronic inflammation is thought to trigger stomach cancer.

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„Pathologist’s advice on How to combat cancer“ series

Part 7: Defense strategies against Lung Cancer

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

Breathing and Lung Cancer

How does lung cancer develop? Like the other cancers that we have discussed so far, lung cancer does not develop in a day. Lung cancer is a common adulthood cancer. It is lifestyle-related because of its intimate relations with breathing. Lung cancer is, therefore, extremely rare in children. So, this means that the development of lung cancer is closely associated with substances in the air we breathe in.

Is the air the same all over the world? The air is probably very different in various places of the world. I think you would agree with this. We have an earnest desire to protect the natural environment of the Earth. We have already seen phenomena that would have a devastating impact on the livelihoods of future generations, unless improvements are made. Air cleanliness in urban and rural areas may considerably differ in terms of concentrations of exhaust fumes. Pollen and dust concentrations may be remarkably higher in rural areas. Forests are known to have a special smell that reduces fatigue. We now have a fairly complete understanding of the types of substances in exhaust gases that are associated with lung cancer.

Basically, these substances are chemically related to oxygen and nitrogen which are the main constituents of air. More specifically, I'm referring to the reactive oxygen species, the "bad" type of oxygen. Nitrogen has a reactive form as well. Reactive nitrogen is found in exhaust fumes. The carcinogenic substances found in tobacco tar are basically clusters of reactive oxygen species; I shall come back to this point later.

Air passage

The air passage from the mouth or nose to the lungs consists of branching tubes, and somewhat resembles a cave. These branching tubes are called respiratory tracts, or airways, because these paths are where air travels back and forth. Air passes through to the lungs, allowing oxygen to enter body, and carbon dioxide to leave the body.

Inside the lungs, the bronchi branch out into bronchial trees, continued by narrower branches called bronchioles, and at the end, there are many alveoli (sacs filled with air), which are shaped like a bunch of grapes. The lungs are located in the chest, on either side of the heart. The lungs can expand when the pressure in the chest cavity is lower than the pressure in the air outside. The lungs inflate and deflate each time you breathe. The weight of the right lung is about 250 grams, and the left lung is about 200 grams. The lung is a light-pink, air-filled organ that is relatively light for its volume.

Glandular cells and Ciliated cells

Considering the structures from bronchi to the alveoli as one unit, the right lung is divided into three sections called the upper, middle, and inferior lobes, while the left lung is divided into two sections. The internal walls of these bronchi and alveoli are lined with several types of epithelial cells. The bronchial epithelial cells consist of ciliated epithelial cells (which have fine hairs on the surface), columnar epithelial cells, and goblet cells (which secrete sticky liquid). The epithelium of the alveoli consists of two types of cells: alveolar type I cells and alveolar type II cells. These are called glandular cells, and these cells may develop into adenocarcinoma of the lung, a type of lung cancer.

The cilia in the ciliated epithelium move in a powerful wave-like motion from the back of the bronchi towards the direction of the mouth. This movement removes foreign materials that have entered into the deep areas of the bronchi (when air is breathed in) through the production of phlegm. The foreign materials in the air are of varying sizes, and while the larger materials like pollen get stuck on the hairs in the nose, the smaller materials can travel to the far end of the lungs.

Exhaust fumes, tobacco smoke, and asbestos (traditional materials used for brake linings and heat insulation) are microparticles that float in the air, which means they can enter deep into the lungs. When foreign materials enter the alveoli where no cilia are present, it would no longer be possible to remove them. There has been an interesting experiment conducted with ciliated epithelial cells. In this experiment, these cells were cultured in a special plate, and positioned so that the cilia were moving in a fixed direction. The movements of the cilia rapidly decreased when water-soluble substances from tobacco smoke or nicotine were added to the culture solution.

Such changes are predicted to occur in the epithelial cells of the bronchi of smokers. It is widely known that metaplasia also occurs-this is where ciliated epithelial cells are replaced by nonciliated epithelial cells. When this happens, foreign materials accumulate in the mucous membrane of the respiratory tract and cause inflammation. The carcinogenic effects of foreign materials and the reactive oxygen produced by local inflammation of cells can lead to the destruction of epithelial cells and cause damage to DNA associated with the regeneration of cells.

When this process occurs continuously during a latency period, abnormalities occur in the genes that promote cell growth (accelerators), in the genes that inhibit cell growth (brakes), or in the genes that cause programmed cell death (apoptosis), leading to cancerous changes in the epithelial cells.

Equally important as ciliated cells is a rich supply of immune cells (which trigger immune responses) in the respiratory tract mucosa. They are known as white blood cells. These cells are associated with chronic inflammation, and are thus closely associated with diseases such as allergies and asthma. They also trigger inflammation associated with tobacco and exhaust fumes, and are a major factor in the onset of cancer. Biobran can properly regulate these immune responses. Experiments on animals have indicated that it may be effective in alleviating symptoms of hay fever and asthma.

Mass production of cigarettes and the outbreak of Lung Cancer

The dissemination of the cigarette that led to its widespread use as we see today started in the beginning of the 20th century. Back in those times, lung cancer was very rare. Lung cancer was thought to be a rare cancer that occurred in animals under experimental conditions, and it was believed that it only occurred when special carcinogens were administered to these animals to trigger its onset. Compared to the days where people were puffing on a pipe, the amount of tar intake rapidly increased with the spread of cigarette smoking. This shift towards cigarette smoking occurred due to the development of automated machinery for the production of cigarettes.

It is a well-known fact that, in the 20th century USA, the rising curves of cigarette consumption and mortality rates are interrelated with a 20-year difference. In Japan, this trend occurred together with improvements in the economic situation after World War II. Moreover, the trend closely resembles the ways of which lung cancer is currently rising in countries in Eastern Europe and Africa.

Today, smoking not only increases the risk of lung cancer but also of other cancers such as cancers of the respiratory tract, breast, digestive tract, pancreas, and bladder. The tar in cigarettes is absorbed into the body and circulates around the entire body. When substances in

tar are excreted into urine, they will remain in the bladder for some time and affect the epithelial cells of the bladder during this time.

Unfortunately, secondhand smoking also increases the risk of cancer in people who are near smokers. Smokers often show symptoms of mild chronic bronchitis. Symptoms such as dry cough and increased phlegm frequently manifest. Complications such as lung fibrosis (idiopathic interstitial pneumonia) and emphysema arise. People with lung fibrosis have a high susceptibility to developing lung cancer, which is evidence that chronic inflammation stimulates the onset of cancer.

The toxic substances that enter the body damage the intravascular cells (cells inside blood vessels) due to the production of reactive oxygen species. This leads to local inflammation or the formation of blood clots. Smoking is also a factor in arteriosclerosis, and is intimately associated with angina pectoris and myocardial infarction, as well as cerebrovascular disease. Therefore, it is not an overstatement to say that tobacco smoking is associated with an increased risk of almost all types of lifestyle-related diseases.

Based on the knowledge that has been acquired through medical evidence, it is a major problem that the insurance premiums are the same for smokers and non-smokers. In North America, many insurance companies have different premiums for smokers and non-smokers. In the United States, tobacco companies have often lost lawsuits filed against them for the damage to health caused by cigarettes.

Awareness of the risk of Lung Cancer

The first step towards the prevention of cancer and lifestyle-related diseases is for smokers and passive smokers to do a self-assessment of their risk of cancer, and to become aware that they are at high risk. People who are in close contact with exhaust fumes are not only exposed to polyaromatic hydrocarbons, which are carcinogens similar to tobacco tar, but are also exposed to asbestos used in car brakes.

Therefore, people who work in the automobile industry should be aware that they are at high risk of developing lung cancer and pleural mesothelioma (a malignant tumor that develops in the mesothelial cells, which are cells that cover the surface of the lung and thoracic cavity). Pleural mesothelioma is a malignant tumor that is particularly difficult to cure. That is why it is necessary to upgrade from the usual chest X-ray and take a chest CT scan every few years.

Extra-early detection of Lung Cancer

For a long time, chest X-ray was a part of lung cancer screening, and its use was aimed at early detection of lung cancer. However, the detection rate is low, and it is becoming evident that in many cases, the cancer is no longer in its early stages by the time it gets detected. This information is based not on my own judgment, but on recent information from various academic papers.

Studies conducted in Japan have shown that chest X-rays were effective for the early detection of lung cancer, but the study results did not show that they were remarkably effective. The problems of X-ray image (radiogram) interpretation lay in the backdrop of this situation. The doctor's skill level has a large influence on the interpretation of radiograms, which means that there is a possibility that some cancerous changes may go undetected depending on the doctor in charge of the diagnosis. In actual fact, lung cancer mortality rates have not improved despite the widespread use of chest X-ray exams.

It has been pointed out that the outcomes after surgery for the smallest lung cancer found on X-ray exams is evidently worse than the outcomes after surgery for early stage lung cancer found in

CT (computed tomography) scans. In both Japan and America, the statistics reveal a grave situation; the prevalence rate and mortality rate are hardly different for lung cancer.

