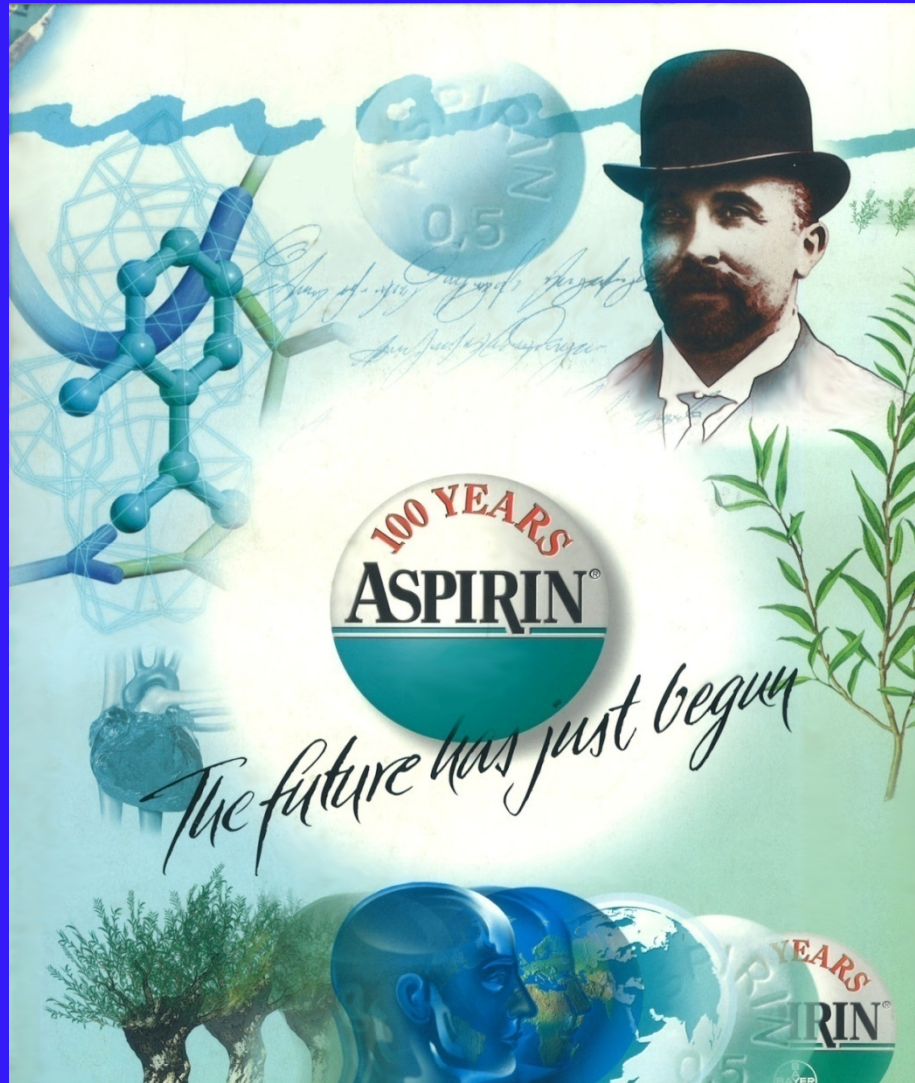


Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention

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London, United Kingdom

100 year Celebration Book from Bayer with Felix Hoffman (1997)



Sulindac for polyposis of the colon^W

Waddel WR, Loughry RW

J Surg Oncol. 1983 Sep;24(1):83-7

Four members of a Gardner's syndrome family had rectal and colon polyposis treated with nonsteroid anti-inflammatory drugs. Three of these patients had had subtotal colectomy and ileoproctostomy and the residual polyps arose in the rectal mucosa. The polyps almost completely disappeared when sulindac was administered. Indomethacin therapy over the course of a preceding year was ineffective in one of these patients. One patient (case 4) had diffuse polyposis in an intact colon. After sulindac therapy for a year, only three small mucosal polyps could be identified by air contrast barium enema and colonoscopic examination. These observations confirm those of Pollard and Luckert [1,2] on rats with chemically induced polyposis of the intestinal tract.

Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis

**Nugent KP, Farmer KC, Spigelman AD, Williams CB, Phillips RK
Br J Surg. 1993 Dec;80(12):1618-9**

Twenty-four patients with familial adenomatous polyposis who had previously undergone prophylactic colectomy and had advanced duodenal polyposis were entered into a randomized trial to assess the effect of the non-steroidal anti-inflammatory drug sulindac on duodenal and rectal polyps. Polyp size and number were assessed by videotaped duodenoscopy (and rectoscopy in 14 patients) at entry and after 6 months of treatment; the tapes were compared by two assessors who were unaware of the randomization and the shuffled chronological order of the recordings. Mucosal cell proliferation was measured by in vitro incorporation of 5-bromo-2'-deoxyuridine. Sulindac therapy was associated with a reduction in epithelial cell proliferation in the duodenum (median labelling index (LI) 15.8 versus 14.4 per cent, $P = 0.003$) and a trend towards duodenal polyp regression ($P = 0.12$). In the rectum, cell proliferation showed a marked reduction (median LI 8.5 versus 7.4 per cent, $P = 0.018$), and significant ($P = 0.01$) polyp regression was seen. Rectal polyposis was less severe than that in the duodenum and responded more dramatically. Sulindac is a possible treatment for patients in whom rectal polyps have failed to show significant regression after ileorectal anastomosis and who are unsuitable for pouch surgery; it may be useful in early duodenal polyposis or as an adjunct after duodenal clearance.

Estimated benefits of long-term (about 20 years) aspirin use on colorectal neoplasia in the general population

	Number of studies	Number of cases	Relative Risk (95% CI)	Risk (%) to age 74 (general population)	Estimated absolute benefit to age 74 (per 1000)
Colorectal cancer					
Case-control	12	14279	0.89 (0.86-0.93)
Male	4.64	5.1
Female	3.83	4.2
Cohort	12	9250	0.82 (0.77-0.88)
Colorectal adenoma					
Case-control	5	15213	0.87 (0.77-0.98)
Male	30	51
Female	25	42.5
Cohort	2	1845	0.72 (0.61-0.85)

NSAIDs – Colorectal Cancer

Case-control studies

Kune et al, 1988
 Rosenberg et al, 1991
 Muscat et al, 2003 (Males)
 Muscat et al, 2003 (Females)
 Peleg et al, 1994
 Reeves et al, 1996
 La Vecchia et al, 1997
 Rosenberg at al, 1998
 Friedman et al, 1998
 Neugut et al, 1998
 Juarranz et al, 2002
 Sansbury et al, 2005
 Vinogradova et al, 2007

