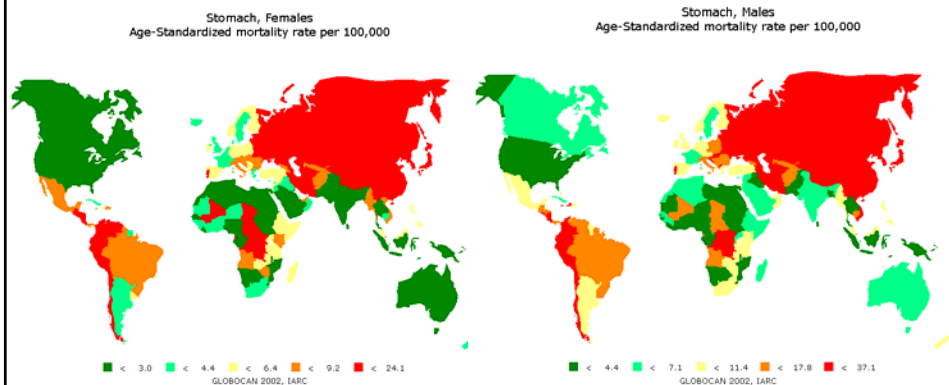


# H. Pylori, Cox-2 inhibitors and Prevention of Gastric Cancer

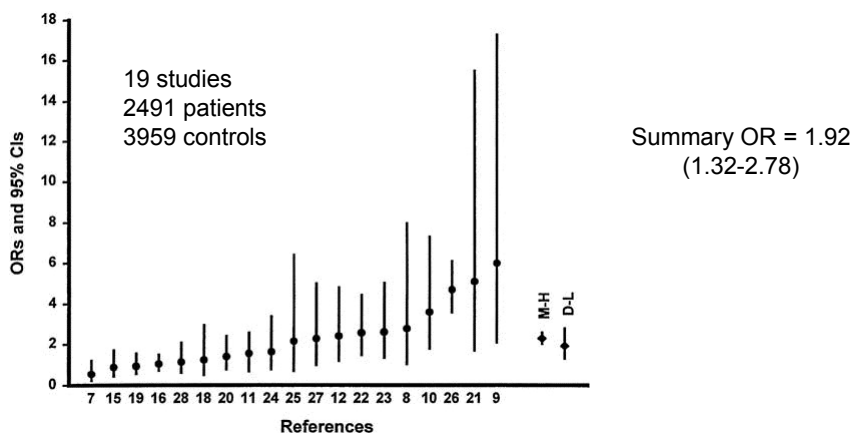
Joseph Sung MD, PhD  
Institute of Digestive Disease  
The Chinese University of Hong Kong



