Is there an association between Helicobacter Pylori cytotoxin Cag A seropositivity and risk for gastric cancer?

Ann. Ital. Chir., LXXIII, 6, 2002

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Abstract

Background: *Since discovered in 1990, Cag A, a protein expressed by specific strains of Helicobacter pylori, was thought able to explain why only a few Helicobacter infected patients develop peptic diseases and gastric cancer. However, clinical trials provide discordant results.*
Materials and Methods: *In this study we evaluate Helicobacter pylori and Cag A seropositivity in 35 cancer affected patients, in 36 gastritis affected patients and in 40 healthy blood donors by means of two comercially available fluorescence enzyme-immunoessay (ELISA).*
Results: *Odds ratios determination strongly suggests that Cag A bearer Helicobacter strains play a pathogenetic role in gastric diseases (OR 4.23, 95% CI 3.22-5.24 for cancer versus healthy volounteers, OR 3.2, 95% CI 2.19-4.21 for gastritis versus asymptomatic patients), but is unable to demonstrate a direct carcinogenic activity (cancer-gastritis difference is not significant: OR 1.32, 95% CI 0.39-1.25).*
Conclusions: *Cag A seropositivity can be considered a risk factor for peptic disease, and only indirectly for gastric carcinoma. The paper also discuss some sampling, laboratory and statistical bias that can explain a wide eterogenity of the results reported in the literature.*
Key-words: Gastric cancer, gastroduodenal pathology, atrophic gastritis, Helicobacter pylori, Cag A cytotoxin.

Riassunto

LA SIEROPOSITIVITÀ PER CAG A AUMENTA IL RISCHIO DI CANCRO GASTRICO NEI PAZIENTI INFETTI DA HELICOBACTER PYLORI?

Premessa: *Ritenendosi l'Helicobacter pylori potenzialmente implicato nella patogenesi del carcinoma gastrico, ma risultando soltanto una minoranza dei pazienti HP+ affetti da neoplasia, si è ritenuto di riconoscere nella proteina Cag A, sintetizzata soltanto da alcuni ceppi batterici, un fattore capace di attivare l'HP in senso carcinogenetico. I numerosi studi clinici effettuati al fine di confermare questa ipotesi hanno peraltro dato risultati contradditori.*
Materiali e Metodi: *in questo studio si è valutata la sieropositività per Helicobacter pylori e per Cag A con test Elisa disponibili sul mercato in 35 pazienti con carcinoma gastrico, in 36 pazienti con gastrite e in 40 soggetti sani.*
Risultati: *il confronto tra i 3 gruppi di pazienti median-*

Introduction

Since Helicobacter Pylori was recognised as cancerogenic agent by the IARC in 1994[1], the search of a pathogenic factor explaining why this worldwide infection shows only in few cases cancerogenic ability became the goal of many researches. In 1990 Cover for the first time characterized a 120-Kd Helicobacter protein with vacuolizing cytotoxic activity[2], and Crabtree one year later suspected the presence of gastric mucosal IgA against that protein to be associated with active gastritis and peptic ulceration[3]. The protein was named Cag A (cytotoxin-associated gene A).
We actually know the nucleotide sequence and the molecular structure of Cag A and the immune response to it[4], while its role in Helicobacter infection remains unclear. The gene is part of a 40-Kb DNA insertion named PAI (pathogenicity island)[5], that codes almost 40 proteins. Cag A is a hydrophilic, highly immunogenic, surface-exposed protein; it is not a toxin, but allows Vac A, a 87-Kd protein, to cause vacuolation in cell culture in vitro and mouse gastric epithelium damage in vivo[6].
Whether Cag A seropositivity is effectively associated or not with enhanced risk of a more severe inflammation, gastric chronic atrophy, intestinal metaplasia and intestinal-type gastric cancer, as strongly suggested by experimental studies, is still under debate. Some clinical trials,

Pervenuto in Redazione il 25 Giugno 2001

te la determinazione dell'odds ratio dimostra che i ceppi di Helicobacter portatori di Cag A incidono significativamente nel favorire l'insorgenza di patologia gastrica (OR pari a 4.23 con intervallo di confidenza al 95% 3.22-5.24 per i pazienti con cancro rispetto ai soggetti sani, OR pari a 3.2 con intervallo di confidenza al 95% 2.19-4.21 per i pazienti con gastrite rispetto ai soggetti sani), ma non può confermare un'attività carcinogenica diretta di Cag A (la differenza tra pazienti con cancro e pazienti con gastrite non è significativa: OR 1.32 con intervallo di confidenza al 95% 0.39-1.25).
Conclusioni: *La sieropositività per Cag A deve essere considerata un fattore di rischio per patologia peptica, e solo indirettamente per il carcinoma gastrico.*
Parole-chiave: carcinoma gastrico, patologia gastroduodenale, gastrite atrofica, Helicobacter pylori, citotossina Cag A.

