

ORIGINAL ARTICLE

Genome wide array comparative genomic hybridisation analysis of premalignant lesions of the stomach

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Background: Gastric cancer is one of the most frequent malignancies in the world, ranking fifth in the Netherlands as a cause of cancer death. Surgery is the only curative treatment for advanced cases, but results of gastrectomy largely depend on the stage of the disease. A better understanding of the mechanisms of progression from a preneoplastic condition through intraepithelial neoplasia to invasive cancer may provide information relevant to designing focused prevention strategies.

Methods: Because the pattern of chromosomal aberrations in precursors of gastric cancer is unclear, 11 gastric polyps with intraepithelial neoplasia (three hyperplastic polyps and eight adenomas) were analysed by microarray comparative genomic hybridisation to study chromosomal instability in precursors of gastric cancer.

Results: Chromosomal aberrations were detected in all specimens. Adenomas showed no more chromosomal aberrations than did the hyperplastic polyps. The most frequent aberrations were gain of 7q36 and 20q12, and loss of 5q14–q21 in the adenomas, and loss of 15q11–14, 1p21–31, and 21q11–21.2 in the hyperplastic polyps. The most frequent chromosomal aberration in common to both types was loss of 9p21.3.

Conclusion: Hyperplastic polyps showed many chromosomal aberrations, confirming that neoplastic transformation can occur in these lesions. These observations are consistent with the existence of two morphologically and genetically distinct pathways to gastric cancer—the hyperplastic polyp pathway and the (intestinal type) adenoma pathway. The relative contribution of each to gastric carcinogenesis in general, and how they compare to patterns of chromosomal aberrations in the more prevalent flat foci of intraepithelial neoplasia remain to be determined.

Gastric cancer is one of the most frequent malignancies in the world, and even the most frequent in some areas, such as Japan. The prognosis of this malignancy remains very poor. In the Netherlands, gastric adenocarcinoma ranks fifth as a cause of cancer death, with approximately 2200 new cases annually.¹ Surgery is the only possible curative treatment for advanced cases, but results of gastrectomy largely depend on the stage of the disease. Detection and removal of gastric mucosal neoplasias in an early or even pre-malignant stage can contribute to improved disease outcome. This notion has led to population based screening strategies in high incidence countries.^{2,3} However, in low and average risk countries the success of population based screening seems less obvious. A better understanding of the mechanisms leading to the progression from intraepithelial neoplasia (formerly termed dysplasia) to cancer may provide new insights that are relevant for designing focused prevention strategies.

According to the Correa model, the pathogenesis of the most frequent form of gastric adenocarcinoma (the intestinal type) morphologically follows a sequence of *Helicobacter pylori* infection causing active and subsequent chronic active gastritis, leading to mucosal atrophy and intestinal metaplasia in a small number of cases, followed by intraepithelial neoplasia, and ultimately invasive adenocarcinoma.^{4–6} One of the key features in the pathogenesis of many solid cancers, including gastric carcinoma, is chromosomal instability, a condition that can be analysed by comparative genomic hybridisation (CGH). CGH yields in a single experiment, an overview of the DNA copy number changes (gains and losses) present in a tumour, it can be applied to formaldehyde fixed, paraffin wax embedded material, and is well suited for the analysis of premalignant lesions.⁷ In the stomach, intraepithelial neoplasia mainly presents as small lesions, often admixed with non-

tumour cells, which are less suitable for CGH. In a few cases, intraepithelial neoplasia presents as larger polypoid lesions; that is, adenomas.