## Ca Stomach Mortality Male vs Female

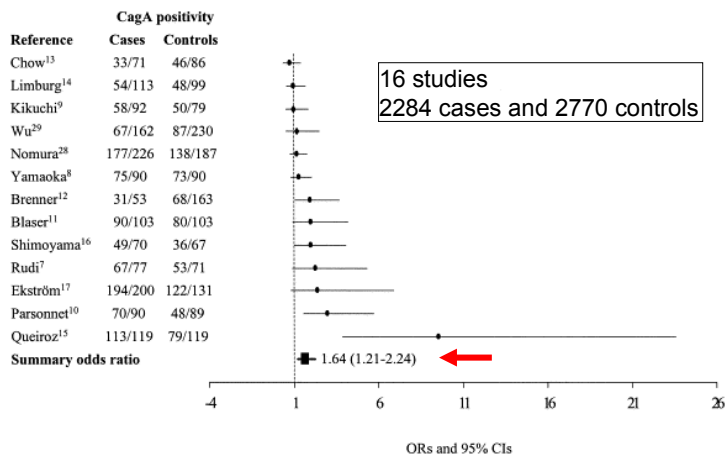


## HP seropositivity and Gastric Cancer



Huang JQ et al. Gastroenterol 1998

## cagA and Gastric Cancer



Huang JQ et al. Gastroenterol 2003

# H. pylori and Gastric Cancer

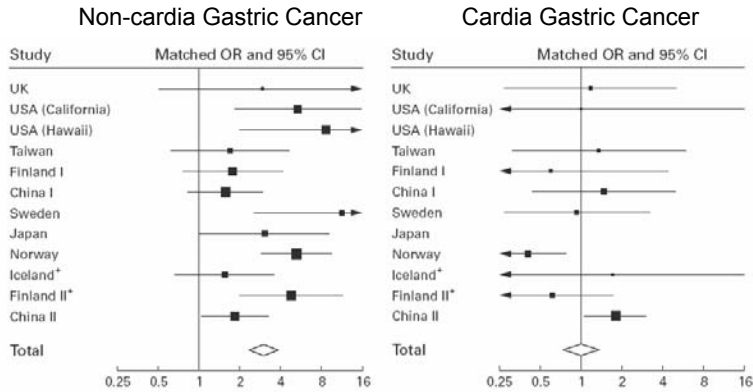
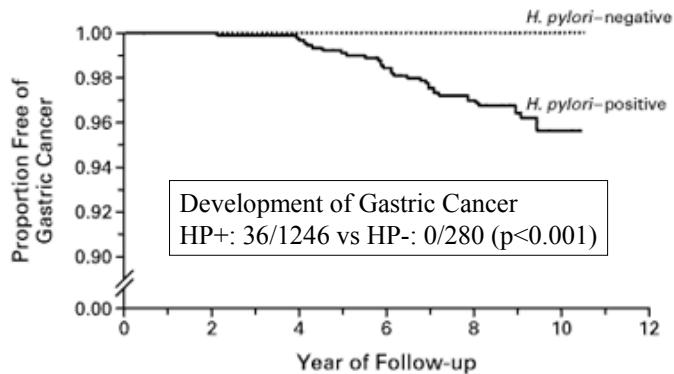


Figure 2 Matched odds ratios (OR) and 95% confidence intervals (CI) for the association between *Helicobacter pylori* infection and non-cardia gastric cancer, overall and by study. The area of the square is proportional to the study size. The diamond shows the OR value for all studies combined, with 95% CI represented by the horizontal points. \*Unpublished data.

Figure 3 Matched odds ratios (OR) and 95% confidence intervals (CI) for the association between *Helicobacter pylori* infection and cardia cancer, overall and by study. The area of the square is proportional to the study size. The diamond shows the OR value for all studies combined, with 95% CI represented by the horizontal points. \*Unpublished data.

Helicobacter & Cancer Collaboration Group. GUT 2001

# HP & Gastric Cancer



No. AT RISK	0	2	4	6	8	10	12
H. pylori-negative	280	272	251	245	213	57	
H. pylori-positive	1246	1219	1086	907	782	258	

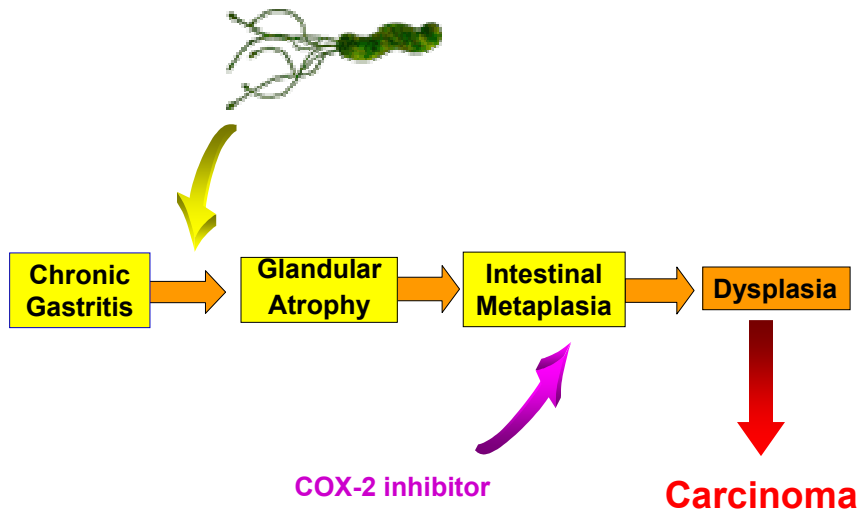
Uemura et al. NEJM 2001

## Atrophy/IM and risk of gastric cancer

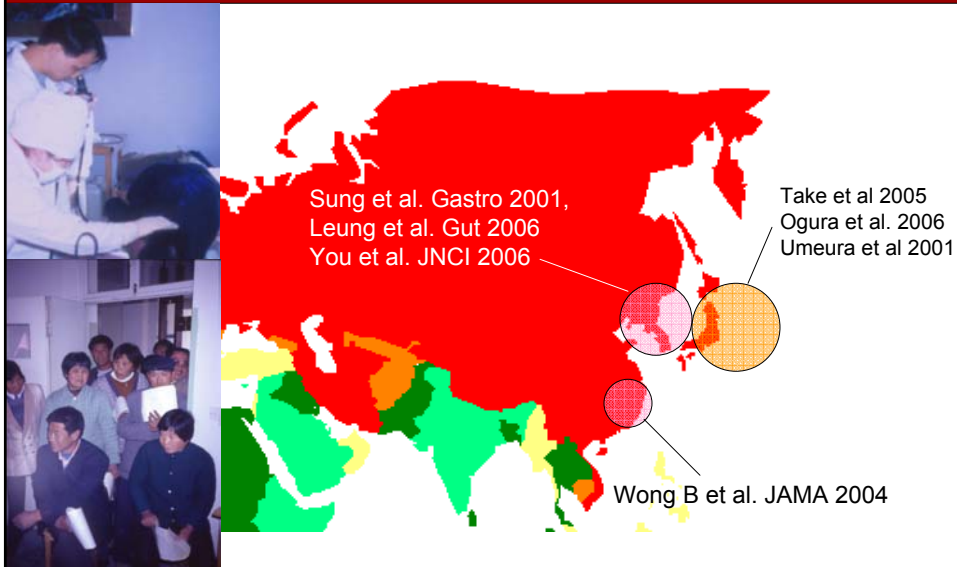
Baseline Histology	All HP+ (n=1246)	HP+ & GC (N=36)	RR (95% CI)
<b>Atrophy</b>			
None or mild	381	3 (0.8%)	1.0
Moderate	657	18 (2.7%)	1.7 (0.8-3.7)
Severe	208	15 (7.2%)	4.9 (2.8-19.2)
<b>Intestinal Metaplasia</b>			
Absent	782	6 (0.8%)	1.0
Present	464	30 (6.5%)	6.4 (2.6-16.1)