differing in methods and end-point evaluations, failed to etablish this relationship. The majority of these studies retrospectively evaluate Cag A positivity in cancer patients and in control groups, by means of serologic or bioptic tests, with different conclusions (Tab I).
In this study we compare Helicobacter pylori and Cag A seropositivity in gastric cancer patients with similar groups of patients affected by gastritis and healthy blood donors, and we discuss Cag A cancerogenic properties with the aim to confirm or exclude the role of Cag A bearer Helicobacter in the pathogenesis of chronic gastritis and gastric cancer.

Materials and methods

35 patients operated on for gastric cancer were enrolled; there were 23 males and 12 females; age ranged from 39 to 84, with mean age of 66 (group 1, gastric cancer patients); control groups were composed by 36 age and gender-matched patients who underwent gastric endoscopic examination that excluded the presence of a malignancy and diagnosed gastritis (group 2, peptic disease patients) and by 40 healthy volounteers, hospitalized for non gastric pathology (group 3, healthy patients); we recorded age, gender, and, in the neoplastic group, size and site of the tumor, histological type according to Lauren (either intestinal or diffuse type), staging, type and year of resection.
During a regular 6 months-follow-up we took two blood samples from cancer patients, and so we did at the time of endoscopic examination or during hospital stay for both peptic disease affected and healthy patients. Serum samples were stored at -20° C until laboratory testing. Helicobacter status was determined by serum specific IgG antibodies using a commercially available fluorescence

Tab. I

Author	*n cases*	*n controls*	*source*	*method*	*only HP+*	*subgrups*	*results (OR, 95%CI)*
Crabtree (1993)	55	47 neg	serum	W.blot	yes	no	S (3.86, 2.6-4.9)
Shimoyama (1998)	81	81 neg	serum	Elisa	no	no	S (1.93, 1.01-3.68)
Queiroz (1998)	119	119 neg	tissue	PCR	yes	yes	S (9.05, 3.6-26.8)
Klaamas (1996)	182	306 a	serum	Immunoblot	no	yes	NS
Rudi (1997)	77	71 a	serum	Immunoblot	yes	no	S (1.61, 1.06-2.45)
Yamaoka (1999)	90	90 a	serum	Elisa	yes	yes	NS (1.16, 0.54-2.5)
Maeda (2000)	80	80 a	serum	Elisa	no	no	S (10.4, 4.23-29.7)
Blaser (1995)	103	103 n.s.	serum	Elisa	yes	yes	S (2.3, 1.0-5.2)
Parsonnet (1997)	90	89 n.s.	serum	Elisa	yes	yes	S (3.54, 2.82-4.26)
Shimoyama (1997)	58	58 n.s.	tissue	PCR	yes	no	NS
Chow (1998)	67	224 n.s.	serum	Elisa	no	no	NS (1.4, 0.7-2.8)
Mitchell (1996)	48	180 m	serum	W.blot	yes	no	NS
Kikuchi (1999)	103	201 m	serum	Elisa	no	no	NS
Yamaoka (1999)	156	268 m	tissue	PCR	yes	no	NS
Basso (1998)	17	71 p.d.	tissue	PCR	yes	no	S (3.58, 1.47-5.69)
Basso (1998)	21	71 p.d.	serum	W.blot	no	no	NS (1.1, 0-2.4)
Shiesh (2000)	40	130 p.d.	serum	W.blot	yes	no	NS
Baiocchi (2000)	35	40 neg	serum	Elisa	no	yes	S(4.23, 3.22-5.24)
Baiocchi (2000)	35	36 p.d.	serum	Elisa	no	yes	NS (1.32, 0.39-1.25)
Baiocchi (2000)	35	76 m	serum	Elisa	no	yes	S (2.29, 1.47-3.10)

Neg: negative (like showed by endoscopic examination);
a: aymptomatic;
n.s: not specified;
m: mixed (asymptomatic and benign peptic disease);
p.d.: peptic disease;
Only HP: yes if only HP positive patients are considered for Cag A evaluation;
Subgroups: yes if cancer subgroups analysis (e.g. intestinal or diffuse, proximal or distal...) showed relevant differences.

enzyme-immunoessay (Helori-test IgG, Eurospital, Trieste, Italy) that is reported to have 94.4% sensitivity and 86.9% specificity. According to data reported by testing 150 adult patients, we choose as limit value 22 of HP index for positive, and 18-22 for border-line. A second anti Helicobacter IgG kit was employed as control (Behring).