What this means is that the preventive measures and treatments performed for lung cancer in the past up until the present have been very ineffective, indicating the urgent need for improvements in these areas. In fact, the medical checkups for employees organized annually by companies have not necessarily contributed to the early detection (i.e., the detection of tumors while they are still very small and treatable) of lung cancer. Wide availability of a test with a higher sensitivity than chest X-ray exams is urgently required.

The current reality in most medical institutions is that if lung cancer is suspected, a chest X-ray is used for screening and confirmation. If no abnormalities are found at this stage, CT scans will not be performed.

Recently in Japan, several institutions have presented initial data on lung CT scan screening. CT scans were performed in studies involving 2,000 to over 10,000 Japanese people aged 50 years and above (details such as age composition, male to female ratio are unknown). Abnormalities were detected in 3 to 6 people out of every 1,000 people. Unfortunately, not all of them were lung cancers in early stages; some of them had already advanced to later stages. As you can see, the sensitivity of chest X-rays is not ideal for detecting early stage cancer that is still treatable.

It is hoped that high-sensitivity CT scans and PET (positron emission tomography) scans will help screen for early stage lung cancer. These advanced technologies can generate 3D images of the lung (akin to computer graphic images) using a series of sectional images, and these images can be taken in just 10 seconds or so, while holding one's breath. The amount of radiation exposure has been reduced to the lowest possible level. At the Fujimoto Hayasuzu Hospital (Head: Toshiro Fujimoto), a hospital in Miyazaki prefecture, integrating the use of PET scans, CyberKnife and Gamma Knife has allowed them to steadily improve their outcomes.

Early stage lung cancer caused by smoking generally grows slowly, so if your first CT scan or PET scan shows no abnormalities, you can be rest assured for at least 4 or 5 years after that. If you take these tests, I recommend that you ask for a copy of the test images and report of the findings. These documents are official documents, like a personal history of health, and they will be very important when obtaining a second opinion.

Surgical treatment

These days, many cases of early stage lung cancer can be treated by limited surgery without requiring open chest surgery. In this surgery, local anesthesia is administered to the intercostal space (the space between ribs) closest to the tumor, and several small opening are made around this area. While looking through a thoracoscope, surgical equipment is used to remove the area of the lung with the tumor, and the area is sewn back together with a device to ensure that air does not leak through.

Tumors often recur in heavy smokers, so thoracoscopic surgery is useful for finding and removing such tumors while they are small, and in their earlier stages. If the cancer is limited to one lobe of the lung, it is possible to remove just that lobe (lobectomy). When the cancer is spread across different lobes, it will be necessary to remove the entire lung on one side, which is a major surgery.

Pathological diagnosis of Lung Cancer

Lung tissues that are removed during surgery are usually preserved in formalin and chemically processed (fixation). As the lung is inflated in its original state, keeping it inflated makes it easier to conduct tests and analyses. Therefore, a needle is inserted at various points of the removed tissue and formalin is injected into these points to inflate the lung tissue before fixing it.

The formalin-fixed lung tissue is analyzed by a pathologist, and is processed into a form that facilitates examination. The samples of lung tissue, which have been resized into an appropriate size for microscopic examination, are processed in several stages using various chemicals and embedded in paraffin. Using a microtome (a mechanical device for slicing specimens, and which has a knife that can be adjusted by increments of 1/1,000 mm), the lung tissue embedded in paraffin can be made into thin slices with a thickness of several microns. In fact, the resulting lung tissue slices are thinner than the Somei Yoshino cherry blossom petals.

These slices are spread onto glass slides. The tissue and cells are stained using several different dyes, and examined under a microscope. The pathologist examines the sample, checking the type of cancer and the surrounding lung tissues. The pathologist's report states the patterns of growth of the cancer, whether the cancer has been completely removed, whether the cancer has spread to lymph nodes, veins, and the surface of the pleura, or whether it has metastasized to any lymph nodes.

Lung cancer and anticancer agents

There are two major types of lung cancer: small-cell lung cancer and non-small-cell lung cancer. Treatment methods vary depending on which type of lung cancer patients have. Non-small-cell lung cancer is a particularly malignant cancer; anticancer agents have very little effect on this type of cancer. Some anticancer agents exert their effects on the nucleus or DNA, while other anticancer agents, such as Iressa, have an effect on cell-surface molecules involved in cell proliferation.

The similarity between these two types of anticancer agents is that both function to suppress the proliferation of cells. Among the different types of lung cancers, adenocarcinoma is the most difficult to treat using anticancer agents. The pharmaceutical company that developed Iressa publicly announced that Iressa was not effective in lung cancer. On the contrary, the Ministry of Health Labour and Welfare in Japan appears to acknowledge Iressa's effectiveness in lung cancer. However, their viewpoint remains unclear due to the lack of scientific evidence.

Sputum cytology

Screening for lung cancer includes a test category called sputum cytology. This is a test that examines cells in sputum. Cells from the respiratory tract or lungs can break off together with secretions from these areas, and these cells can be found in sputum. The laboratory technician for sputum cytology and a team of pathologists determine whether the cells are healthy or not.

Sputum cytology complements the weaknesses of CT scans. Computed tomography (CT) generates three-dimensional images using a series of X-ray images. CT scans can be used to visualize very small masses inside the lung, bronchi, and bronchial walls, and are known to be particularly effective for detecting changes inside the lung. However, it is considered difficult for CT scans to detect early stage bronchial cancer because this type of cancer spreads thinly on the mucosal surface of large respiratory tracts.

In this case, it is useful to use sputum cytology, which microscopically examines the atypical epithelial cells that have broken off from the mucosal surface. It is necessary to examine sputum coughed up on three consecutive days, rather than just one day.

Food and lung cancer prevention

As I have mentioned earlier, the latency period of 10 or more years leading up to lung cancer can be thought of as a period for preventing cancer. It is not a bad idea to rely on food and good quality supplements as a means of reducing the amount of reactive oxygen produced in the body. Reducing chronic inflammation of the respiratory tracts is required for the prevention of factors that promote cancer, based on scientific evidence.

Certain foods have antioxidant effects. Fruits are especially recommended as they have various beneficial effects. In a recent, internationally-acknowledged epidemiological study, researchers found that fruits were effective, although they did not identify a specific fruit to be particularly effective. In contrast, the effectiveness of vegetables was unclear in this study. We can only anticipate that there are benefits of antioxidants contained in vegetables. We are also hoping to find detoxification and enzyme effects of garlic, curry spices (e.g., turmeric), natural pigments in dark colored vegetables (such as carotene, and xanthine), and trace metals such as selenium and zinc.

Biobran is a supplement that has been found to have antioxidant and anti-inflammatory effects, and it has also been shown to be effective in alleviating the adverse effects that arise from treatments with anticancer agents. I believe that the supplement may be worth trying, not only for lung cancer but for all types of adulthood cancers. In the next article, I will be discussing strategies for the treatment and prevention of breast cancer.

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„Pathologist’s advice on How to combat cancer“ series

Part 8: Strategies for Breast Cancer Prevention

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

The breast is one of the key organs of reproduction. After a woman conceives and delivers a baby, the breast provides nourishment for the child's growth. Hormones control the production and excretion of breast milk, as well as other functions such as breast development and cell proliferation. Estrogen is one of the key hormones in breast activity, in other words growth and maturation, but it can also be responsible for the development of breast cancer and serve as an obstacle for breast cancer treatment. Progesterone is another key hormone for lactation, but it is also implicated in breast cancer development. The irony is that these hormones, when in balance, are indispensable for healthy breasts, yet can also be the key factor in triggering cancer.

Ovaries, because of their role in production of estrogen and progesterone, are also implicated in breast cancer development right up until menopause, because then production of both hormones declines coincidentally under the upper control of hypothalamus and pituitary gland. Yet even after menopause, especially the more adipose cells of the breast, the more they store and release estrogen. For this reason, maintaining a healthy weight with reasonably low fat stores (including in the breast) will lower the risk of developing breast cancer. A low-fat and moderate-calorie diet is recommended as part of a breast cancer prevention lifestyle.

A diet high in pork, beef and dairy, rather than a vegetarian diet, will increase breast cancer risk. Recent research has revealed that the burnt portion of meats and smoked foods contain chemicals that are implicated in breast cancer development. If a person does frequently consume these high risk foods, it would be wise to start breast cancer screenings at age 40.

Additionally, women who start menarche at younger age, who had a greater number of years than average from the menarche to menopause, or who were never pregnant or delivered a child, are at higher risk of breast cancer. Women who are predisposed to weight gain are also at higher risk. Body Mass Index (BMI) is a good measurement for healthy weight. A BMI of 20- 24 is considered healthy, and if a woman is more than 120% of their ideal weight, as according to the BMI, breast cancer screening should be more frequent.

(*BMI is calculated by dividing body weight(kg) by square value of body height(m). 20-24 is regarded as a medium build. Ex. weight 70kg, height 1.6m; $70/1.6 \times 1.6 = 27.3$ = obesity)

A woman who consumes a diet high in vegetables, fruit and soy, with low consumption of beef, pork and dairy, and an ideal BMI, is generally going to have a lower risk of breast cancer. Even under ideal circumstances, a woman should start breast cancer screenings by age 50.