Uemura et al. NEJM 2001

## *H. pylori* associated gastric carcinogenesis



## Hp Eradication and Prevention of Gastric Cancer: studies in China



## Intervention trial in Linqu

Population: 3400 aged 35-64, from 1995 to 2003 (7.3 years)

- Two-week treatment for H.pylori infection  
Omeprazole 20mg + Amoxicillin 1g Bid
- Daily nutritional supplementation  
VC 250mg + VE 100IU + Selenium 37.5ug Bid
- Garlic preparation (400mg Bid)

You WC et al, JNCI 2006

## Hp treatment reduces severe atrophy, IM, dysplasia & GC after 7 years

Year, treatment group	Dysplasia or gastric cancer		Severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer	
	OR (95% CI)	P	OR (95% CI)	P
1999				
<i>H. pylori</i> treatment	1.13 (0.89 to 1.44)	.32	0.77 (0.62 to 0.95)	.016
Vitamins	1.10 (0.89 to 1.37)	.39	1.32 (1.12 to 1.57)	.001
Garlic	0.98 (0.79 to 1.22)	.86	0.99 (0.84 to 1.18)	.94
2003				
<i>H. pylori</i> treatment	1.07 (0.88 to 1.31)	.49	0.60 (0.47 to 0.75)	<.001
Vitamins	1.03 (0.87 to 1.23)	.71	1.14 (0.96 to 1.37)	.14
Garlic	1.02 (0.86 to 1.21)	.83	1.08 (0.90 to 1.29)	.40

Hp treatment has not reduced the combined prevalence of dysplasia & gastric cancer

You WC et al, JNCI 2006

## Histopathologic severity improves after treatment of *H. pylori*

Treatment	1994–1999				1994–2003			
	Regression, N(%)	No change, N(%)	Progression, N(%)	P <sub>trend</sub> *	Regression, N(%)	No change, N(%)	Progression, N(%)	P <sub>trend</sub> *
<i>H. pylori</i> treatment								
Active	230 (22)	440 (42)	375 (36)	.63	165 (17)	383 (39)	440 (45)	.006
Placebo	222 (21)	453 (43)	385 (36)		120 (12)	388 (39)	486 (49)	
Vitamins								
Active	305 (20)	669 (43)	590 (38)	.043	210 (14)	630 (43)	619(42)	.40
Placebo	327 (21)	724 (46)	531 (34)		259 (17)	582 (39)	642 (43)	
Garlic								
Active	321 (21)	693 (44)	549 (35)	.46	236 (16)	602 (41)	622 (43)	.78
Placebo	311 (20)	700 (44)	572 (36)		233 (16)	610 (41)	639 (43)	

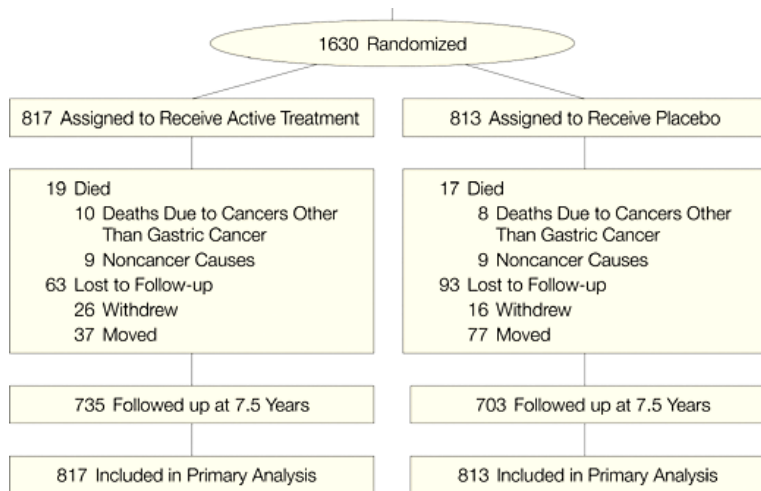
\*Cochran–Armitage–Mantel trend test stratified by sex and age (35–39, 40–44, 45–54, and ≥55 years). Scores for regression, no change, and progression were –1, 0, and 1, respectively.