“A better understanding of the mechanisms leading to the progression from intraepithelial neoplasia (formerly termed dysplasia) to cancer may provide new insights that are relevant for designing focused prevention strategies”

Hyperplastic polyps almost never occur in normal gastric mucosa, but almost always against a background of chronic active gastritis.^{8,9} They are thought to result from regeneration after mucosal damage—for example, as a result of *H pylori* induced gastritis. Hyperplastic polyps in principle are reactive in nature, but on rare occasions they may contain intraepithelial neoplasia or even adenocarcinoma.^{8,10–13} Little is known about the molecular background through which hyperplastic polyps develop. Microsatellite instability¹⁴ and mutation of the K-ras oncogene¹⁵ have been reported to occur in a subset of hyperplastic polyps. Both adenomas and hyperplastic polyps can yield enough DNA for CGH. A few studies have already analysed chromosomal imbalances in premalignant gastric lesions by chromosome based CGH, and some chromosomal regions with frequent gains or losses have been identified.^{16–18} However, this information was obtained by chromosome based CGH, a technique with a limited resolution of 3–10 Mb.

Abbreviations: CGH, comparative genomic hybridisation; DAPI, diaminophenylindole; SCC, saline sodium citrate

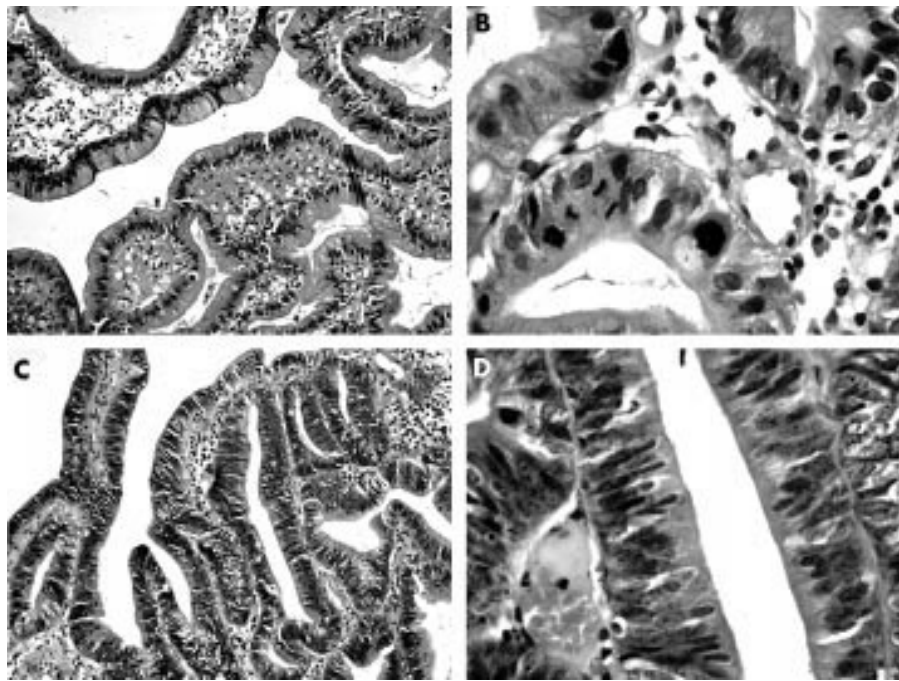


Figure 1 (A) Gastric hyperplastic polyp at $\times 10$ magnification showing villous and tubular structured lines with cylindrical epithelium and disturbed differentiation. The stroma is oedematous, with a chronic inflammatory infiltrate. (B) At $\times 40$ magnification, the epithelium of the same hyperplastic polyp shows severe atypia, with enlarged nuclei that are hyperchromatic and polymorphic. (C) At $\times 10$ magnification of a tubulovillous adenoma, multiple mitoses can be seen, many of which are atypical; there are irregular crypts and leaf-like projections. (D) At $\times 40$ magnification, the epithelium of the same adenoma shows mucin depletion, crowding, and stratification of atypical nuclei.

Microarray based CGH has a much higher resolution, as we have demonstrated previously in the analysis of the 20q13.2 amplicon that is frequently found in gastric cancer.¹⁹ Such higher resolution may allow the detection of smaller chromosomal changes.

Therefore, in our present study, gastric adenomas and some rare cases of hyperplastic polyps with intraepithelial neoplasia were analysed by microarray CGH to study the presence of chromosomal instability in precursors of gastric cancer.

