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Special Session:
Reducing Incidence + Mortality of Major Cancers

Reducing the Incidence and Mortality of Colorectal Cancer: Ready for General Use?

Prof. Dr. med. Hans-Jörg Senn and Prof. Dr. med. Florian Otto
Tumor- and Breast Center ZeTuP + St.Gallen Oncology Conferences
CH-9006 St.Gallen / Switzerland

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The Epidemiology of Colorectal Cancers, 2012 I

- Colo-Rectal Cancer (CRC) is a major health concern with >1‘000‘000 new cases annually and some 500‘000 annual death expected worldwide in 2012.
- Around 230‘000 new cases and >110‘000 deaths from CRC are expected across Europe during 2012 !
- Mortality rates from CRC have been decreasing slowly in both, men and women, over the past decades, which reflects declining incidence rates and also improvement of early detection and (adjuvant) treatment (Cancer Facts and Figures, USA, 2011).
- Nervertheless, CRC incidence and death rates remain unacceptably high, calling for further improvements!

The Epidemiology of Colorectal Cancers, 2012 II

- Colo-Rectal Cancer (CRC) has a natural history from pre-malignant precursors to malignancy that spans, on average, 15-20 years, thus:
- Providing a favorable and long „window of opportunity“ for effective preventive interventions.
- CRC clearly meets the criteria of a neoplastic disease, suitable for chemopreventive interventions:
- It emerges slowly over time, it is highly prevalent and it is associated with considerable morbidity and mortality!
- In addition, CRC is a suitable target for several classes of chemopreventive drugs, that prevent or delay the evolution from adenomas to adeno-carcinomas.

What is „Chemoprevention“? How defining it?

- Chemoprevention is the use of synthetic or natural agents to suppress, reverse or prevent the carcinogenic process from progressing to invasive cancer (N. Arber, 2007).
- **Chemoprevention, however, has many faces:**
- Adding an artifical (usually chemical) compound/drug
- Adding „natural“, ev. dietary compounds, in more than normal quantity (not so easy to implement and control….!)
- Eliminating unnecessary/noxious (dietary) compounds
- Eliminate toxic compounds (diet, air pollution, working place etc. >>> needs political action)
- Any combination of these

Basket of Chemopreventive Drugs Against CRC

These agents can be broadly classified in 4 categories:

1. Anti-Inflammatory Drugs:

   Aspirin, NSAID‘s, COX-2-Inhibitors

2. Signal-Transduction-Modulators (Research!):

   EGF, IGF-Receptor- and VEGF-Inhibitors, etc.

3. Epigenetic Modulators (Research):

   Estrogen-Receptor and Histone Deacetylase Inhib., Rosiglitazone, etc.