### Risk of Developing Gastric cancer:

*H. pylori* treatment (19/1130; 1.7%) vs placebo (27/1128; 2.4%) (adjusted  $P = .14$ )

You WC et al, JNCI 2006

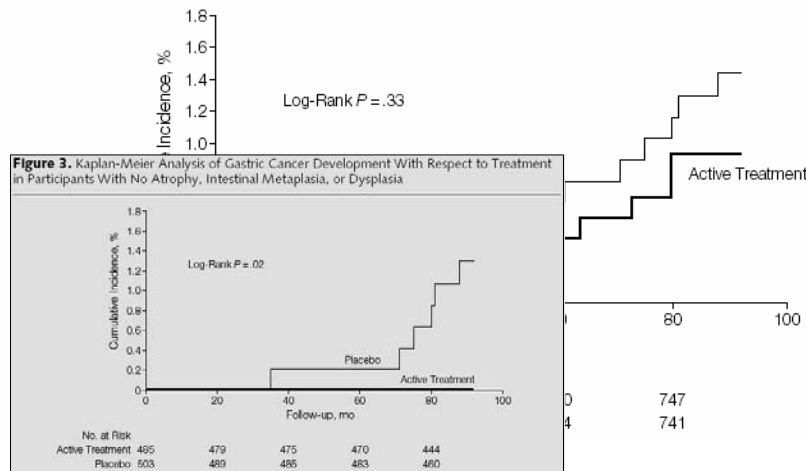
# Changle, China



Wong et al, JAMA 2004

## HP eradication and prevent gastric cancer development only before atrophy, IM or dysplasia

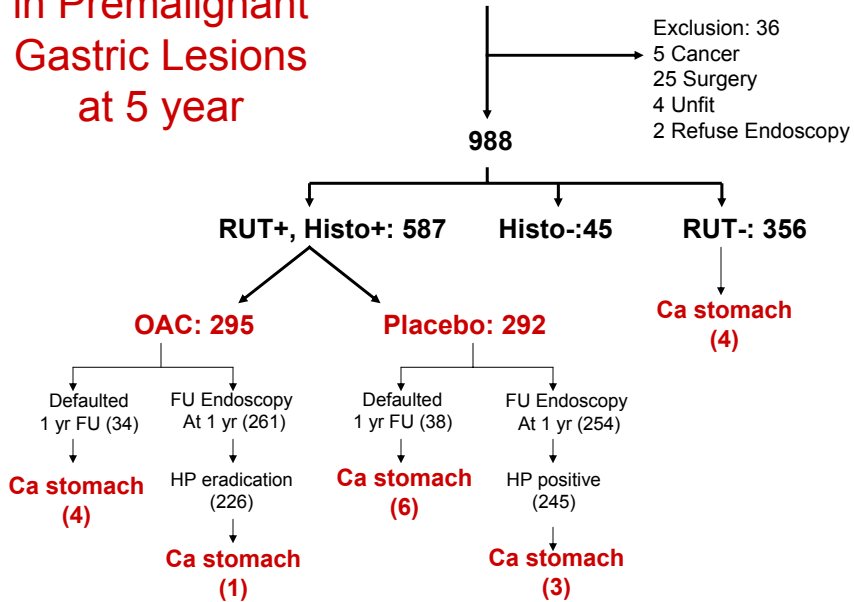
**Figure 2.** Kaplan-Meier Analysis of Gastric Cancer Development With Respect to Treatment



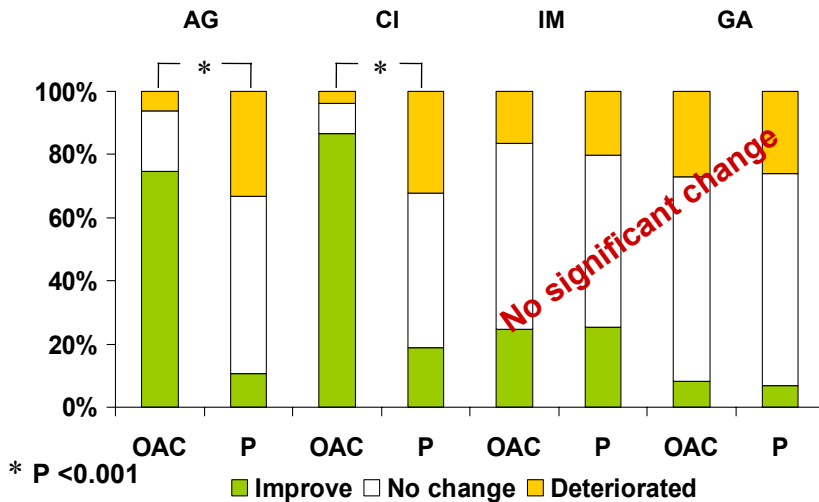
Wong et al, JAMA 2004

## HP eradication in Premalignant Gastric Lesions at 5 year

Screening: 1024



## H. pylori eradication on changes of premalignant gastric lesions at 1 year



Sung et al. Gastroenterol 2001

## H. pylori and progression of IM

**Table 3** Odds ratio (OR with 95% confidence interval (CI)) for progression of intestinal metaplasia (IM) according to *Helicobacter pylori* treatment and/or final *H pylori* status