MATERIAL AND METHODS

Material

Our study comprised 11 gastric polyps with intraepithelial neoplasia (three hyperplastic polyps, and eight adenomatous polyps). Of the patients, six were male, and five were female. Two hyperplastic polyps contained low grade intraepithelial neoplasia and one showed high grade intraepithelial neoplasia (fig 1). It should be noted that hyperplastic polyps with intraepithelial neoplasia are exceptions. Three adenomas contained low grade, and five high grade intraepithelial neoplasia. Four adenomas showed a tubular architecture and four were tubulovillous.

DNA was isolated from paraffin wax embedded, archival tissue samples from the specimens described above. The samples were obtained from the archives of the department of pathology of the VU University Medical Centre, Amsterdam in The Netherlands, and from the department of pathology of the Klinikum Bayreuth in Germany. For each tumour tissue sample, DNA was extracted from 15 paraffin wax sections (10 μ m thick), dissecting the area of interest (that is, the dysplastic areas) by scraping the tissue of a microscope slide with a scalpel blade, allowing a maximum of 25% non-tumour cell contamination. This approach yielded sufficient amounts of DNA of good quality to perform CGH without the need for prior amplification. Normal human male genome DNA was isolated from lymphocytes obtained from a blood bank. DNA isolation was performed following the manufacturers instructions (Qiamp tissue kit; Qiagen Inc, Valencia, California, USA), with some modifications as described previously.²⁰

Microarrays

Microarrays were produced as described previously.²¹ In short, DNA isolated from BAC clones was amplified using ligation

mediated polymerase chain reaction to generate representations of these human BAC DNAs. The DNA samples were spotted on chromium coated microscope slides using a custom built arrayer. A genome wide scanning array was used as described previously.²¹⁻²³ The array comprised DNA samples from 2275 BAC and P1 clones spotted in triplicate, evenly spread across the whole genome at an average resolution of 1.4 Mb. Chromosome X clones ($n = 61$) were discarded from further analysis because all tumour samples were hybridised to male reference DNA, leaving 2214 clones for each array to be evaluated.

Comparative hybridisation

Test and reference genomic DNA (300–500 ng of each) were labelled by random priming (BioPrime DNA labelling system; Gibco BRL, Gaithersburg, Maryland, USA) in a 50 μ l reaction with Cy3 dCTP (Amersham Pharmacia Biotech, Piscataway, New Jersey, USA) and Cy5 dCTP (Amersham Pharmacia Biotech), respectively, as described previously.²¹ Non-incorporated nucleotides were removed using a Sephadex G-50 spin column. Labelled DNA (~600–1000 ng of input DNA) was mixed with Cot-1 DNA (80–100 μ g; Gibco BRL) and ethanol precipitated. The precipitated DNA was dissolved in hybridisation mix (50 μ l) to achieve a final composition of 50% formamide, 10% dextran sulfate, 2 \times saline sodium citrate (SSC), 4% sodium dodecyl sulfate, and 500 μ g yeast tRNA. The hybridisation solution was heated to 70°C for 10–15 minutes to denature the DNA, and then incubated at 37°C for approximately 60 minutes to allow blocking of the repetitive sequences. A ring of rubber cement was applied closely around the array to form a well into which we added 50 μ l of slide blocking solution containing 250 mg salmon sperm DNA. After a 30 minute incubation period at room temperature, approximately three quarters of the blocking solution was removed, and the denatured and reannealed hybridisation mixture was added. The arrays were placed on a slowly rocking table (~1 revolutions/minute) at 37°C to allow hybridisation to occur over 48–72 hours.