In North America, breast cancer rates continue to increase with no signs of slowing. Breast cancer has been labeled as so-to-speak an epidemic, and national campaigns have been enacted to reverse the trend. Even in Japan, there is concern about increased breast cancer rates, which has been attributed to the growing popularity of Western diets laden with fat. Only certain types of fats, such as animal fats like butter and lard, are implicated as increasing cancer risk, and traditionally vegetable based fat was recommended as a healthy substitution. It was thought that vegetable fats would also help prevent heart attacks and cerebral vascular accidents, however it has now been recognized that vegetable fats can also cause problems. Vegetable fats found in salad dressing, cooking oil, margarine, and vegetable shortening were once thought to be low in saturated fats and cholesterol. However, research reveals that consumption of small amounts of artificial trans-fats, as can be found in some processed vegetable oils, also correlates with increased mortality from heart disease and breast cancer.

In response to these health concerns, the FDA requires food labels to state the levels of trans fat in a single serving. In North America, some margarines are available without trans fats. Another reflection of fat awareness is the popularity of olive oil, due to its squalene and “good” fat content.

In fact, fatty acids can be divided into beneficial fat and bad fat, similar to cholesterol. We need to pay attention to how fats are processed. When we look at the quality of fats found in prepared salad dressing, margarine, white bread, cake, biscuits, snacks, and ice cream, we should consider eating less of them, just as with beef and pork.

The popularity of soybean consumption is considered one of the primary reasons why the morbidity of breast cancer is still lower in Japan than in North America. Soy beans contain various chemicals that are effective in preventing cancer. Among them, the most significant are isoflavones, specifically genistein. Genestein is a very strong phytoestrogen that counteracts estrogens cell proliferation activity and helps maintain healthy breast tissue.

Traditional Japanese soy products, including tofu (soy bean cake), natto (fermented soy bean), miso soup (soup seasoned with fermented soy bean paste), atsugae (fried soy bean cake), and kinako (soy bean powder), contain phytoestrogens and other various chemicals which are effective in controlling cancer. Hopefully those foods are fully utilized in a diet focused on cancer prevention.

One of the most important factors in fatty food with regards to cancer formation is bile secreted from the liver. Bile is composed of cholic acids and cholesterol made from cell membranes of our reformed cells, especially from red blood cells destructed daily in the spleen. In the body, bile is so-called detergent or soap. Bile might be changed in the gut by bacterial flora to be carcinogenic, for instance, methylcholanthrene and others. Therefore, the more food may be oily, the more bile may be secreted and the more gut juice may be changed to be carcinogenic.

Breast cancer examination

Breast cancer examination in the physician's office may include palpation of the mammary glands, imaging, such as mammogram and the more sensitive digital mammography, ultrasound and MRI, which does not use radiation. Each of these methods has pros and cons. Self-examination can be done monthly by lying down and palpating the breasts gently not with the fingers, but with palm of the hand, by massaging the breasts in a circular motion. If a lump is palpated, even if it is small, it should be examined by a physician.

The National Cancer Institute (NCI) in the US recently released a report about research that was conducted on Chinese women in Shanghai, which concluded that palpation did not aid in early detection of breast cancer. However, it should be noted that the difference in breast size between Asian women and Caucasian women in North America is quite significant, and tumors in smaller breasts can be detected more easily with palpation. So despite the report's conclusion that palpation is not effective for early detection, women should not be discouraged from regular self-examination. This research also appropriately emphasizes the importance of routine breast examination with mammography or ultrasonography. MRI is strongly recommended because mammography can be painful.

When a woman feels a lump in her breast, or discovers secretion in her bra, she should visit a gynecologist/oncologist, or a surgeon. Fortunately for women, the number of clinics with female gynecologists is increasing. If a lump is discovered, a biopsy may be taken from the mammary gland. Stereotactic biopsy enables more exact localization of tumor. Then histopathological examination on the tumor sample can be done after a fine needle biopsy or resection. There may also be cytodiagnosis on mammary gland secretions. Most breast cancers are hormone-dependent, specifically estrogen- or progesterone-dependent. Breast cancer has receptors for female hormones, and may be hormone-dependent, although some breast cancers are not

dependent on any kind of hormones. In pathological analysis, those hormone receptors can be detected, which helps doctors decide what specific medicine should be administered.

Genetic testing has become more commonly utilized in clinical medicine to help predict prognosis. The test results are reflective of health status and copies of the results should be maintained by the patient.

Breast cancer and hormone receptor

As stated previously, breast cancer can be estrogen and/or progesterone dependent. In the case of breast cancer surgery, it is essential to determine whether or not cancer cells have receptors to these hormones. This can be diagnosed through pathology tests as part of the immunohistochemical examination. The lab evaluation should be kept at the hospital where the surgical procedure occurred, as the results help determine the course of treatment. Cell growth receptor, Her-2, is also one of the most important items to evaluate the outcome of the patients.

There is a study that compared the effects of the combination of an anticancer drug and tamoxifen versus tamoxifen alone. The purpose of tamoxifen is to reduce estrogen levels. This study was conducted on patients with breast cancer without lymph node metastasis, who had surgical intervention and determination of estrogen receptor status. In cases of estrogen receptor-positive breast cancer, chemotherapy showed no effects, and no difference in outcome was seen between patients receiving the drug combination versus patients receiving tamoxifen alone. As for both groups, the seven-year survival rate was slightly less than 90%, and 80% of the group overall maintained good health. On the other hand, in the cases of estrogen receptor-negative breast cancer in patients without lymph node metastasis, the combination of anti-cancer drugs and tamoxifen was more effective. The seven-year survival rates of this group were 85-90%, and those patients maintained good health. But with tamoxifen alone, 70% of patients had a seven-year survival rate and maintained good health.

The interpretation of the results of this study and the different treatments should be explained to breast cancer patients to help them make truly informed choices. Doctors need to explain these results because the effect of chemotherapy on cancer is not nearly as straightforward as the effects of antibiotics on a bacterial infection. In order to cure a bacterial infection, there are no choices other than antibiotics, but with cancer, chemotherapy is not the only option and patients need to understand the alternatives and the expected outcome of each. It is important for physicians to take adequate time to consult with their patients.

Another method to attack breast cancer cells involves blocking estrogen receptors. This acts to starve cancer cells by blocking the supply of estrogen, and this method can be used with postmenopausal women who naturally have lower estrogen production from the ovaries. One should take into consideration that subcutaneous fat throughout the body continuously supplies estrogen, therefore, reducing fat through exercise will help prevent breast cancer.

Aromatase, an enzyme found in subcutaneous fat, can elevate estrogen levels by converting androgens to estrogen. An aromatase inhibitor cuts off the supply of estrogen by inhibiting this enzyme, and suppresses the growth of estrogen receptor-positive breast cancer cells. One aromatase inhibitor is called Letrozole, and results from a Phase III clinical trial examined the effects of this medicine. The report found that letrozole showed better results than tamoxifen regarding the five-year survival rates after breast cancer resections.

Choices for cancer treatment methods

It is important to educate a patient on their cancer treatment options. In the initial consultation when a person is told they have cancer, they may experience shock and have difficulty processing and absorbing the information they are given. In the long run, a cancer patient has

many issues to deal with, such as scheduling appointments, choosing doctors, learning about their illness and simply dealing with their own personal affairs.

Most cancer patients do not have a background in medicine or oncology, so it is very important that they take the necessary time to learn about the variety of options for their type of cancer, evaluate the possible outcomes, such as success rates and risks, and work with their doctor to come up with a plan that makes them comfortable. Too often a patient feels they have no choice other than to blindly follow their doctor's instructions. However in most cases, it is not necessary to rush into treatment or make rash decisions. Instead it is much more important to go through the process of learning about their illness in order to make an educated decision.

There are many choices regarding cancer treatments, and unfortunately there is not one clearly reliable choice. Surgery is more than 80% effective as treatment for solid tumor, but other possible treatments do not necessarily have significantly different rates of success..

Be sure to have a good support system during the process of developing a treatment plan; this includes not only a trustworthy doctor, but also a nurse, a person who specializes in the medical system, and a good technical resource. This is a process that focuses on information gathering and analyzing statistics. From the perspective of the patient, analyzing medical data such as survival rates is the equivalent of gambling on his life. For example, if a patient was told there was a five year survival rate of 50%, they may be shocked at the concept that only half of the patients survive five years. What this doesn't take into consideration is that survival rates only determine whether a person will live or die over a period of time, and do not reflect other important pieces of information such as the possible adverse effects of a treatment such as chemotherapy.

Chemotherapy may be effective by preventing the spread of solid tumors, but in many cases, it does not effectively extend the person's lifespan. Sometimes it only adds a few months or a year.