Assessement of Cag A status was performed in HP positive and negative patients, even if we agree with others Authors that consider Cag A positivity in HP negative patients a laboratory bias (false positive Cag A or false negative HP serology: this happened in 1% of our determinations). An enzyme immunoessay was employed (Helori CTX IgG, Eurospital, Trieste, Italy), whose reported sensibility and sensitivity are 94.1% and 97.9%. Values >7.5 units were considered positive, while 5-7.5 units were border-line. A second, hightly specific (100% when compared with Western blotting) but less sensible (93.7%) immunoessay was tested (Cag A-IgG EIA WELL, Radim, Roma, Italy), dividing results into positive if >15, border-line if 10-15 and negative if <10.

Statistical analysis was performed by odds ratio determination with 95% confidence intervals.

HP and Cag A positivity prevalence were compared in the three groups. Between cancer patients, we considered subgroups such as young and old patients, proximal and distal, intestinal and diffuse, high and low-staged, old and recently operated cancers.

Results

As shown in Table IIa and IIb, Helicobacter pylori infection was significantly associated with gastric cancer and with gastritis. Odds ratios were 2.04 and 2.86 with confidence intervals of 1.08-3.00 and 1.86-3.85 for gastric cancer and gastritis respectively, both versus healthy subjects. Subgroups of gastric cancer patients were compared, demonstrating a greater association with HP for older patients and for those affected by distal and advanced malignancies. Table IIc shows the lack of difference in HP seropositivity between cancer and gastritis patients, but it becomes significant considering only distal cancer patients (OR 2.10, CI 1.13-3.07). We didn't observe differences between Hp IgG determination performed by different diagnostic kits.

Cytotoxin Cag A seropositivity analysis showed a significant difference between gastric cancer group and healthy volounteers (OR 4.23, 95% CI 3.22-5.24), and a less strong association between gastritis and healthy patients (OR 3.2, 95% CI 2.19-4.21) (Tab. IIIa and IIIb). The difference between gastric cancer and peptic disease affected patients was not significant (OR 1.32, CI 0.39-1.25) (Table IIIc). Subgroup evaluation showed a stronger Cag A seropositivity for distal and intestinal cancers, but only in early cancers the difference was significant (OR 2.75, 95% CI 1.43-4.07). Similar results were observed when the second determination kit (Radim) was employed.

To assess the influence of control group choice on statistical analysis, we determined association in Cag A seropositivity between gastric cancer and a control group of mixed gastritis affected patients and healthy donors (tab 3d), showing a significant relationship, stronger for distal, intestinal and early cancer subgroups (all subjets, OR 2.29, 95% CI 1.47-3.10).

Tab. II – HP SEROPREVALENCE

Tab. IIA – GASTRIC CANCER VERSUS HEALTHY BLOOD DONORS

	HP+(GC)	*HP+(HD)*	*OR*	*95% CI*	*p value*
All subjects	71%	55%	2.04	1.08-3	S
Proximal	30%		0.35	0-1.78	NS
Distal	88%		6.00	4.65-7.35	S
Intestinal	71%		2.04	0.91-3.17	NS
Diffuse	63%		1.43	0.06-2.80	NS
Stage I-II	68%		1.80	0.58-3.02	NS
Stage III-IV	73%		2.29	1.10-3.48	S
<60 years	57%		1.09	0-2.71	NS
>60 years	75%		2.45	1.4-3.5	S
1999-2000	85%		4.90	3.28-6.52	S
Before 1999	62%		1.33	0.26-2.40	NS

Tab. IIB – GASTRITIS VERSUS HEALTHY BLOOD DONORS

	HP+(G)	*HP+(HD)*	*OR*	*95% CI*	*p value*
All subjects	77%	55%	2.86	1.86-3.85	S

Tab. IIC – GASTRIC CANCER VERSUS GASTRITIS

	HP+(G)	*HP+(HD)*	*OR*	*95% CI*	*p value*
All subjects	71%	77%	0.71	0-1.64	NS
Proximal	30%		0.12	0-1.62	NS
Distal	88%		2.10	1.13-3.07	S
Intestinal	71%		0.71	0-1.73	NS
Diffuse	63%		0.50	0-1.72	NS
Stage I-II	68%		0.62	0-1.71	NS
Stage III-IV	73%		0.80	0-1.84	NS
<60 years	57%		0.38	0-1.83	NS
>60 years	75%		0.85	0-1.81	NS
1999-2000	85%		1.71	0.62-2	NS
Before 1999	62%		0.46	0-1.5	NS

GC: gastric cancer;
HD: healthy donors;
G: gastritis;
1999-2000: operated on in 99-00;
<1999: operated on before 1999.

