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RAPID COMMUNICATION

Alteration of sister chromatid exchange frequencies in gastric cancer and chronic atrophic gastritis patients with and without *H pylori* infection

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Abstract

AIM: To determine, by counting sister chromatid exchange (SCE) frequencies, whether genetic impairment and DNA damage have an effect on the pathogenesis of gastric cancer (GC).

METHODS: Analysis of SCE is a cytogenetic technique used to show DNA damage as a result of an exchange of DNA fragments between sister chromatids. We analyzed SCE frequency in 24 patients with GC, 26 patients with chronic atrophic gastritis (CAG), and 15 normal controls. The presence of *H pylori* was confirmed by urease test, toluidine-blue stain and hematoxylin-eosin stain.

RESULTS: SCE was significantly increased in *H pylori*-negative GC patients, and in *H pylori*-negative CAG patients compared with controls (7.41 ± 1.36 and 6.92 ± 1.20, respectively, *vs* 5.54 ± 0.8, $P < 0.001$). There was no difference in the SCE frequency between *H pylori*-negative GC patients and *H pylori*-negative CAG patients ($P > 0.05$). On other hand, the SCE frequencies in *H pylori*-positive GC patients were higher than those in *H pylori*-positive CAG patients (9.20 ± 0.94 *vs* 7.93 ± 0.81, $P < 0.01$). Furthermore, *H pylori*-positive GC patients had a higher SCE frequency than *H pylori*-negative GC patients (9.20 ± 0.94 *vs* 7.41 ± 1.36, $P < 0.001$). Similarly, a significant difference was detected between *H pylori*-positive CAG patients and *H pylori*-negative CAG patients (7.93 ± 0.81 *vs* 6.92 ± 1.20, $P < 0.05$).

CONCLUSION: We suggest the increased SCE in patients reflects a genomic instability that may be operative in gastric carcinogenesis.

Key words: Gastric carcinoma; Chronic atrophic gastritis; Pathogenesis; *Helicobacter pylori* infection; Sister chromatid exchange

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INTRODUCTION

Gastric cancer is the second leading cause of cancer death and the fourth most common cancer in terms of new cases worldwide[1]. The development of gastric cancer in humans has been shown to be a multi-step process, ranging from chronic gastritis to atrophy, intestinal metaplasia, dysplasia and finally, invasive cancer[2-5].

Multiple genetic and epigenetic alterations in oncogenes, tumor suppressor genes, cell-cycle regulators, cell adhesion molecules, DNA repair genes and genetic instability, as well as telomerase activation, are implicated in the multi-step process of gastric carcinogenesis. p53, a tumor suppressor gene is thought to play a critical role in the multistep process of gastric carcinogenesis[6-9]. Inactivation of p53 by 17p (p53), loss of heterozygosity (LOH) and mutation seems to be an early event in neoplastic progression in gastric carcinomas, because it develops in diploid cells before aneuploidy and other LOH events involving chromosomes 1, 5, 6, 7, 10, 11 and 12[10,11].

H pylori is an important human pathogen, responsible for most cases of chronic gastritis, peptic ulcer, gastric cancer and gastric mucosa-associated lymphoid lymphoma[12-16]. Evidence that it acts as a carcinogen has come mainly from epidemiological studies[17-19] and animal studies[20]. The working group of the Agency for Research on Cancer reported in 1994 that *H pylori* is indeed a group-1 carcinogen[21].

H pylori is a carcinogen in humans, although it is not thought to cause gastric cancer directly. It may, however, provide a suitable environment, by causing chronic gastritis and intestinal metaplasia, for neoplastic changes. *H pylori* infection leads to changes in many factors, such as the vitamin C content of gastric juice, the levels of reactive oxygen metabolites in the tissues and epithelial cell proliferation, which are important in the pathogenesis of gastric cancer[22].

The sister chromatid exchange (SCE) phenomenon is widely used as a reliable and sensitive indicator of chromosome (DNA) instability, since the SCE patterns can reveal a general genome instability[23]. Variations in DNA repair mechanisms or detoxifying enzymes have been implicated as causing genetic susceptibility associated with cancer[24]. SCE in peripheral lymphocytes has been widely used to assess exposure to mutagens and carcinogens[25-27]. The SCE frequency was found to be significantly higher in individuals with Werner syndrome, Bloom's syndrome, and myelodysplastic disease than in their control groups. These diseases are known to be associated with genomic instability[28,29].