The average two year survival rate for rapidly progressing breast cancer has not improved in the past 50 years, despite advances in chemotherapeutic drugs. But still, it is important to use the statistics that are available to choose an appropriate chemotherapy drug for this disease. The progression of the cancer can be tracked with pathology tests to determine whether it is spreading rapidly, moderately, slowly, or if it is dormant. The long term effects of the drug on the body cannot be predicted however.

Survival rates tend to be general statistics, but more precise predictions can be made by eliminating specific characteristics of patients. An important question to ask is "what if a patient doesn't do any treatment?". Modern medicine doesn't conduct research which compares a treatment versus no treatment (or placebo), therefore survival rates for absence of treatment have not been developed. The lack of scientific research on absence of treatment is one of the significant limitations of modern medicine.

When given the diagnosis of cancer, it is important to take into consideration the survival rate statistics and adverse effects of chemotherapy drugs, and use that information to make a decision. It is appropriate to have concerns about side effects of chemotherapy, but to not decline those drugs based solely on that concern. New treatments continue to be developed, so be sure to be open to the new information offered by the support team.

After leaving the hospital, many patients require support not only from their medical team, but also people involved in medical services and their family. Immediate support is essential for a patient who needs long term cancer treatment. The current medical system is lacking in these peripheral services and the current health insurance system cannot afford to establish new programs for assistance.

The concept of "informed consent" has been promoted in order to preserve the dignity and rights of the patients. This philosophy has progressed into patients demand for medical information

disclosure and establishing patient's rights for them to be actively involved in their treatment. Informed consent does not adequately protect the patient, as contemporary medicine is complex and the patient must go far beyond simply having faith in their doctor. Patients need to thoroughly evaluate all the treatments options that are offered and make their decision based on impartial information.

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„Pathologist’s advice on How to combat cancer“ series

Part 9: Strategies for Prostate Cancer Prevention

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

Introduction

Breast cancer is influenced by female hormones such as estrogen, and conversely, prostate cancer is influenced by androgenic hormones because of the physiological dependence.

The prostate, about the size of a walnut, is part of the glandular system, like salivary glands or the breast, and secretes fluid which prolongs the lifespan of sperm. The prostate is situated right below the bladder in men and surrounds the urethra. Women also have remnants of a prostate.

Dysuria, which sometimes occurs in older men, is caused by an enlarged prostate and constricted urethra. This is known as prostate hypertrophy which is benign and occurs in many older men. Sometimes it is complicated by cancer, but dysuria that is caused by cancer indicates that the cancer has already progressed considerably. From this perspective it is important to determine whether dysuria is caused by prostate hypertrophy or prostate cancer.

In an examination to rule out prostate cancer, serum PSA and ultrasonography are very important tools. Serum PSA levels may be slightly higher when prostate hypertrophy is accompanied by inflammation. But in the primary stage of prostate cancer, PSA shows a slight abnormality, and it should be emphasized that if the PSA level is constantly higher over normal range, even if very slight, further examination should be done as a precaution.

Diagnosis may be made through prostatic fine needle biopsy. Under local anesthesia, fine needle biopsy is given through the urethra or rectum. High tech imaging tests including ultrasonography and CT scans have made progress. By utilizing these technologies, it is also possible to partition the prostate into smaller sections, and identify the exact location of cancer in imaging in 3D.

Pathological tissue examination is conducted from core biopsies, and final microscopic diagnosis is made. As stated in the breast cancer article, requesting a copy of the pathological tissue examination report is recommended as the public document.

What is prostate cancer?

The prostate develops, functions, and is maintained under the influence of androgenic hormones. Some cancer cells in the epithelial tissue of the prostate have androgen receptors, but others don't. Prostate cancer prevention may include antioxidants, similar to other cancer prevention methods, and treatments using anti-hormones like antiandrogens, which are specific to treating prostate cancer. Taking it a step further, the ultimate treatment method for progressive prostate cancer is removing the testes, which generate androgens and female hormones.

When I started studying pathology, prostate cancer was rarely seen in the prime of life, and the majority of cases were seen in elderly people by chance at autopsy. Under these circumstances, the small prostate cancer is called occult cancer or latent cancer. On the other hand, nowadays in Japan, prostate cancer in young patients was seen infrequently, but of those, most progressed very rapidly, then metastasized and were fatal.

There is a highly suggestive report that was released in the early 80s. This research was conducted on white and black males in the US, Colombians, and Japanese (living in Hawaii or

Japan). These patients died from causes other than cancer, and were autopsied so that their potential prostate cancer could be examined carefully.

In each group, the number of cases with potential prostate cancer was almost same, but fatal cases were seen more significantly in black males in the US group, then white males in the US group, which was followed by the Columbian group, Japanese men in Hawaii, and Japanese men in Japan respectively.

These results indicate two facts. Prostate cancer can be divided into two groups; one is moderate cases which are common all over the world, and the other is more malignant cases that are influenced by external environments, including dietary habits and food selection.

Significant external influences that affect prostate cancer developments are the following: 1) the amount of vegetable and fruit consumption for antioxidant properties, 2) consumption of fat, specifically the amount and type 3) degree of consumption of soy products and 4) amount of fish and sea vegetables that are consumed.

The report by the National Cancer Institute of the US in 1998 shows that regarding prostate cancer morbidity, Japanese and Chinese males are among the lowest cohorts and American males are among the highest. In particular, the prostate cancer morbidity rate of black males in the US was about 13 times higher than that of Japanese males. As I mentioned, epidemiological research indicated that the prostate cancer morbidity of Japanese males rapidly increases after moving to North America. Considering these facts, we can theorize that eating habits may greatly affect the development of prostate cancer.

Research results show that the consumption of beef and meat, fatty foods, and too much calcium raise the risk of developing prostate cancer. A researcher in New Zealand studied the relationship between prostate cancer morbidity and methods of cooking beef, pork and chicken, and the amount of heterocyclic amines contained in the burnt portions of grilled foods. It turned out that men who eat grilled beef steaks that were burnt are at higher risk of prostate cancer than non-burnt meat. Chicken is least likely to cause prostate cancer. Meat with fat tissue is needed to be digested with larger amount of bile for suspension. Bile secreted in the gut might be altered to be carcinogenic by intestinal flora by chance so that such a substance must be dangerous to the colon mucosa and also must be absorbed into the blood to any excretory glands such as the prostate, breast or pancreas.

Additionally, dietary fiber is helpful to prevent not only breast cancer, but also prostate cancer. In the following I will discuss some other health promoting foods.

Lycopene

Lycopene, a carotenoid (red pigment), along with other materials found in tomatoes, have shown preventive effects against prostate cancer in animal experiments. Lycopene is an antioxidant and is effective for preventing other cancers as well.

BioBran, extracted from rice bran, is also antioxidant, and is expected to have immunomodulatory functions along with those of an antioxidant.

Dr. Pfeifer, a distinguished oncologist in Aeskulap Clinic in Switzerland, uses BioBran as one of the methods to treat progressing prostate cancer which is androgen receptor-negative. Those cancers are the most treatment-refractory ones in prostate cancer, and tend to be resistant to anticancer drugs. It has been gradually discovered that we can find nutrients that fight against cancer from natural sources, such as tomatoes and rice bran.

Soy Bean

Many epidemiological studies show that the low prostate cancer morbidity of Japanese males is mainly attributed to their large consumption of soy bean products. Soy bean contains lignans (dietary fiber), isoflavones (phytoestrogen), and other phytonutrients, such as saponins. Lignans are also present in whole-grain bread, sesame seeds and various other seeds, berries (strawberry, blueberry and others), vegetables, and green tea. As I mentioned previously, androgen promotes growth of prostate cancer cells and female hormones inhibit canceration of prostate epithelial cells. It is indicated that soy phytoestrogens may also inhibit canceration of prostate cells.

Genistein, one kind of isoflavone, not only has antioxidant effects, but also sets the function of Epidermal Growth Factor Receptor (EGFR) to "OFF". It has been reported to reduce arterializations and be involved in growth factor (TGF β). Refer to previous descriptions about soybeans and breast cancer for more detailed information.

A research study conducted on 8,000 Japanese Americans living in Hawaii reported that prostate cancer morbidity was the lowest in the group of men who consumed a lot of *tofu* (soy bean cake). In the comparison to the isoflavone volume in the blood between Japanese males and Finnish males, who show higher prostate cancer morbidity, Japanese males showed 7-110 times higher levels.

It has been shown that soy isoflavones may reduce prostate cancer. Soy isoflavones help us maintain good health, because they are effective not only for prevention of prostate, breast, and large bowel cancer, but also reduce brain, heart and blood vessel diseases by reducing cholesterol levels in blood. But soy also contains unhealthy components. A study shows that animals that consumed a lot of raw soybeans developed pancreas cancer, caused by trypsin, a digestive enzyme inhibitor. Soybeans should always be well-cooked.

Omega-3 unsaturated fatty acid

A research study was conducted in Sweden involving twins who were born between 1886 to 1925, and questionnaires were given to them between 1961 and 1967. In follow-up research, the relationship between prostate cancer morbidity and age, degree of obesity, eating habits (consumption of beef, pork, smoked meat and ham, fruits, and vegetables), smoking history, drinking history, sedentary work, lifestyle, exercise, and others parameters were evaluated.