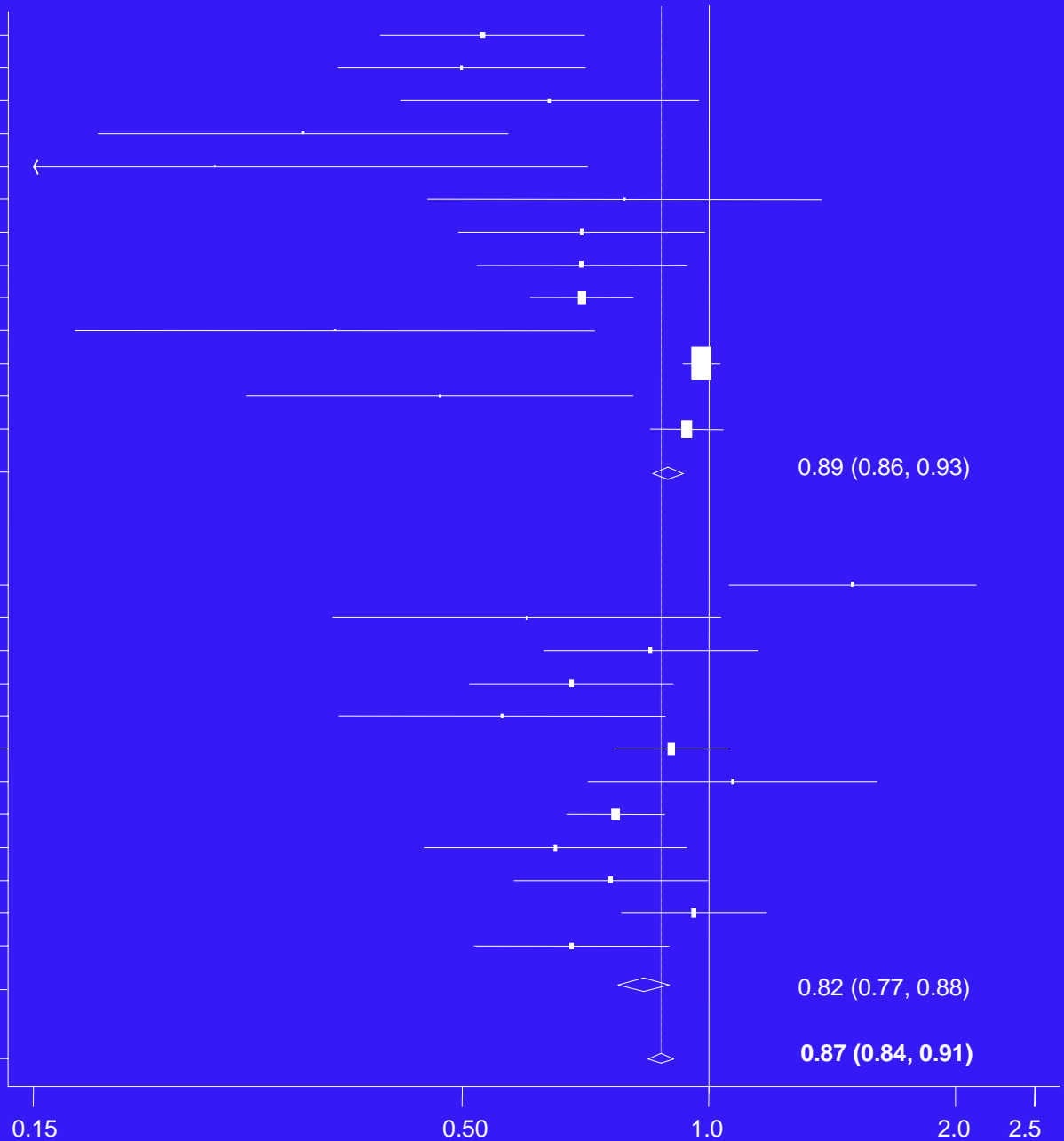
Combined

Cohort studies

Paganini-Hill et al, 1989
 Thun et al, 1991, 1993
 Schreinemachers and Everson, 1994
 Giovannucci et al, 1994
 Giovannucci et al, 1995
 Garcia Rodriguez and Huerta Alvarez, 2001
 Ratnasinghe et al, 2004
 Chan et al, 2005
 Larsson et al, 2006
 Mahipal et al, 2006
 Allison et al, 2006
 Jacobs et al, 2007

Combined

Overall Combined

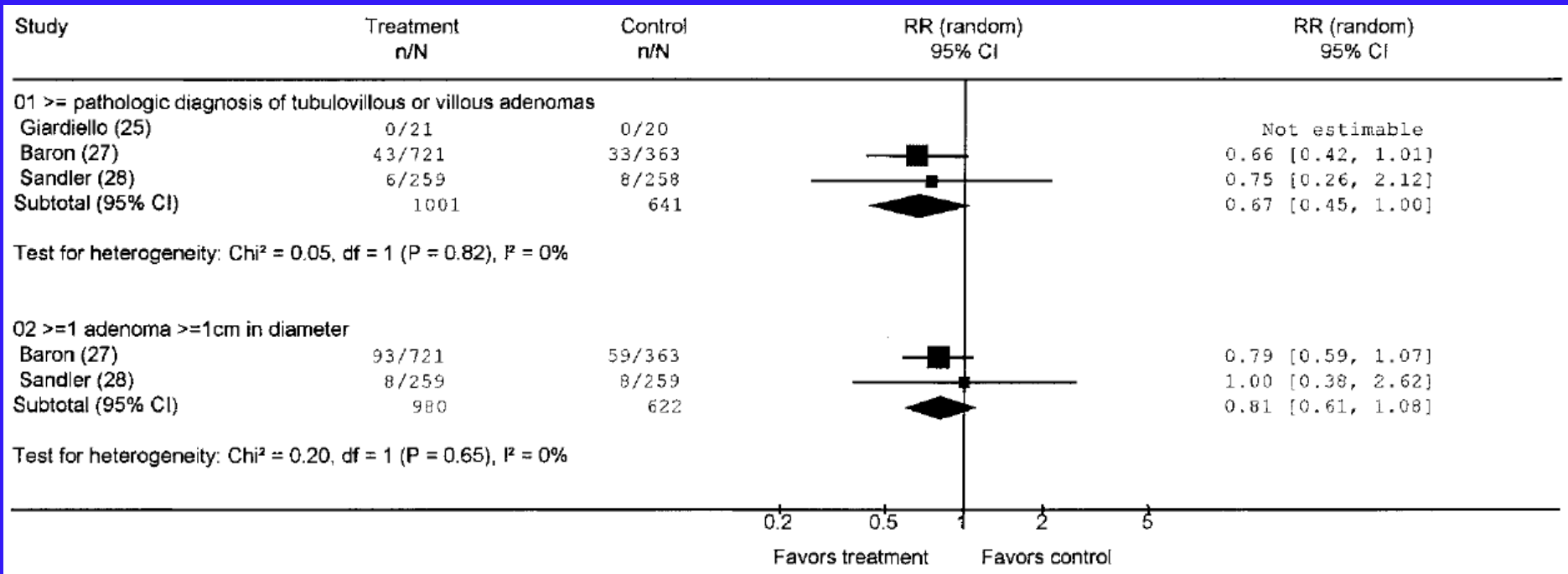


Relative Risk

Bosetti et al 2009

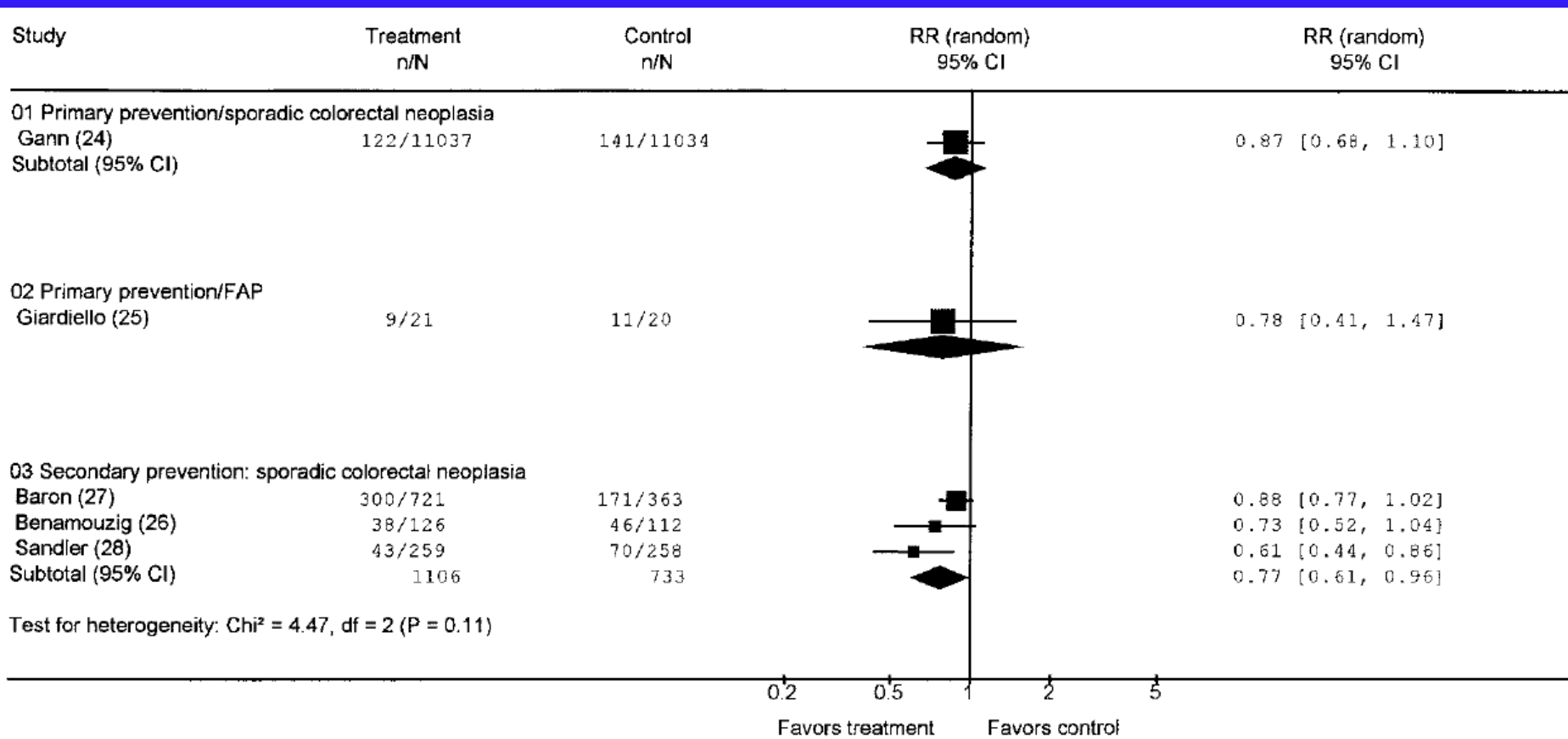
Number of patients that develop higher risk adenomas

