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Perspectives on Stomach Cancer

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INTRODUTION

More so than any other malignant tumor, stomach cancer has generated a great deal of interest among cancer epidemiologist because of the gradual decline in its incidence and death rate in the United States from 1930 to 1990 in both males and females. Once, stomach cancer was the leading cause of cancer death in males and the second leading cause after uterus cancer in females in the 1930s. Today its death rate has dropped to less than one eighth after 60 years and is still declining. Certainly the disease is no longer a major threat to the public health in the United States.

On the other hand, in Korea the relative frequency of stomach cancer among cancer is about 28 percent in males, the first in the rank, and about 18 percent in females, the second in the rank, and stomach cancer is the leading cause of cancer death in Korea. In fact, the death rate due to stomach cancer in Korea is the highest in the world. The detection of stomach cancer is still in increasing trend, presumably due to early diagnosis through the introduction of the health insurance system, improved diagnostic technology, and public awareness of the disease. The possibility of a true increase in the incidence and mortality rate cannot be discounted. In the United States the age-adjusted death rate due to stomach cancer is 3.8 per 100,000 population. However, it is a dismal 39.2 per 100,000 population in Korea, which is ten times more than that of the United States.

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POSSIBLE CARCINOGENIC FACTORS

Naturally the decline in its incidence in the United States points to a non-genetic etiology and makes to look into possible roles of environmental factors, personal life styles, habits and behavior, or dietary factors. This declining incidence also provides a hope for a reduction of mortality due to stomach cancer among the Korean population as well, in the future.

In the United States, exposure to external environmental factors, such as chemicals, physical forces, and radiation, has increased considerably since the 1930s in the general population, and other industrialized countries have also shown a progressive decline in the incidence of stomach cancer. These findings suggest that stomach cancer is not caused by such external environmental factors. It is also fairly certain that personal life styles and habits, such as cigarette smoking, and alcohol intake, are not major contributing factors.

Epidemiologic studies from China, Poland, Italy, and Japan have shown that a high consumption of certain foods has been associated with an increased incidence of stomach cancer(Sugimura and Wakabayashi, 1990 ; Boeing et al, 1991 ; Palli et al, 1991 ; Yu and Hsieh, 1991). Salt-preserved vegetables, salted and dried fish, sausages, charred foods, and charcoal/gas cooked meats have been suspected to have cancer-promoting effects. On the other hand, the high consumption of fresh fruits, green vegetables, radishes, onions, cheese, and non-white breads, and increased intakes of vitamin C and beta carotene have been associated with a decreased incidence of stomach cancer. In view of this data, the possible carcinogenic effect of certain traditional Korean foods and dietary habits should be examined by a carefully controlled study. In addition, it would be important to perform a prevention trial study on a large population using

prophylactic administration of vitamin C and beta carotene to determine their cancer-protective effect in high risk patients.

Helicobacter pylori is a gram-negative microaerophilic spiral bacteria which can colonize in the gastric mucosa for years. The infection can result in chronic diffuse superficial gastritis, which sometimes progresses to chronic atrophic gastritis. Chronic atrophic gastritis is known to be a precursor to stomach cancer. *Helicobacter pylori* antibodies(IgG) are present in 94% of stomach cancer patients and the higher level of this antibody titer is associated with a higher risk of stomach cancer(Nomura et al, 1991 ; Parsonnet et al, 1991). Serologic assays for specific IgG antibodies have been documented to be accurate for the diagnosis of *Helicobacter pylori* infection(Evans et al, 1989). However, this data should be interpreted with caution since only a small fraction of patients showing evidence of infection with *Helicobacter pylori* has developed stomach cancer. This infection is suspected to be a cofactor in the pathogenesis of stomach cancer rather than a sole etiologic agent.

Acute and chronic gastritis and peptic ulcer disease have also been common among Koreans, and *Helicobacter pylori* may have an important role in the pathogenesis of these diseases. Accordingly, it seems prudent to do a large scale epidemiologic study to evaluate the relationship between *Helicobacter pylori* infection and the incidence of stomach cancer in Korea. Further, well-designed controlled studies, which employ appropriate antibiotics and anti-ulcer regimens for the treatment of *Helicobacter pylori* infection, are needed to determine a possible favorable effect on the incidence of stomach cancer.

STOMACH CANCER IN KOREAN IMMIGRANTS IN THE UNITED STATES

The incidence of stomach cancer in Japanese immigrants in the United States seems to be considerably less than that of Japanese natives, but is still significantly higher than that in Americans(Tominaga, 1985). Preliminary observation within Korean communities in the United States suggests that Korean immigrants experience a similar decline(Sawyers and Eaten, 1992). The dietary habits of many Korean immigrants have been modified although they still continue to consume a great deal of their original native diet, which includes dried and salt-preserved fish, and pickled vegetables. The trend of a declining incidence of stomach cancer, if proved to be true in large scale epidemiologic studies among immigrants in the United States, may support the critical importance of diet and dietary habits.