This follow-up research was conducted on 6272 persons with an average age of 50, for up to 30 years after (average research period was 21.4 years). During this research period 466 men developed prostate cancer, and 340 of them died because of it. In the group of people who ate fish more frequently, exercised, abstained from smoking, and ate a lot of vegetables and fruits, they showed a lower morbidity rate of prostate cancer. The specific kinds of fish were mainly cold-water fish, such as herring, salmon, and mackerel, which contain abundant omega-3 fatty acids.

But the group of people who rarely ate fish showed two- to- three times higher morbidity than the previous group. The consumption of fish caused a significant difference in prostate cancer morbidity. This fact didn't change after being modified for genetic factors in twins or lifestyle habits.

Similar results have been reported recently, one after another. Omega-3 fatty acids found in fish oil are recognized for reducing growth of androgen-receptor positive prostate cancer cells, dose dependently. This function seems to have no relation to whether a patient has androgen receptors or not, and effects DNA directly.

Based on these results, a study was conducted on patients with untreated prostate cancer. Patients were given low-fat meals supplemented with fatty acids, with a high proportion of omega-3 and omega-6 for three months. Patients were followed with genetic testing, erythrocyte

membrane fatty acid analysis, adipose tissue biopsy from the lumber region, histopathological analysis of prostatic biopsy, and cyclooxygenase (COX-2) levels. Regarding the fatty acid analysis of fat and red blood cell membranes, omega-3 levels were shown to increase rapidly. Histopathological pictures improved, and COX-2 decreased. These results indicate that reducing COX-2 levels helps to reduce prostate cancer, as with colon cancer, which may be due to omega 3 fatty acids.

Alpha-linolenic acid

An epidemiological study comparing health status and dietary patterns specific to a country or region shows that the morbidity of prostate cancer is correlated with the total amount of fat contained in meals and the consumption of saturated fat. This research is helpful to find indirect carcinogenic factors. It has also been shown that increased consumption of omega-6 derived from animal fat is also related to a higher risk of prostate cancer.

I mentioned in the previous section that omega-3 fatty acids found in fish oil may reduce the risk of developing prostate cancer. Those researchers have been influenced by the fact that morbidity of prostate cancer is low among Japanese and Inuit. A large-scaled study of 50,000 people who took a questionnaire, were followed over a four year period. People were segregated into two groups, one that developed prostate cancer and a group that didn't, and their eating habits were studied. The results indicated that alpha-linolenic acid, an essential fatty acid found in plants rather than fish, was shown to be correlated with an increased risk of prostate cancer, which is admittedly contrary to conventional wisdom. Further research should be done, although a second study reported similar findings.

In Uruguay, South America, morbidity of prostate cancer is high, followed by that of lung cancer, and 35.2 people per 100,000 in the population will develop this disease (1990-1992). The reasons implicated are high beef consumption and alpha-linolenic acid consumption. Five of six studies, which have been reported recently, conducted additional tests and reconfirmed the relationship between alpha-linolenic acid and the rising morbidity of progressing prostate cancer. We do need to acknowledge these results.

In conclusion, it is recommended to consume less meat that is "burnt", less beef and pork, and increase intake of fish and olive oil. But omega-6 and alpha-linolenic acids that are found in vegetable oil should be consumed in moderation.

Compared to North America where the main sources of oil are extracted from soybean or rapeseed, the olive oil-consuming region around the Mediterranean Sea shows relatively lower morbidity rates of prostate cancer. It has been reconfirmed that olive oil is one of the healthiest oils out of the many available varieties. Alpha-linolenic acid is contained in mayonnaise, store-bought salad dressing, margarine, butter, beef and pork. Habitual intake of those foods may enhance the risk of developing prostate cancer. It is important not to consume excess amounts of vegetable oil sourced from salad dressing.

Soy products, garlic, and fish are recommended as part of a healthy diet. Tomato sauce and tomato puree are better than fresh tomatoes. Tomato ketchup may be a good second choice. It is good to take garlic, vitamin D, vitamin E, and a small amount of selenium (a trace mineral). Absorbable forms of calcium should be taken moderately. Beef and pork, especially when burnt, should be avoided.

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„Pathologist’s advice on How to combat cancer“ series

Part 10: Strategies for preventing Liver Cancer (Hepatocellular Carcinoma)

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

Occurrence of Hepatocellular Carcinoma

I have so far been talking about cancer formation in the adult that would develop as a lifestyle related disease wherever it is in our body in this series. The occurrence of hepatocellular carcinoma does not fall into that category. As a matter of fact, a certain trigger of its occurrence as an initiator of cancer formation is not a lifestyle related disease, but an infection-related disease. However, its promoter is most probably thought to be life-style related disease in terms of chronic inflammation for more than 20 years. This is the reason why I mention in this chapter and is to accord with clients' claim.

The initiator of its occurrence in Japan is highly suggestive of chronic viral infection such as hepatitis B virus (HBV) or hepatitis C virus (HCV), leading to liver cirrhosis as a consequence of chronic inflammation in the liver for more than 20 years.

In the western countries, hepatocellular carcinoma could occur as a consequence of long term alcohol abuse with chronic inflammation, leading to the same condition as viral infection in the liver. These two factors are considered to be the major causes of liver cirrhosis with chronic inflammation and eventually, more than 90% of the cases with advanced stage of chronic hepatitis or liver cirrhosis will develop hepatocellular carcinoma.

Therefore, people without chronic viral infection or alcohol abuse are certainly not concerned about the risk of developing liver cancer. People who are predisposed to occur hepatocellular carcinoma are quite different groups from the normal population. In accordance with modern medical history, chronic inflammation due to a parasitic worm species called *Schistosoma japonica* in Asian countries has also been an important cause of liver cirrhosis followed by hepatocellular carcinoma. Nowadays in Japan, this is considered as a disease of the past.

Cell population of the liver function

The liver is composed of hepatocytes and bile duct cells, representing function of the liver. The former is the proper function of the liver called epithelial cells capable of the liver function. HBV or HCV could infect hepatocytes. Hepatocellular carcinoma is derived from hepatocytes.

On the other hand, bile duct cells is the inner cells of the bile duct, through which bile excreted by the hepatocytes flows to the gut. Bile duct carcinoma, or cholangio- cellular carcinoma is derived from the bile duct cells. This cancer is not related with HBV nor HCV and quite rare compared with the former in terms of the prevalence rate in Japan as well as other developed countries.

Hepatitis B and hepatitis C viruses

First of all, I have to discuss about chronic hepatitis caused by the two major viruses. Before the discovery of these viruses, there had been a number of scientific struggles to investigate the infectious routes to humans for a couples of decades since 1950s. These viral infections appeared to be closely related to blood transfusions. HBV (DNA group) was discovered in the contaminated blood samples by Dr. Blumberg in 1970s.

His work earned him the Nobel prize. HCV(RNA group) was discovered in the 1990s by a new sophisticated discipline. Tests for detection of these viral markers in the blood have been quite useful in checking for viral contamination of blood samples. Thereafter, incidence of these viral

infection via blood transfusions have decreased revolutionarily. However, it should be emphasized that sexual intercourse or vertical transmission from some carrier-mothers to their children can also be a potential route as a parenteral route of infection in a small group of patients.

Host-parasite relationship

Generally speaking, relationships between animal species or plants and any virus have strict selectivity of infections, in terms of molecular interaction between them. HBV or HCV is able to infect only hepatocytes from humans or chimpanzee. As you can see, avian or swine influenza virus can only infect each specific species.

However, only mutated viruses could infect human beings. Since birds with mutated avian influenza virus could be flying over the oceans or continents for a short period, we, people over the earth, should absolutely be scared about the great outbreak. HIV mutated from Simian IV (SIV) and SARS transformed from corona virus follow the same pattern.

There is a strict molecular rule between host and parasite relationship in viral infections as mentioned just above. The host has a defense system against viral infection by utilizing the immune system. If the so-called acute infection and immune system response can handle viruses, then they will be eliminated via production of antibodies against them. However, the immune system of our body has a lot of weakness regarding infectious agents, especially HBV or HCV.

These agents have a tendency to not be eliminated, but instead to induce a course of chronic inflammation in the liver, transforming normal lobules to pseudo-lobules in the hepatic functional units. This condition is called liver cirrhosis, or fibrosis of the liver caused by scar formation, with inflammation and on-going viral persistence.

Free radicals released by inflammatory cells and DNA damage

Free radicals, generated by inflammatory cells such as macrophages and neutrophils, could cause continuing damage to hepatocytic DNA, and then the damaged DNA replicates followed by summing up randomly to damage exon sites in terms of mutated genes. This cause and effect is a common pattern in cancer development. Hepatocellular carcinoma tends to be a lifestyle-related disease in adults, which I have mentioned in previous articles. Therefore, chronic inflammation is one of the key attributes in the development of cancer.

