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Japanese Journal of Clinical Oncology

Recent development of gastric cancer prevention

Journal:	*Japanese Journal of Clinical Oncology*
Manuscript ID:	JJCO-12-0116.R1
Manuscript Type:	Review Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Kato, Mototsugu; Hokkaido University Hospital, Division of Endoscopy Asaka, Masahiro
Sub-category:	Gastrointestinal Medicine
Keywords:	GI Medicine, GI-Stomach-Basic, GI-Stomach-Med

Recent development of gastric cancer prevention

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Key words: screening, photofluorography, endoscopy, pepsinogen, *H. pylori* eradication

Running title: Gastric cancer prevention

Funding: No funding source

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Abstract

Mass screening program using photofluorography has been used as a secondary prophylaxis of gastric cancer in Japan. However, we are at a turning point for reconsidering the strategy of gastric cancer prevention because of various problems with photofluorography. The shift from current secondary prophylaxis to primary prophylaxis is now required. After Japanese multicenter randomized controlled trial showed that *H. pylori* eradication reduced the incidence of metachronous gastric cancer after endoscopic resection of early gastric cancer, primary prophylaxis of gastric cancer has gained greater attention. The combination of *H. pylori* eradication as a primary prophylaxis and screening as a secondary prophylaxis is necessary for the elimination of gastric cancer in Japan. Strategy of test, treat and screening for *H. pylori* infection is effective at reducing the incidence and mortality of gastric cancer in communities with high incidence of gastric cancer. We have proposed a program of risk stratification based on the presence of *H. pylori* infection with or without atrophic gastritis followed by targeted interventions.

Mini-abstract

We are at a turning point for reconsidering the strategy of gastric cancer prevention because of current mass screening using photofluorography. The shift to primary prophylaxis is necessary in Japan.

Introduction

The final goal of cancer prevention is to reduce cancer incidence and mortality. Cancer prevention consists of primary and secondary prophylaxis. Primary prophylaxis includes avoiding exposure to known cancer-causing agents, enhancement of host defensive mechanisms, modifying life style, and chemoprevention. (1) Secondary prophylaxis consists of screening and treatment for early stage of cancer.

Although the age-adjusted mortality of gastric cancer has decreased in the last few decades, gastric cancer is the second leading cause of death from cancer in Japan. (2) Gastric cancer accounted for 12.5% of approximately 344,000 cancer deaths in 2009. Mass screening for gastric cancer has been conducted nationwide for all residents aged 40 years and over since 1983 under the Health Service Law for the Aged. (3) Photofluorography using barium meal has been the main screening method for gastric cancer. The purpose of cancer screening includes detection of gastric cancer in its early stage and intervention in its natural development through appropriate treatment. However, the evidence that *Helicobacter pylori (H. pylori)* eradication prevents the development of metachronous gastric cancer after endoscopic resection of primary gastric cancer was provided through a Japanese multicenter randomized controlled trial. (4) Ideally, removal of the cause of the cancer before its occurrence will become part of the strategy of primary prevention of gastric cancer.

Primary prevention of gastric cancer

The methodology of primary cancer prevention has an epidemiological approach and a chemical approach. The epidemiological approach includes elucidation of cancer-causing agents and cancer-preventive agents among foods, drinks and modern living habits in developed countries. The aim of the epidemiological approach is to reduce cancer incidence and mortality by exclusion of causal factors and supplementation of preventive factors that are associates with anti-carcinogenesis. Dietary salt intake, refraining from smoking, and consumption of vegetables and fruits are known as preventive methods in the field of nutrition. (5) The chemical approach includes chemoprevention for inhibition of cancer using various chemicals. The aim of the chemical approach is to extermination causal microorganism and to stop cancer development using administration of chemical substances that have direct anti-carcinogenesis. Eradication treatment of *H. pylori* infection using antimicrobial agents and non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin are used as chemoprevention for gastric cancer. (1).