Randomised trials



Asano & McLeod, Diseases of the Colon & Rectum, 2004

Number of patients that develop ≥ 1 adenoma randomised trials



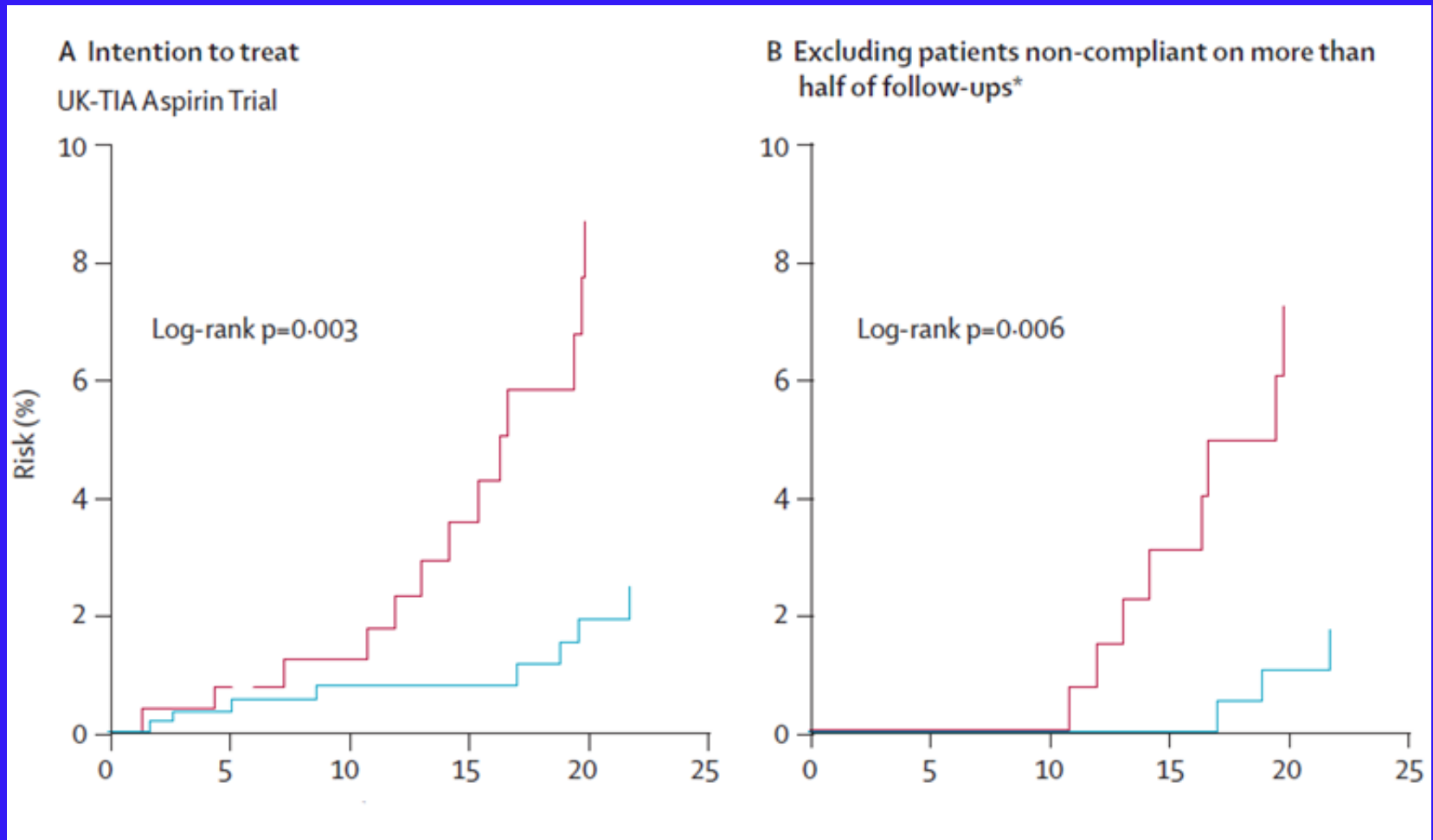
Incidence of colorectal cancer and adenomas

Randomised trials of aspirin for cancer prevention

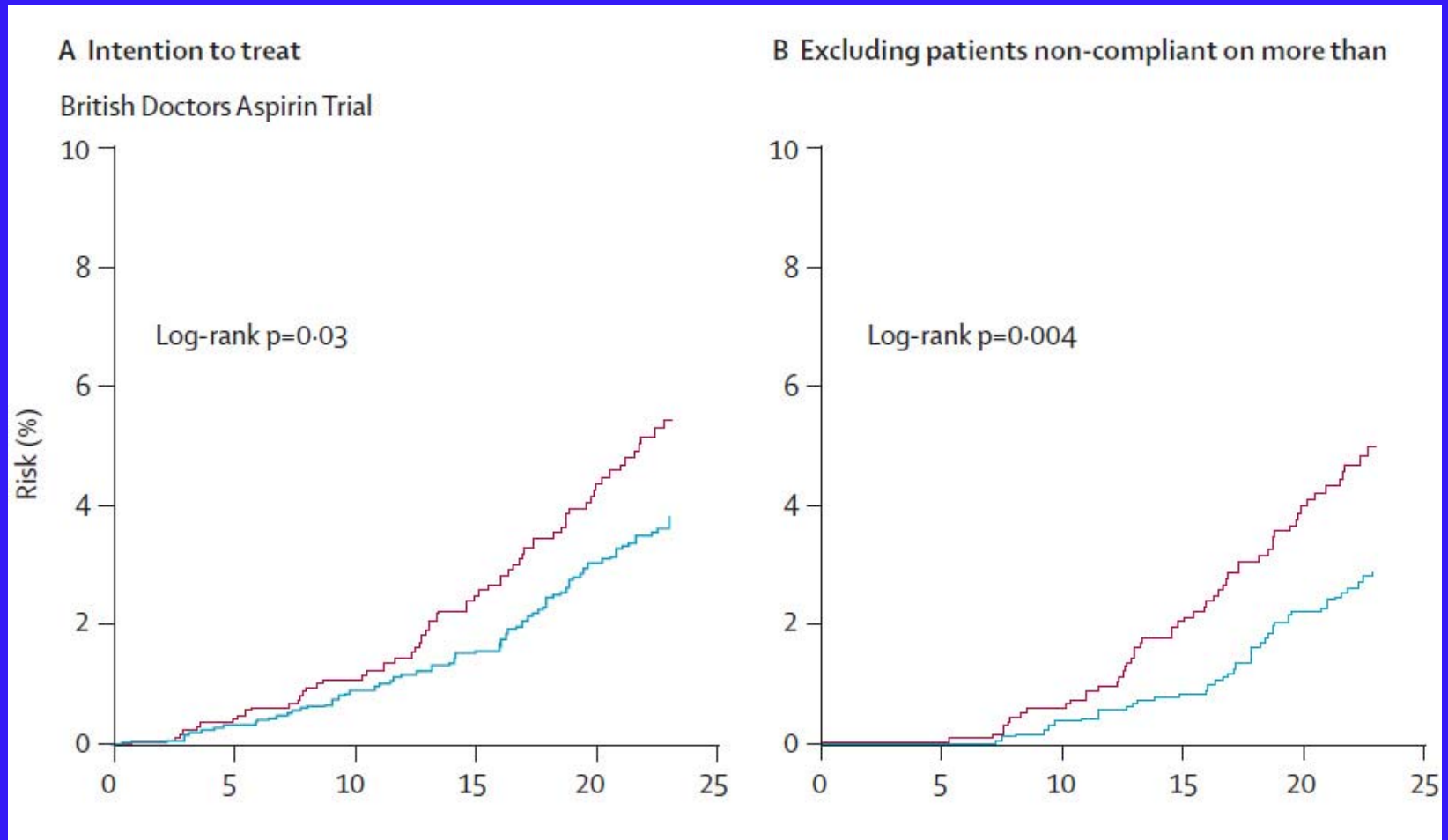
	Duration of treatment (years)	Follow-up (years)	Number of participants	Number of cases	Relative risk* (95% CI)
Invasive colorectal cancer†					
Women's Health Study ¹²					
100 mg qod	10	10	19 934	133	0.97 (0.77-1.24)
Placebo	10	10	19 942	136	..
Physicians' Health Study ¹³					
325 mg qod	5	12	11 037	173	1.03 (0.83-1.28)
Placebo	5	12	11 034	168	..
British Doctors Aspirin Trial ¹⁴					
500 mg	5-6	23	3 429	92	0.70 (0.51-0.97)
No treatment	5-6	23	1 710	64	..
UK Transient Ischaemic Attack Aspirin Trial ¹⁴					
300 mg or 1200 mg	1-7	23	1 632	37	0.82 (0.49-1.38)
Placebo	1-7	23	817	23	..
Colorectal adenomas‡					
Baron et al 2003 ¹⁵					
85 mg	3	3	377	140	0.81 (0.69-0.96)
325 mg	3	3	366	160	0.96 (0.81-1.13)
Placebo	3	3	355	171	..
Sandler et al 2003 ¹⁶					
325 mg	1	2.5	259	43	0.65 (0.46-0.91)
Placebo	1	2.5	258	60	..
APACC Trial ¹⁷					
160 mg or 300 mg	4	1	126	38	0.73 (0.52-1.04)
Placebo	4	1	112	46	..