Clinically, there is significant difference in the possible outcome of cirrhosis with or without chronic inflammation leading to hepatocellular carcinoma when cirrhosis is caused by HBV versus HCV. Specifically, the latter with a likely tendency to continue chronic inflammation to cause hepatocellular carcinoma after 10 years later since beginning of liver cirrhosis. On the other hand, in the cases with cirrhosis caused by hepatitis B, development of hepatocellular carcinoma tends to be slow down after 5 years. Inflammation levels in the liver can be measured by liver biopsy evaluated and diagnosed by board-certified pathologists in Japan like me.

After developing cirrhosis, strong inflammatory reactions are likely to lead to hepatocellular carcinoma. In light of this, one should consider traditional Chinese medicine that suppresses inflammation, or functional foods like BioBran, which are anti-inflammatory, after developing cirrhosis.

On the other hand, various medicines have been developed to cure hepatitis by killing the virus, but they are not effective enough on some specific viruses. In order to prevent hepatocellular carcinoma, it is critical and important not only to eliminate the virus, but also to suppress inflammatory processes.

Even if a patient does occur hepatocellular carcinoma, various supportive approaches, including ideal eating habits, functional foods, and improving lifestyle will help delay the progression of cirrhotic process, and support liver function followed by delay carcinogenesis of the cirrhotic liver.

Application of BioBran, a modified rice bran, for preventing development of hepatocellular carcinoma as an anti-inflammatory supplement

Elimination of HBV or HCV in its chronic phase of infection is still quite hard, even with sophisticated drug treatment. Chronic hepatitis caused by chronic viral infection is also considered to be a significant cause of hepatocellular carcinoma. This is the same kind of consequence that occurs with chronic inflammation in other organs in the life style related disease. This consequence may most probably lead to cancer development, as mentioned in previous chapters.

BioBran is a product of rice bran and basically is a compound of polysaccharides, namely arabinoxylan. BioBran is an enriched plant-fiber, specifically arabinoxylan, which is a kind of polysaccharide compound. This supplement has been investigated in in vitro and in vivo studies, as well as in several clinical studies. A number of papers have been published in the peer-reviewed journals regarding its function. This supplement has a potent immunomodulating action by supporting immune homeostasis and the body's natural healing powers. Allergies are considered as over-active immune responses consisting of chronic inflammatory reactions due to a variety of causes which can be uniquely regulated or modulated by this supplement. Long term modulation of these over-reactions is necessary, especially for cancer prevention, because decreasing chronic inflammation prevents cancer promotion.

Moreover, recently, Dr.Ghoneum and Vietnamese clinicians published clinical studies concerning efficacy of suppression of cancer cell growth of hepatocellular carcinoma by BioBran in the journal named Anticancer Research.

Conclusions

When we look back to the history of medical research, it is very important to ask the question "is hepatocellular carcinoma in human caused by HBV or HCV viral genome?" Ultimately, there is no direct evidence that viral genome is built into host DNA or RNA, or causes infected hepatocytes to become cancerous growth. I would like to answer "No" to the above question as described in my hypothesis, based on current knowledge. Therefore, decrease of chronic inflammation by BioBran or other immunomodulators whatever it is prevents promotion of cancer formation in terms of chemoprevention.

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„Pathologist’s advice on How to combat cancer“ series

Part 11: Uterine Cancer

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Introduction

Regardless to say that the uterus is a precious organ not only for women, but also for human beings. Uterine development relies on female hormones that are secreted by the ovaries. Hormonal homeostasis is so impressive that uterine condition must feedback to the hypothalamus situated in the deep area of the brain by whatever the whole bunch of information it is in the blood and whatever impulses they are through autonomic nervous system from the periphery. Moreover, the hypothalamus is the center of hormonal control influenced from the outside the world through five senses so that it controls the lower hormonal gland, such as the ventral gland of the pituitary, which secretes ovarian stimulating hormones targeting the ovary. The uterus is said to reflect one's reproductive age because it atrophies rapidly after menopause. Hormone replacement therapy, which has recently attracted attention for its anti-aging attributes, is helpful to maintain feminine features and alleviate menopausal syndromes.

Men have the remnant of a uterus, but its development is suppressed by male hormones. It has been said that women think with their uterus and in ancient times. Greeks created the word “hysteria”, which means uterus. Looking back on human history, it would be reasonable to say that the uterus symbolizes the female gender as much as the breasts. However, I'm afraid that this statement may be construed as sexual discrimination in contemporary Japan.

Uterine cancer is divided into two kinds, uterine cervical cancer and endometrial cancer. Among developed nations, as well as in Japan, rates of morbidity and mortality from uterine cervical cancer are decreasing. On the other hand, those of endometrial cancer are gradually on the rise. The reasons for this escalation are clear and I will explain them in detail later in terms of hypothalamus by subcultural influence from the outside.

The assumption is, initially, that cervical cancer is related to viral infections and is dependant on genital hygiene and sexual education. However, endometrial cancer depends on female hormones. Those hormones are strongly influenced by diets high in beef, pork, dairy, and sweets with creamy or whip flavor in addition to sexual influence. Women are exposed to excessive female hormones in this contemporary lifestyle. Female internal environment is unconsciously getting with excessive female hormones. I will talk about this issue in detail in the next essay.

Uterine cervical cancer

In this essay, I would like to talk about uterine cervical cancer. When the uterus is healthy and not in the state of pregnancy, it is in the shape and size of an eggplant, with a small empty space in it. It is as if the eggplant was placed upside-down, with its stem-side down. The position of the “stem” is equivalent to where the uterine cervix is situated. It is connected to the vagina, with the external part being the pudendum. Where the bulbous, round part of the eggplant would be is where the uterine tubes are connected, one on each side, at the top, which is bolstered underneath by the bladder. The slit-like empty space in the uterus is covered with the endometrium, which is where the fetus is nourished during pregnancy.

When a woman is not pregnant, the endometrium (uterine lining) is shed about once every month, which is called menstruation. In this hormonal cycle, the endometrium goes through the proliferative phase by estrogen and eventually becomes fertile by progesterone.

The endometrium is connected to the uterine cervix where the “stem” of the eggplant would be located, which protrudes into the vagina. Those organs are closely connected, and the hygienic

environment of the “vulva-vagina-uterine cervix”, which is related to sexual intercourse, has a great influence on uterine cervical cancer development. In order to protect the important uterus, the inside of the vagina is kept acidic by lactic acid fermentation created by resident bacterium, including Doederlein bacillus. This particular bacterium is believed to be a good one. The acidic environment it creates may prevent various attacks from outside pathogens. But the invasion of viruses and infection cannot be prevented completely. In order to keep this sensitive environment clean, proper genital and sexual hygiene is indispensable.

Human papillomavirus (HPV)

Many Japanese women have human papillomavirus coexisting in the pelvic area. About one third of the adult females in Japan is estimated. The AIDS virus, avian flu and other types of viruses may exist, but you don't need to be fearful of every virus. Since the beginning of time, there have been many different kinds of viruses that peacefully coexist with human beings. HPV is one of those types of viruses. Virus (parasite) and host relationship was elaborately mentioned in the previous chapter (Liver cancer).

Women's bodies can tolerate the coexistence of this virus under normal immune conditions when HPV parasitizes epithelial cells of the vagina and uterine cervix. Epithelial cells infected with HPV are typically not damaged under ordinary circumstances.

Maintaining the immune balance is very important for the immune system, but balance can be lost for instance lowered in a part of immune systems, then virus can grow rapidly followed by damage of cells infected by virus leading arachidonic acid derived from the cell membrane, which cause inflammation in the cervical area as a mechanical result of sexual intercourse. If the inflammation is chronic or occurs repeatedly, leukocytes are attracted to the area, causing various symptoms. Leukorrhea may increase and the patient may feel pain or heaviness in the pelvic area. If inflammation becomes chronic, the inflammatory cells (leucorrhea) attack not only pathogens, but also the patients own body, because leukorrhea is a natural phenomenon like a chemical reaction. One should give up the presumption that “your own cells are always on your side”.

Leukorrhea attacks pathogens with a very strong weapon called “active oxygen” or free radicals. But at the same time, they also destroy epithelial cells which HPV parasitize. Those epithelial cells then regenerate themselves.

In chronic inflammation, this process occurs repeatedly and when epithelial cells proliferate, those cells are undergoing DNA replication and are at their most vulnerable. In this process, the DNA of epithelial cells in the uterine cervix is parasitized by HPV and the cells are gradually damaged and may become malignant.

It is obvious that when HPV infection and inflammation are prevalent, it will progress to malignant changes in epithelial cells. It may depend on the individual as to how long this process will take, but usually it can be from 10 to 15 years, as was found in a clinical study conducted in New Zealand. This process can be traced with a light microscope, referred to as cytodiagnosis in pathology and this examination is also used in uterine cancer. Cells that have been scraped off as well as inflammatory cells can be examined with a microscope and a pathologist determines if they are benign or malignant. Even if a malignant diagnosis is given, it doesn't mean the patient should undergo surgery immediately. Observation is of utmost importance on this stage especially for women in their mid-20s to mid-30s. I have heard that vaccinations for uterine cervical cancer will be put into practical use. HPV have more than 10 subtypes and pathogenicity of them are researched. Vaccines have been produced in accordance with their pathogenicity. Now in Japan vaccination of some of them has been proactical. However, its protective efficacy will be anticipated only around 50% so that cancer formation is closely related not only to its viral infection but also to chronic inflammation.

