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Role of Genetic and Environmental Risk Factors in Gastric Carcinogenesis Pathway

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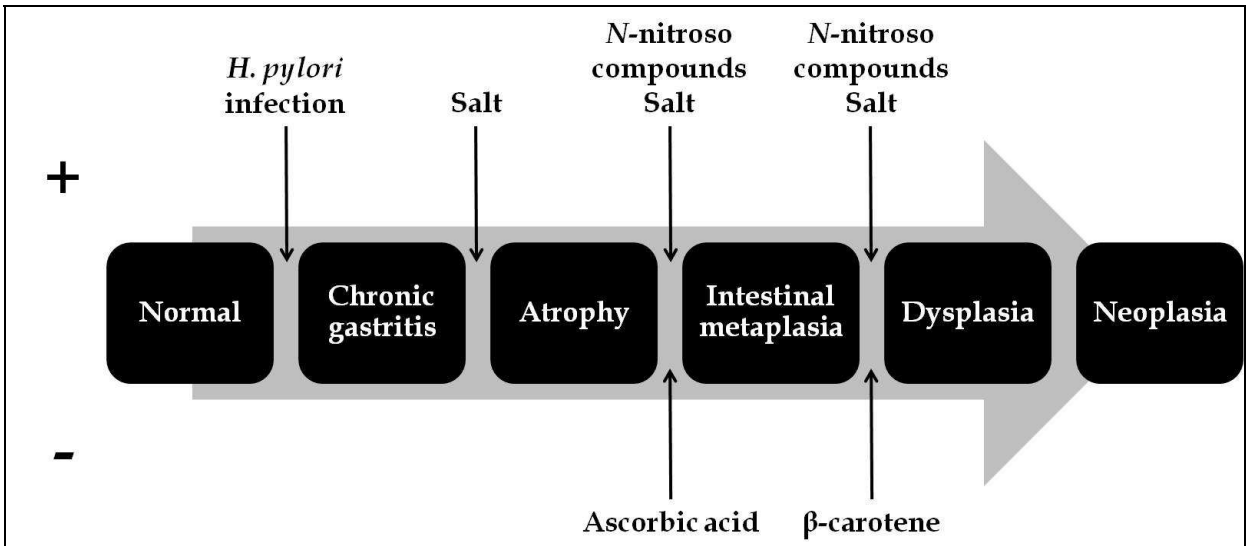
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1. Introduction

Gastric carcinoma has been considered an aetiologically heterogeneous entity, with the role of its potential determinants differing with tumour location (Cavaleiro-Pinto et al., 2011; Helicobacter and Cancer Collaborative Group, 2001; Huang et al., 1998; Huang et al., 2003; Ladeiras-Lopes et al., 2008; Larsson et al., 2006; Lunet et al., 2007; Tredaniel et al., 1997; World Cancer Research Fund & American Institute for Cancer Research, 2007) and histological type (Helicobacter and Cancer Collaborative Group, 2001; Huang et al., 1998; Ladeiras-Lopes et al., 2008; Larsson et al., 2006; Lunet et al., 2007; World Cancer Research Fund & American Institute for Cancer Research, 2007). Regarding the latter, Laurén proposed an histo-clinical classification (Laurén, 1965) comprising two main histological types – diffuse and intestinal – with different frequency and distribution across populations (Muñoz & Asvall, 1971; Muñoz & Connelly, 1971). Most gastric carcinomas belong to the intestinal type, representing between 52% and 82% of all gastric cancers (Kaneke & Yoshimura, 2001; Laurén & Nevalainen, 1993; Wu et al., 2009). A higher incidence of intestinal type tumours was observed in males, blacks and older subjects, while the diffuse type had a similar incidence in both genders and was more frequent in younger individuals (Correa et al., 1973; Ekström et al., 2000). Also, there was a wide geographical variation in the frequency of intestinal type tumours, whereas the occurrence of diffuse adenocarcinomas was more uniform across regions (Laurén & Nevalainen, 1993). In addition, the decrease in cancer incidence among migrants from high- to low-risk areas was observed predominantly for tumours of the intestinal type (Correa et al., 1973). These findings were taken as evidence of a relatively greater impact of environmental factors in the aetiology of intestinal type carcinomas, while the diffuse type was considered more dependent on the genetic profile of the individuals (Tahara, 2004). Pelayo Correa (Correa et al., 1975) proposed a model for the development of the intestinal type tumours, according to which the precancerous lesions occur in sequential steps: chronic atrophic gastritis, intestinal metaplasia, and dysplasia. It provided a framework for understanding the role of different environmental and constitutional factors in gastric carcinogenesis, which has evolved with the epidemiologic findings on this topic.

2. Gastric carcinogenesis models

In his initial model (Correa et al., 1975), Correa postulated that both deleterious and protective exposures could modulate the progression towards intestinal type cancers, by acting in different stages of the pathway. With the rediscovery of *Helicobacter pylori* in 1984 (Marshall & Warren, 1984) and the gradual recognition of its role as a carcinogen, the model was redefined to accommodate the causal relation between *H. pylori* infection and gastric cancer (Correa, 1992), assuming that its effects were exerted at the early phases of gastric carcinogenesis (Figure 1).



+ positive associations (increase the risk of gastric cancer); - negative associations (decrease the risk of gastric cancer).

Fig. 1. Gastric carcinogenesis model for the carcinomas of Laurén intestinal type, according to the proposed by Pelayo Correa (Correa, 1992)

The models proposed by Pelayo Correa more than 15 years ago still provide the essential framework for research on gastric carcinogenesis. The understanding of potentially alternative pathways, the more accurate definition of the endpoints for research, and the identification of the carcinogenesis steps where each of the gastric cancer causal components may act will contribute for a better understanding of cancer aetiology and support the development of preventive strategies.

2.1 The effect of risk factors for gastric cancer across the carcinogenesis pathway

The research on the determinants of gastric cancer precursors has been less extensive than for the cancer endpoints. In Table 1 we present a summary of the systematic reviews and meta-analyses of research conducted to assess the determinants of the lesions that precede the cancer. The contribution of these findings for improvement of the currently accepted gastric carcinogenesis model will be discussed in the following sections of this chapter.