qod = every other day. *Risk relative to placebo (reference) group. †Incidence of colorectal cancer in randomised primary prevention trials assessing aspirin. ‡Incidence of colorectal adenomas in randomised secondary prevention trials assessing aspirin.

Risk of Colorectal Cancer in Patients Allocated Aspirin (blue line) vs No Aspirin (red line) in the UK-TIA Aspirin Trial



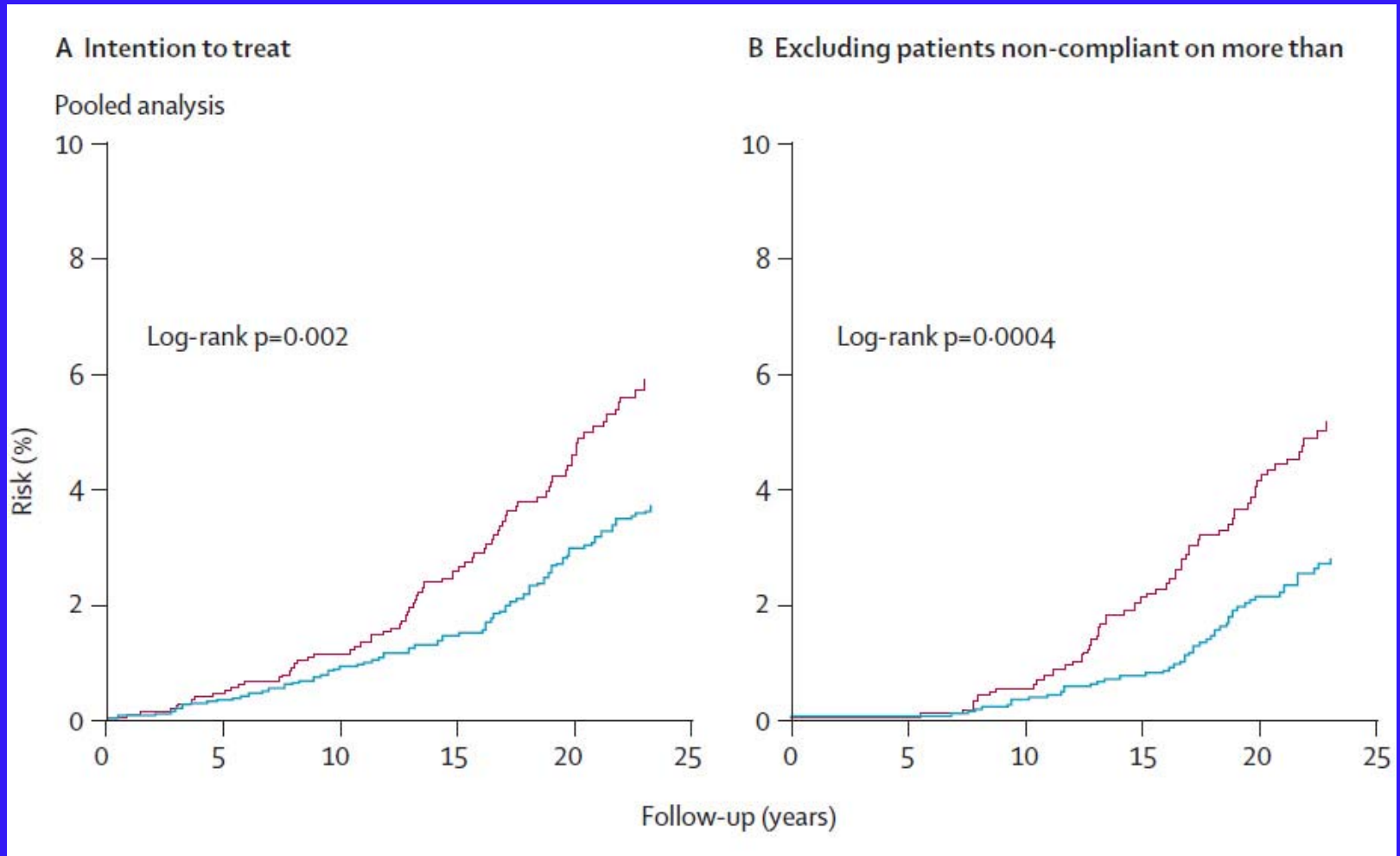
Risk of Colorectal Cancer in Patients Allocated Aspirin (blue line) vs No Aspirin (red line) in the British Doctors Aspirin Trial