	IM deterioration	No IM deterioration	OR (95% CI)	p Value
OAC group	104 (45.2%)	116 (56.6%)	0.63 (0.43–0.93)	0.018
Placebo group	126 (54.8%)	89 (43.4%)	1.0 (referent)	
OAC+HP –ve	68 (37.6%)	96 (55.5%)	0.48 (0.32–0.74)	<0.001
Placebo+HP+ve	113 (62.4%)	77 (44.5%)	1.0 (referent)	
HP+ve at 5 y	146 (65.8%)	97 (47.3%)	2.14 (1.45–3.16)	<0.001
HP–ve at 5 y	76 (34.2%)	108 (52.7%)	1.0 (referent)	

HP+ve, *H pylori* infected; HP–ve, *H pylori* negative.  
OAC, omeprazole, amoxicillin, and clarithromycin.

Leung and Sung. Gut 2004

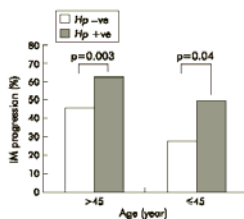
## Factors associated with IM progression

**Table 4** Factors predicting intestinal metaplasia (IM) progression: multivariate logistic regression

Factor	OR (95% CI)	p Value
Persistent HP+ve	2.13 (1.41–3.23)	<0.001
Age > 45 y	1.92 (1.18–3.11)	0.009
Duodenal ulcer	0.25 (0.09–0.66)	0.005
Alcohol use	1.67 (1.07–2.62)	0.03
Drinking water from well	1.74 (1.13–2.67)	0.01

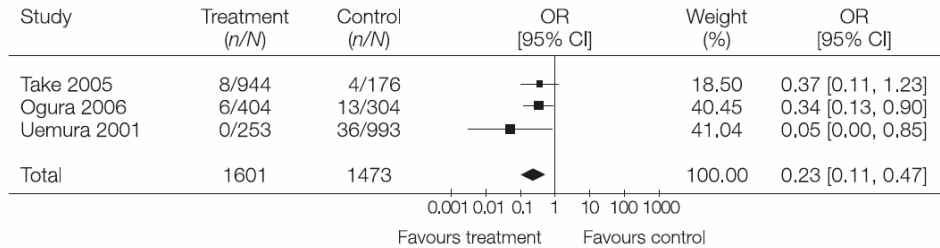
HP+ve, *H pylori* infected.

Values are odds ratios with 95% confidence interval (OR (95% CI)).