Author, year (ref)	Exposure	Outcome	Databases searched	Number of studies included	Main results
Adamu, 2010 (Adamu et al., 2010)	<i>H. pylori</i> infection	CAG incidence	MEDLINE, EMBASE	14	<u><i>H. pylori</i>-infected vs. uninfected</u> RR=5.0 (95%CI: 3.1-8.3) Includes studies with follow-up periods ranging from 5 to 32 years
Peleteiro, 2010 (Peleteiro et al., 2010b)	<i>IL1RN</i> VNTR <i>IL1B-511</i> <i>TNFA-308</i>	CAG prevalence IM prevalence	PubMed	15	<u><i>IL1RN</i> VNTR (22 vs. LL)</u> CAG and IM: OR=2.27 (95%CI: 1.40-3.70) CAG: OR=1.65 (95%CI: 1.02-2.66) IM: OR=2.27 (95%CI: 1.14-4.51) <u><i>IL1B-511</i> (TT vs. CC)</u> CAG and IM: OR=1.34 (95%CI: 0.87-2.07) CAG: OR=1.20 (95%CI: 0.70-2.05) IM: OR=1.94 (95%CI: 1.14-3.31) <u><i>TNFA-308</i> (AA vs. GG)</u> CAG and IM: OR=0.93 (95%CI: 0.35-2.43)
Dias-Neto, 2010 (Dias-Neto et al., 2010)	Salt intake	IM prevalence	PubMed	17	<u>Salted/salty meat intake (highest vs. lowest exposure)</u> OR=1.68 (95%CI: 0.98-2.90) <u>Preference for salted/salty foods or use of table salt (highest vs. lowest exposure)</u> OR=1.53 (95%CI: 0.72-3.24)
Weck, 2008 (Weck & Brenner, 2008)	<i>H. pylori</i> infection	CAG prevalence evaluated by: - gastroscopy with biopsy - PG I only - PG I/PG II ratio	MEDLINE	66	<u><i>H. pylori</i>-infected vs. uninfected</u> Gastroscopy with biopsy: OR=6.4 (95%CI: 4.0-10.1) PG I only *: OR=0.9 (95%CI: 0.7-1.2) PG I/PG II ratio: OR=7.2 (95%CI: 3.1-16.8) Combination of PG I and PG I/PG II ratio: OR=5.7 (95%CI: 4.4-7.4)

Author, year (ref)	Exposure	Outcome	Databases searched	Number of studies included	Main results
		- combi- nation of PG I and PG I/PG II ratio			All methods: OR=4.7 (95%CI: 3.7-6.0) All methods, except PG I only: OR=6.1 (95%CI: 4.8-7.7)
Peleteiro, 2008 (Peleteiro et al., 2008)	<i>H. pylori</i> infection Smoking	IM prevalence	PubMed	22	Systematic review for identification of estimates for IM prevalence among <i>H.</i> <i>pylori</i> -infected subjects in different populations and ecological analysis of the association with smoking
Rokkas, 2007 (Rokkas et al., 2007)	<i>H. pylori</i> eradica- tion	CAG incidence IM incidence	MEDLINE	8	Pearson correlation coefficient = 0.45 (p=0.02) <u><i>H. pylori</i>-eradicated vs. placebo</u> CAG in the antrum: OR=0.554 (95%CI: 0.372- 0.825) CAG in the corpus: OR=0.209 (95%CI: 0.081- 0.538) IM in the antrum: OR=0.795 (95%CI: 0.587- 1.078) IM in the corpus: OR=0.891 (95%CI: 0.633- 1.253) Includes studies with follow-up periods ranging from 10 to 137 months

CAG – chronic atrophic gastritis; RR – relative risk; VNTR – variable number tandem repeat; IM – intestinal metaplasia; OR – odds ratio; PG – pepsinogen.

* the magnitude of the association depends on the method used to assess atrophy; previous studies showed that PG I alone had a low sensitivity for serological definition of chronic atrophic gastritis (Miki, 2006).

† systematic reviews and meta-analyses were identified through PubMed search, from its inception to December 2010, under the following expression (*gastritis OR chronic OR atroph* OR intestinal metaplasia OR dysplasia*) AND (*gastric OR stomach*) AND (*helicobacter pylori OR gene OR polymorphism OR SNPs OR smoking OR tobacco OR cigarette OR salt OR antioxidant OR diet OR lifestyle OR environmental OR behaviour*) AND (*meta-analysis OR "systematic review"*).

Table 1. Summary of systematic reviews and meta-analyses † addressing the role of genetic and environmental factors on the occurrence of gastric precancerous lesions

2.1.1 The role of *Helicobacter pylori* infection

The association between *H. pylori* infection and gastric cancer is well established, with several meta-analyses reporting an odds ratio of approximately 2 (Figure 2). The prevalence of *H. pylori* infection is high (74% in developing and 58% in developed countries, on average) and nearly two-thirds of all gastric cancers occurring worldwide are attributed to it (Parkin, 2006). Pelayo Correa proposed that *H. pylori* infection acted at the early phases of the carcinogenesis based on the fact that the inflammatory reaction could disappear after clearance of the bacteria with antibiotic treatment (Correa, 1992), and this has received support from several lines of evidence. On the one hand, the longer the lag between the assessment of *H. pylori* infection status and the diagnosis of gastric cancer, the stronger is the association between infection and cancer (Helicobacter and Cancer Collaborative Group, 2001; Huang et al., 1998), as *H. pylori* clearance tends to occur with the progression to the cancer endpoint (Gao et al., 2009; Kokkola et al., 2003). Case-control designs tend to underestimate the relation between infection and gastric cancer, but studies that used more sensitive methods to detect past infection or restricted the analysis to less advanced cases yielded stronger relative risk estimates (Brenner et al., 2004; Ekstrom et al., 2001; Mitchell et al., 2008; Peleteiro et al., 2010a). On the other hand, this is also in accordance with the stronger associations observed between *H. pylori* and precancerous lesions (Table 1) than with gastric cancer, as depicted in Figure 2.