Flossmann, et al, Lancet 2007

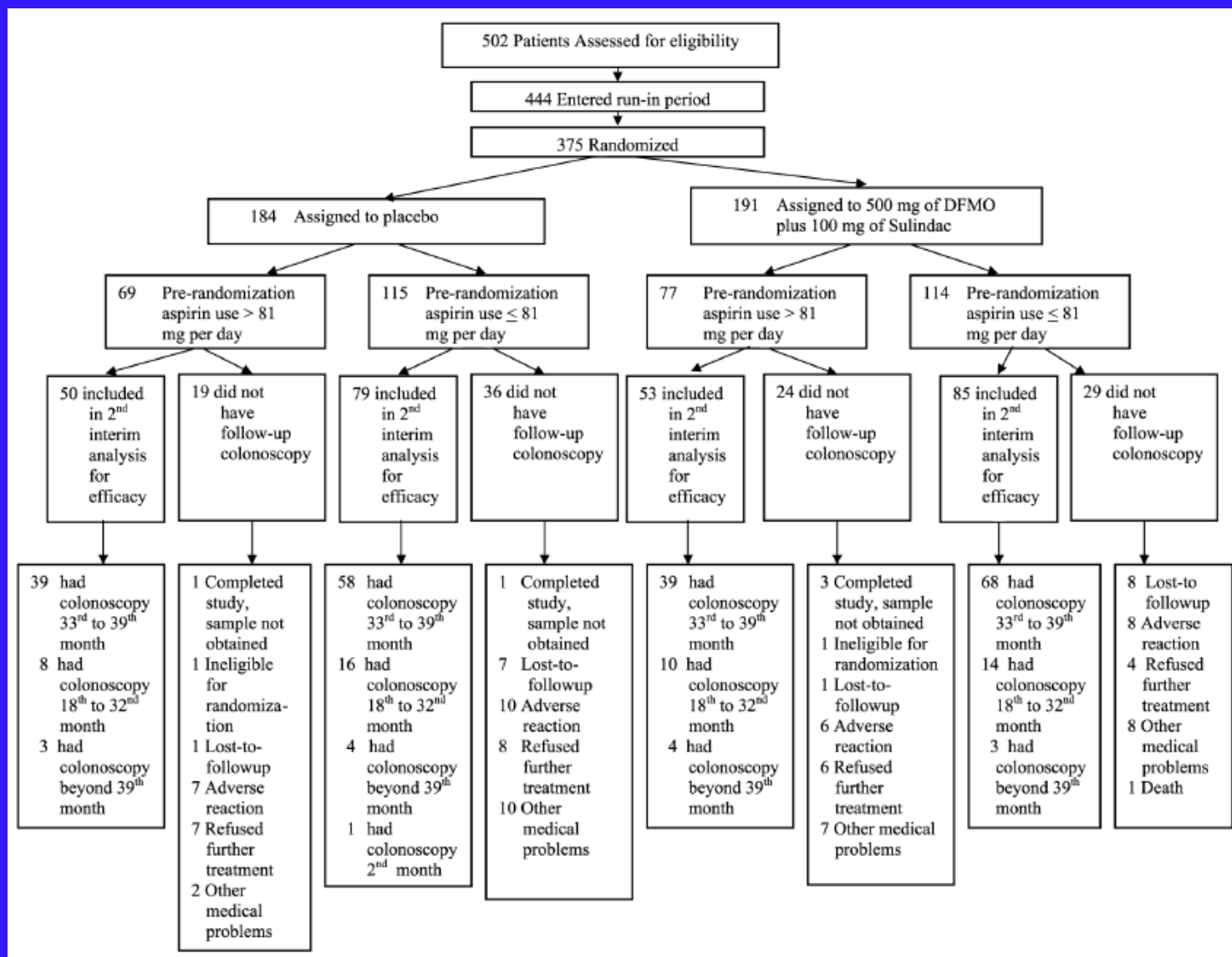
Risk of colorectal cancer

Combined UK-TIA Aspirin Trial & the British Doctors Aspirin Trial



Flossmann, et al, Lancet 2007

DFMO & Sulindac - Study Schema



Risk of adenomas; evidence of substantial effect in active arm

	Follow-up colonoscopy 2 to 39 mo after beginning treatment (n = 267)		Follow-up colonoscopy 33 to 36 mo after beginning treatment (n = 204)	
	Placebo (n = 129)	DFMO/sulindac (n = 138)	Placebo (n = 97)	DFMO/sulindac (n = 107)
Detection of any adenoma				
Cumulative incidence of adenomas detected at end of the treatment (%)	53 (41.1)	17 (12.3)	42 (43.3)	12 (11.2)
Risk ratio* (95% CI)		0.30 (0.18–0.49)		0.26 (0.15–0.46)
P		<0.001		<0.001
Detection of advanced adenomas [†]				
Cumulative incidence of advanced adenomas detected at end of the treatment (%)	11 (8.5)	1 (0.7)	9 (9.3)	1 (0.9)
Risk ratio* (95% CI)		0.085 (0.011–0.65)		0.10 (0.013–0.78)
P		0.001		0.004
Detection of advanced adenomas with size ≥ 1 cm				
Cumulative incidence of advanced adenomas with size ≥ 1 cm detected at end of the treatment (%)	9 (7.0)	1 (0.7)	7 (7.2)	1 (0.9)
Risk ratio* (95% CI)		0.10 (0.013–0.81)		0.13 (0.016–1.03)
P		0.004		0.02
Detection of multiple adenomas (>1)				
Patients with >1 adenoma, incidence (%)	17 (13.2)	1 (0.7)	15 (15.5)	1 (0.9)
Risk ratio* (95% CI)		0.055 (0.0074–0.41)		0.060 (0.0081–0.45)
P		<0.001		<0.001
Sensitivity analysis imputing adenoma for patients without an end-point determination [‡]				
Cumulative incidence of adenomas detected at end of the treatment (%)	76/184 (41.3)	39/191 (20.4)		
Risk ratio* (95% CI)		0.49 (0.36–0.69)		
P		<0.001		

Nonsteroidal Anti-inflammatory Drugs Effects on Mortality After Colorectal Cancer Diagnosis

Jason A. Zell, Argyrios Ziogas, Leslie Bernstein, Christina A. Clarke,
Dennis Deapen, ; Joan A. Largent, Susan L. Neuhausen, Daniel O. Stram,
Giske Ursin, and Hoda Anton-Culver
Cancer 2009;115:5662–71

BACKGROUND: Nonsteroidal anti-inflammatory drug (NSAID) use has been associated with a decreased colorectal cancer (CRC) risk. However, to the best of the authors' knowledge, the effects of NSAID on clinical outcomes after CRC diagnosis are not well defined. The authors investigated the association between prediagnosis NSAID use and mortality after CRC diagnosis among women in the California Teachers Study cohort.

METHODS: Women aged <85 years participating in the California Teachers Study, without a prior CRC diagnosis at baseline (1995-1996), and who were diagnosed with CRC during follow-up through December 2005, were eligible for analysis of the association between prediagnosis NSAID use and mortality. NSAID use (including aspirin and ibuprofen) was collected through a self-administered questionnaire. Cancer occurrence was identified through California Cancer Registry linkage. Multivariate Cox proportional hazards regression models were used to estimate hazards ratios (HR) for death and 95% confidence intervals (95% CIs).

RESULTS: Among 621 CRC patients who were identified, 64% reported no prediagnosis regular NSAID use, 17% reported use of 1 to 6 days/week, and 20% reported daily use. A duration of NSAID use <5 years was reported by 17% of patients and a use of 5 years was reported by 18%. **Regular prediagnosis NSAID use (1-3 days/week, 4-6 days/week, and daily) versus none was associated with improved overall survival (OS) (HR, 0.71; 95% CI, 0.53-0.95) and CRC-specific survival (HR, 0.58; 95% CI 0.40-0.84) after adjustment for clinically relevant factors. Prediagnosis NSAID use 5 years (vs none) was found to be associated with improved OS (HR, 0.55; 95% CI, 0.37-0.84) and CRC-specific survival (HR, 0.40; 95% CI, 0.23-0.71) in adjusted analyses.**

CONCLUSIONS: When used regularly or over a prolonged duration before CRC diagnosis, NSAIDs are associated with decreased mortality among female CRC patients.

Univariate and Multivariate Adjusted Overall Survival Analysis and CRC-Specific Survival Analysis for CRC Cases by Self-Reported Frequency of NSAID and Aspirin Use

	Reported NSAID Frequency		Reported Aspirin frequency	
	No Regular NSAID Use	Regular NSAID Use	No Regular Aspirin Use	Regular Aspirin Use‡
Overall mortality				
No. of events	150	72	167	54
No. at risk	397	224	456	164
Unadjusted HR (95% CI)	1 (reference)	0.83 (0.63-1.10)	1 (reference)	0.89 (0.65-1.21)
Adjusted HR (95% CI)*	1 (reference)	0.71 (0.53-0.95)	1 (reference)	0.74 (0.54-1.01)
CRC-specific mortality				
No. of events	103	42	113	32
No. at risk	397	224	456	164
Unadjusted HR (95% CI)	1 (reference)	0.71 (0.49-1.01)	1 (reference)	0.77 (0.52-1.14)
Adjusted HR (95% CI)*	1 (reference)	0.58 (0.40-0.84)	1 (reference)	0.62 (0.41-0.94)

Zell, et al, Cancer 2009

Univariate and Multivariate Adjusted Overall Survival Analysis and CRC-Specific Survival Analysis for All Colorectal Cancer Cases by Self-Reported Duration of NSAID and Aspirin Use