4. Many other agents such as curcumin, selenium, calcium, fibers, statins, etc. (no or minor effects).

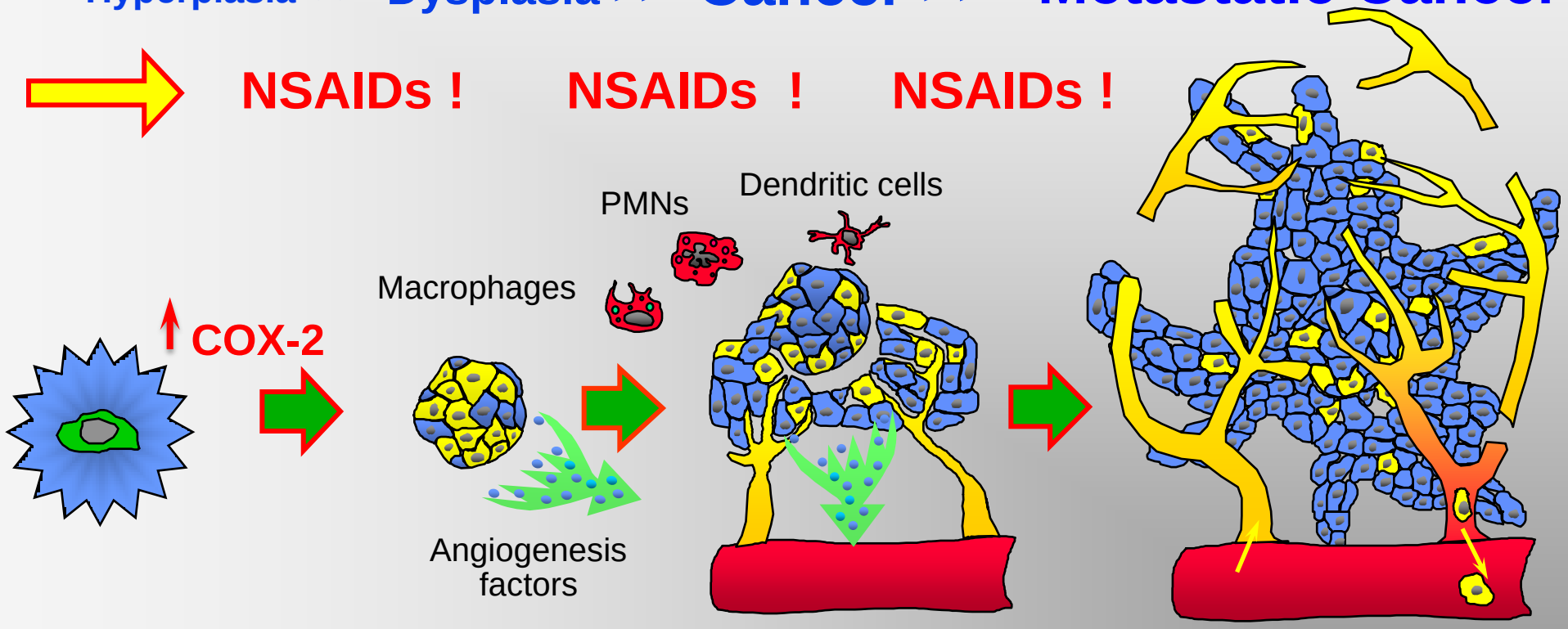
The Most Promising Chemopreventive Drugs Against CRC

- The hitherto most promising chemopreventive drugs against CRC are Aspirin and NSAID‘s (Baron 2004, Arber 2008/10, Meyskens 2008, Cuzick 2009, Roswell 2010).
- Extensive epidemiological observations and preclinical studies revealed, that inhibition of CRC-carcinogenesis by NSAID‘s is mediated via modulation of prostaglandin-production by the rate-limiting COX-enzymes.
- NSAID‘s reduce the risk of CRC through a mechanism of inhibiting COX-2, frequently over-expressed in premalig-nant colonic adenomas and in CRC (Levine 2009).
- Preventive effect of NSAID‘s against CRC is supported by >200 animal + many human trials (Arber 2010).