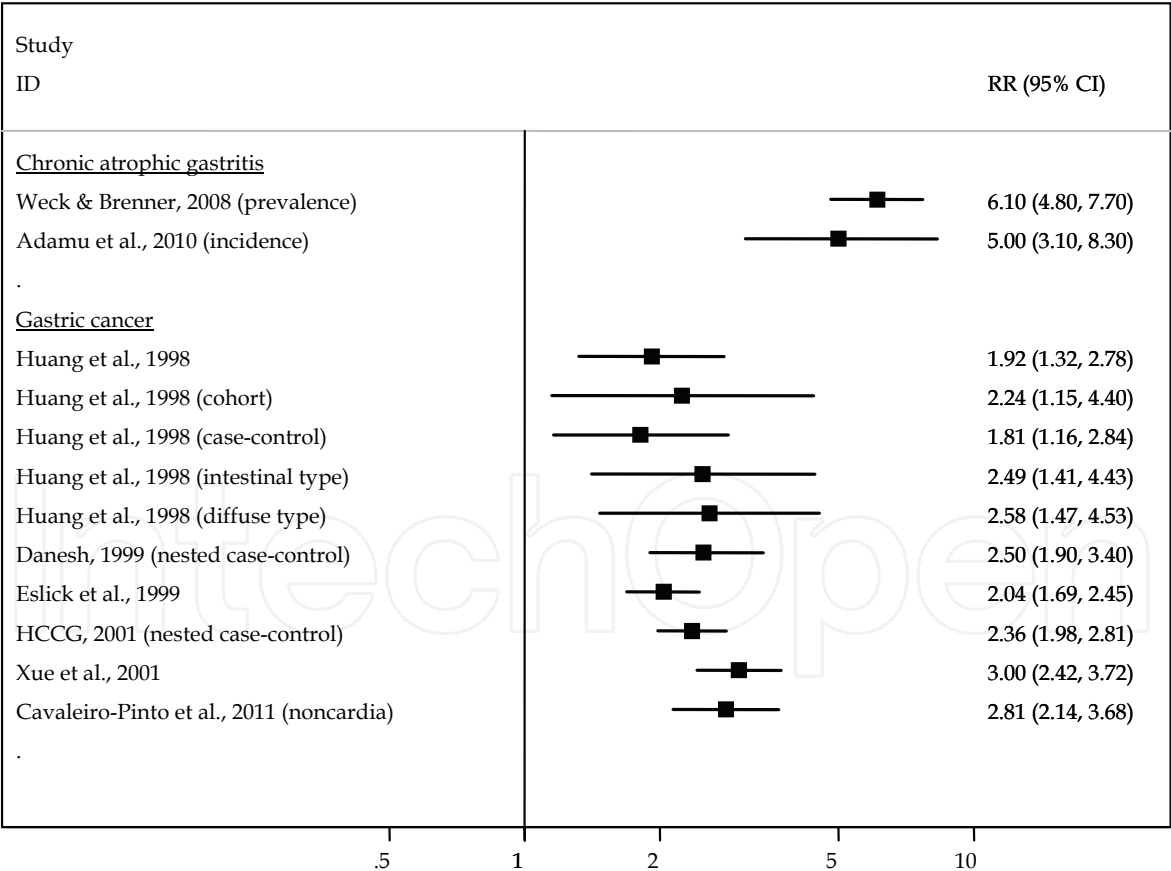
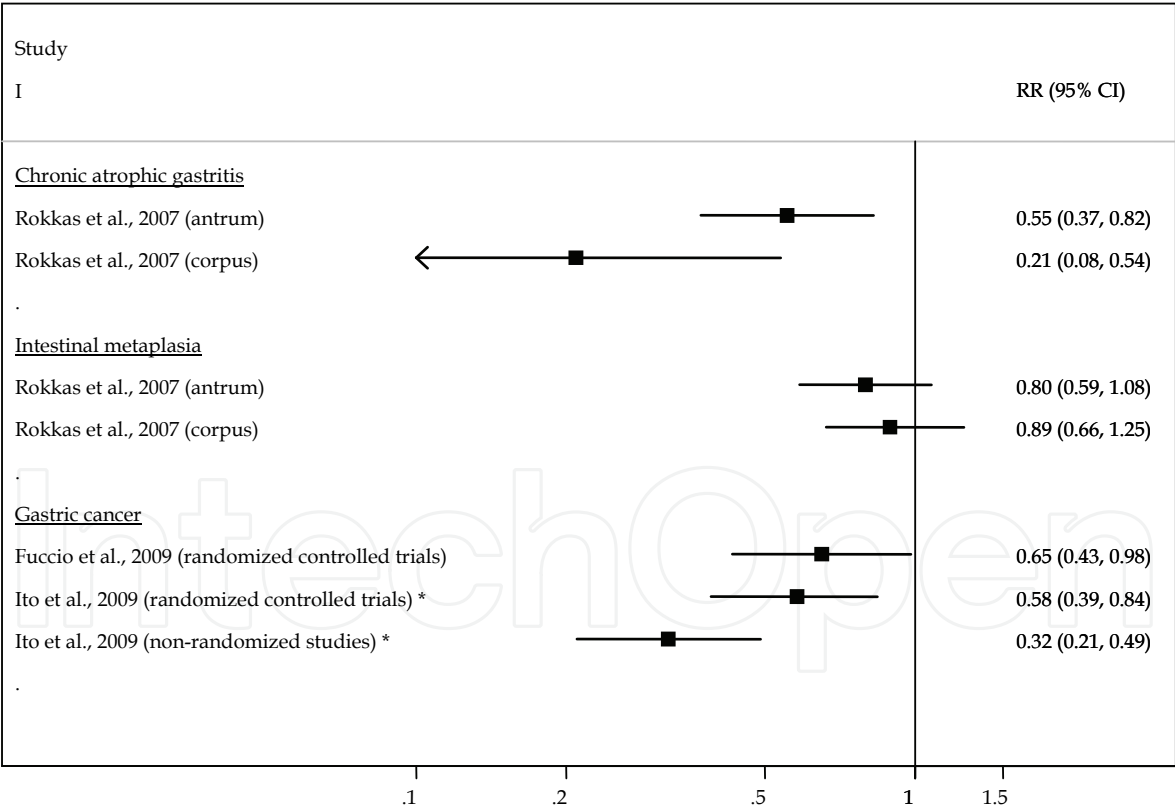


Fig. 2. Meta-analyses on the association between *Helicobacter pylori* infection and chronic atrophic gastritis, and gastric cancer (Adamu et al., 2010; Cavaleiro-Pinto et al., 2011; Danesh, 1999; Eslick et al., 1999; Helicobacter and Cancer Collaborative Group, 2001; Huang et al., 1998; Weck & Brenner, 2008; Xue et al., 2001).