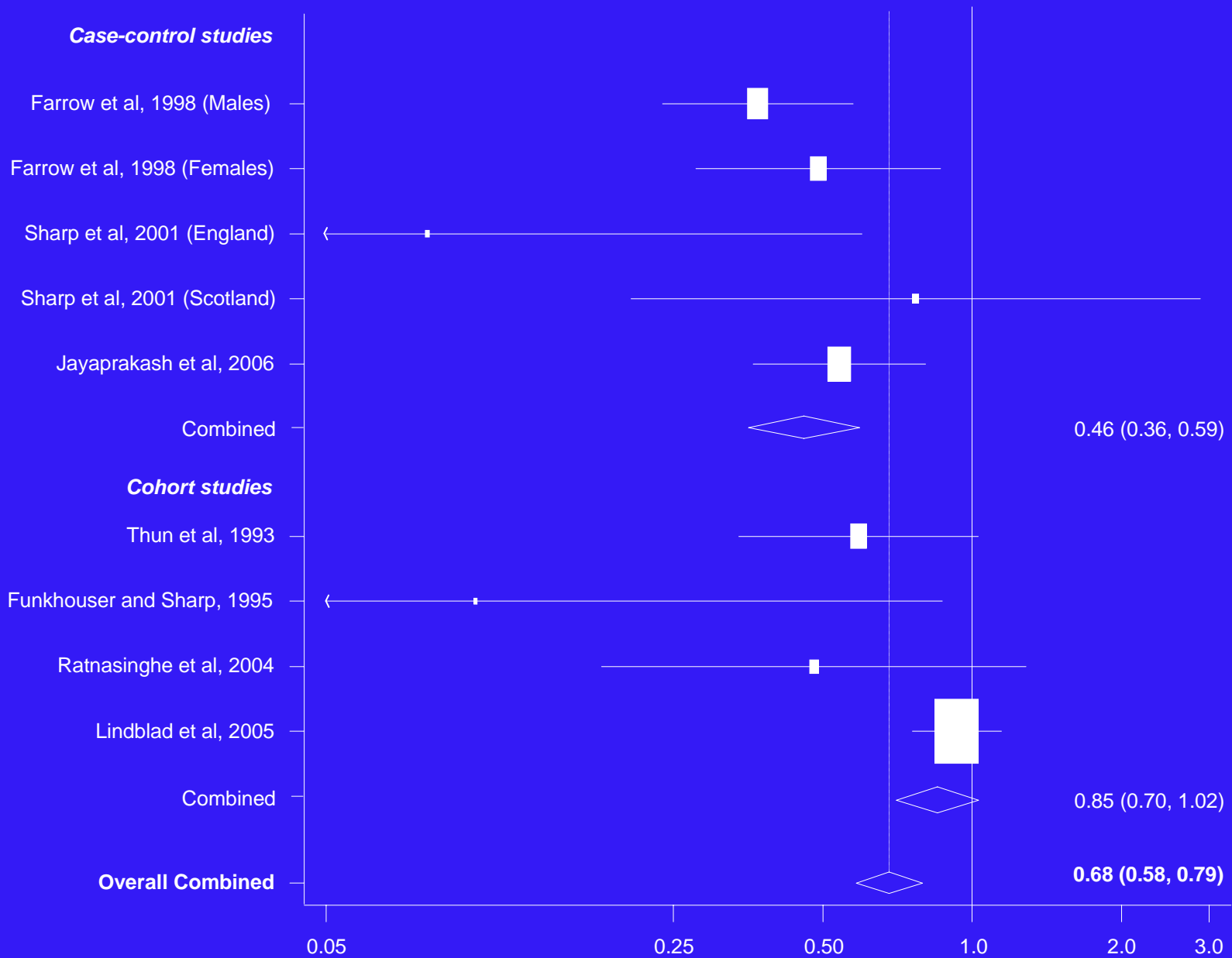
	Reported NSAID Duration			Reported Aspirin Duration		
	None	<5 Years	≥5 Years	None	<5 Years	≥5 Years
Overall mortality						
No. of events	150	30	42	167	26	24
No. at risk	397	105	111	456	65	92
Unadjusted HR (95% CI)	1 (reference)	0.94 (0.66-1.34)	0.67 (0.45-0.99)	1 (reference)	1.06 (0.70-1.60)	0.71 (0.46-1.08)
Adjusted HR (95% CI)†	1 (reference)	0.83 (0.58-1.19)	0.55 (0.37-0.84)	1 (reference)	1.02 (0.67-1.55)	0.53 (0.34-0.83)
CRC-specific mortality						
No. of events	103	24	24	113	18	11
No. at risk	397	105	111	456	65	92
Unadjusted HR (95% CI)	1 (reference)	0.87 (0.56-1.35)	0.50 (0.29-0.87)	1 (reference)	1.08 (0.66-1.78)	0.48 (0.26-0.88)
Adjusted HR (95% CI)*	1 (reference)	0.73 (0.46-1.15)	0.40 (0.23-0.71)	1 (reference)	1.03 (0.62-1.72)	0.33 (0.18-0.63)

Zell, et al, Cancer 2009

Estimated benefits of long-term (about 20 years) aspirin use in general population – Upper GI

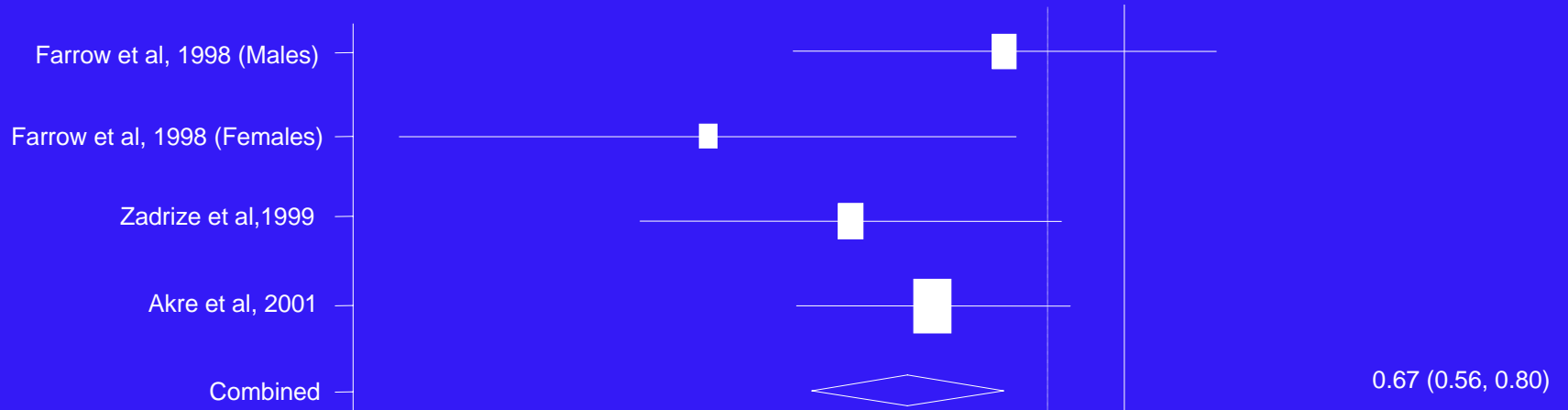
	Number of studies	Number of cases	Relative Risk (95% CI)	Risk (%) to age 74 (general population)	Estimated absolute benefit to age 74 (per 1000)
Oesophagus					
Case-control	3	836	0.46 (0.36-0.59)
Male	0.81	4.4
Female	0.33	1.8
Cohort	4	1118	0.85 (0.70-1.02)
Stomach					
Case-control	3	1557	0.67 (0.56-0.80)
Male	1.10	3.6
Female	0.41	1.4
Cohort	4	1376	1.03 (0.89-1.19)

NSAIDs – Oesophageal Cancer

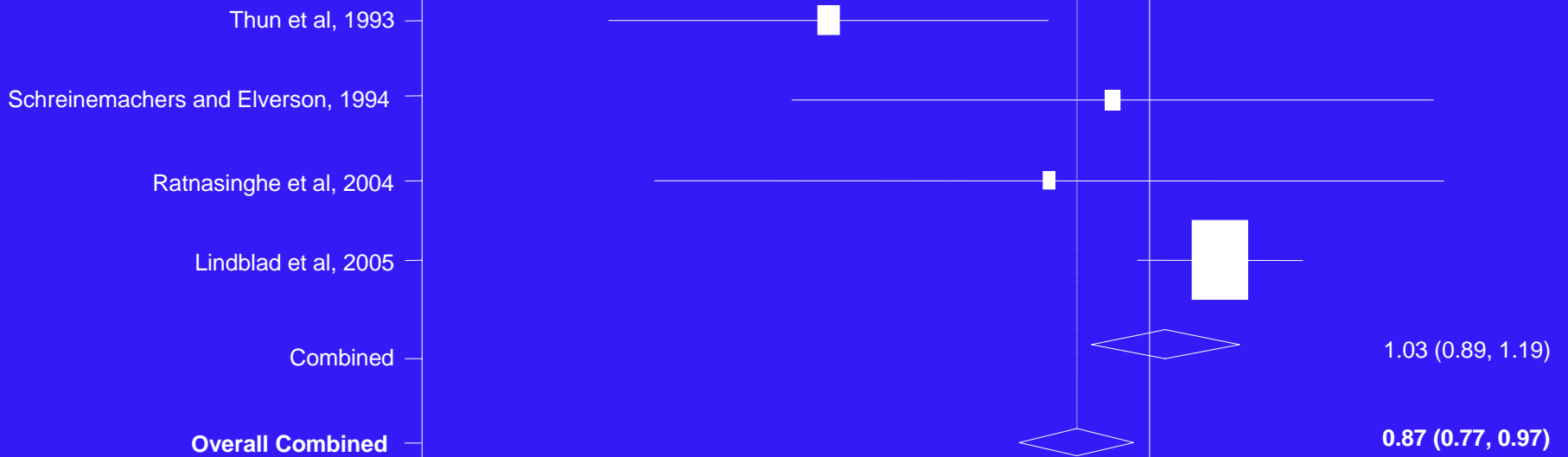


NSAIDs - Stomach cancer

Case-control studies



Cohort studies



Overall Combined

0.87 (0.77, 0.97)