1) Diet and nutrition

The World Cancer Research Fund and the American Institute for Cancer Research issued a report about food, nutrition, physical activity, and the prevention of cancer in 2007. (6) In this expert study, causal factors and preventive factors for gastric cancer were analyzed from many manuscripts as below. Non-starchy vegetables, particularly allium vegetables, as

well as fruits probably protect against stomach cancer. Salt, and also salt-preserved foods, are probably causes of this cancer. Limited evidence suggests that pulses, including soya and soya products, and also foods containing selenium protect against stomach cancer. There is also limited evidence suggesting that chilis, processed meat, smoked foods, and grilled (broiled) and barbecued (charbroiled) animal flesh are causes of stomach cancer. Infection with the bacterium *Helicobacter pylori* has been established as a necessary cause of almost all cases of gastric cancer. It has been estimated that most cases of this cancer are preventable through appropriate diet and associated factors.

Trends in age-standardized incidence and mortality of gastric cancer worldwide have declined in the last few decades. The most likely reason for this trend is a marked change of life style. A reduced intake of salted, pickled, and preserved foods, increased consumption of fruit and vegetables, and widespread use of refrigeration contributed to decline in gastric cancer incidence. (7) Animal model study demonstrated dose-dependent enhancing effects of salt in gastric chemical carcinogenesis in *H. pylori*-infected Mongolian gerbils associated with alteration of the mucous microenvironment. (8) However, enhancing effects of salt were not found in *H. pylori*-negative Mongolian gerbils. Reduction of salt intake has the possibility of preventing gastric carcinogenesis in *H. pylori* infected patients.

Consumption of fresh fruits and vegetables was reported to have significant reduction of gastric cancer risk in several prospective studies. Ten-year follow-up of the Japan Public

Health Center (JPHC) study cohort showed that intake one or more days per week of yellow vegetables, white vegetables, and fruit reduced gastric cancer risk compared with less than one day per week. (9) In meta-analysis of relevant published cohort studies until 2004, an inverse association was observed between fruit intake and gastric cancer incidence (relative risk 0.82; 95% CI : 0.73-0.93) and this was stronger for follow-up periods of more than 10 years (RR: 0.66; 95% CI: 0.52–0.83). (10) For vegetables, the relative rate was significantly reduced to 0.71 (95% CI: 0.53-0.94) when considering only those with the longer follow-up. Vegetables and fruits include those rich in nutrients such as ascorbic acid, carotenoid, and beta-carotene that may be protective against gastric carcinogenesis. Ascorbic acid is an important anti-oxidant that inhibits tumor cell mitotic activity without affecting normal cell growth. (11) Carotenoid is also a powerful antioxidant that protects against damage caused by free radicals. (12) Because beta-carotene, a precursor of retinol, has anti-cancer effects, it is expected to prevent gastric carcinogenesis. (13) Green tea contains polyphenols, more commonly known as catechins. Catechins include ~~includes~~ epigallocatechin-3-gallate (EGCG) that was proved to inhibit carcinogenesis in both in vitro and in vivo studies. (14)(15) However, these epidemiological associations do not establish beyond doubt that dietary interventions will reduce gastric cancer incidence.

2) Chemoprevention

NSAIDs including aspirin possess the action which obstructs cyclo-oxygenase-2 (COX-2). Expression of COX-2 has been detected not only in colon cancer but also in other

organ cancer. Chemoprevention using COX-2 inhibitors has been investigated in every organ. Overexpression of COX-2 is strongly found in non-cardiac cancer and well-differentiated stomach cancer. The preventive effect of NSAIDs for gastric cancer has been observed in some animal model experiments.

The results from a cohort study and a meta-analysis showed that use of any aspirin reduced significantly the risk of non-cardiac cancer (Hazard ratio HR: 0.64, 95% CI: 0.47-0.86), but no inhibition of cardiac cancer risk (HR: 0.82, 95% CI: 0.67-1.04). (16) Use of other NSAID reduced significantly the risk of non-cardiac cancer (HR: 0.68, 95% CI: 0.57-0.81) and cardiac cancer (HR: 0.80, 95% CI: 0.67-0.95). Multivariate analysis of a nationwide retrospective cohort study in Taiwan suggested that regular NSAID use was an independent protective factor for gastric cancer development (HR: 0.79, 95%CI: 0.69-0.90) (17) Long-term administration of selective COX-2 inhibitor reduced the incidence of metachronous cancer development after endoscopic resection of early gastric cancer with the same degree of effectiveness as *H. pylori* eradication. (18) Although NSAIDs are one of the candidate agents for chemoprevention of gastric cancer, the safety of long-term NSAIDs use is required for chemoprevention with NSAIDs in general population.

