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ORIGINAL RESEARCH

Intestinal Metaplasia and the Risk of Gastric Cancer in an Immigrant Asian Population

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Abstract: The development of intestinal metaplasia (IM) has been purported to be a critical step in the pathogenesis of gastric cancer. However, the natural history of IM in migrant human populations has not been well elucidated. The purpose of this study was to determine the risk of gastric cancer posed by IM in Asian immigrants undergoing gastric cancer screening. A retrospective review of Asian immigrants found to have IM during screening was conducted over an 18-month period. In total, 222 patients were found to have IM. Altogether, 24% had a history of smoking, 48% had a family history of gastric cancer, and 52% had a history of *Helicobacter pylori* (*H. pylori*) infection with a 96% eradication rate. Patients with stable IM (SIM) were then compared with those who developed high risk pathology (HRP), specifically dysplasia and/or adenocarcinoma. Thirty-five patients (16%) were included in the HRP group, 31 with dysplasia (14%) and 4 with adenocarcinoma (2%). Of those with dysplasia, 55% demonstrated regression to IM over the course of follow-up. Patients in the SIM group were more likely to be female (60% vs. 31%, $P = 0.002$) and more likely to have had a normal biopsy during follow-up (32% vs. 9%, $P = 0.005$). Odds ratios for IM stability were 3.3 (95% CI 1.5–7.0) and 5.0 (95% CI 1.5–17.1) for female gender and presence of a normal biopsy, respectively. Intestinal metaplasia in immigrant Asian populations is predominantly a stable histologic finding associated with a low rate of persistent dysplasia and adenocarcinoma.

Keywords: intestinal metaplasia, gastric cancer, Asian

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Introduction

Gastric intestinal metaplasia (IM) is defined as the replacement of normal differentiated gastric mucosa with mucosa histologically identical or intestinal epithelium.[1] The importance of IM in the pathogenesis of gastric cancer was first recognized in the 1970s by Correa from histological data gathered in migrant populations a decade earlier.[2] These findings led to the development of the so-called Correa sequence, which describes the series of histological events believed to precede the development of gastric cancer, particularly of the intestinal subtype.[3,4] The sequence begins with development of superficial gastritis, predominantly due to *Helicobacter pylori* (*H. pylori*) infection. Chronic superficial gastritis then leads to the development of atrophic gastritis and subsequently IM which confers a 45- to 90-fold increased risk of developing gastric cancer as compared with normal subjects.[3,5] Further progression to dysplasia and adenocarcinoma is governed by a multiplicity of genetic anomalies and environmental factors.[6]

Molecular studies demonstrate that aberrant expression of *CDX-1* and *CDX-2*, genes that regulate the differentiation of gastric epithelial cells, occurs in IM and can be identified in over 95% of intestinal type gastric cancers in Asian patients.[7,8] Several other proteins, including TGFα and EGF receptor, have also been implicated in the development of IM, but their specific roles are still unclear.[9] Microsatellite instability is also a common finding in IM, being seen in up to 40% of lesions in some series.[3,10]

The primary environmental factor associated with IM and gastric cancer is *H. pylori* infection. Classic studies have demonstrated an odds ratio (OR) of 2.97 for developing non-cardia gastric cancers when infected with *H. pylori*.[11,12] However, a recent study of non-cardia gastric cancers demonstrated the presence of *H. pylori* in 93% of lesions by immunoblot analysis, thought to be more sensitive than traditional ELISA assays, with an associated OR of 21.4.[13] The precise mechanism by which *H. pylori* infection leads to IM and gastric cancer is unclear but may relate to DNA damage caused by reactive oxygen species produced by inducible nitric oxide synthase within inflammatory cells. Exogenous carcinogens, such as nitroso compounds, may also play a role in a susceptible host.[14]

Further evidence for the role of genetic and environmental influences comes from epidemiological studies characterizing the geographical distribution of gastric cancer. In Asia, the rate of gastric cancer is as high as 70 cases per 100 000 males, whereas in North America the rate is less than 6 cases per 100 000 males.[11] This wide discrepancy in prevalence is thought to be due to a higher endemic infection rate with *H. pylori* in Asia as compared with North America, as well as differences in diet and genetic polymorphisms.[8,9,11] Interestingly, a decrease in gastric cancer risk is seen in migrant populations from high risk regions who move to low risk regions, a trend that appears to depend on the age at the time of migration.[15] This likely relates to environmental changes in the new country of residence, but studies on this subject are lacking. Despite this trend, there are little available data on the risk posed by the development of IM in these migrant populations, and it is unclear what, if any, influence this should have on gastric cancer screening guidelines in North America. Therefore, we conducted a retrospective review of Asian immigrants who underwent gastric cancer screening in a tertiary teaching hospital serving an inner-city population to determine the rate of IM, dysplasia, and gastric adenocarcinoma.