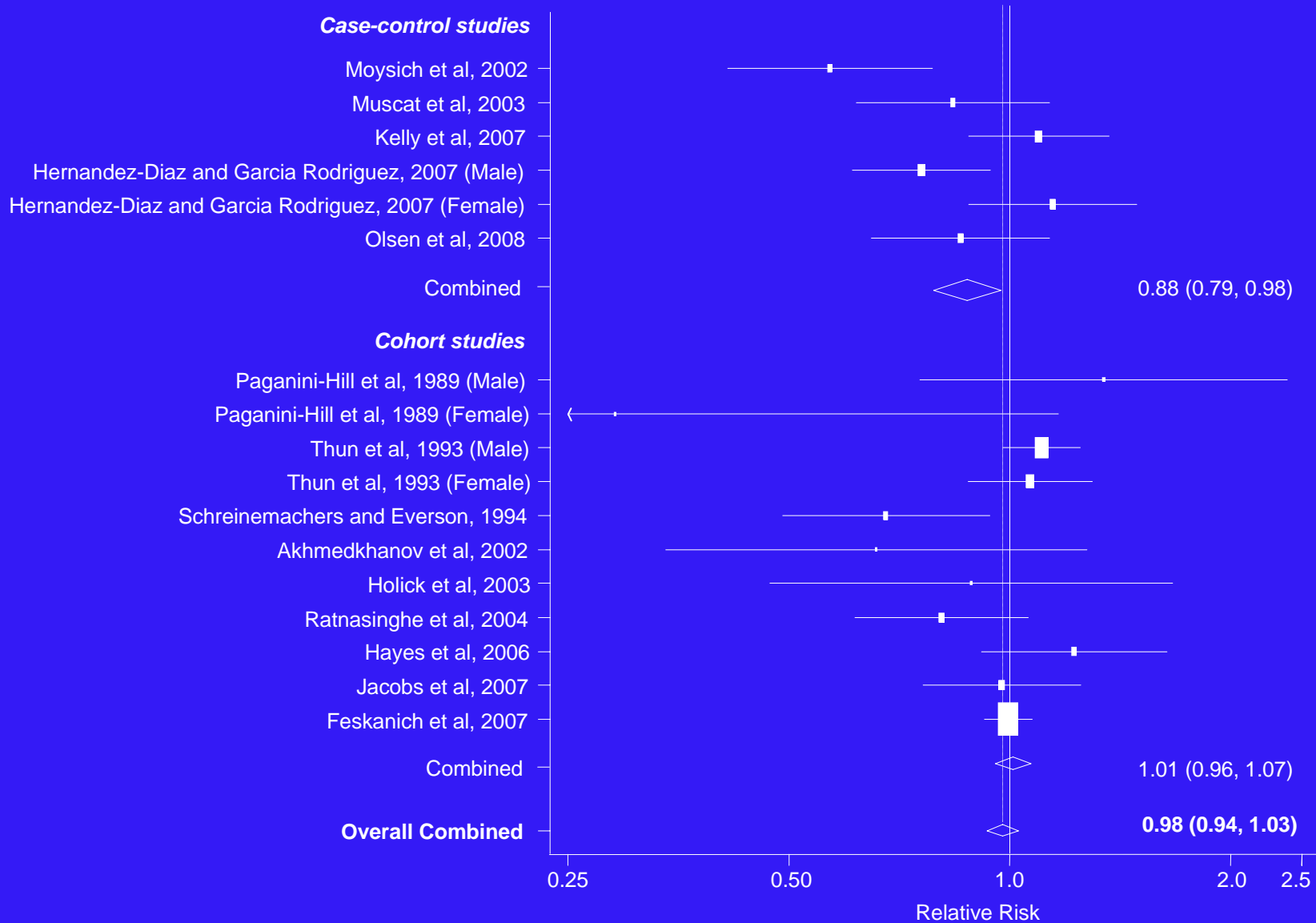
Bosetti et al 2009

Relative Risk

Estimated benefits of long-term (about 20 years) aspirin use in general population – Lung cancer

	Number of studies	Number of cases	Relative Risk (95% CI)	Risk (%) to age 74 (general population)	Estimated absolute benefit to age 74 (per 1000)
Lung					
Case-control	5	8782	0.88 (0.79-0.98)
Male		6.69	8.0
Female		5.89	7.1
Male, current smoker		15.9	19.1
Lifelong non-smoker		0.4	0.5
Cohort	9	4672	1.01 (0.96-1.07)

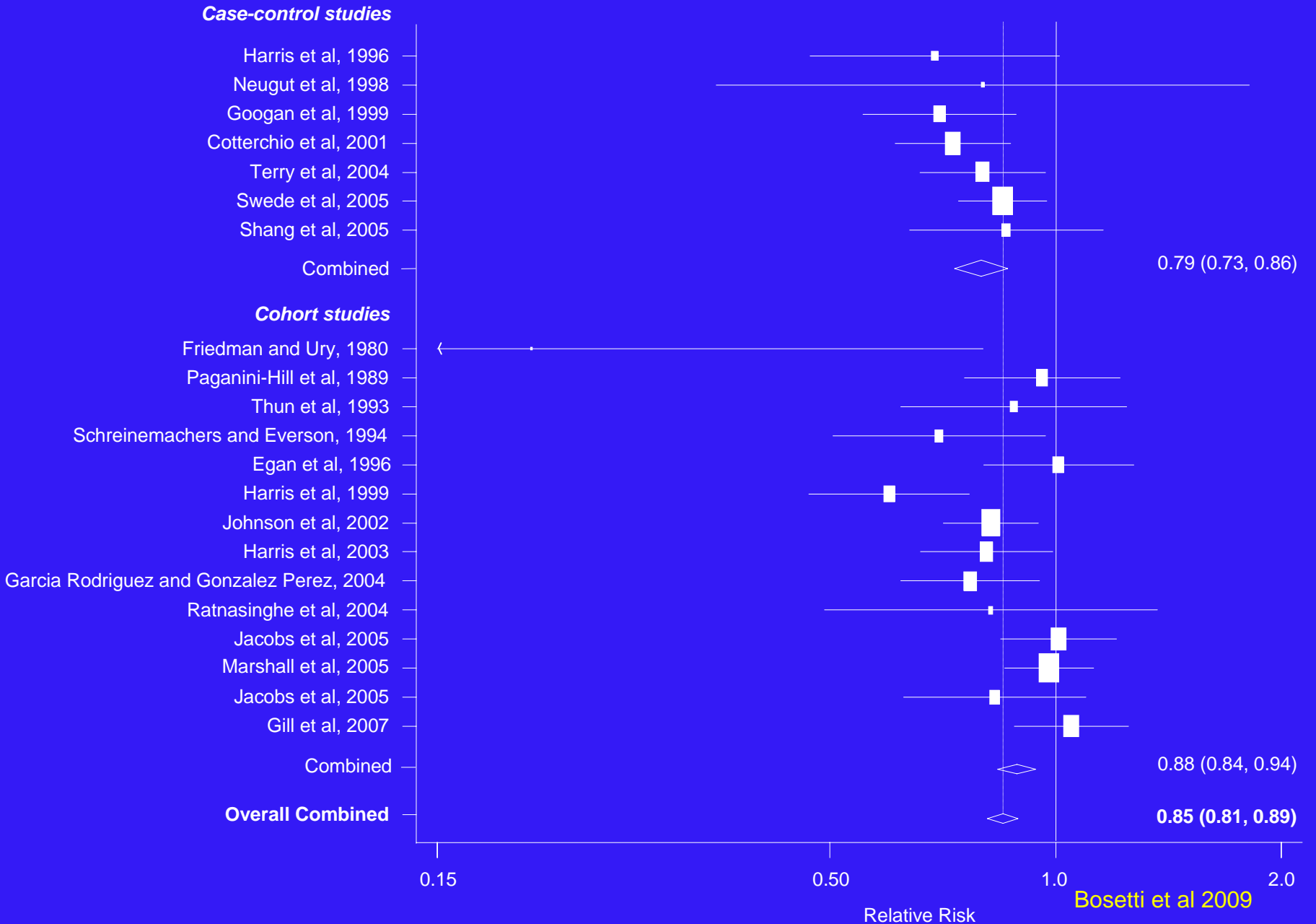
NSAIDs – Lung cancer



Estimated benefits of long-term (about 20 years) aspirin use in general population – Breast & Ovary