Epithelial cells parasitized by HPV can spread from the vagina to the uterine cervix, but cancerous changes are limited only to the uterine cervix. This phenomenon is very suggestive, in that HPV parasitism may be an initiator, but chronic inflammation related to sexual intercourse is the promoter of cancerous changes. Screening exam for vaginal smear called Pap smear exam is quite effective for checking cytodiagnosis of atypical cells desquamated from the cervical mucosa. Credibility of this exam is dependent upon expert technologists and pathologists. Epithelial cells infected by HPV with inflammation appear to be atypical. This condition is supposed to be in the premalignant consequence. In the course of its following-up, targeted cervical biopsy is recommended and diagnosed by board certified pathologist. In conclusion, avoidance of viral infection and of chronic inflammation should absolutely be recommended. Even if in case of HPV infection, chronic inflammation should be treated.

I think that a functional food such as BioBran should be recommended to alleviate inflammation to regulate immune balance in women who are experiencing persistent inflammation, because it inhibits cancer promotion. An anti-inflammatory drug like aspirin is not recommended because it has adverse effects.

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„Pathologist’s advice on How to combat cancer“ series

Part 12: Endometrial Cancer

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

Fatty or dairy food and excessive biliary secretion in the gut

The statistics for uterine cancer rates have remained steady. As I mentioned in the previous essay, uterine cervical cancer rates are decreasing, but endometrial cancer is on the rise. This trend is common among developed nations, and the reasons can be speculated. Nature of both cancers of the uterus is quite different from the light microscopic point of view. The former is mainly squamous cell carcinoma just the same as esophageal cancer or skin cancer in part. The latter is mainly adenocarcinoma just the same as colon or prostate cancer, namely cancer of the exocrine glands. The reasons for decreased cervical cancer are already mentioned the previous chapter. The most important reasons are improvements in genital hygiene and the advancement of sexual education. I have explained previously that virus infection as a major initiator and chronic inflammation as a major promoter in the genital area are the major causes for this kind of cancer. In order to get rid of such virus of the cervical cancer, vaccination against such virus as HPV type 16 to young-adult women has been practical, although it has been anticipated to be at most around 50% in the developed countries.

On the other hand, endometrial cancer is influenced by female hormones, which are significantly impacted by diet, environment and social or cultural settings. In accordance with a number of evidence data, I would like to point out that dairy or fatty meal should be digested absolutely by help of bile from the liver derived from the daily reform of red blood cells, totally around 100 grams. Bile secreted into the gut is useful to be detergent like soap and to help digest fatty food by lipoenzymes from the pancreas or small intestine. During the course of the intestinal tract, bile is often changed into the various substances such as carcinogenic substances like methylcholanthrene in the colon by bad intestinal flora, such as anaerobic clostridium. These substances not only influence directly to the colonic epithelium leading to colon cancer in site, but also are absorbed into the blood and transported to the exocrine glands of our body, such as endometrium and breast in the female, or prostate in the male.

What is endometrial cancer?

In the previous essay, I described the shape and position of the uterus. In this essay I would like to give a brief explanation on its functions from the hormonal perspective.

The whole uterus is made up of thick muscles called smooth muscle, and its inside is covered with soft epithelial tissue, called the endometrium. The fertilized ovum implants in the soft tissue. Two kinds of female hormones from the ovaries, estrogen and progesterone, regulate the condition of the endometrium and smooth muscle. The endometrium changes cyclically every month due to the effects and interactions of these hormones. This cycle is meant to prepare the uterus for conception. When the endometrium doesn't receive a fertilized ovum, it completes the cycle by shedding the epithelial tissue with hemorrhage, which is known as menstruation. After menstruation, cells of the endometrium are influenced by estrogen to proliferate again. Estrogen promotes normal cell growth, but in some cases it can become a dangerous carcinogenic factor.

About two weeks later, progesterone is secreted from the corpus luteum of the ovaries, which causes the endometrium to become thick and moist for implantation of fertilized ovum. The ovaries respond to the signals given by the hypothalamus and pituitary gland. The hypothalamus is strongly affected by hormone levels in the blood (that had been secreted from the ovaries), and by brain activity, including emotional reactions.

The system to regulate the endometrial cycles is called the feedback system, and consists of the ovaries, hypothalamus and pituitary in the brain. The endometrium is continuously controlled by hormones and the autonomic nervous system, influencing two patterns of cell behavior: cell proliferation (cell growth) and differentiation (maturation and function). Estrogen strongly promotes cell-proliferation while progesterone maintains proliferated cells and controls function of secretions. Therefore, the endometrium is constantly in an environment that encourages cell growth, a condition that is predisposes one to cancer.

Sex hormones are strongly influenced by diet and social or cultural environments. Adolescents are in their reproductive years, and are affected by Western diets that are high in fat, meat, and dairy, in addition to being influenced by sexual precocity closely related to social subcultures. Those scenarios are some of the influential factors for development of endometrial cancer.

Endometrial cancer screening

Early detection of endometrial cancer is generally made through a relatively easy and simple test, that being cytodiagnosis of endometrium and vagina tissue, or Pap smear, which is standard in a gynecological and cytopathological exam. But some women may be uncomfortable with this screening. Whether the cells are benign or malignant, they are diagnosed by a skilled and experienced laboratory personnel and board-certified pathologist using a light microscope. Endometrial cancer is in many cases detected relatively early, because it is accompanied by subjective symptoms such as increased leukorrhea. Besides, progression is relatively slow and is sometimes curable. Therefore, creating opportunities for screening examination is very important.

If a woman suspects such symptoms, she should undergo a screening from a gynecologist. If heteromorphous cells are detected, extensive screening is conducted by taking a tiny portion of the endometrial tissue. This exam is called an endometrial biopsy, which is a type of histopathological test. This test report is regarded as an official document, and a copy should be maintained by the patient for their own records.

Endometrial cancer may sometimes accompany gynecological health problems, such as irregular menstruation or hypermenorrhea. If a woman is having troubles with menopausal symptoms, cytoscopy is recommended as a precautionary measure.

What is endometriosis?

Endometriosis is not cancer, but it is very troublesome and recurrent during menstruation. The rate of endometriosis has been increasing.

In this illness, small or large patches of endometrial tissue may appear and proliferate in other parts of the body. When these tissues grow into the muscular wall of the uterus, it is called adenomyosis, and when it spreads to other areas, it is called endometriosis. These changes are influenced by the cyclical hormone exchanges under the physiological circumstances, such as proliferative or secretory phases, which are the same as the endometrium itself.

Those endometrial tissues respond to hormones according to the menstrual cycle. Therefore menstruation occurs at those displaced patches of endometrial tissue, causing lower abdominal pain, heavy cramps, or anemia. At present there is no specific medicine to eliminate endometriosis.

Hormone replacement therapy

Endometrial cancer and endometriosis have long existed, but the morbidity is rapidly increasing these days in developed nations, including Japan. It may be partly attributed to changes of diets and social or cultural environments, but there is no scientific evidence for it. Some preventive measures should be found and it is clear that female hormones are a key factor for these illnesses.

Hormone replacement therapy (HRT) is becoming prevalent in the US for treating menopausal syndrome. HRT prescriptions have declined significantly since the Women's Health Initiative study in the mid 90s found that HRT was responsible partly for gynecological cancers or ischemic change of the heart. Menopause is a physiological phenomenon caused by permanent cessation of ovarian function, which signifies the end of reproduction functions.

The average life expectancy of the Japanese was once 50 years around 1950, but now it has rapidly increased up to 90 years and at present Japanese people can enjoy their lives far beyond 50 years. Therefore, in such an age it is natural that women are seeking some method to maintain their youth. Hormone replacement therapy may be used to meet those demands.

However, mentioned above, it has been revealed that long-term hormone replacement therapy enhances the risk of endometrial cancer. It may also cause thrombosis and acute ischemic cardiac diseases, including cardiac infarction and angina pectoris. The use of hormone replacement therapy is being re-examined in the US.

Conclusions

Endometrial cancer occurs infrequently, and fortunately its progress is rather slow. However, its incidence in Japan has insidiously risen up, mentioned above. The level of its malignancy varies from benign to malignant. Early detection and early treatment are required; therefore planning to undergo a gynecological exam is important.

A screening exam should be done several times in one's 50s. If no problems are detected, screening once every five years there on may be adequate. It is also important to select an appropriate hospital and laboratory. The level of gynecological as well as pathological care is important, but at the same time, the medical level of a hospital is determined by the quality of the pathological examination and diagnosis. An ideal hospital should have a pathologist as a permanent member of their staff. These facets of a medical system aren't visible to the general public, but can be seen by researching a facility's website. When selecting which hospital to use, it is important to have this information.