Several groups of investigators have suggested active oxygen species may be implicated in the production of high basal SCE frequencies in chromosome instability syndrome cells, because oxygen free radicals are thought to be responsible for chromosome damage in these cells[30]. Oxidative damage to DNA over time can cause changes to both the structure and function of chromosomes. These changes in the genetic code may lead to cancer and other chronic diseases[31,32]. The mutagenic effects of reactive oxygen species (ROS) have been detected in human lymphocytes by using the SCE technique; elevated ROS in cells can cause an increase in mitotic recombination frequency[33]. Recently, the genotoxicity of ROS has been well established, and oxidative stress has been shown to cause genomic damage[34,35].

The aim of this study was to determine, by counting SCE frequencies, whether genetic impairment and DNA damage have an effect on the pathogenesis of GC.

MATERIALS AND METHODS

Patients

This study was conducted between February 2007 and June 2007 in the Erzurum State Hospital. We performed SCE analysis in 24 non-smoking (8 females and 16 males) patients with GC (age, mean ± SE: 62.2 ± 5.94 years), 26 non-smoking (7 females and 19 males) patients with CAG (age, mean ± SE: 54.3 ± 12.27 years), and 15 healthy, non-smoking (6 females and 9 males) controls (age, mean ± SE: 51.26 ± 6.27 years). Nine of the 24 GC patients were infected with *H pylori*. Nine of the 26 CAG patients infected with *H pylori*. The presence of *H pylori* was confirmed by the urease test, toluidine-blue stain and hematoxylin-eosin stain. The patients were selected from non-smoking and nonalcoholic subjects. None of the subjects had a history of viral infection, bacterial infection or any metabolic diseases. The patients had not been treated with chemotherapy or radiotherapy during the last 4 mo. The patient and control groups were chosen for their similar habits. The hospital Ethical Committee approved the human study. All patients were analyzed prior to treatment.

Sister chromatid exchange analysis

For SCE analysis, 2 mL of heparinized blood was drawn from each individual. Cultures were established by adding 0.5 mL of blood to 5 mL karyotyping medium (Biological Industries, Beit Haemek, Israel) with 2% phytohaemagglutinin M (PHA) (Biological Industries, Beit Haemek, Israel), and incubating for 24 h at 37℃. A 5-bromo-2'-deoxyuridine (BrdU) (Sigma, USA) solution at a final concentration of 5 μg/mL was added. Lymphocytes were cultured in the dark for 48 h and metaphases were blocked during the last 2 h with colcemid (Biological Industries, Beit Haemek, Israel) at a final concentration of 0.1 μg/mL. Further processing included hypotonic treatment, fixation, slide preparation and fluorescein plus Giemsa (FPG) staining for the detection of SCE[36]. Fifty second-division metaphases were scored on coded slides by a single observer as the number of SCEs/cell per subject. The SCE data were analyzed statistically by Student's *t*-test.

RESULTS

The associations of GC and CAG with SCE frequencies in *H pylori*-positive and negative groups are shown in Table 1. According to these results, there was no difference in mean SCE frequency between *H pylori*-negative GC patients and *H pylori*-negative CAG patients (7.41 ± 1.36 *vs* 6.92 ± 1.20 per metaphase, respectively; $P > 0.05$); however, the mean SCE frequencies of both patient groups were significantly higher than that of the control group (5.54 ± 0.8 per metaphase, $P < 0.001$ for both patient groups). On the other hand, the mean SCE frequency of *H pylori*-positive GC patients was significantly higher than that of *H pylori*-positive CAG patients (9.20 ± 0.94 *vs* 7.93 ± 0.81 per metaphase, respectively; $P < 0.01$). Furthermore, the mean SCE frequency in *H pylori*-positive GC patients was higher than that in *H pylori*-negative GC patients (9.20 ± 0.94 *vs* 7.41 ± 1.36 per metaphase, respectively $P < 0.001$). Similarly, *H pylori*-positive CAG patients had a higher mean SCE frequency than *H pylori*-negative CAG patients (7.93 ± 0.81 *vs* 6.92 ± 1.20 per metaphase, respectively $P < 0.05$).