A direct correlation between *H. pylori* prevalence and gastric cancer rates is not observed when countries with different patterns of infection and gastric cancer risk are considered, namely because some of them present low gastric cancer incidences despite the high prevalences of infection, the so-called African and Asian enigmas (Holcombe, 1992; Miwa et al., 2002). In the latter settings, the cancer precursor lesions, especially intestinal metaplasia, are also less frequent than expected given the high prevalence of infection (Campbell et al., 2001; Carrilho et al., 2009; Kalebi et al., 2007; Kidd et al., 1999; Oluwasola & Ogunbiyi, 2004), supporting the hypothesis that *H. pylori* infection acts before their development (in earlier steps of the carcinogenesis) and that other genetic and/or environmental exposures modulate the progression towards cancer (Campbell et al., 2001; Louw et al., 2001; Lunet & Barros, 2003; Mitchell et al., 2002).

2.1.1.1 The impact of *Helicobacter pylori* eradication

Since the recognition of the causal link between *H. pylori* and gastric cancer, research has focused on the potential of eradication of the infection as preventive tool. Some clinical trials concluded that *H. pylori* eradication reduces gastric cancer risk (Fuccio et al., 2009; Ito et al., 2009) (Figure 3). However, one of the trials (Wong et al., 2004) analysed separately the subjects with and without precancerous lesions, and eradication of *H. pylori* infection was significantly associated with a decreased risk of developing gastric cancer only among the



* this report refers to a systematic review but does not include a meta-analysis, and summary estimates were computed by the authors of this chapter based on the results presented for each individual study.

Fig. 3. Meta-analyses on the association between *Helicobacter pylori* eradication and incidence of chronic atrophic gastritis, intestinal metaplasia, and gastric cancer (Fuccio et al., 2009; Ito et al., 2009; Rokkas et al., 2007).

latter, supporting the hypothesis of the effects of infection in the early stages of gastric carcinogenesis. This is also in accordance with the lack of association between eradication and cancer in a trial conducted in Colombia, which only included subjects with gastric precancerous lesions at baseline evaluation (Correa et al., 2000; Mera et al., 2005).

Also, a meta-analysis from Rokkas *et al.* (Rokkas et al., 2007) estimated the long-term impact of *H. pylori* eradication on the incidence of gastric precancerous lesions (Table 1), with significant reduction in chronic atrophic gastritis risk but not for intestinal metaplasia (Figure 3).

Taken together, these results support the irreversibility of intestinal metaplasia, since *H. pylori* eradication must occur before a point of no return in order to be effective. This represents one more piece of evidence of an early role for *H. pylori* infection in the gastric carcinogenesis, as it leads to intestinal metaplasia but must be complemented with other factors for progression towards cancer.

2.1.2 The role of lifestyle factors

Although *H. pylori* infection is the most important gastric cancer determinant, only a small proportion of infected subjects will reach this endpoint (Hsu et al., 2007; Uemura et al., 2001), and several other potential causal components have to be considered.

2.1.2.1 Smoking

Stomach cancer is now considered a tobacco-related cancer, with 17% of cases among men and 11% among women being attributed to it in the more developed countries (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004). Compared to never-smokers, current smokers have a 20% (among women) to 62% (among men) higher risk of gastric cancer, while gastric cancer is 16% (among women) to 34% (among men) more frequent in former smokers (Ladeiras-Lopes et al., 2008). This shows that the interruption of the exposure to tobacco contributes to a reduction in gastric cancer risk, supporting that its effects are exerted at the later steps of carcinogenesis. Furthermore, the risk of cancer was higher in subjects quitting smoking more recently (summary RR for studies with a mean/median follow-up time < 10 vs. ≥ 10 years: 1.39, 95%CI: 1.30-1.49 vs. 1.09, 95%CI: 0.95-1.25, among men) (Ladeiras-Lopes et al., 2008), in accordance with the hypothesis that smoking acts predominantly by promoting the progression from the more advanced precursor lesions to cancer.

Among lifestyle exposures, the relation between smoking and precancerous lesions, especially intestinal metaplasia, has been the more extensively studied, but no systematic reviews of studies quantifying this association are available. The individual reports that have been published yielded relative risk estimates ranging from 1.42 to 4.91 (Kim et al., 2008; Mesquita et al., 2006). An ecological analysis showed a strong correlation between apparent tobacco consumption and the frequency of intestinal metaplasia among *H. pylori*-infected subjects (Peleteiro et al., 2008), suggesting that the low cigarette consumption observed in developing countries may be a contributory factor for the disruption of the carcinogenesis pathway, precluding the progression to the more advanced lesions. This was also supported by another ecological analysis that showed lower gastric cancer incidence rates in settings with high prevalence of infection and low apparent tobacco consumption than in those where smoking was more frequent (Lunet & Barros, 2003).

Taken together, these results are indicative of a role for smoking in the stages closer to cancer.

2.1.2.2 Salt

The proposed mechanisms by which salt can cause gastric cancer are either the direct damage of the gastric mucosa causing excessive cell replication or an indirect effect by increasing of the mutagenic potential of *N*-nitroso compounds, which is compatible with the action of salt intake at the initial and late stages of gastric carcinogenesis, respectively (Correa, 1992). More recently, it was shown that the damage caused by salt may also increase gastric *H. pylori* colonization (Fox et al., 1999; Nozaki et al., 2002), which is also supportive of an early role in the pathway.