After hybridisation, slides were washed once in 50% formamide, 2 \times SSC, pH 7.0, at 45°C for 15 minutes, and once in PN buffer (0.1M sodium phosphate, 0.1% nonidet P40, pH 8.0) at room temperature for 15 minutes. Excess liquid was drained from the slides and the array was mounted in 90% glycerol,



Figure 2 Overview of chromosomal aberrations in gastric adenomas (n=8; black bars) and hyperplastic polyps (n=3; grey bars), as detected by array comparative hybridisation. Bars on the left of the ideograms (850 bands resolution) indicate losses, and on the right gains. None of the cases showed amplifications (high level gains).

10% phosphate buffered saline, 1mM diaminophenylindole (DAPI) solution to counterstain the DNA targets.

Image acquisition and data analysis

UCSF SPOT software²⁴ (<http://jainlab.ucsf.edu/Projects.html>) was used to automatically segment the spots based on the DAPI images, perform local background correction, and to calculate various measurement parameters, including \log_2 ratios of the total integrated Cy3 and Cy5 intensities for each spot. A second custom program, SPROC (<http://jainlab.ucsf.edu/Projects.html>), was used to associate clone identities and a mapping information file with each spot, so that the data could be plotted relative to the position of the BACs on the September 2000 or August 2001 freeze of the draft human genome sequence (<http://genome.ucsc.edu/>). The SPROC output consists of \log_2 transformed averaged fluorescence ratios of the triplicate spots for each clone, standard deviations of the triplicates, and plotting position for each clone on the array. Ratios of clones for which only one of the triplicates remained after SPROC analysis were excluded from further analysis.

Chromosomal aberrations were classified as a gain when the normalised \log_2 transformed fluorescence ratio was higher than 0.2, and as a loss when this ratio was below -0.2. Neighbouring clones with a similar \log_2 transformed fluorescence

ratio exceeding these borders were regarded as belonging to the same chromosomal gain or loss, respectively. Multiple gains and losses were counted as separate events.

RESULTS

Chromosomal aberrations were detected in all three gastric hyperplastic polyps and eight adenomas studied. Figure 2 and table 1 provide an overview of the copy number changes.

The mean numbers of events, gains, and losses were comparable between the hyperplastic polyps (6.7, 2.0, 4.7, respectively) and the adenomas (5.4, 2.5, 2.9, respectively). The five lesions with low grade intraepithelial neoplasia showed a mean of 3.8 events (SD, 1.3), and the six with high grade intraepithelial neoplasia a mean of 7.3 CGH events (SD, 3.7). Within the adenomas, the three with low grade intraepithelial neoplasia showed a mean of 3.3 events (SD, 1.5), and the five with high grade intraepithelial neoplasia a mean of 6.6 chromosomal aberrations (SD, 3.7) for each case. Of the three hyperplastic polyps, the two with low grade intraepithelial neoplasia showed a mean of 4.5 (range, 4–5) chromosomal events and the one hyperplastic polyp with high grade intraepithelial neoplasia showed 11.0 events.

In the adenomas, the most frequent aberrations were gain of 7q36 and 20q12 (in four and three of the eight cases, respectively), and losses of 5q14–21 (in three of the eight cases), whereas in the hyperplastic polyps, loss of 15q11–14, 1p21–31, and 21q11–21.2 (each in two of the three cases) were most prevalent. The most frequent chromosomal aberration that both types of polyps had in common was loss of 9p (five of 11 cases), with a common region of overlap at 9p21.3.