Discussion

Helicobacter infection is very common, affecting 60% of adult people in developed countries and even more in developing ones. It is certainly associated with peptic disease, because of its ability to damage gastric mucosa and induce an inflammatory reaction that differ in intensity among the patients. It has been suggested that Helicobacter infection is a risk factor for gastric cancer[7-9]. However, the great majority of Helicobacter infected people does not develope a gastric malignancy, questionning about the existence of specific strains with cancerogenic properties. Experimental studies showed that infection of Helicobacter possessing the Cag A protein is associated with changes in epithelial cells turnover, increasing gastric cell proliferation[10] and diminishing cells viability in vitro[11]. Bioptical histologic studies confirmed in these cases a more severe leukocytes infiltration, leading to an higher mucosal concentrations of IL-1 beta and IL-8 and to a more frequently expressed inducible nitric oxid synthase mRNAs[12-14]. Similar modifications of gastric cells could not be determined considering total Helicobacter pylori population[15].

However, a lot of clinical studies were made, that reached opposite conclusions. Retrospective studies, comparing Cag A+ Helicobacter infection rate in cancer patients and in control groups, are the most frequently performed. A wide variation in Cag A sampling and determination methods, including serum (Elisa or Western blotting) or tissue analysis (taken from biopsies, or isolated, or resected specimens) and in statistical elaboration make difficult to compare the different results. In Tab I we synthetize some data derived from literature [16-31], reporting for every trial the control group constitution, the source of data and the laboratory method employed, and analysing all the results by odds ratios determination. The control group composition shows great influence on the results: 75% of the studies comparing cancer with healthy or asymptomatic patients, but only 30% of studies considering as control peptic disease affected patients or mixed healthy and dispeptic patients showed significant differences, presumably because of the well described peptic disease inducing ability of Cag A+ Helicobacter. A second factor influencing significativity is the source of sampling: bioptic studies are normally conduced on a population that required endoscopic examination because of symptoms, overestimating Cag A seropositivity in control group; on the other side serological studies expose to laboratory bias: Elisa is generally sensible when compared with Western blotting[32], but the comparaison of serological and tissue analysis shows a 17-25% of false negative[20], and a 10% of false positive results[33], and Figura found 13 of 19 patients examined coinfected by multiple Helicobacter strains, that can overestimate Cag A prevalence (even if the predominant strain is Cag A negative, serological analysis shows a Cag A seropositivity)[34].

The main goal of our study was assessement of Cag A+ Helicobacter infection role in gastric cancer development by eliminating the surmentionned confounding factors. Groups were designed considering well defined features, such as histologically diagnosed cancer and gastritis for group 1 and 2, and the complete absence of gastric symptoms, gastric drug absumption and previous endoscopic examinations for group 3. We decided to investigate serological status of patients because it is difficult to obtain tissue specimens from really asymptomatic people, that does not receive an endoscopic examination, and because the bias of serologic determinations arise in all the groups considered, thus not affecting the comparaison. The employment of Elisa test was decided on the basis of its wide availability in daily clinical practice.

We found a significant association between HP and Cag A seropositivity and both gastric cancer and peptic disease (Tab. IIa, IIIa and IIb, IIIb). Gastric cancer patients are more frequently Cag A seropositive that gastritis affected patients, but the difference is not significant. If we consider as control all non cancer patients (gastritis and healthy) the difference become significant (Tab. IIId), but it is clear that the evaluation of cancer versus healthy and gastritis alone is of some better value in disease's pathogenesis understanding.