Many methodological limitations preclude valid measurements of salt consumption (Chen et al., 1990), and the excretion of sodium in urine over a 24-h period is the method that reflects more accurately the sodium ingested from different sources (World Cancer Research Fund & American Institute for Cancer Research, 2007). The latter, however, was used only in an ecological study assessing the association between salt and intestinal metaplasia (ECP-EURONUT, 1994).

The summary estimates for the relation between total salt use and gastric cancer obtained in the World Cancer Research Fund meta-analysis correspond to a relative risk of approximately 2 (Figure 4). However, only 17 of the 71 studies identified trough systematic review were included in the meta-analysis, due to the large heterogeneity in the presentation of results (World Cancer Research Fund & American Institute for Cancer Research, 2007).

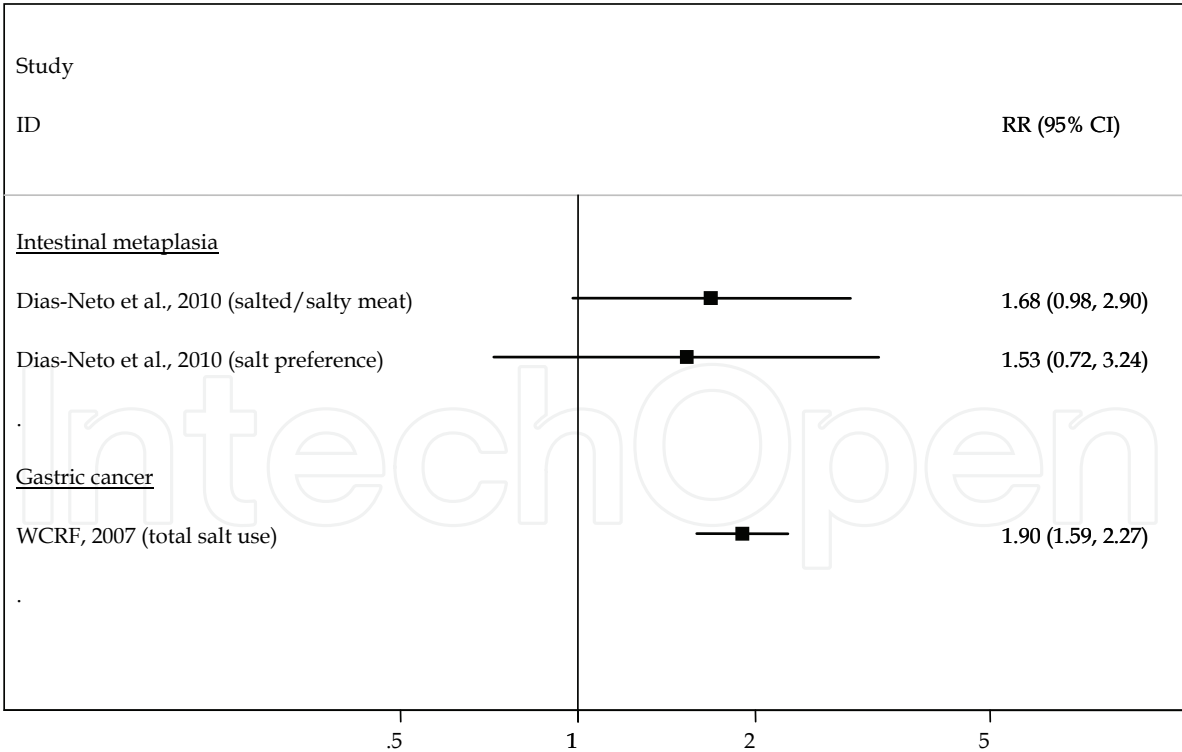


Fig. 4. Meta-analyses on the association between salt intake and intestinal metaplasia, and gastric cancer (Dias-Neto et al., 2010; World Cancer Research Fund & American Institute for Cancer Research, 2007).

In the meta-analysis conducted by Dias-Neto *et al.* (Dias-Neto et al., 2010), salted/salty meat intake and preference for salted/salty foods or use of table salt were associated with an approximately 60% increased risk of intestinal metaplasia (Figure 4), but the authors concluded that the large methodological heterogeneity and in the presentation of the results did not allow a more comprehensive quantitative synthesis or a conclusive overall interpretation of the findings.

The evidence currently available on this topic precludes definite conclusions on the magnitude of the effects of salt consumption, overall and in different steps of carcinogenesis.

2.1.2.3 Antioxidants

Based on the inverse association between ingestion of fresh fruits and vegetables and gastric cancer observed in epidemiological studies, antioxidants such as ascorbic acid and beta-carotene were postulated to play a protective role in the stages closer to cancer by acting as free-radical scavengers (Correa, 1992). This protective effect of fruits and vegetables, however, seems to be weaker than initially expected. The summary estimates from several meta-analyses on this topic are closer to 1 when derived from cohort studies, ranging from 0.89 to 0.95 for fruits intake and from 0.89 to 0.98 for vegetables consumption (Figure 5).