DISCUSSION

Gastric cancer is a very common disease with a poor outcome in most cases. The disease is strongly associated with colonisation with *H pylori*. Although several precursor lesions for gastric adenocarcinomas have been recognised, we know very little about the pattern of chromosomal aberrations in these precursors of gastric cancer, or the role of these lesions in the process of progression to cancer.^{16–18} This is largely because most of the time biopsies from flat intraepithelial neoplasias, the most common precursor of gastric cancer, are too small for CGH analysis or contain too many contaminating non-tumour cells. Therefore, gastric adenomas provide a better opportunity for surveying the pattern of chromosomal changes occurring during the pathogenesis of gastric cancer, although probably only a minority of all gastric cancers actually arise from adenomas. A certain analogy exists with the adenoma-carcinoma sequence in the large intestine, although adenomas are much less prevalent in the stomach than in the colon. For hyperplastic polyps, the situation is even less clear. In general, hyperplastic polyps are thought to be reactive in nature, rather than neoplastic. Nevertheless, a few studies report the occurrence of cancer in gastric hyperplastic polyps.^{11–13} In our present study, we were able to analyse chromosomal changes in three hyperplastic polyps with intraepithelial neoplasia. It should be stressed that intraepithelial neoplasia in hyperplastic polyps of the stomach is an exceptional finding, and therefore these data cannot simply be extrapolated to gastric hyperplastic polyps in general. Nevertheless, the analysis of these lesions is meaningful because it allows the comparison of DNA copy number changes in different types of precursors of gastric cancer. To our knowledge, our study is the first to analyse precursors of gastric cancer with the sensitive and high resolution microarray CGH technique. Given the lack of knowledge on chromosomal changes in precursors of gastric cancer, and the fact that these lesions are difficult to study, even the analysis of a relatively small number of samples with an advanced technique like microarray CGH can yield relevant information.

Table 1 Array comparative genomic hybridisation data and clinicopathological characteristics

Tumour ID	Lesion	Sex	Type	Grade of intraepithelial neoplasia	Chromosomal aberrations	
					Gains	Losses
1	A	M	Tubulovillous	Low grade	–	5q12–21 5q33–34 3q13.3–24 9p21–22 18
2	A	F	Tubulovillous	High grade	8 20q13.1	–
3	A	M	Tubulovillous	High grade	7q36 11q13 14q32.2 16q22 16q24 17q21.1–qtel 20q13.1	4q28 5q14–23 9p 18
4	A	M	Tubular	Low grade	7 20	5p15.2
5	A	M	Tubulovillous	High grade	7 11q13 16q24 17q25	5q14–23 5q34 13q14.3–33
6	A	M	Tubular	Low grade	13q32 17q24–25.1	–
7	A	M	Tubular	High grade	4q13–21	7q11 19q12–13.1 22q13.2–qter
8	A	F	Tubular	High grade	7q35–36	6p24 6q14–16 6q22.1–23.2 9p21–23 13q12 13q31
9	HP	F	–	Low grade	20q11.2	1p21–31 8p22–23.1 11p11.2–12
10	HP	F	–	High grade	10q22 13q 15q22–25 19	1p21–31 4p15.2–16.3 9 15q11–14 17p–q11.2 18p 21q11–21.2
11	HP	F	–	Low grade	15	4p15.1 4q32–35 9p21.3 21q11–21

A, adenomatous; HP, hyperplastic polyp.

We found chromosomal instability in all the gastric adenomas and hyperplastic polyps with intraepithelial neoplasia analysed. The most frequent aberration in these 11 gastric polyps was loss of 9p21.3, which is in concordance with other observations.¹⁸ Two well known tumour suppressor genes (p15 and p16 (ink4/arf)) are located at this chromosomal region. Adenomas did not show more chromosomal aberrations than did the hyperplastic polyps with intraepithelial neoplasia. Apart from the loss of 9p21.3, hyperplastic polyps showed a different genetic profile to adenomas, with gain of 7q36 and 20q12 and loss of 5q14–21 as the most common events in the adenomas, compared with gain of 15q11–14 and loss of 1p21–31 and 21q11–21.2 in the hyperplastic polyps.