Cag A seropositivity is confirmed to be a relevant disease-related factor, but the lack of significativity in cancer-gastritis comparaison might induce some prudence in assessement of its status of cancer-related factor. We can suppose that some gastric cancers arise from Helicobacter-related peptic pathology, but the demonstration of this hypotesis needs a perspective evaluation of chronic atrophic gastritis affected patients. The only perspective study was conduced by Kuipers and Coll.[35] by serum and endoscopic bioptic sampling before and after a mean follow-up period of 11.5 years; in 58 patients enrolled, a Cag A seropositivity-atrophic gastritis strong relationship was seen at the end of the observation period, during which a great number of Cag A seropositive and a few of seronegative patients evolved into atrophic gastritis. One patient showed an evolution from atrophic gastritis to intestinal metaplasia and to gastric cancer. In 1975 Correa described the epidemiological model that consider intestinal type gastric cancer, like defined by Lauren, directly subsequent to atrophic gastritis and intestinal metaplasia[36]; according to the Correa model, our data show a better correlation between distal and intestinal subgroups of gastric cancer with Cag A + infection. So, 25 years later, we know that the first step isn't only the exposure to food carcinogens but also to Helicobacter infection, and we can suppose Cag A positive strains of Helicobacter to be strictly related with cancerogenic cascade. By this way, Cag A seropositivity can be considered an indirect risk factor for cancer development, causing atrophic gastritis and intestinal metaplasia. The existence of a different Helicobacter-related cancerogenic pathway, directly from normal mucosa to

Tab. III – CAG A SEROPREVALENCE

Tab. IIIA – GASTRIC CANCER VERSUS HEALTHY BLOOD DONORS

	CagA+(GC)	*CagA+(HD)*	*OR*	*95% CI*	*p value*
All subjects	51%	20%	4.23	3.22-5.24	S
Proximal	40%		2.66	1.18-4.14	S
Distal	56%		5.09	3.99-6.19	S
Intestinal	62%		6.50	5.33-7.67	S
Diffuse	45%		3.33	1.92-4.74	S
Stage I-II	69%		8.80	7.50-10.10	S
Stage III-IV	37%		2.33	1.12-3.54	S
<60 years	43%		3.00	1.32-4.68	S
>60 years	53%		4.61	3.54-5.68	S
1999-2000	57%		5.33	4.02-6.64	S
Before 1999	48%		3.63	2.48-4.78	S

Tab. IIIB – GASTRITIS VERSUS HEALTHY BLOOD DONORS

	CagA+(G)	*CagA+(HD)*	*OR*	*95% CI*	*p value*
All subjects	44%	20%	3.2	2.19-4.21	S

Tab. IIIC – GASTRIC CANCER VERSUS GASTRITIS

	CagA+(GC)	*CagA+(HD)*	*OR*	*95% CI*	*p value*
All subjects	51%	44%	1.32	0.39-1.25	NS
Proximal	40%		0.83	0-2.25	NS
Distal	56%		1.59	0.57-2.61	NS
Intestinal	62%		2.03	0.94-3.12	NS
Diffuse	45%		1.04	0-2.39	NS
Stage I-II	69%		2.75	1.43-4.07	S
Stage III-IV	37%		0.73	0-1.86	NS
<60 years	43%		0.93	0-2.56	NS
>60 years	53%		1.44	0.46-2.42	NS
1999-2000	57%		1.66	0.42-2.90	NS
Before 1999	48%		1.13	0.06-2.20	NS

Tab. IIID – GASTRIC CANCER VERSUS MIXED CONTROL PATIENTS

	CagA+(GC)	*CagA+(HD)*	*OR*	*95% CI*	*p value*
All subjects	51%	32%	2.29	1.47-3.10	S
Proximal	40%		1.44	0.09-2.79	NS
Distal	56%		2.76	1.83-3.68	S
Intestinal	62%		3.52	2.51-4.53	S
Diffuse	45%		1.80	0.52-3.08	NS
Stage I-II	69%		4.77	3.61-5.93	S
Stage III-IV	37%		1.26	0.22-2.30	NS
<60 years	43%		1.62	0.05-3.19	NS
>60 years	53%		2.50	1.62-3.38	S
1999-2000	57%		2.89	1.9-3.88	S
Before 1999	48%		1.97	1.08-2.86	S

GC: gastric cancer;
HD: healthy donors;
G: gastritis;
1999-2000: operated on in 99-00;
<1999: operated on before 1999.

gastric cancer, was never showed, and is not suggested by our data.

The comparaison of the three groups of patients, cancer, peptic disease affected and healthy patients, supports the pathogenic and cancerogenic properties of Helicobacter pylori infection, as previously assessed and officially recognized by the International Agency for Cancer Research, and suggests the association can be stronger for Helicobacter strains possessing Cag A. To clearly assess the role of this protein in gastric malignancies development further studies are needed, in whom all underscored confounding factors are taken into account. A surveillance protocol of Cag A positive Helicobacter infected people developing chronic atrophic gastritis with intestinal metaplasia is recommended. At the moment, Cag A seropositivity must be considered a relevant risk factor for peptic disease development.