DISCUSSION

Gastric cancer is still a common cause of cancer-related deaths worldwide, despite improved diagnostic and therapeutic implications. Hence, early diagnosis has critical importance. Cancer results from accumulated genetic or

Table 1 SCE frequency in *H pylori*-positive and -negative groups of patients and healthy controls (mean ± SE)

		Sex F/M	*n*	Age, yr	Age at diagnosis, yr	SCE
GC Patients	*H pylori*-positive	3/6	9	53.77 ± 10.27	53.33 ± 9.26	9.20 ± 0.94
	H pylori-negative	5/10	15	63.20 ± 6.98	63.06 ± 7.06	7.41 ± 1.36
CAG Patients	*H pylori*-positive	2/7	9	51.33 ± 11.21	50.11 ± 15.16	7.93 ± 0.81
	H pylori-negative	5/12	17	57.23 ± 13.58	56.65 ± 13.65	6.92 ± 1.2
Controls		6/9	15	51.26 ± 6.27		5.54 ± 0.8

GC: Gastric cancer; CAG: Chronic atrophic gastritis.

epigenetic alteration(s) in a variety of genes that directly or indirectly control cell division, cell differentiation, and cell death[37]. The development of gastric cancer in humans has been shown to be a multi-step process, ranging from chronic gastritis to atrophy, intestinal metaplasia, dysplasia and finally invasive cancer[2-5].

Exposure of cells to a variety of genotoxic and cytotoxic agents has the potential to elicit prolonged and dynamic changes that compromise the stability of the cellular genome[38]. Many of these changes, whether induced directly or indirectly by DNA damage, lead to increases in gene mutation and amplification, reduced cloning efficiency, elevated micronuclei, sister chromatid exchanges, and multiple karyotypic abnormalities[38].

Cytogenetic tests have been widely used in medicine for the assessment of a causal association between disease and cytogenetic damage. In the present study, we investigated whether cytogenetic abnormalities participate in the pathogenesis of GC. SCE, as an indicator of DNA damage, might reflect an instability of DNA or a deficiency of DNA repair. Therefore, it could be used to investigate any causal association between various diseases and any cytogenetic damage[39-41].

SCE is known to be increased by exposure to various genotoxic carcinogens[42] and seems to reflect the repair of DNA lesions by homologous recombination[43]. Important sources of exposure include diet, general environment, medical exposure to ionizing radiation, and internal generation of genotoxic species. Internal phenomena, such as metabolism, errors of DNA replication, inflammation and oxidative stress, may be of importance. Inflammatory diseases, oxidative stress and radiation exposure have been associated with the generation of clastogenic factors, which may be quite persistent[44-46] and might play an important role in carcinogenesis.

Numerous studies have clarified the relationship between *H pylori* infection and gastric cancer[14-16]. Epidemiological studies have shown that *H pylori* infection is an important risk factor in gastric cancer[22,47]. Several *H pylori* virulence-associated genes have been found in Western populations to be associated with an increased risk of gastric cancer and precancerous lesions[48]. Studies from Japan have confirmed IL-1β polymorphisms do contribute to the gastric acid secretory response to *H pylori* infection, and subsequently to clinical sequelae[49,50]. A polymorphism in the IL-1β gene cluster, which has both pro-inflammatory and potent acid suppressive effects, is associated with an augmented cytokine response to *H pylori* infection that increases the risk of gastric atrophy, gastric ulcer, and gastric cancer[3,51].

Tsai *et al*[52] reported alterations in gene expression associated with cell damage, inflammation, proliferation, apoptosis, and intestinal differentiation in gastric tissues, taking into account *H pylori* status. More changes in gene expression, possibly associated with persistent *H pylori* infection and progression of preneoplasia, were observed in the placebo group. No gene was upregulated over time in tissues from the treatment group. This observation is consistent with current knowledge that *H pylori* infection induces cell hyperproliferation, inflammation, and genomic instability[53].