Not surprisingly, when comparing these data with those previously obtained by microarray CGH in a series of gastric

cancers (unpublished data, 2002), it is clear that the mean number of events, gains, and losses was lower in the hyperplastic polyps (6.7, 2.0, and 4.7, respectively) and the adenomas (5.4, 2.5, and 2.9, respectively) than in the 35 gastric carcinomas (16.0, 7.9, and 7.1, respectively). In addition, no amplifications were detected in the hyperplastic polyps and the adenomas, whereas in the carcinomas a mean of 1.0 amplification/case was detected. Interestingly, several of the chromosomal changes in the gastric carcinomas also occurred in some of the adenomas and hyperplastic polyps, including the loss of 9p21.3 that occurred in both adenomas and hyperplastic polyps. Some of the other cancer related chromosomal aberrations in our present series appeared to be more specifically related to the type of polyp. For example, gain of 15q11–14 (one of 35 carcinomas), loss of 1p21–31 (four of 35

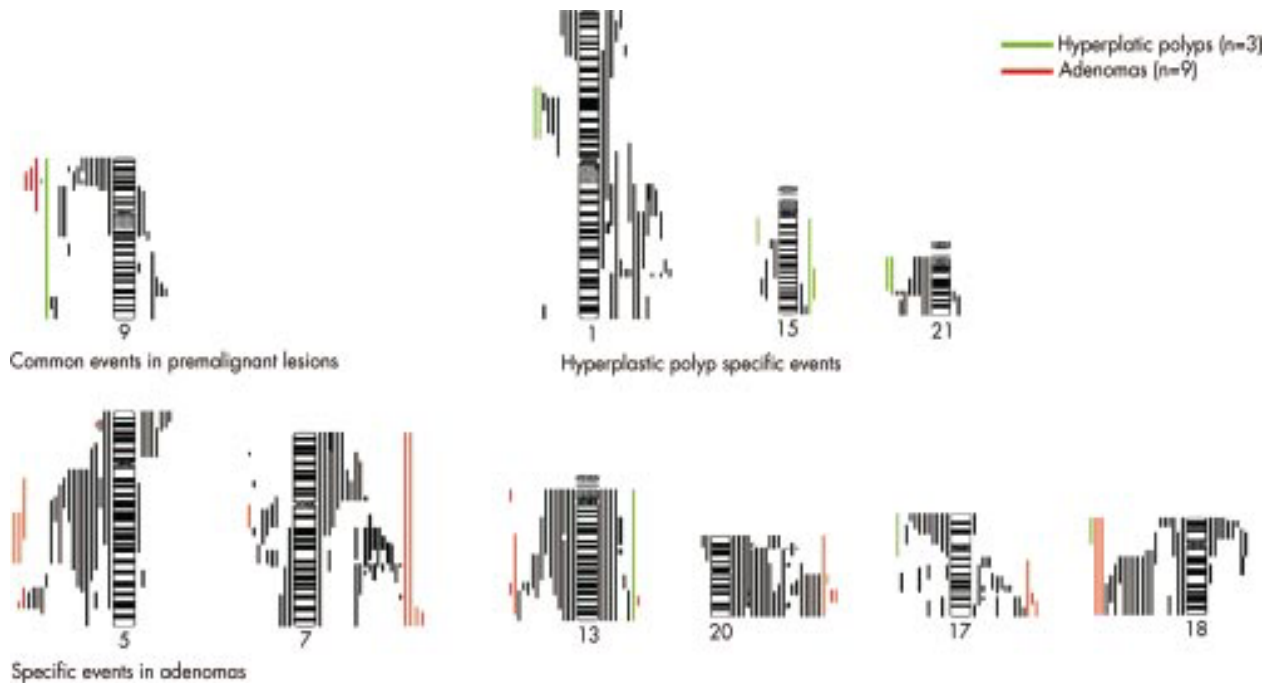


Figure 3 Frequent chromosomal copy number changes in premalignant lesions (both adenomas and hyperplastic polyps) in comparison with gastric adenocarcinomas. The most frequent aberration in the precursor lesions is loss of 9p21.3. Furthermore, gain of 15q11–14 (one of 35 carcinomas), loss of 1p21–31 (four of 35 carcinomas), and loss of 21q11–21.2 (five of 35 carcinomas) were only seen in the hyperplastic polyps, whereas loss of 5q14–21 (12 of 35 carcinomas), loss of 5q34 (seven of 35 carcinomas), gain of 7q36 (two of 35 carcinomas), loss of 13q31 (10 of 35 carcinomas), gain of 17q25 (five of 35 carcinomas), loss of chromosome 18 (18p in seven and 18q in 16 of 35 carcinomas), and gain of 20q12 (19 of 35 carcinomas) were only seen in adenomas.