COX-2 and NSAIDs: Involved in All Stages of CRC-Carcinogenesis

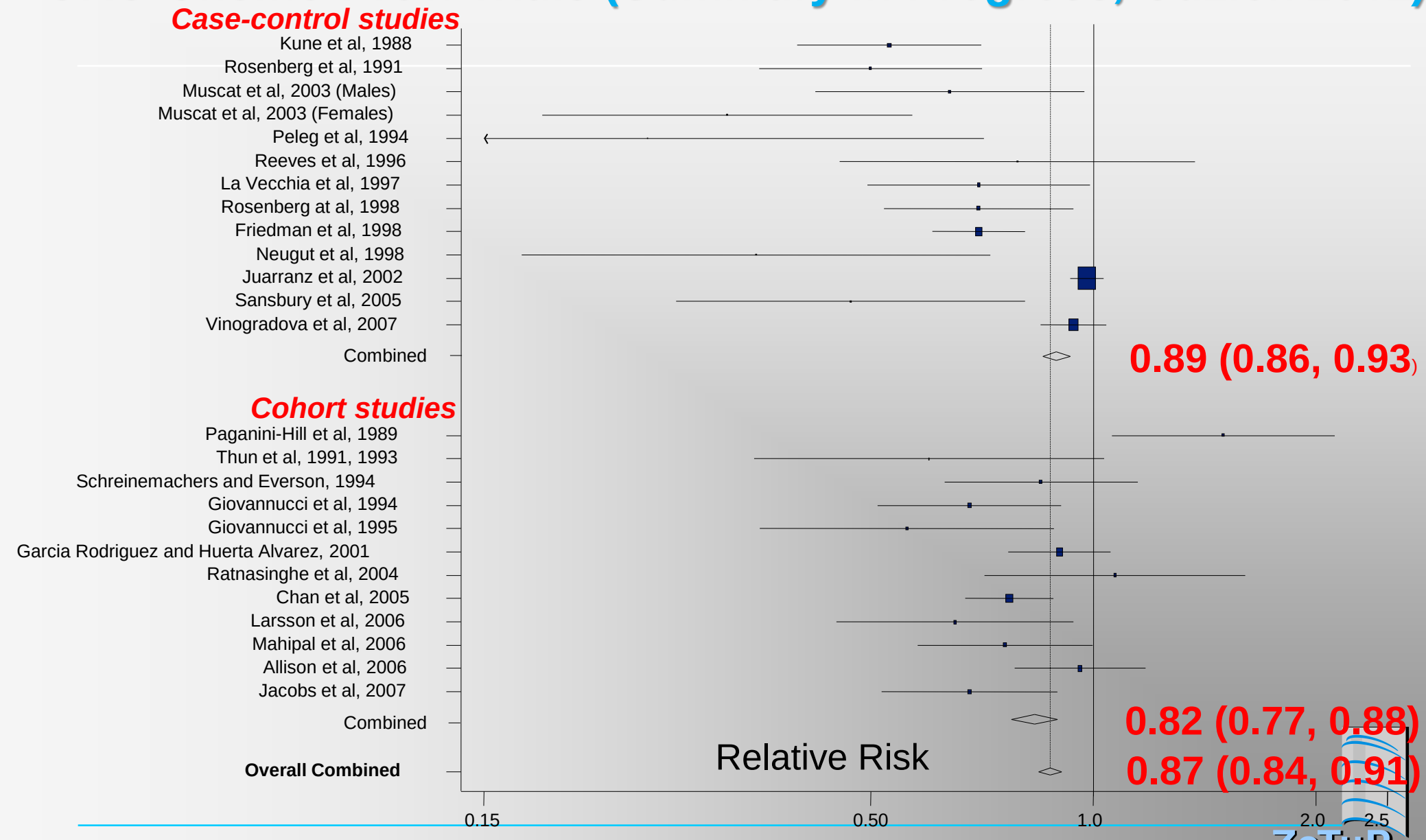
Hyperplasia >> Dysplasia >> Cancer >> Metastatic Cancer

NSAIDs ! NSAIDs ! NSAIDs !