Methods

A retrospective chart review was conducted of all immigrant Asian patients who underwent screening gastroscopy in an academic gastroenterology practice at St. Michael's Hospital in Toronto between March 1, 2010, and October 31, 2011. St. Michael's Hospital is a tertiary teaching hospital affiliated with the University of Toronto, is located in downtown Toronto, and serves a demographically diverse inner-city population. Patients were referred to our practice by community general practitioners for the specific purpose of gastric cancer screening based on elevated risk due either to ethnic background or family history of gastric cancer. Patients undergoing gastroscopy for screening purposes had biopsies taken at the time of the procedure in a random fashion in order to rule out intestinal metaplasia, dysplasia, or adenocarcinoma. Any suspicious lesions such as nodules were also biopsied at the discretion of the endoscopist. The frequency of repeat gastroscopy was determined by

the gastroenterologist. If high risk pathologic changes were identified, patients underwent appropriate therapy (eg, endoscopic mucosal resection or partial gastrectomy) and then continued with screening. If total gastrectomy was required, patients were excluded from screening.

St. Michael's Hospital maintains a searchable electronic database of all pathology specimens obtained at the hospital. This database was searched to generate a list of all gastric biopsy specimens taken in our practice over the specified time period. Specimen identification numbers were then entered into a central electronic pathology database to obtain specifics regarding patient information. Patient names from this list were reviewed, and name recognition was employed to determine those of Asian descent. Consultation notes were then reviewed to determine if these identified patients were born outside of Canada. Patients not born outside of Canada, or those whose place of birth could not be determined, were excluded. Patients were included in the study if they were immigrants of Asian descent and had IM on any biopsy by review of all documented pathology reports. Demographic data including age, gender, ethnicity, and number of years resident in Canada were reviewed. Clinical information including smoking history, family history of gastric cancer, and history of *H. pylori* infection and treatment was recorded. Endoscopic data including number of procedures, specimens taken at endoscopy (biopsy versus endoscopic mucosal resection), and number of years of follow-up were reviewed. Histopathologic data including the presence of *H. pylori*, IM, dysplasia, and adenocarcinoma were reviewed.

Patients were then divided into two groups for statistical analysis. The stable IM (SIM) group comprised those patients who had documented IM on at least one biopsy with no evidence of high risk pathology (ie, dysplasia and/or adenocarcinoma) on any biopsy over the selected time period. The high risk pathology (HRP) group comprised those patients who developed dysplasia and/or adenocarcinoma during the selected time period on a background of established IM. Statistical analysis was performed using SAS software (SAS Institute Inc, NC, USA). Continuous non-parametric data was analyzed using the Wilcoxon rank-sum test. Discrete categorical data was analyzed using the χ^2 test except in the case of smoking history where Fisher's exact test was used. All data were collected and analyzed in accordance with the guidelines of the research ethics board of St. Michael's Hospital.

Results

In total, 436 patients underwent screening gastroscopy over the selected time period of which 328 were determined to be immigrants of Asian descent. Of the 328 Asian patients, 222 (68%) had biopsy-confirmed IM at some point in their clinical history, and 90% of those patients had persistent IM on their most recent biopsy. Fifty-five percent of patients were female. The vast majority (89%) of patients were Korean, followed by Japanese (5%), Chinese (4%), and Vietnamese (2%). The mean age at immigration was 37 ± 17 years, and the mean duration of residency in Canada was 15 ± 11 years. Twenty-four percent had a history of smoking, 48% had a family history of gastric cancer, and 52% had a history of *H. pylori* infection. Ninety-six percent of patients with a history of *H. pylori* infection had documented eradication. Seven patients (3%) had endoscopic mucosal resection (EMR) of nodules with all specimens demonstrating IM. Six of the 7 EMR specimens (86%) demonstrated high risk pathology: 3 with low grade dysplasia (LGD), 1 with high grade dysplasia (HGD), 1 with both LGD and HGD, and 1 with both HGD and intramucosal adenocarcinoma.