carcinomas), and loss of 21q11–21.2 (five of 35 carcinomas) were seen only in the hyperplastic polyps, whereas loss of 5q14–21 (12 of 35 carcinomas), loss of 5q34 (seven of 35 carcinomas), gain of 7q36 (two of 35 carcinomas), loss of 13q31 (10 of 35 carcinomas), gain of 17q25 (five of 35 carcinomas), loss of chromosome 18 (18p in seven, and 18q in 16 of 35 carcinomas), and gain of 20q12 (19 of 35 carcinomas) were seen only in adenomas (fig 3).

Several studies have pointed to the risk of gastric cancer arising in hyperplastic polyps, and a genetic predisposition for cancer prone hyperplastic polyps in the stomach has even been described.²⁵ However, it is important to realise that intraepithelial neoplasia, and probably also chromosomal instability, is a very rare event in gastric hyperplastic polyps. Consequently the hyperplastic polyps studied here are not representative of gastric hyperplastic polyps in general. Nevertheless, the findings could be informative for the pathogenesis of gastric cancer. Interestingly, *H pylori* infection plays a role in the pathogenesis of both hyperplastic polyps and gastric cancer.²⁶ The microarray CGH results of one of the hyperplastic polyps analysed in our study underlines the hypothesis that neoplastic transformation can occur in these lesions. Despite the fact that histologically this lesion was a true hyperplastic polyp, with high cylindrical, foveolar type of epithelium and an oedematous stroma with chronic inflammatory infiltrate, it showed portions with severe nuclear atypia, and in these areas there were many chromosomal aberrations, and the pattern of changes was similar to that seen in cancer.

“Several of the chromosomal aberrations reported here have been reported before in gastric premalignant lesions, indicating that these changes are relevant”

These observations are consistent with the existence of two morphologically and genetically different pathways to gastric cancer; that is, the “hyperplastic polyp with intraepithelial

neoplasia type” pathway and the “adenoma type” (intestinal type) pathway (fig 3). To a certain extent, this parallels the situation in the large intestine where alternative routes through hyperplastic polyps have also been proposed, although histological hyperplastic polyps of the stomach and large intestine are different lesions.²⁷ What the relative contribution of each of these pathways is to gastric carcinogenesis in general, and how they compare to patterns of chromosomal aberrations in the more prevalent flat foci of intraepithelial neoplasia, remain to be determined. However, the fact that the chromosomal changes seen in both types of polyps also belong to the more prevalent ones seen in gastric cancer, in addition to the fact that several of the chromosomal aberrations reported here have been reported before in gastric premalignant lesions, indicate that these changes are relevant.^{16–18} Further studies on larger series should reveal the

Take home messages

- The most frequent chromosomal aberration in common to both types of gastric polyp with intraepithelial neoplasia was loss of 9p21.3
- Both types of polyp showed many chromosomal aberrations and the adenomas showed no more chromosomal aberrations than did the hyperplastic polyps
- The fact that different chromosomal aberrations were seen in each type of polyp is consistent with the existence of two morphologically and genetically distinct pathways to gastric cancer—the hyperplastic polyp pathway and the (intestinal type) adenoma pathway
- Larger studies might reveal the relative contribution of each of these pathways to the development of cancer, and might provide detailed knowledge of the molecular pathways involved. This may lead to new diagnostic approaches for early detection of gastric cancer, or even reveal molecular targets that may provide opportunities for pharmacological intervention in tumour progression

relative contribution of each of these pathways, and might provide detailed knowledge of the molecular pathways involved, which may open up possibilities for new diagnostic approaches for early detection of gastric cancer, or even reveal molecular targets that may provide opportunities for pharmacological intervention in tumour progression.

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