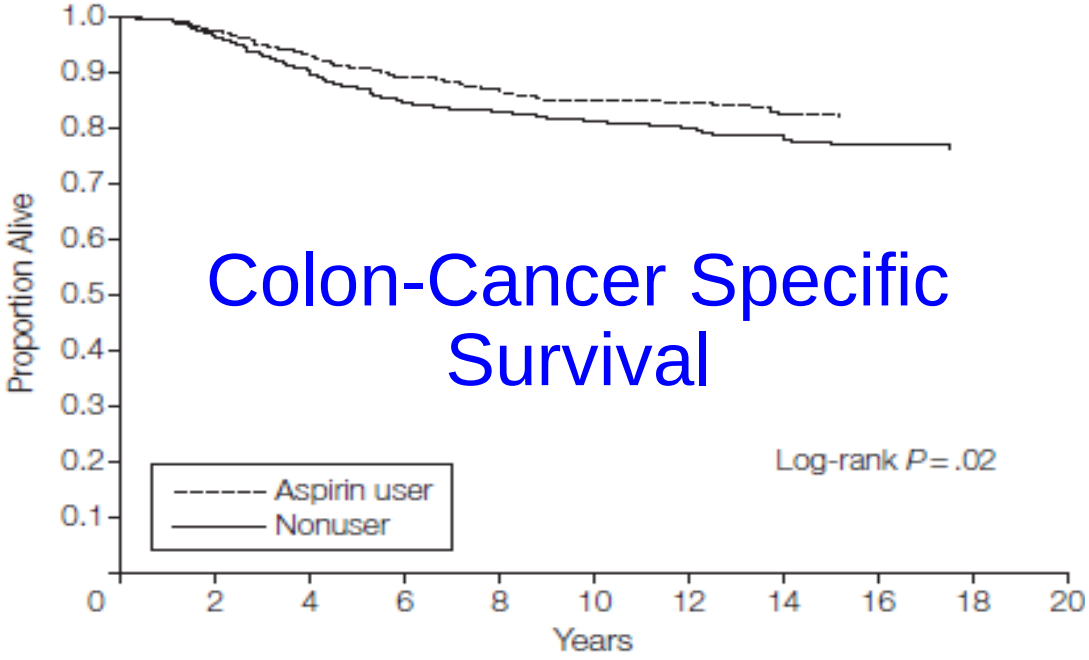


(Adapted from N. Arber, Internat. GI-Cancer-Conf. Barcelona, 2012)

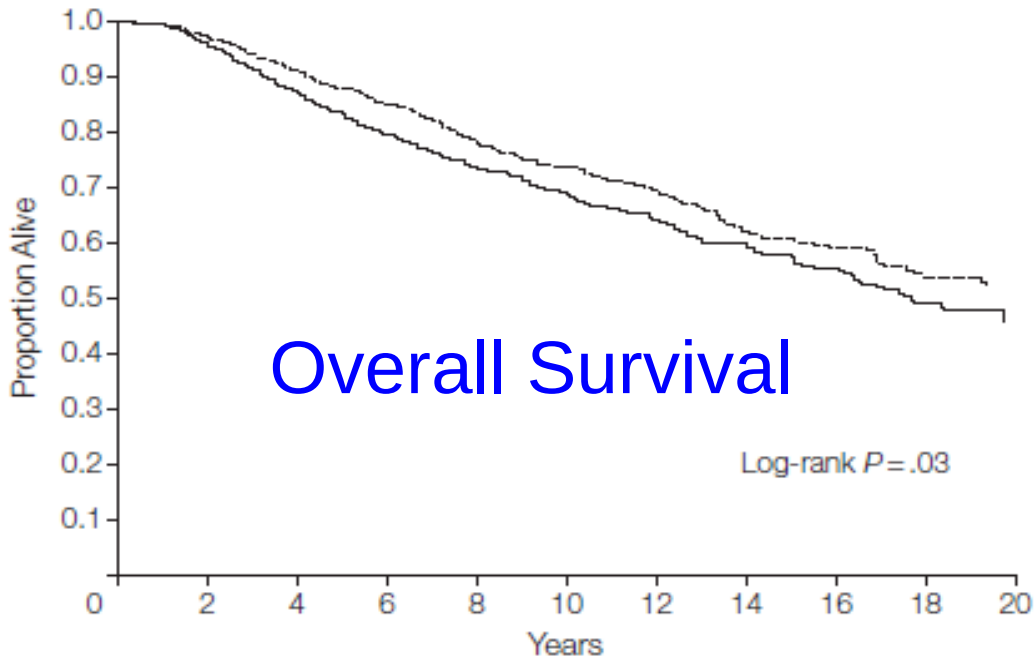
CRC-Chemo-Prev. Trials (Summary in Progress, Cuzick 2012)



Aspirin Significantly Reduces Mortality of CRC (Cohort-Trial, Chan AT et al)



Colon-Cancer Specific Survival



Overall Survival

Nonuser	730	600	541	341	199	75
Aspirin User	549	534	437	274	158	81

730	600	541	341	199	75
549	534	437	274	158	81

- CRC-specific mortality risk reduced by 29%
  - HR= 0.71 (0.53-0.95)
- Overall mortality risk reduced by 21%
  - HR= 0.79 (0.65-0.97)

From Chan AT, et al. JAMA. 2009;302(6):649
(Cohort-Trial)