Thirty-one patients (14%) developed dysplasia, and 4 patients (2%) developed adenocarcinoma. These 35 patients comprised the high risk pathology (HRP) group, while the remaining 187 patients comprised the stable IM (SIM) group. Of those with dysplasia in the HRP group, only 7 patients (23%) demonstrated either persistence of dysplasia or progression of dysplasia to a higher grade, while 17 patients (55%) demonstrated regression of dysplasia to IM. The remaining 7 patients had no prior biopsies to allow conclusions to be drawn regarding progression. Representative histologic photos of focal and extensive IM, low-grade dysplasia and intramucosal adenocarcinoma from the study population are presented in Figure 1.

There was no difference in median age between the SIM and HRP groups (67 years [IQR 57–73] vs. 69 years [IQR 60–72] respectively, $P = 0.50$; Table 1).

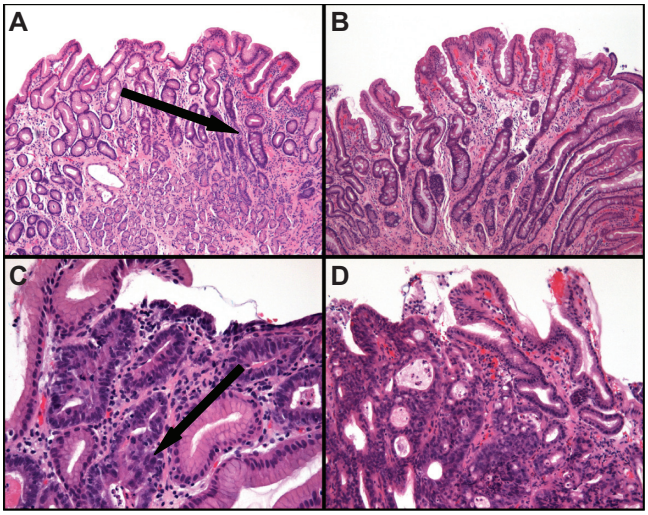

Figure 1. Representative histology from the study population demonstrating (**A**) focal intestinal metaplasia (arrow), (**B**) extensive intestinal metaplasia, (**C**) low grade dysplasia (arrow) and (**D**) intramucosal adenocarcinoma.

There was no difference in median duration of endoscopic follow-up between the SIM and HRP groups (4.0 years [IQR 2.0–8.0] vs. 4.0 years [IQR 1.0–7.0] respectively, $P = 0.88$; Table 1). However, patients in the HRP group did undergo significantly more screening gastroscopies than patients in the SIM group over that time period (4 [IQR 3–6] vs. 3 [IQR 2–4] respectively, $P = 0.001$; Table 1). Patients in the SIM group were more likely to be female than patients in the HRP group (60% vs. 31% respectively, $P = 0.002$; Table 1). Patients in the SIM group were more likely to have had a normal biopsy over the course of their follow-up than patients in the HRP group as well (32% vs. 9% respectively, $P = 0.005$; Table 1). Odds ratios for stability of IM were 3.3 (95% CI 1.5–7.0) and 5.0 (95% CI 1.5–17.1) for female gender and presence of a normal biopsy, respectively.

Although twice the number of patients in the HRP group were smokers as compared with the SIM group, this difference was not statistically significant (20% vs. 10% respectively, $P = 0.08$; Table 1). No significant differences between the SIM and HRP groups were noted with respect to family history of gastric cancer (41% vs. 37% respectively, $P = 0.70$; Table 1), history of *H. pylori* infection (52% vs. 54% respectively, $P = 0.79$; Table 1), or confirmed eradication of *H. pylori* (50% vs. 51% respectively, $P = 0.85$; Table 1).