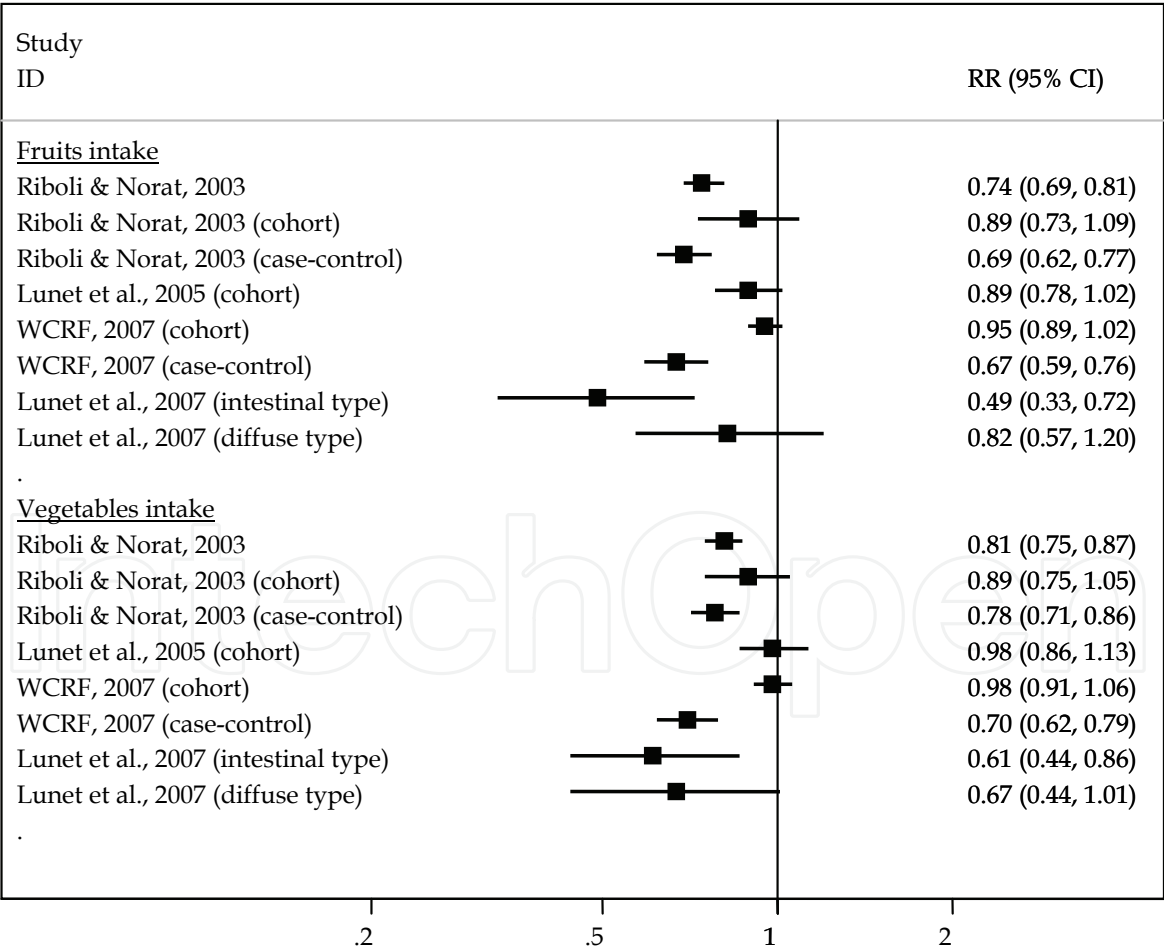


Fig. 5. Meta-analyses on the association between fruits and vegetables intake and gastric cancer (Lunet et al., 2005; Lunet et al., 2007; Riboli & Norat, 2003; World Cancer Research Fund & American Institute for Cancer Research, 2007).

However, a stronger protective effect was observed in studies with a follow-up of 10 or more years (OR=0.66, 95%CI: 0.52-0.83 for fruits and OR=0.71, 95%CI: 0.53-0.94 for vegetables in incidence studies) (Lunet et al., 2005), which may be seen as evidence of a relatively early effect of these factors in the gastric carcinogenesis pathway. Research on this topic having cancer precursor lesions as the outcome has seldom been conducted, with few studies reporting conflicting results regarding chronic atrophic gastritis and intestinal metaplasia (Jedrychowski et al., 1999; Kato et al., 2004; Kuwahara et al., 2000; Sierra et al., 2008).

Chemoprevention trials have found no evidence of a beneficial effect for antioxidant supplementation on gastric cancer prevention (Bjelakovic et al., 2004; Druesne-Pecollo et al., 2010).

Although it is plausible that naturally occurring antioxidants may inhibit the carcinogenesis progression, there is limited evidence on the specific steps where these factors may act.

2.1.2.4 N-nitroso compounds

N-nitroso compounds were hypothesized to act in gastric carcinogenesis by promoting the synthesis of carcinogens via nitrosation reactions (Correa, 1992). Processed meat is often an important source of exposure to carcinogenic N-nitroso compounds, and a meta-analysis of studies that quantified the association between processed meat consumption and stomach cancer found stronger associations for case-control studies (case-control *vs.* cohort: OR=1.63, 95%CI: 1.31-2.01 *vs.* OR=1.24, 95%CI: 0.98-1.56) (Larsson et al., 2006). The relation between these exposures and cancer precursor lesions has seldom been addressed (Sobala et al., 1991; You et al., 1996) and the effect of these compounds in the gastric carcinogenesis pathway remains to be fully understood.

2.1.3 The role of genetic factors

The genetic profile of the individuals was not included in the first versions of the model proposed by Correa (Correa, 1992; Correa et al., 1975) but, along with the advent of new technologies and their use in epidemiological research, several studies addressing the association between genetic polymorphisms and gastric cancer have been conducted. In the aetiological model of gastric cancer, individual genetic susceptibility may be critical in a variety of processes relevant to gastric carcinogenesis, namely mucosal protection, inflammatory response, carcinogen detoxification, antioxidant protection, DNA repair and oncogenes and tumour suppressor genes expression. The most widely studied polymorphisms, and for which more promising results have been achieved, are those related to proinflammatory cytokines, namely within interleukin-1 (*IL1*) and tumour necrosis factor α (*TNFA*) gene clusters.

2.1.3.1 Cytokine gene polymorphisms

H. pylori infection induces both interleukin-1 β (IL-1 β) and tumour necrosis factor- α (TNF- α) production, and these cytokines inhibit gastric acid secretion, leading to the development of gastric precancerous lesions and cancer (El-Omar et al., 2000; Hwang et al., 2002). The *IL1B* gene codes for the IL-1 β and the *IL1RN* gene for an anti-inflammatory cytokine, interleukin-1 receptor antagonist (IL-1ra). Polymorphisms within the *IL1B* gene increase IL-1 β expression and IL-1ra binds to the IL-1 receptors, modulating the pro-inflammatory effects of IL-1 β . Regarding the *IL1RN* gene, a variable number tandem repeat (VNTR)

polymorphism has been detected within intron 2, and five allelic variants have been identified in the number of repeats varying from 2 to 6 (El-Omar, 2001; Gonzalez et al., 2002). The ability of *H. pylori* to infect and remain in the human stomach induces a chronic inflammatory response, which may be of variable magnitude depending on the genetic make-up of the host. Most of the single nucleotide polymorphisms (SNPs) studied are situated in the gene promoter region and play important roles in modulating gene expression and thus the inflammatory response.