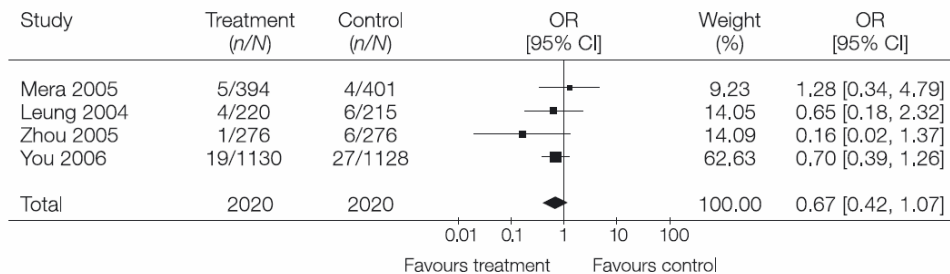
Leung and Sung. Gut 2004

## What is the consensus? Summary of non-randomized trials



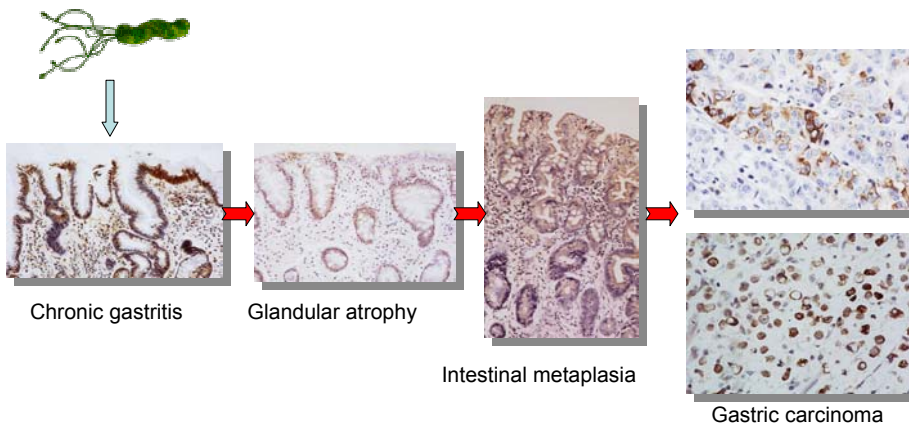
Fuccio, APT 2007

## What is the consensus? Summary of Randomized trials



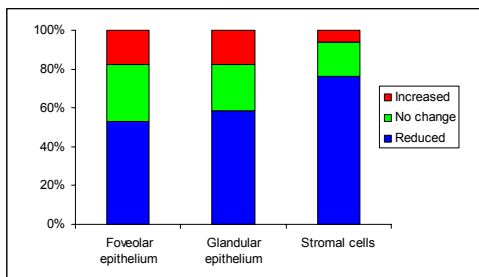
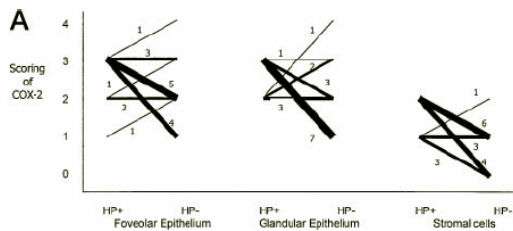
Fuccio, APT 2007