Discussion

Gastric cancer is the fourth most common cancer worldwide, with 876 000 new cases diagnosed annually, and the second leading cause of cancer-related mortality with 647 000 deaths annually, accounting for 10.4% of all cancer deaths.[11,16] Two-thirds of these cases occur in patients from developing countries, with the highest rates being observed in patients from Asia including Japan, Korea, and China.[11] The majority of patients have incurable disease at the time of diagnosis and a median survival of less than one year.[17]

Although the incidence of gastric cancer is low in North America, migrant populations arriving from regions of high gastric cancer incidence pose a distinct challenge with respect to the need for gastric cancer screening. National census data from 2006[18] demonstrate that people of Asian descent comprise 5.4% of the population of Canada, nearly 1.6 million residents. A recent study showed that the number of gastroscopies required to detect 1 case of upper GI cancer was 41, and to prevent 1 cancer-related death was 571, with an associated cost of US $16

Table 1. Demographic characteristic comparison of the study population.

	SIM	HRP	*P*
Median age [IQR] (years)	67 [57–73]	69 [60–72]	0.50
Female (%)	60	31	0.002
Median follow-up duration [IQR] (years)	4.0 [2.0–8.0]	4.0 [1.0–7.0]	0.88
Median *n* of gastroscopies [IQR]	3 [2–4]	4 [3–6]	0.001
Normal biopsy during follow-up (%)	32	9	0.005
Smoking history (%)	10	20	0.08
H. pylori infection (%)	52	54	0.79
H. pylori eradication (%)	50	51	0.85
Family history of gastric cancer (%)	41	37	0.70

Abbreviations: SIM, Stable IM group; HRP, High risk pathology group; IQR, Interquartile Range.

577 per life-year gained in a North American model of gastroscopy referral patterns.[19] The economic burden to North American health care systems of screening these immigrant Asian populations cannot be understated.

Moreover, the clinical value of population-based screening for gastric cancer has not been established. National population-based gastric cancer screening programs have been instituted in both Japan and Korea, but disparities in participation rates and follow-up make it difficult to establish an effect on mortality.[20–22] While there is retrospective evidence of decreased mortality with endoscopic surveillance of pre-malignant gastric lesions from the UK,[23,24] substantive prospective data are lacking. In a position statement from 2006, the American Society for Gastrointestinal Endoscopy (ASGE) could not uniformly recommend routine endoscopic surveillance for gastric cancer.[25] Furthermore, strong epidemiological data suggest that the baseline risk of gastric cancer is reduced in traditionally high risk populations who have immigrated to regions of low gastric cancer incidence.[15,26] Taken together, these findings cast doubt on the economic feasibility and preventative utility of gastric cancer screening programs in North America in immigrant Asian populations.

While there are extensive data on the molecular biology of IM, the clinical importance of IM in human populations is less clear and data regarding the actual cancer risk posed by the presence of IM are lacking.[27] Histopathologic studies have shown that gastric IM may progress to dysplasia but may also regress to normal epithelium[28,29] even in those who have not been treated for *H. pylori*[30–32] However, these studies are based on biopsy evaluation for IM; many cases of regression may simply be due to sampling error in patients with patchy or focal IM. A cohort study by de Vries et al[33] demonstrated a gastric cancer incidence rate of 1.2% at 5 years and 1.8% at 10 years in Dutch patients with IM. However, to our knowledge, no studies have looked specifically at IM in immigrant Asian populations in North America.

In this study, the prevalence of IM and the associated risk of gastric cancer were assessed retrospectively in a cohort of Asian immigrants in Toronto who were referred for gastric cancer screening. Over two-thirds of patients in our study had IM, confirming findings in other studies[29] that IM is a common histologic abnormality. However, the proportion of patients with IM who developed gastric adenocarcinoma was approximately 2% over a median follow-up of 4 years, in line with findings in the de Vries et al study. When patients with biopsy-proven dysplasia were evaluated, fewer than a quarter of the patients showed persistent histologic abnormalities on their most recent biopsy. Thus, IM diagnosed at endoscopy in high risk Asian immigrant populations appears to be a stable histologic finding with a low associated risk of progression to dysplasia or adenocarcinoma in the vast majority of patients.