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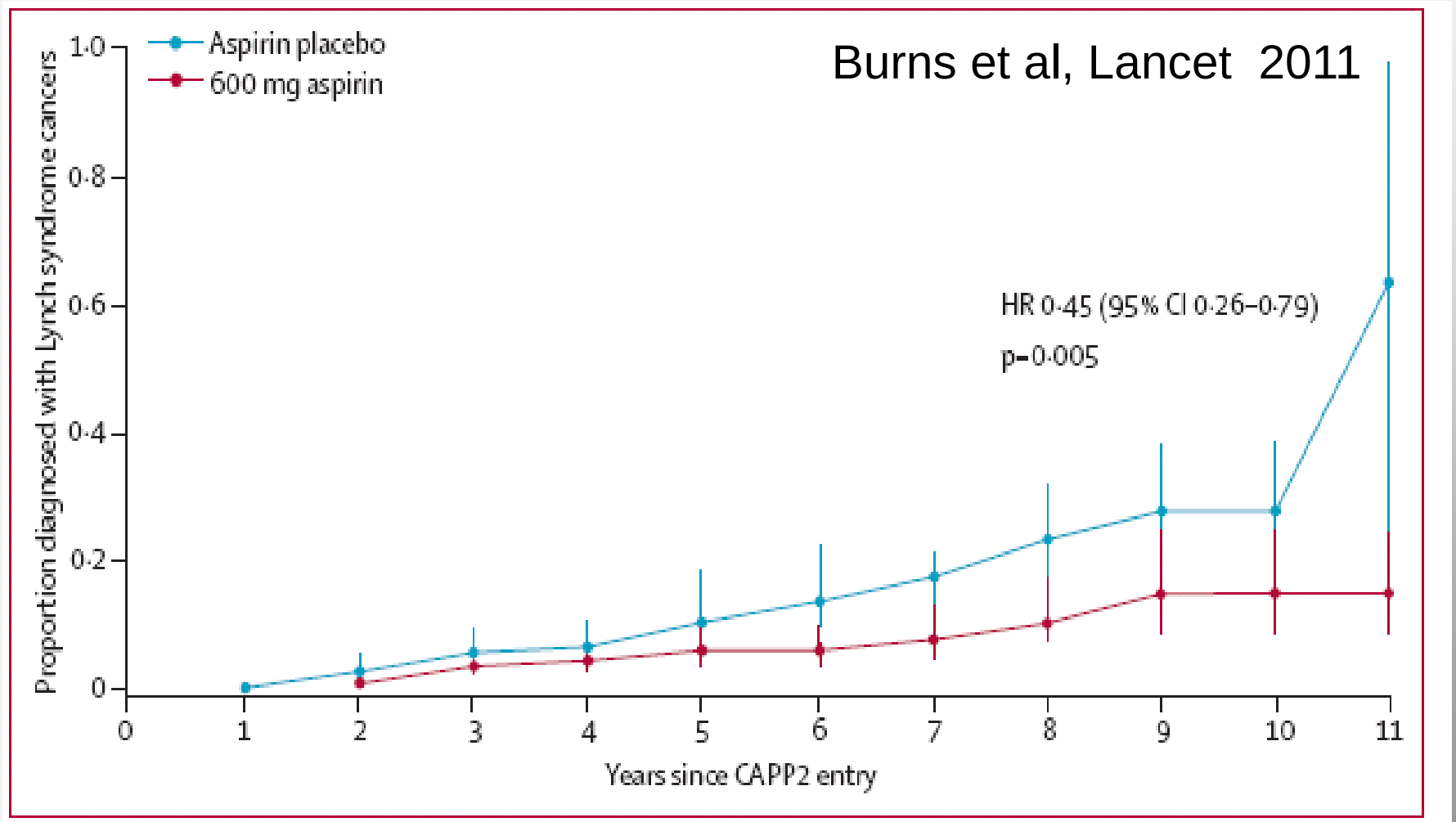
„Contradictory“ Results in Chemoprevention-Trials against CRC with ASA (esp., if analysed too early)