3) *H. pylori* eradication

Gastric carcinogenesis is a multi-factorial process including environmental factors, socioeconomic conditions, and living habits. However, almost all gastric cancers including

both intestinal type and diffuse type arise from mucosa infected by *H. pylori*, and these tumors very rarely arise from gastric mucosa without inflammation. *H. pylori* plays the most important role in gastric carcinogenesis. (19) In experimental research in which cancer was induced in Mongolian gerbils through *H. pylori* inoculation plus administration of low-dose chemical carcinogens, *H. pylori* eradication suppressed the incidence of gastric cancer. (20) Animal experiment also suggested that eradication at an earlier period was effective as reducing gastric carcinogenesis compared with middle or late period. (21)

a) Cohort study

Five Japanese cohort studies, in which eradicated and non-eradicated subjects underwent endoscopic follow-up to assess development of gastric cancer, have been reported. (22)-(26) The results of four cohort studies for peptic ulcer patients have suggested an inhibitory effect of *H. pylori* eradication on gastric cancer incidence. One cohort study based on an employer-sponsored medical examination did not have significant results during 9 years of follow-up using X-ray examination. These different results depended on the incidence rates of gastric cancer (Table 1). The incidence rates of gastric cancer in studies with significant results are higher than those of studies without significant results. A large-scale retrospective cohort study in Taiwan showed that early *H pylori* eradication is associated with decreased risk of gastric cancer in patients with peptic ulcer diseases (HR:0.78, :95%CI: 0.60-0.99). (27) Since one-year difference of eradication timing affects

the incidence rate of gastric cancer, early eradication is crucial. Most of the positive cohort data of gastric cancer prevention by *H. pylori* eradication was investigated in the subjects with peptic ulcer. Patients with especially gastric ulcer have higher risk of gastric cancer incidence than general population. One cohort study without peptic ulcer showed that significant reduction in cancer incidence after eradication was observed only in pepsinogen test-negative subjects with mild atrophic change. (25) To confirm these cohort results, a randomized controlled study based on general population is necessary.

b) Randomized controlled study

A double-blind randomized study in China showed that gastric cancer still occurred after successful eradication of *H. pylori* and that *H. pylori* eradication did not lead to significant decrease in the incidence of gastric cancer. (28) In Fujian Province, where the mortality rate due to gastric cancer is high, 1,630 people with *H. pylori* infection were randomly assigned to an *H. pylori* eradication therapy group or a placebo group, and were followed for 7.5 years. During follow-up, development of gastric cancer was observed in 7 subjects from the *H. pylori* eradication therapy group and 11 subjects from the placebo group, with no significant difference between the 2 groups (P=0.33). For the subgroup without precancerous lesions (atrophy, intestinal metaplasia, and dysplasia), however, the incidence of gastric cancer was significantly lower in the *H. pylori* eradication therapy group than in the placebo group (P=0.02). This study suggested that preventive effect of *H. pylori*

eradication for gastric cancer is sufficient only in patients without atrophic change.

Meta-analysis of five randomized controlled studies that compared eradication treatment with no treatment in H. pylori-positive patients was reported whether *H. pylori* eradication treatment reduce the incidence of primary gastric cancer. (29)-(33) Over a follow-up period ranging from 4 to 10 years, 33 of 3,112 patients (1.0%) who received eradication treatment developed gastric cancer compared with 50 of 3,031 controls (1.6%). This difference yielded a relative risk of 0.65 (95 % CI: 0.42 – 1.01) (P = 0.05). (34) Interventional studies to investigate preventive effect of primary gastric cancer require large sample number and long-term observation period in order to get significant results (Table 2, Table 3).