The frequency of SCE is increased in patients with carcinoma of cervix uteri, nasopharyngeal carcinoma, prostate carcinoma, ovarian carcinoma, acute leukemia, chronic lymphocytic leukemia and breast cancer[54-59]. Concerning gastric cancer, in one of the earliest studies SCE was increased to similar levels in patients with GC and those with CAG. However, the mean frequencies of both groups were significantly higher than that of the control group[60]. Furthermore, Gulten *et al*[61] reported increased SCE frequencies in a group of gastritis patients infected with *H pylori*.

In our study, we found significantly elevated SCE frequencies in both *H pylori*-negative GC patients and *H pylori*-negative CAG patients compared with controls. However, there was no difference in SCE frequency between *H pylori*-negative GC patients and *H pylori*-negative CAG patients. This result is consistent with the study of Zhou L *et al*[60]. On the other hand, *H pylori*-positive CAG patients had a higher SCE frequency than *H pylori*-negative CAG patients. This finding is consistent with the study of Gulten *et al*[61]. Similarly, *H pylori*-positive GC patients had a higher SCE frequency than *H pylori*-negative GC patients. Furthermore, the SCE frequencies in *H pylori*-positive GC patients were higher than those in *H pylori*-positive CAG patients. These findings clearly indicate the significance of simultaneous application of SCE for the screening of high-risk individuals. In addition, the results suggest the genotoxic effect of *H pylori* infection is a risk factor for gastric cancer. Intense *H pylori* infection may contribute more to DNA damage and promote carcinogenesis in patients with gastric cancer. Furthermore, chronic *H pylori* infection is also associated with increased gastric cell turnover, which is probably of importance in malignant transformation[62,63].

Our study, which showed increased SCE frequencies in the lymphocytes of CAG patients, could support these observations, as the induction of changes in DNA that lead to mutations play a role in carcinogenicity. Establishment of inherited susceptibility factors is

important to recognize individuals at a higher risk of developing gastric cancer, so that they may benefit from early detection and prevention programs.

Recent studies have demonstrated a significantly increased risk for the development of gastric carcinoma in patients with CAG[3,4,64,65]. Patients with CAG have a markedly increased risk of GC, but the mechanism underlying this increased risk is not well understood. Chronic inflammation has been associated with the development of chromosomal aberrations in both disorders that progress to neoplasia, such as ulcerative colitis[66], and Barrett's esophagus[67]. Our results confirm and extend these findings to patients with CAG. Many investigators have demonstrated genomic instability and abnormalities in patients with CAG and GC[60,61,64,65]. Our analysis suggests that chromosomal instability (DNA) is present at very early stages of neoplastic progression in CAG and GC patients. This instability may be permissive for the generation of other genomic aberrations associated with gastric cancer progression.

In conclusion, our results suggest increased chromosomal instability may be associated with the pathogenesis of early gastric cancer. In addition, our findings indicate that the genotoxic potential of *H pylori* infection is a risk factor for gastric cancer. Thus, SCE is a promising biomarker for assessing the risk of neoplastic progression in gastric carcinoma.

COMMENTS

Background

It is known there is an increased sister chromatid exchange (SCE) frequency in neoplastic diseases. Gastric cancer is still a common cause of cancer-related deaths worldwide, despite improved diagnostic and therapeutic implications. Hence, early diagnosis has critical importance.

Research frontiers

Analysis of SCE is a cytogenetic technique used to show DNA damage as a result of an exchange of DNA fragments between sister chromatids. Therefore, in this study, we aimed to determine, by assessing SCE frequencies, whether genetic impairment and DNA damage have an effect on the pathogenesis of GC.

Innovations and breakthroughs

Our results suggest increased chromosomal instability may be associated with the pathogenesis of early gastric cancer. The identification of increased SCE frequency in patients with gastric lesions may be helpful in the early diagnosis of gastric cancer.

Applications

SCE analysis has come into use as a sensitive means of monitoring the DNA damage. SCE analysis may be used as a marker to estimate the risk of gastric cancer.

Terminology

Sister chromatid exchange (SCE): SCE is known to result from reciprocal DNA interchange in homologous loci of sister chromatids during the replication process.

Peer review

This study indicated genetic impairment and genetic instability may play an important role in gastric cancer. In addition, these findings show the genotoxic potential of *H pylori* infection is a risk factor for gastric cancer.

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