## COX-2 expression in different stages of gastric carcinogenesis



Sung JJY, *Am J Pathol* 2000

## Changes in COX-2 expression 12 months after HP eradication

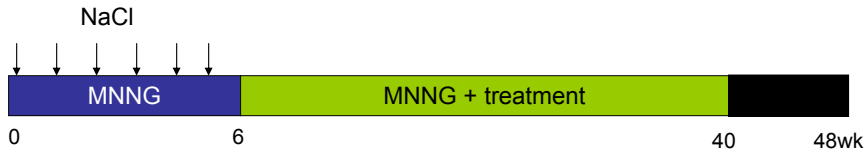


Sung JJY, *Am J Pathol* 2000



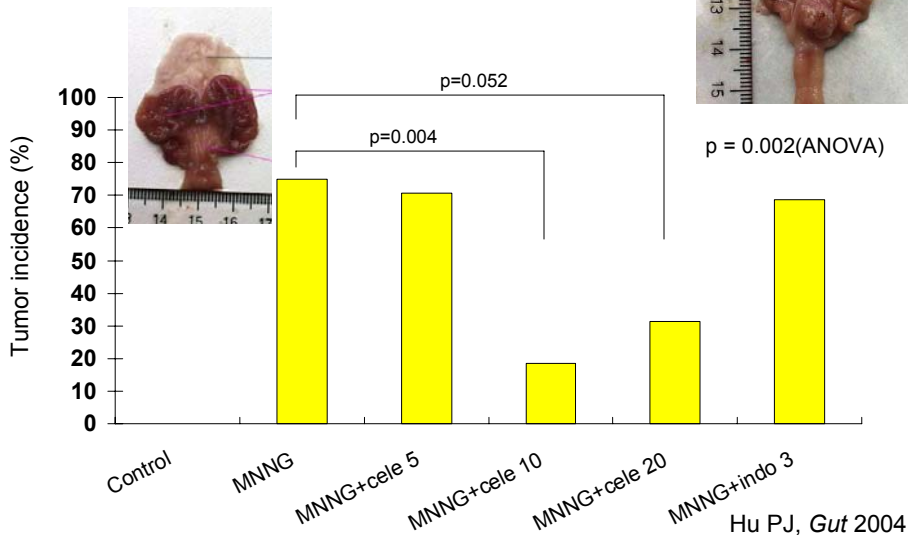
# Does Cox-2i prevent Ca Stomach

- Animals: 4-wk old male Wistar rats
- Gastric cancer induced by NaCl and MNNG

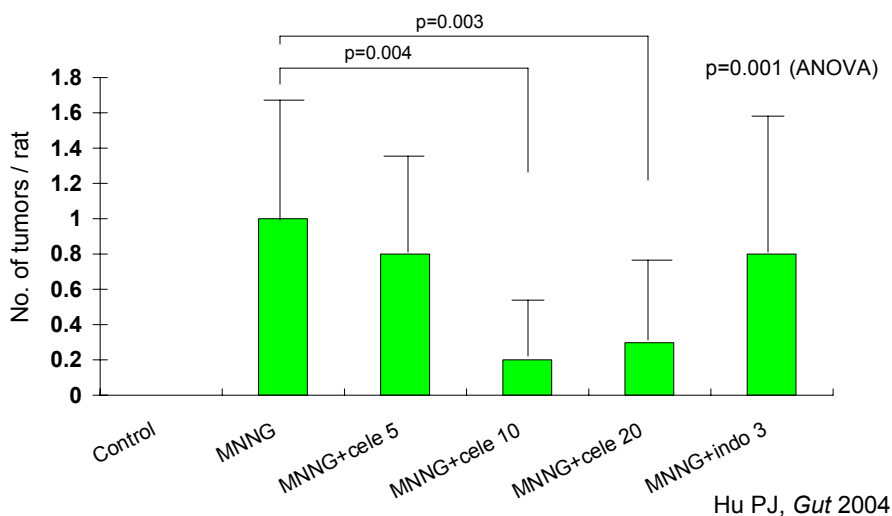


Group	Treatment	Total no. of rats
A	Control	5
B	MNNG alone	16
C	MNNG + celecoxib 5mg/kg/d	17
D	MNNG + celecoxib 10mg/kg/d	16
E	MNNG + celecoxib 20mg/kg/d	16
F	MNNG + indomethacin 3mg/kg/d	16

## Tumor incidence (% of rats with gastric cancer)



## Tumor Multiplicity (No. of tumors / rat)



## Tumor volume



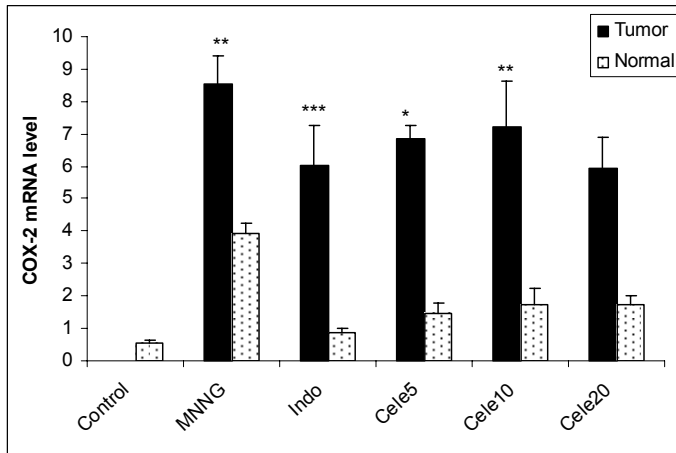
Group	Treatment	Total no. of rats	Mean Tumor volume* (± SD)
A	Control	5	0
B	MNNG alone	16	2805 ± 5540
C	MNNG + celecoxib 5mg/kg	17	188 ± 378 <sup>#</sup>
D	MNNG + celecoxib 10mg/kg	16	2 ± 7 <sup>#</sup>
E	MNNG + celecoxib 20mg/kg	16	39 ± 111 <sup>#</sup>
F	MNNG + indomethacin 3mg/kg	16	359 ± 860

\*p=0.009 (ANOVA)

<sup>#</sup> p<0.05 vs group B

Hu PJ, *Gut* 2004

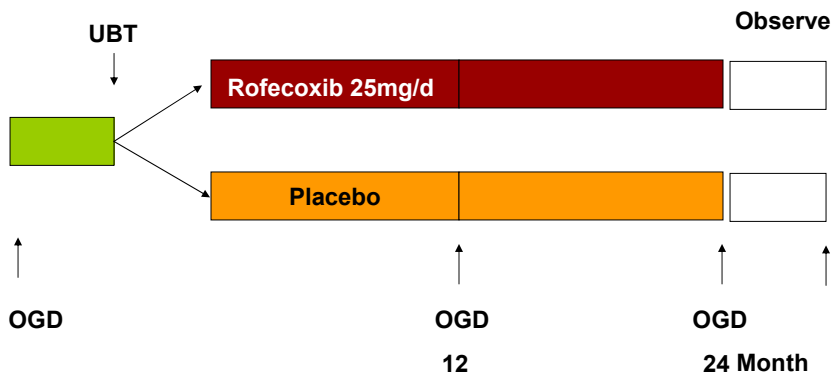
# Cox-2 expression in different treatment groups