Previous meta-analyses have shown an increased gastric cancer risk associated with polymorphisms in *IL1RN*, *IL1B-511* and *TNFA-308* (Figure 6). The *IL1RN**22 genotype increases the risk of gastric precancerous lesions, suggesting a role for this polymorphism in the early stages of gastric carcinogenesis, while positive associations between *IL1B-511* TT genotype and gastric precancerous lesions only became apparent when studies addressing intestinal metaplasia as the outcome were considered (Figure 6). These associations were

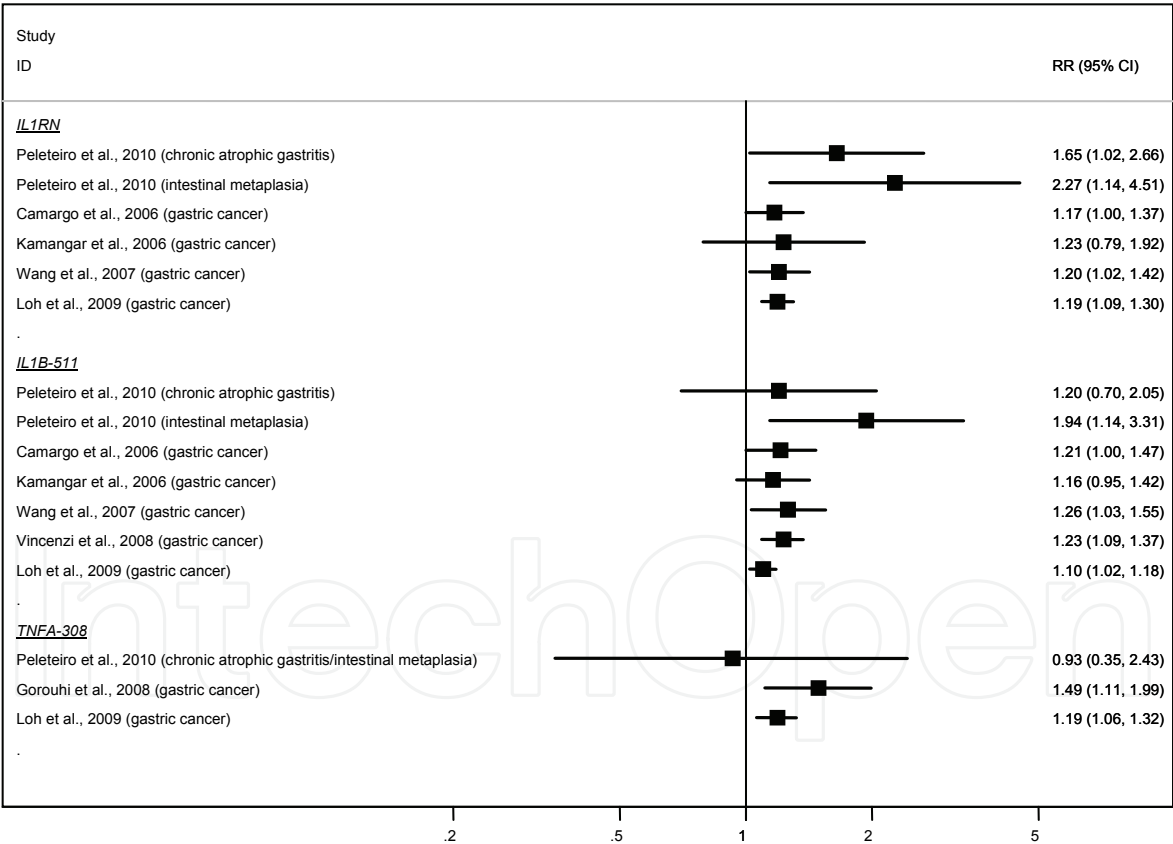


Fig. 6. Meta-analyses on the association between cytokine gene polymorphisms and chronic atrophic gastritis, intestinal metaplasia, and gastric cancer (Camargo et al., 2006; Gorouhi et al., 2008; Kamangar et al., 2006; Loh et al., 2009; Peleteiro et al., 2010b; Vincenzi et al., 2008; Wang et al., 2007).

stronger among studies conducted in samples with high *H. pylori* prevalence, in accordance to what is known about the gene function and its potential interaction with infection. No overall association was found for *TNFA*-308 AA genotype (Figure 6).

2.2 Other markers of gastric cancer development

The currently available evidence shows no substantial aetiological differences between the main Laurén subtypes, despite the relatively small number of studies addressing the effect of environmental exposures on the risk of gastric cancer according to histological subtypes (Figures 2 and 5). This may partially reflect misclassification of the histological type, due to inter-observer variability, the type of specimen available for diagnosis, and the proportion of tumours classified as unknown (Carneiro et al., 2007).

An additional concern is the ability for the classification proposed by Laurén to define aetiologically homogeneous subgroups of gastric cancer cases. The cascade of events that involve intestinal differentiation is mediated by CDX1 and/or CDX2 (Guo et al., 2004), and may result in the development of both intestinal and diffuse gastric carcinoma (Almeida et al., 2003). In particular, CDX2 expression is regarded as a marker of the intestinal epithelial phenotype, and the transdifferentiation of normal epithelia has been experimentally induced by changes in local environment (Marchetti et al., 2003), which supports the hypothesis that environmental exposures may modulate the CDX2 expression. This may be seen as an early marker of intestinal differentiation, that may be used as an endpoint occurring in the gastric carcinogenesis pathway even earlier than chronic atrophic gastritis or intestinal metaplasia. Research relying on these tools to define the outcomes is still scarce (Yuasa et al., 2009; Yuasa et al., 2005), but may be important to understand the aetiological heterogeneity of gastric cancer.