Second and third generation Korean immigrants appear to be more adapted to the western style diet and consume much less of the traditional Korean diet than their parents. Therefore, epidemiologic studies on the incidence of stomach cancer in this population may also provide a very important guideline in addressing the issue of improving diet and dietary habits of native Koreans for the future.

NOVEL APPROACHES WITH CHEMOTHERAPY

The potential cure of stomach cancer can be best achieved by early detection of the disease and surgical intervention. Although there is disagreement among surgeons about the best surgical approaches, improved survival has not been conclusively linked with more aggressive surgery. Nonetheless, the five-year survival rate after surgical resection of stage I stomach cancer is above 80 percent(Alexander et al, 1993). Undoubtly, early diagnosis should be the cornerstone of a successful management.

Radiation therapy can benefit certain patients by reducing the recurrence rate and improving longevity(Childs et al, 1968 ; Gastrointestinal Tumor Study Group, 1982). However, the cure for stage II and III stomach cancer is often illusory despite radical surgery. And even after a very aggressive surgical approach the disease frequently relapses in a short time after surgery. Often, the disease is more advanced than initially thought when the patient is surgically explored.

Traditionally, chemotherapy has been employed in metastatic disease. Although stomach cancer is a relatively chemosensitive tumor, the response rate is approximately 50% (10% complete and 40% partial) at best, and the median survival is a meager 9 to 10 months(Sawyers and Eaten, 1992 ; Preusser et al, 1988 ; Wils & Bleiberg, 1989). Better results can be achieved with combination chemotherapy than with a single agent. Regimens that have shown promising results are FAM(5-fluorouracil, doxorubicin, and mitomycin-C)(MacDonald et al, 1980 ; Gastrointestinal Study Group, 1982), EAP(etoposide,

doxorubicin, and cisplatin)(Preusser et al, 1989; Lerner et al, 1992), FAMTX(5-fluorouracil, doxorubicin, methotrexate, and leucovorin)(Kelson et al, 1992), FAP(5-fluorouracil, doxorubicin, and cisplatin)(Wagener et al, 1983), and FP(5-fluorouracil, and cisplatin)(Kim et al, 1993; Kim et al, 1989).

More recently, oncologists have become bolder and more progressive in utilizing multimodality approaches because aggressive surgery hasn't consistently translated into an improved prognosis and new chemotherapeutic treatments have become available. Neoadjuvant chemotherapy, which is preoperative chemotherapy to make it more palatable for surgical intervention, intraoperative chemotherapy, immediate postoperative chemotherapy, and intraperitoneal chemotherapy, and adjuvant chemotherapy are being explored by some oncology groups(Douglass, 1989; Kelsen, 1991; Atiq et al, 1993; Wilke et al, 1989).

Further down the road, more innovative treatments will be explored. These include gene therapy(Rosenberg, 1992), monoclonal antibody treatment(Zhang et al, 1992; Kasprzyk et al, 1992), and dose-intensity chemotherapy with the support of autologous bone marrow and peripheral stem cell transplants along with hematopoietic growth factors, such as erythropoietin, G-CSF, and GMCSF(Shea et al, 1992). New antitumor agents, such as taxol, taxotere, topoisomerase 1 inhibitors, may prove to have a role in the treatment of advanced stomach cancer.

PERSPECTIVES FOR KOREANS

Stomach cancer in the Korean population is a serious health problem and is a menace for Korea. It is tragic to see a large portion of the population succumb, often still young in age, to a disease that can be largely controlled with proper national policy and education. A three-pronged attack against stomach cancer should be seriously considered.

First, it is imperative to improve the dietary habits of the general population. Consumption of healthy foods, such as fresh vegetables and well-refrigerated meats and protein products instead of salt-preserved, dried or smoked ones, should be encouraged through educational programs to the public. Additionally a national policy should be formulated for the standardization of dietary products, and a formal recommendation on a healthy diet for the prevention of stomach cancer should be established and its implementation overseen by a government health agency.

Second, an emphasis on appropriate surgical intervention after establishing the diagnosis of early stage of stomach cancer and the value of adjuvant chemotherapy and radiation therapy should be addressed in medical school curricula and postgraduate medical education of physicians. In addition, well-controlled research protocols in search of more effective adjuvant chemotherapy regimens should be carefully designed and evaluated by a cooperative oncology group.

Third, since chemotherapy has shown a value for remission induction and improvement in the quality of life and longevity in a good number of patients, it is humanly to make optimum regimes available to eligible patients with stomach cancer, even in the advanced stage, hopefully with the financial support of a government-funded national health program.

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