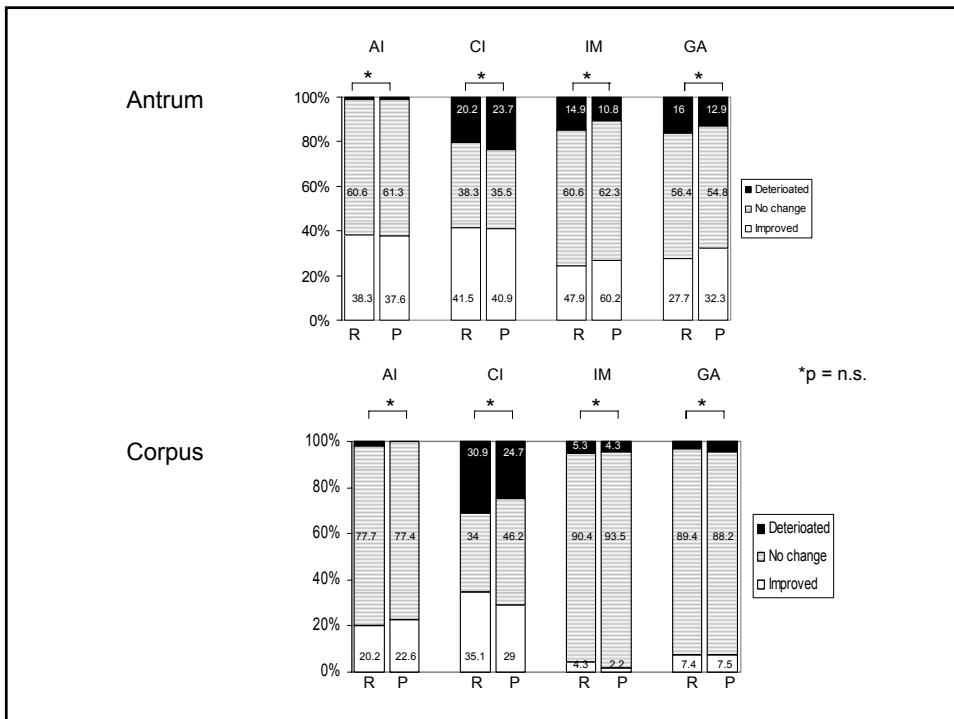
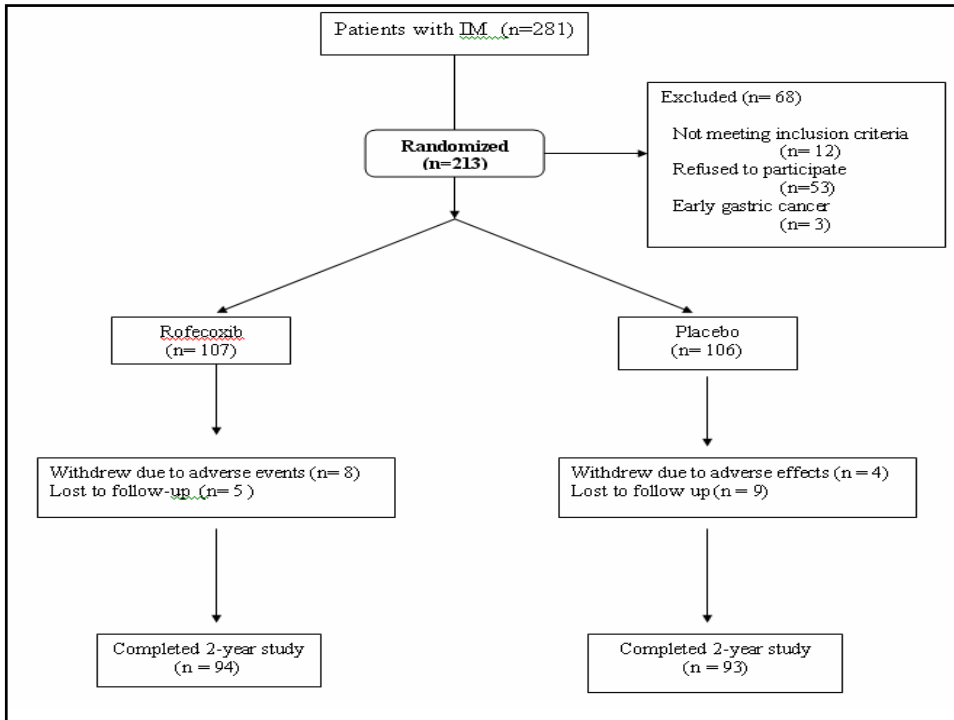
\*p=0.02; \*\*p<0.002; \*\*\*p<0.0001  
 Between different tumors: p>0.05  
 Between different normal tissues: p<0.0001  
 #(MNNG normal vs all other normal: p<0.01)

Hu PJ, *Gut* 2004

# Does COX-2i causes regression of Intestinal metaplasia?



Leung et al. *DDW* 2006



## Interventional trial in Linq

**Population: 1024 aged 34-64, from 2003 to 2006**

- ◆ **Two-week treatment for *H.pylori* infection**  
**Omeprazole 20mg + Amoxicillin 1g Bid**
- ◆ **Celecoxib 200mg Bid**

You et al (in progress)

## Conclusions

- Non-cardiac gastric cancer is associated with (cagA positive) *H. pylori* infection
- Over-expression of COX-2 is found in gastric cancer and pre-malignant lesions

## Conclusions

- Eradication of *H. pylori* alone *may* reduce the risk of gastric cancer, especially before atrophy and IM
- The use of COX-2 inhibitors have been found to reduce gastric cancer in animal model but not (yet) in human studies