- Cancer Prevention Study II (Jacobs 2007):
  69‘810 males and 76‘303 females, with Aspirin 325 mg/T),
  signific. lower incidence of CRC, already after 5 y. MFU
- Physicans‘ Health Study (Gann et al, 1993 and later):
  >22‘000 M.D.‘s USA. No effect after 5 y., but later at 10y.+!
- British Doctors Aspirin Trial (Flossman 2007):
  No decrease in CRC for ASA for at least 5 y., but later ++
- Women‘s Health Study (Cook et al, 2005):
  >100‘000 females: No effect of ASA at 10 y. of MFU
- Cuzik et al: ASA in Cancer Prevention (Lancet-O, 2011):
  Consensus: Evidence clearly shows a chemopreventive effect of Aspirin and other NSAID‘s on CRC….

CAPP2 trial: Time to First CRC in Lynch Syndrome Patients with > 2yrs ASA treatment (N = 508)



Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial.

METHODS: In the CAPP2 randomised trial, carriers of Lynch syndrome were randomly assigned in a two-by-two factorial design to 600 mg aspirin or aspirin placebo or 30 g resistant starch or starch placebo, for up to 4 years. Randomisation was in blocks of 16 with provision for optional single-agent randomisation and extended postintervention double-blind follow-up; participants and investigators were masked to treatment allocation. The primary endpoint was development of colorectal cancer. Analysis was by intention to treat and per protocol.

RESULTS: 861 participants were randomly assigned to aspirin or aspirin placebo. At a mean follow-up of 55·7 months, 48 participants had developed 53 primary colorectal cancers (18 of 427 randomly assigned to aspirin, 30 of 434 to aspirin placebo). Intention-to-treat analysis of time to first colorectal cancer showed a hazard ratio (HR) of 0·63 (95% CI 0·35-1·13, p=0·12). Poisson regression taking account of multiple primary events gave an incidence rate ratio (IRR) of 0·56 (95% CI 0·32-0·99, p=0·05). For participants completing 2 years of intervention (258 aspirin, 250 aspirin placebo), per-protocol analysis yielded an HR of 0·41 (0·19-0·86, p=0·02) and an IRR of 0·37 (0·18-0·78, p=0·008). No data for adverse events were available post intervention; during the intervention, adverse events did not differ between aspirin and placebo groups.

INTERPRETATION: 600 mg aspirin per day for a mean of 25 months substantially reduced cancer incidence in a randomised trial, after 56 months MFU, in carriers of hereditary colorectal cancer (Lynch-Syndrome). Further studies are needed to establish the optimum dose and duration of aspirin treatment.

Lancet. Oct 27, 2011 (Burns, et al, UK)

Toxicity of Chemopreventive Drugs against CRC: Problems with NSAID's and Aspirin

- Gastrointestinal (GI) toxicity constitutes the clinically most relevant problem, inducing siginifcant morbidity and even (very) low mortality in treated risk populations, esp. elderly males!
- These GI-toxicities include: Upper GI adverse events, esp. stomac ulcerations, bleeding, perforation, obstruction and hepatic injury (usually reversible and dose-dependent).
- These GI-events are mostly attributable to COX-inhibition, resulting in reduced prostaglandin-levels in gastric mucosa, and topical irritant effects (Akara 1005, Arber 2009).
- Selective COX-2-inhibitors were claimed to be devoid of these side-effects (Wallace + Vrong 2008), but these claims have not been fulfilled, and in addition – they were later even accused to induce increased cardiovascular toxicity!

CRC-Chemoprevention with COX-2-Inhibitors: Potential, Problems and Tragedy

- Thus - although selective COX-2-inhibitors would have been ideal candidates for CRC-chemoprevention, they fell in „disgrace“ due to their increased cardio-vascular toxicity (as compared to ASA) in 2005 the USA:
- Three large, international, multicenter, placebo-controlled trials (NCI-APC Adenoma Prevention with Celexocib-trial; Pre-Scap-trial by Pfizer and APPROVe Rofecoxib-trial by Merck) were all terminated prematurely due to substantial concerns about „cardio-vascular safety“.
- Celexocib at least remained in clinic as a preferential CRC-preventive drug in patients with FAP (usually young patients without CVD and other comorbidities).