In order to delineate predictors of IM progression, we categorized the patients into two groups: those who had IM without dysplasia or adenocarcinoma (the stable IM or SIM group) and those who had IM and dysplasia or adenocarcinoma (the high risk pathology or HRP group). No differences in median age or duration of follow-up were noted between the two groups, although patients in the HRP group underwent more gastroscopies during follow-up than did those in the SIM group (Table 1). Comparison studies of the two groups demonstrated that the variables with the strongest association to stable IM were female gender and the presence of a normal biopsy at some point during follow-up. Low risk of progression in females with IM appears to agree with well-established epidemiological data that males are typically at twice the risk of gastric cancer than females.[11,34,35] Indeed, the proportion of females in the SIM group in our study was approximately twice that of males. More than three times as many patients in the SIM group had a normal biopsy (ie, a biopsy with no IM, dysplasia, or adenocarcinoma) at some point during their follow-up when compared with the HRP group. Given that the biopsies taken were random, it may be inferred that the presence of a normal biopsy suggests relatively limited mucosal disease, while the absence of a normal biopsy suggests more diffuse mucosal disease. Theoretically, the more widespread the IM, the higher the probability of any individual metaplastic cell (or group of cells) becoming dysplastic or neoplastic. This would agree with findings in other studies that have shown that the topographical extent of IM correlates to the risk of gastric cancer.[36,37]

Although the proportion of smokers in the HRP group was twice that of the SIM group, this difference did not reach statistical significance, which may be related to small sample size or Type II error, but this finding is in agreement with the lack of a conclusive link between gastric cancer and smoking.[38] No association was found with respect to family history of gastric cancer, which may also be related to small sample size. Patients with a family history of gastric cancer have been shown to be at higher risk of developing IM, but the risk of developing adenocarcinoma has been less well elucidated[39] although a positive family history may predispose to disease at a younger age or to the presence of synchronous lesions.[40] Furthermore, the study subjects were all immigrants from an endemic region, and the mean age of the study population was approximately 65, potentially making family history a less important risk factor in this particular study. A history of *H. pylori*, even when treated, was not associated with IM progression in our study. As in previous studies, our findings support the observation that the presence or absence of *H. pylori* likely does not change the natural history of IM once it has been established.[30,32,41]

While this study highlights the low risk of gastric cancer in immigrant Asian patients with IM, there are several limitations. The study population is small, and, hence, other important factors may not have been identified due to sample size limitations. The retrospective nature of the study does not allow for causality to be determined conclusively for the associations that were identified. Moreover, other potentially important variables with prognostic value, such as age at immigration or number of years of residency in Canada, could not be accurately ascertained due to the lack of sufficient data. Also, referral bias cannot be excluded in our data given that the entirety of the data comes from a single academic GI practice in an urban setting. Furthermore, the high proportion of Korean patients in our study, as compared with other Asian ethnic subgroups, may not be representative of other immigrant populations across North America. There is also significant heterogeneity in the sub-classification of IM among the different pathologists interpreting the biopsies in this study, a factor that cannot be overcome in a retrospective study and that may have important prognostic implications for IM progression. Nevertheless, this study identifies patient characteristics that appear to impart a propensity to IM stability and, hence, can aid the gastroenterologist in decision making regarding the need for, and the frequency and duration of, gastric cancer screening for Asian immigrant patients. Further areas of study may include comparisons with non-Asian immigrants as well as to second and third generation Asian patients. The effect of duration of residency, age of immigration, and dietary changes can also be assessed, ideally with larger prospective studies.

Conclusion

Intestinal metaplasia in immigrant Asian populations is predominantly a stable histologic finding associated with a low rate of progression to dysplasia and adenocarcinoma. The strongest associations with IM stability in this study were female gender and presence of a normal biopsy during screening. As no screening guidelines for gastric cancer have been established in North America, specific recommendations regarding screening are difficult to make. Screening practices should be administered in a judicious manner by the consultant gastroenterologist in conjunction with open patient communication. Findings from this study suggest that female patients and those who have had a normal biopsy may be at lower risk of progression to gastric cancer, even in high risk populations, and perhaps do not require screening gastroscopy as frequently as other high risk patients. This study may serve as the impetus for further correlative and prospective studies, which may have significant implications for screening practices in North America for these high risk populations.

Author Contributions

Conceived and designed the experiments: AA, CS, CBM, AG, YIK. Analysed the data: AA, CS, CBM, AG, YIK. Wrote the first draft of the manuscript: AA. Contributed to the writing of the manuscript: AA, CS, CBM, AG, YIK. Agree with manuscript results and conclusions: AA, CS, CBM, AG, YIK. Jointly developed the structure and arguments for the paper: AA, CS, CBM, AG, YIK. Made critical revisions and approved final version: AA, CS, CBM, AG, YIK. All authors reviewed and approved of the final manuscript.

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Competing Interests

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Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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