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

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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.

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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].
is indeed a -negative GC patients. 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°C. 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[20]. 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 pmeta/ 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 pmeta/ 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 pmeta/ 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 pmeta/ 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 pmeta/ 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        | 9.20 ± 0.94 |
| H pylori-negative  | 5/10 | 15     | 63.20 ± 6.98         | 7.41 ± 1.36 |
| CAG Patients |    |         |                      |           |
| H pylori-positive | 2/7 | 9       | 51.33 ± 11.21        | 7.93 ± 0.81 |
| H pylori-negative  | 5/12 | 17     | 57.23 ± 13.58        | 6.92 ± 1.2  |
| Controls         | 6/9 | 15     | 51.26 ± 6.27         | 5.54 ± 0.8  |

GC: Gastric cancer; CAG: Chronic atrophic gastritis.

epigentic 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[48]. 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[50].

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[39,40].

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[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[34-39]. 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[60]. 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[60,61,64,65]. 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[64], and Barrett’s esophagus[63]. 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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