This series of essays have continued over the course of two years and is coming close to the end. Only a few essays are remaining. The purpose of this essay was not to describe cancer in

detail, but to give advice on each individual's strategy for cancer prevention and treatment. This is why I decided to discuss some of the more common types of cancer. I think self-care is the ultimate goal of future medicine, in which people become independent, rather than blindly follow their doctors' instructions, and take care of themselves by improving their own diets and taking supplements appropriately. I would like to promote my idea "Shoku 食=eat followed by I 医=medicine 同源 Dougen=Same Root and Stem" expressed in the Japanese famous proverb-like phrase, "*I-Shoku-Dougen 医食同源*" which has converse means against my idea "To eat adequate food or take supplement like BioBran is fundamentally important. Do not depend upon medicine, as much as possible", that is my own hearty advice to you!

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„Pathologist’s advice on How to combat cancer“ series

Part 13: Strategies for Treatment of Advanced Cancer in Adults (1)

by Yuzo Endo MD, PhD in field of Pathology and Clinical Immunology

In my previous essays, I have mentioned several adult cancers that occur relatively frequently in Japanese people over fifties and are closely related to lifestyle. I mentioned that every morbidity of those cancers has been increasing considerably these days, except for the morbidity of gastric cancer, uterine cervical cancer and esophageal cancer. Hormone-dependent cancers such as breast cancer as well as prostate cancer, and pancreatic cancer were so far not discussed. It is also important that some other cancer, categorized as head and neck cancer, has been also attracting attention recently. I would like to talk about those cancers near future in the next essay series.

My discussions have focused on strategies for cancer prevention in adult, mainly suggesting to improve diet and use supplements in terms of chemo-prevention and integrative medicine. In this essay I would like to go into more detail on these subjects.

What is chemo-prevention for cancer in adult?

Interest in food and supplements rose within the medical movement beginning in the 1970s, which developed into complementary and alternative medicine (CAM), or integrated medicine. This includes the term "chemo-prevention", which is a trend for medical ideology in terms of precaution claim of efficacy even without elaborate basis of scientific evidence. Chemo-prevention includes anti-oxidant function and detoxification of redox reaction with the use of vitamins or natural resources from plants, herbs or natural inorganic chemicals as trace elements in our body. Its meaning is "strategies for cancer prevention and treatment mainly with the use of natural resources except for anti-cancer drugs". It was led by European and US governments with a focus on development of anticancer drugs, and CAM. This movement of CAM became accepted by the public in 1990s. DSHEA is one of the most initiative acts in the United States of America to promote the health promotion campaign not only throughout the US, but also into the world. DSHEA is an abbreviation of Dietary Supplement Health and Education Act, which has begun and held from Jan.25, 1994 on. This act has been impacting throughout the world ever since. However, public officers as well as politicians related to the public health in Japan unfortunately have never had a shrewd receptors for it more than 17 years.

In the US, some prestigious medical schools have educational institutions that specialize in CAM . The education and research of CAM is supported by the government. In Japan, it is unfortunate that this movement has made little progress. This is the reason why I have referred to improving

the diet in this series. I hope my suggestions will contribute to even very small progress of Japanese medicine in general.

This alternative movement has advanced to include naturopathy and homeopathy. Naturopathy involves various folk remedies, herbs, traditional Chinese medicine, aromatherapy, thalassotherapy and others. Homeopathy is so unique that ultimate dilution of remedy in term of dilution dimension of Avogadro number might be even one molecule of remedy chemicals effective on some receptor of cell in our body. It reminds me that salmon returning from the ocean to the river where this salmon hatched out and grew up can discriminate the very specific amino acids or peptides in the river waters in terms of sensing the dilution level of Avogadro number in the ocean.

I sometimes feel that “medical treatment” is becoming so comprehensive that it wouldn't be overstating to say that medicine is a “borderless field”. However, generally speaking, such stuffs mentioned above are not based upon scientific evidence, upon the precaution claims. Double-blind control study in clinics is the first choice to evaluate the efficacy. On the other hand, case control study is also recommended to evaluate clinical trials by supplements. Simultaneously, experimental research including in vitro as well as in vivo studies should be necessary.

The example is as follows. The National Institute of Health in the US has a National Center for CAM, which subsidizes research and education of this field, in addition to conducting clinical trials. For example, there was a clinical suggestion from Cuba that shark cartilage was effective in halting cancers progress and metastasis by inhibiting nutritional support to cancer cells and blocking proliferation of blood capillaries. A clinical trial was conducted to examine this theory, and its effectiveness was not proven. This conclusion was reported on an international medical magazine.

On the contrary, Dr.J.Markus and his colleagues published a case report in the authorized journal named *Dermatol Surg* 2006: 32; 145-147. The title of this report is “Metastatic hemangiopericytoma of the skin treated with wide local excision and MGN-3. MGN-3 is an official name of BioBran.

What is advanced cancer?

I have mentioned that “cancer doesn't develop in a day”. Cancer development usually takes more than ten years, sometimes over twenty years. Once a clump of cancer becomes large enough to be recognized by sight, it accelerates in its progression. If it develops in the digestive system, the cancer on the surface of mucosa spreads and develops in the wall of the stomach or large bowel, and finally into lymph vessels, termed lymph node metastasis or into blood vessels leading to hematogenous metastasis, termed remote metastasis. In the worst cases, cancer proliferates and invades directly through the wall into the peritoneum, followed by cancerous peritonitis. When the cancer grows into the lymph system, it spreads to nearby lymph nodes and finally to the whole body through blood vessels. Once cancer gets into a blood vessel, it spreads over the whole body, which is called remote metastasis.

Clinically speaking, patients with cancer should be categorized in stage classification, such as Stage I (early stage), Stage II, Stage III and Stage IV (advanced stage) in accordance with tumor size, lymph node metastasis, or metastasis to the remote organ etc. Stage classification is standardized throughout the world in terms of stage classification by WHO or World Congress of anti-cancer society.

Even in case of advanced cancer, primary solid tumor mass as well as metastatic site should be resected as much as possible. Local administration of anticancer drugs to the metastatic sites once was practical followed by no recall. However, even though efficacy of anticancer drugs in general might be so limited, I am wondering whether or not chemotherapy or radiotherapy should once be considered again.

Effects of anticancer drugs

Administration of anticancer drugs might be appropriate, in theory, for the purpose of eliminating cancer cells which may have already spread over the whole body. But this theory is only applicable if the anticancer drug selectively destroys only cancer cells. Unfortunately, these drugs don't have this selective capability, unlike antibiotics, which can selectively eliminate only bacterial cells.

The concept of anticancer drugs was originally closely related to the manufacturing of toxic gas, named nitrogen mustard. This was the reason why a young US soldier with malignant lymphoma was faced to this toxic gas in the battle field followed by the remission of his disease. The word "cytostatic", which means "slowing cellular growth", was initially used in place of "anticancer". In Japan, strangely speaking, it was called 制癌剤 in Japanese meaning a "drug for making slow in growing of cancer".

The major characteristic of a cancer cell is "uncontrolled cancer growth". The cells that make up our bodies are replicating DNA and growing at various speeds. Among them, hair follicle cells, leucocytes, epithelial cells of the digestive tract and spermatozoa cells proliferate rapidly. If an anticancer drug is administered, those rapidly proliferating cells are also damaged along with damaging of cancer cells.

Adverse effects of anticancer drugs may include hair loss, leucopenia, causing weaker resistance and susceptibility to infections, infertility, gastrointestinal hemorrhage, and nausea. The major effect of an anticancer drug is to attack DNA replication, although indiscriminately.

Currently, molecular target drugs are attracting attention. These do not directly attack DNA, but instead focus on a specific part of the cell membrane which has a receptor to a molecule related to cell proliferation.

Limit of efficacy of anticancer drugs

Anticancer drugs are sometimes administered immediately before cancer surgery or just after surgery. This medical technique is called "adjuvant therapy" or "neo-adjuvant therapy". The difference is whether adjuvant is given before or after the surgery.

In case of adjuvant therapy, cancer tissue is removed and observed in a pathological examination with a light microscope. In many cases, anticancer drugs have obviously destroyed most of the cancer cells, but not all of them. As a result, some cancer cells, so-called cancer stem cells, survive and change to become more resistant. In some disastrous cases, most of the cancer cells survive and the patient becomes exhausted and loses his life.

There are so many kinds of anticancer drugs that are very expensive. It is extremely difficult to discern what drug is effective for which symptoms. Just looking back at the history of medicine, we may realize that if an anticancer drug is truly effective like antibiotics, its focus must be more limited. However, the reality is just opposite. There has never been a single miracle of anti-cancer drug. Even under treatment of whole bunch of anticancer drugs, patients with any cancer in Stage IV have a worst prognosis, indicating almost zero % in the survival rate in five years. We should not give up, because there might so far occur spontaneous remission of some advanced cancer reported. I should add that patients after anti-cancer treatment, such as surgery or radiation, must continue to feel scary for its recurrence and to suffer from adverse effect of anticancer drugs.

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