	Number of studies	Number of cases	Relative Risk (95% CI)	Risk (%) to age 74 (general population)	Estimated absolute benefit to age 74 (per 1000)
Breast					
Case-control	7	20380	0.79 (0.73-0.86)
Female		9.46	19.9
Cohort	14	19634	0.88 (0.84-0.94)
Ovary					
Case-control	7	3482	0.78 (0.68-0.91)
Female	1.46	3.2
Cohort	2	449	0.98 (0.80-1.20)

NSAIDs - Breast Cancer



Breast Cancer and Use of Nonsteroidal Anti-inflammatory Drugs: A Meta-analysis

Bahi Takkouche , Carlos Regueira-Méndez , Mahyar Etminan

J Natl Cancer Inst 2008;100: 1439 – 1447

Background Breast cancer is one of the leading causes of mortality among women. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with reduced risk for breast cancer, but results from these studies of the association have been inconsistent.

Methods Studies that examined the association between risk of breast cancer and use of NSAIDs, including aspirin and ibuprofen, that were published between January 1, 1966, and July 1, 2008, were identified using Medline, EMBASE, and other databases. We performed meta-analysis by pooling studies according to the inverse of their variances and performed separate analyses of studies pooled according to aspirin use and ibuprofen use. We evaluated publication bias and study quality.

Results A total of 38 studies (16 case – control studies, 18 cohort studies, 3 case – control studies nested in welldefined cohorts, and 1 clinical trial) that included 2 788 715 subjects were identified. The results of these studies suggest that overall, NSAID use was associated with reduced risk for breast cancer (relative risk [RR] = 0.88, 95% confidence interval [CI] = 0.84 to 0.93). Specific analyses for aspirin (RR = 0.87, 95% CI = 0.82 to 0.92) and ibuprofen (RR = 0.79, 95% CI = 0.64 to 0.97) yielded similar results.

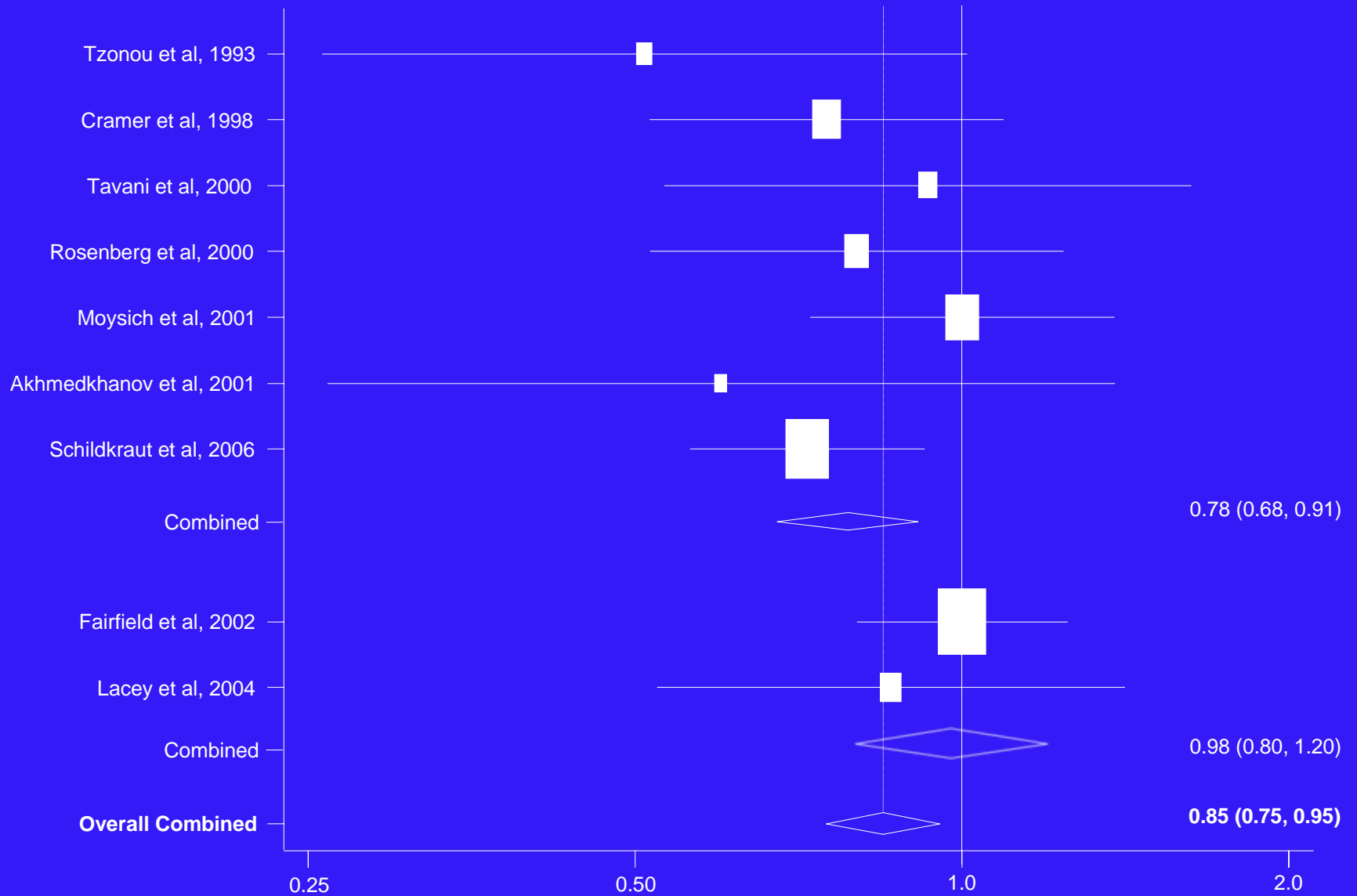
Conclusions This meta-analysis provides evidence that NSAID use is associated with reduced risk for breast cancer. Future research should include careful evaluation of the biologic mechanisms involved in the relationship between NSAIDs and breast cancer.

Nurses Health Study Relative Risk of Breast Cancer Recurrence, According to Aspirin Intake

Model	All Women	Aspirin Intake					P (linear trend)*
		None	Past	Current, 1 Day a Week	Current, 2 to 5 Days a Week	Current, 6 to 7 Days a Week	
Person-years†	44,177	5,521	16,963	4,814	4,847	11,240	
Recurrences†	400	65	191	53	21	67	
Simple model							.0002
Relative risk		1.00	0.89	1.00	0.35	0.44	
95% CI			0.67 to 1.19	0.69 to 1.44	0.21 to 0.58	0.31 to 0.63	
Multivariate model							.03
Relative risk		1.00	1.03	0.91	0.40	0.57	
95% CI			0.76 to 1.39	0.62 to 1.33	0.24 to 0.65	0.39 to 0.82	

Holmes, et al, JCO, 2010

NSAIDs - Ovarian cancer



Conclusions

- Aspirin and other NSAIDs have shown beneficial effects on colorectal, stomach, oesophageal, breast and ovarian cancers in epidemiologic studies and clinical trials for colorectal cancer
- Clinical trials suggest long term follow up and (use??) (>10 yrs) may be necessary to achieve a benefit, suggesting an effect only on the earlier stages of carcinogenesis
- Further evaluation of these agents in prevention trials raises major logistic problems and further follow up of current trials should be a priority
- The minimum effective dose for an anti-cancer effect is not known