C) Metachronous cancer after endoscopic resection

Mucosal gastric cancer is usually resected by endoscopic treatment in Japan. Metachronous gastric cancer after endoscopic resection of primary gastric cancer often develops at another site within the stomach. The incidence rate of metachronous cancer rate has ranged from 2.5 to 14% for different follow-up periods. A large-scale, multi-center, randomized controlled open-label study was conducted to determine whether eradication of *H. pylori* had inhibitory effects on the development of metachronous gastric carcinomas after endoscopic resection. (4) The 542 subjects were randomly allocated to eradication arm (n=271) and control arm (n=271) and examined endoscopically during three years. Metachronous gastric cancer developed in 33 cases, including 9 in the eradication group and

24 in the control group. The incidence of metachronous gastric cancer in eradication group was significantly lower than in control group, even in the analysis ignoring observation period (HR:0.34, 95%CI: 0.16-0.70, p=0.003). Overall results show that *H. pylori* eradication reduces risk of developing new gastric cancer even in the highest risk group. Sub-analysis of previous papers showed that preventive effect of *H. pylori* eradication for gastric cancer incidence was limited to patients without atrophy and metaplasia. 25)28) However, based on the results of this study, *H. pylori* eradication may also be effective in patients who have mucosal atrophy and intestinal metaplasia. Recent retrospective study about metachronous gastric cancer after endoscopic resection of early gastric cancer showed that rates of metachronous cancer were 14.3% in the persistent group and 8.5% in the eradicated group. (35) Although *H. pylori* eradication significantly suppressed incidence of metachronous cancer at 5 years follow-up, there was no significant difference during the overall follow-up period. Because the median of follow-up period in retrospective study was 3.0 year, it seems that more than 5 years follow-up period based on small sample size and great uncertainty. To determine the long-term effect of *H. pylori* eradication on the development of gastric cancer, long-term follow-up analysis of this randomized controlled study was performed. In mean 5 years follow-up period, metachronous gastric carcinoma had developed in 22 patients in the eradication group and 43 in the control group (the hazard ratio 0.497; p=0.008). (Presentation in DDW2012) This result suggested that *H. pylori* eradication prevented the development of metachronous gastric cancers after endoscopic

resection during long-term follow-up. Since participants in this study had a history of gastric cancer, one would expect that they differ from the general population in terms of specific genotypes and environmental factors. Although this could limit the generalisability of the results, this positive data support the use of *H pylori* eradication to prevent the development of gastric cancer.

H. pylori infection has the possibility of both initiating and promoting the development of gastric cancer. (36) It seems that *H. pylori* eradication almost completely suppresses the incidence of gastric cancer before carcinomatous change of cell develops. The potential effect of *H. pylori* eradication on latent cancer (defined as tiny cancers due to chronic *H. pylori* infection that cannot be detected by endoscopy) is not only to slow its growth, but also to almost completely suppress it (zero growth), or to suppress it completely (negative growth). (37) ~~It is expected that *H. pylori* eradication would inhibit the incidence of gastric cancer in patients with severe atrophy and intestinal metaplasia.~~

Secondary prevention of gastric cancer

Five-year survival rate of early stage gastric cancer is more than 95 % according to progression of gastric cancer treatment in Japan. (38) Since the stage of gastric cancer at the time of detection correlates with the prognosis, secondary prevention is important for early detection and early treatment. The aim of secondary prophylaxis is to detect gastric

cancer in its early stage and to protect its natural development through appropriate treatment. The present method of gastric cancer screening is indirect or direct barium meal x-ray examination, a serum pepsinogen check and endoscopic examination (Table 4). The Japanese Research Group for Cancer Screening Guidelines developed the guidelines in 2006 based on evaluation of efficacies of various methods for cancer screening. (39) Although there was no randomized controlled study that used photofluorography in gastric cancer screening, reduction of mortality from gastric cancer was found in five case-control studies, one cohort study, and meta-analysis. Therefore, gastric cancer screening using photofluorography is recommended for population-based and opportunistic screening in Japan. (40) At the same time, no other methods are recommended for gastric cancer screening. However, in spite of many problems in current gastric cancer screening using photofluorography, there is increasing support for gastric cancer screening using endoscopy, serum pepsinogen, and *H. pylori* antibody. Since the number of gastric cancer deaths has not decreased in Japan, it is not advisable to incorporate the use of photofluorography into the current mass screening program. (41)

i) X-ray examination

Barium meal indirect x-ray examination using double contrast radiography was introduced as a mass screening program of gastric cancer in the 1960s in Japan. (3) It is used widely in resident medical examination by municipal districts under the Health Service