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Commento Commentary

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Il cancro gastrico è allo stato attuale il secondo tumore maligno più comune nel mondo e dopo il cancro al polmone ha il più alto indice di mortalità[1].
Nel 1994 l'Agenzia Internazionale della ricerca sul cancro ha definito l'Helicobacter pylori cancerogeno di prima categoria[2] in quanto provoca infiammazione che induce atrofia gastrica e metaplasia intestinale entrambi precursori del cancro gastrico. L'estensione ed il grado di infiammazione dipendono da alcuni fattori inclusa la virulenza dell'agente infettante e la risposta negativa dell'organismo infetto.
Alcuni ceppi dell'Helicobacter pylori, in particolare quelli che comprendono l'isola di patogenicità e sono positivi per CagA, stimolano una maggiore risposta infiammatoria dell'ospite. Il significato di CagA per i pazienti che presentano ceppi di CagA è quello di un più alto livello di IL8, una più intensa risposta infiammatoria ed una più alta incidenza di ulcera peptica e cancro[3].
Studi epidemiologici sono propensi all'esistenza di una relazione tra l'infezione da Helicobacter pylori e cancro gastrico come causa ed effetto, e si basano su 12 studi che analizzano 1228 casi di cancro gastrico accertato in un'analisi sistematica dove è stata trovato un rapporto di indice di previsione di 3(95% Cl:2.3-3.8)[4].
Questo lavoro conferma i dati presenti in letteratura sul rischio crescente di sviluppare il cancro gastrico in pazienti infetti da l'Helicobacter pylori CagA+ con un indice di previsione di 4.23 (95% Cl:3.22-5.24) in pazienti con cancro gastrico a fronte di volontari sani.
Infatti il presente articolo rappresenta uno dei pochi lavori metodologicamente corretti sulla popolazione italiana.
Nel 1994 la NIH Consensus Development Panel ha dichiarato: "Se c'è una relazione casuale tra l'infezione da Helicobacter pylori ed il cancro gastrico, chiaramente altri fattori sono altrettanto importanti nella carcinogenesi gastrica. L'eradicazione dell'Helicobacter pylori solo allo scopo di prevenire il cancro gastrico non è al momento da "caldeggiare"
La discussione sull'argomento è ancora aperta, ma i risultati di questo lavoro ben fatto sono sicuramente incoraggianti per il partito "pro-sradicamento"!!!

Gastric cancer is at the moment the second commonest malignancy in the world and after lung cancer kills more people than any other malignant tumor[1].
In 1994 the International Agency on Research on Cancer defined Helicobacter pylori as a first class carcinogen[2] on the grounds that it induces the inflammation which leads to gastric atrophy and intestinal metaplasia, which are known precursors of gastric cancer. The extent and severity of the inflammation depends on a number of factors, including the virulence of infecting organism and the host response. Certain strains of Helicobacter pylori, particularly those that contain the pathogenicity island and are positive for CagA, stimulate a more aggressive host inflammatory response.
The significance of CagA is that patients which are colonized by CagA positive strains have higher levels of IL-8, a more intensive inflammatory response and a higher incidence of peptic ulceration and cancer[3].
Epidemiological studies favouring the relationship between HP infection and gastric cancer as a cause and effect are based on 12 studies wich included 1228 gastric cancer cases assessed in a systematic review where an Odds Ratio of 3 (95% Cl:2.3-3.8) was found[4]. In a Japanese study which assessed the relationship between gastric cancer and Helicobacter serology in patients aged <40 years an Odds Ratio as high as 13.3 (95% Cl: 5.3-35.6) was found[5].
This paper confirms the data of the Literature on the increased risk of gastric cancer in patients infected by CagA+ Helicobacter Pylori with an OR = 4.23 (Cl:3.22-5.24) in gastric cancer patients vs healthy volunteers.
In fact this is one of the few methodologically correct paper on Italian people.
In 1994 the NIH Consensus Development Panel declared: "if there is any causal relanship between H. pylori infection and gastric cancer, clearly other factors are also important in gastric carcinogenesis. H. pylori eradication for the purpose of preventing gastric cancer can not be reccomended at this time".
The discussion on this argument is still open, but the results of this well done paper are surely encouraging the "Pro-Eradication Party"!!!

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