Histopathological and histochemical studies allowed the identification of two main types of intestinal metaplasia. The complete, also designated type I, and the incomplete, comprising types II and III (Filipe & Jass, 1986). In the classical multistep model of the gastric precancerous process, incomplete follows complete intestinal metaplasia sequentially (Correa, 1992). However, according to the patterns of mucin expression observed within each intestinal metaplasia type, it has been hypothesised that the complete and incomplete types of intestinal metaplasia may represent two alternative pathways, rather than successive steps; or that type II may represent a first step in the pathway, which may evolve to type I or to type III (Reis et al., 1999). The evaluation of specific risk factors for these endpoints may clarify the gastric carcinogenesis pathways and the role of environmental exposures in the aetiology of cancer (Peleteiro et al., 2007; Pintalhao et al., 2010).

3. Conclusion

The accumulated evidence so far led to the gradual acceptance and better understanding of the role of *H. pylori* infection and smoking in gastric carcinogenesis. For other exposures, however, there is much less robust evidence on the magnitude of the associations or their role throughout carcinogenesis. This allows an update of the model proposed by Correa, that still provides the best framework for gastric cancer etiological research, taking into account the evidence generated in the last two decades (Figure 7).

Research relying on more accurate tools to define specific gastric cancer subtypes and the evaluation of specific risk factors for early endpoints in the gastric carcinogenesis pathway may further contribute to the understanding of gastric cancer aetiology.

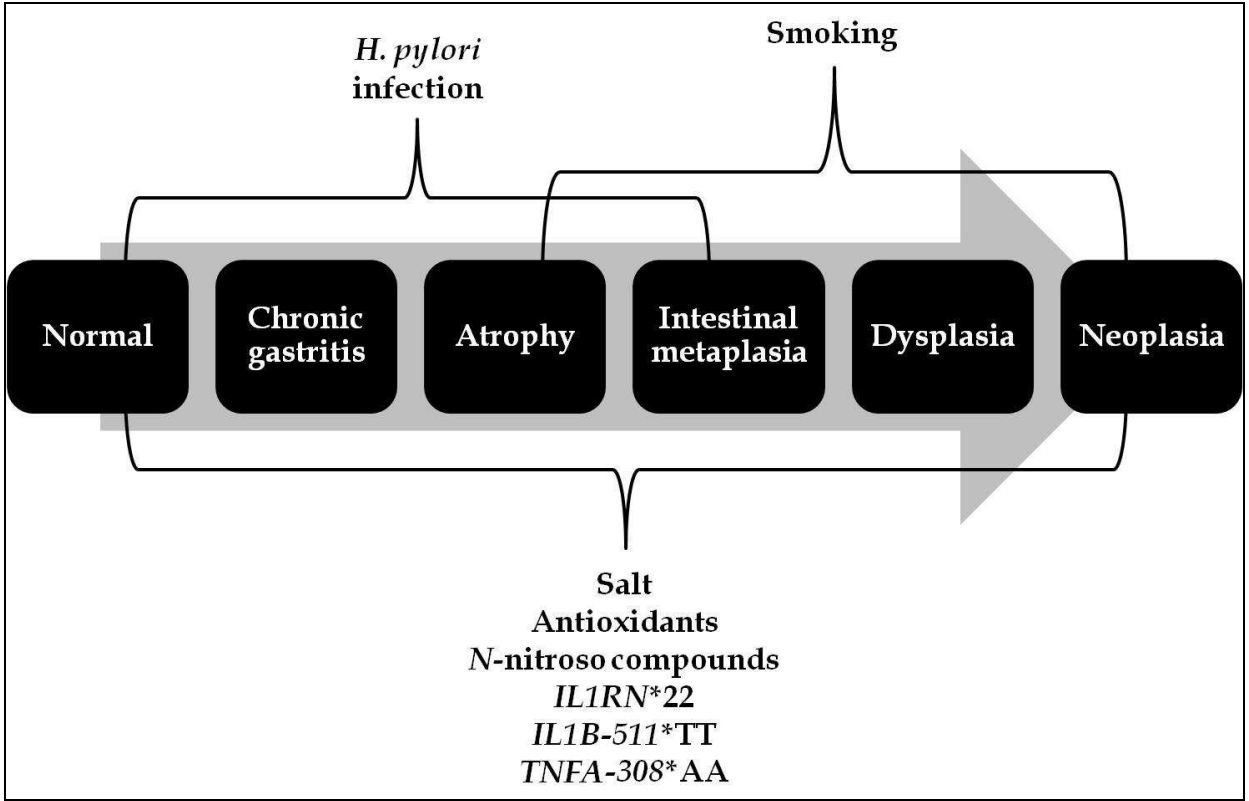


Fig. 7. Framework for the carcinogenesis pathway leading to gastric cancer, taking into account the model proposed by Correa (Correa, 1992) and the more robust evidence gathered up to 2010.

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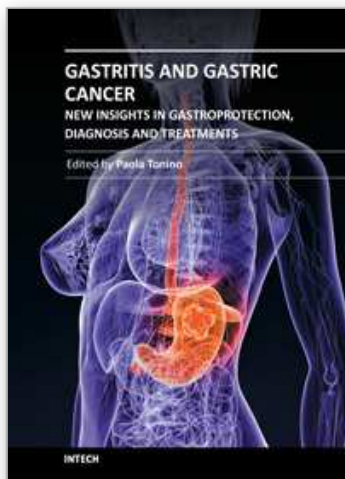
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This book is a comprehensive overview of invited contributions on *Helicobacter pylori* infection in gastritis and gastric carcinogenesis. The first part of the book covers topics related to the pathophysiology of gastric mucosal defense system and gastritis including the gastroprotective function of the mucus, the capsaicin-sensitive afferent nerves and the oxidative stress pathway involved in inflammation, apoptosis and autophagy in *H. pylori* related gastritis. The next chapters deal with molecular pathogenesis and treatment, which consider the role of neuroendocrine cells in gastric disease, DNA methylation in *H. pylori* infection, the role of antioxidants and phytotherapy in gastric disease. The final part presents the effects of cancer risk factors associated with *H. pylori* infection. These chapters discuss the serum pepsinogen test, K-ras mutations, cell kinetics, and *H. pylori* lipopolysaccharide, as well as the roles of several bacterial genes (*cagA*, *cagT*, *vacA* and *dupA*) as virulence factors in gastric cancer, and the gastrokine-1 protein in cancer progression.

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