

# Gastric Cancer: An Opportunity for Prevention



## Cancro Gástrico: Uma Oportunidade para Prevenção

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Gastric cancer is one of the most prevalent cancers worldwide, ranking fourth after lung, breast and colorectal cancers, and it is the second cause of cancer death. The majority of cases occur in developing countries and are more common in males, irrespective of age and geographic area. In Portugal it ranks fifth in cancer deaths and its incidence is the highest in Western Europe.

The most common type of gastric cancer is adenocarcinoma, whose prevalence is related to male gender, increasing age and high prevalence regions, indicating environmental factors as risk factors for the disease. The accepted model for development of this type of cancer involves a cascade of premalignant conditions occurring over several years, due to environmental and host factors, which might progress to premalignant lesions (e.g. dysplasia) and invasive cancer.

Several observational studies have shown that environmental factors play a part and salt, nitrates, tobacco and *Helicobacter pylori* are the most fully described agents. *Helicobacter pylori* is the single main risk factor and considered to promote the development of these precursor conditions and lesions. The first of these may be gastric inflammation that progresses to loss of appropriate glands (atrophy), replacement of original glands with intestinal metaplasia glands that might develop into dysplasia and finally into invasive carcinoma. It is considered that their intragastric extension is also relevant in patients presenting with atrophy or intestinal metaplasia in the corpus, who represent a subgroup of higher risk patients for whom a specific surveillance programme is recommended.

Host factors, in particular genes that regulate expression of proinflammatory agents (interleukin 1  $\beta$ , tumour-necrosis factor) and some innate immunity receptors such as toll-like receptors (TLRs) have been linked to gastric carcinogenesis but as yet without proven clinical implications.

Studies comparing the expression of TLRs and their inhibitors in all premalignant lesions of the gastric carcinogenesis cascade have provided a statistically significant trend for a decrease of TLR inhibitors and a progressive increase of TLR expression, in particular 0.1 for normal mucosa, 1.0 for gastritis, 2.2 for intestinal metaplasia and 2.8 for dysplasia ( $p < 0.001$ ).<sup>1-4</sup> Familial aggregation of gastric cancer might have some role in about 10% of cases, in particular in first relatives of early onset gastric cancer patients. In a case-control study these first degree relatives of gastric cancer patients presented an increased prevalence of *Helicobacter pylori* infection (82% versus 65%,  $p = 0.001$ ) and extensive atrophic gastritis or intestinal metaplasia (19% versus 0%,  $p < 0.001$ ). These results are corroborated in the literature and seem to be independent of the source of controls used, reinforcing the recommendation for screening and treating for *Helicobacter pylori* in these cases and suggesting that a specific surveillance might be desirable, although this is still not consensual.<sup>5,6</sup> Serologic measurement of pepsinogens I and II, normally produced in the gastric mucosa, could be used to screen for high-risk patients harbouring extensive premalignant conditions (e.g. detection of atrophy and/or intestinal metaplasia both in antrum and corpus).<sup>7</sup> It was determined in several studies and in a recent meta-analysis that a pepsinogen I value  $\leq 70$  and a pepsinogen I versus II ratio  $\leq 3$  had a sensitivity of 77% and a negative predictive value of 99% for the diagnosis of dysplasia.<sup>8</sup>

For the endoscopic diagnosis of these premalignant lesions, conventional endoscopy does not present the required accuracy or reproducibility to preclude the need for taking biopsies: even in normal-appearing gastric mucosa, patients with a median pepsinogen I/II ratio of 2.8 have intestinal metaplasia in both the antrum and corpus, and with a ratio of 1.8 more than 50% of the antrum will harbour intestinal metaplasia.<sup>9</sup> Because of this lack of accuracy of

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conventional endoscopy, a detailed endoscopic inspection should be backed up with biopsies. These should involve a minimum of two samples from the gastric antrum and two separate samples from the body, plus biopsies of any suspicious lesions identified.<sup>10</sup>

Recent endoscopic advances such as chromoendoscopy with methylene blue or narrow band imaging are better in terms of both diagnostic accuracy and reproducibility than conventional endoscopy and their use could be justified for the surveillance of a high risk population.<sup>11</sup> Conventional chromoendoscopy with 1% methylene blue gave a diagnosis of dysplasia with a specificity of 81% (95% confidence interval [CI]: 77-85%) and a negative predictive value of 99% (95% CI: 99-100%) along with a kappa statistic of 0.86 for intraobserver and 0.74 for interobserver agreements.<sup>12</sup> These values were validated in another centre which provided very similar results for the diagnosis of dysplasia (sensitivity of 100%, specificity of 99%) and for reproducibility (kappa 0.92, 95% CI: 0.88-0.96) for classification in groups.<sup>13</sup> Electronic chromoendoscopy by narrow band imaging for gastric precursor lesions has been evaluated in several studies, providing different classifications that were combined in a simplified classification. This was prospectively validated in a multicenter endoscopic study, providing diagnostic accuracies for normal mucosa of 83% (95% CI: 75-90%), intestinal metaplasia of 84% (95% CI: 77-91%) and dysplasia of 95% (95% CI: 90-99%). The global reproducibility was kappa = 0.62 and varied between experienced *versus* non-experienced endoscopists (0.75 *versus* 0.60).<sup>14</sup>

Screening for gastric cancer is only cost-effective in high risk countries but in those countries, like Portugal, with an intermediate incidence of this disease, high-risk patients could be offered a specific surveillance programme. These high-risk patients present extensive atrophy or intestinal metaplasia involving the antrum and corpus, diagnosed by pepsinogen assessment or endoscopic biopsy as suggested in a recent consensus guideline.<sup>10</sup> In these cases, endoscopic surveillance should be offered on a 3-yearly

endoscopic schedule, supplemented with magnification chromoendoscopy or narrow-band imaging if available. If, whilst under surveillance, dysplasia is detected without a visible endoscopic lesion, close follow-up should be offered, either immediately in high grade cases or within 12 months for those with low grade. Patients with dysplasia or cancer within an endoscopically visible lesion should undergo staging and resection.<sup>10,15</sup>

This suggestion of surveillance of patients with pre-malignant conditions has only been evaluated by 3 cost-effectiveness studies and a recent review showed the results in the available literature to be contradictory (probably due to different assumptions on progression of precursor conditions). While the incremental cost-effectiveness ratio varied between 1 868 and 72 519 US dollars for intestinal metaplasia (crossing the usually accepted threshold of 50 000 US dollars), for dysplasia incremental values ranged only between 18 600 and 39 800 US dollars. Although the evidence so far is slight, for dysplasia close follow-up seems to be the consensual approach for clinical and cost-effective purposes.<sup>16,17</sup>

In conclusion, gastric cancer is still a prevalent cancer worldwide and a health problem in several countries but different incident rates should lead to different attitudes. While in the Western world population screening is not cost-effective, screening for high-risk patients could lead to a better resource allocation and it could be done either by family history (especially in first relatives of early onset gastric cancer patients), serologic pepsinogen measurement or endoscopic evaluation with biopsies from the antrum and corpus.

For those patients harbouring a high-risk condition such as extensive atrophy or intestinal metaplasia in both the antrum and corpus, our attention and dedication should be unwavering and, although the results from cost-effectiveness studies are contradictory, our best endoscopic surveillance should be offered on a 3-yearly basis, alongside magnification chromoendoscopy or narrow-band imaging, if available.

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