CRC-Chemoprevention with Combination Therapy?

- Although several single agents (ASA, COX-2) have some benefit in CRC-chemoprevention, their effect is modest and/or include a significant toxicity profile (Arber 2009).
- Combining low(er) doses of different preventive agents might therefore be more effective and less toxic (?).
- Such strategies are presently explored in suitable animal cancer chemoprevention models – and seem to prove increasingly effective (Reddy 2006, Arber et al 2009).
- Combination chemoprevention with DMFO and NSAIDs (esp. low doses of celecoxib or sulindac) look particularly effective for CRC prevention (Bertagnoli 2008, Mesykens 2010) > additional trials in progress!

Sulindac+DMFO-Chemopreventive Trial of Sporadic Colo-Rectal Adenomas (NCI-USA)

- Randomised, placebo-controlled, double-blind trial
- In 375 high-risk-patients with a history of 3 or more resected colo-rectal adenomas!
- The trial-pts. were stratified for low-dose Aspirin (81 mg) at baseline and for clinical site.
- Pts. were then randomized between DMFO (500mg/d) + Sulindac (150mg/d) and Placebo daily during 3 years.
- Outcome: Low dose DFMO + Sulindac po markedly reduced the recurrence of new colo-rectal adenomas in high-risk subjects as compared to Placebo (41% vs. 11%) without a significant increase in adverse events!

Monica Bertagnoli et al, Cancer Prev Res 1:32-38, 2008

Personalized Cancer Chemoprevention of CRC with ASA and NSAID's?

- Whenever possible, medical treatments today should be „personalized": Specific therapies should ideally be based on metabolic characteristics of an individual and / or the molecular profile of the target-cancer lesion!
- COX-2-inhibitors seem to preferentially work in or against tumors, which heavily over-express COX-2, but this is not yet fully elaborated, adequately proven and generally accepted (Arber et al, 2008).
- The preventive effect of ASA also seems to work better in individuals, whose colo-rectal adenomas express high levels of COX-2, and less in those devoid of COX-2 (Chan 2007). These correlations need more confirmation!

Development of a Risk Score for Colorectal Cancer in Men

Jane A. Driver, MD, MPH,[a] J. Michael Gaziano MD, MPH,[a,b,e] Rebecca P. Gelber, MD, MPH,[e] I-Min Lee, MBBS, ScD,[b,c]
Julie E. Buring, ScD,[a,b,c,d] Tobias Kurth, MD, ScD[a,b,c] Am J Med, 2007

Simple scoring system for CRC in cohort of >21.000 men (non FAP)

Predictor	Odds ratio (95%CI)	Prediction Score Points
Age (years)		
50-59	2.25 (1.72-2.95)	2
60-69	4.40 (3.36-5.77)	4
>70	6.25 (4.55-8.60)	6
Smoking history (Yes)	1.42 (1.17-1.72)	1
Body mass Index		
25-29.9 kg/m^2	1.26 (1.05-1.52)	1
>30 kg/m^2	1.62 (1.09-2.42)	2
Alcohol use (>once/week)	1.36 (1.08-1.71)	1

Danger: Highest Group (8-10 Points) = >15-fold CRC-Risk!

Aspirin and Cancer – Summary of Present Evidence Cuzik et al, Lancet Oncology 2012 (in press)

Cancer	Observational studies Effect ? RR (95%CI)		Trials Effect ? RR (95%CI)	Best Guess estimate	Cautious estimate	Summary
	Case-control	Cohort	RCT			
Colorectal Ca	**Yes** 0.63 (0.56-0.70)	**Yes** 0.84 (0.78-0.91)	**Yes** 0.93 (0.79-1.1)*	**25-30%**	**20%**	**Definite benefit**
Oesophag. Ca	Yes 0.49 (0.40-0.58)	Trend 0.85 (0.60-1.19)	Yes 0.42 (0.25-0.71)**	40-50%	30%	Definite benefit
Stomach Ca	Yes 0.60 (0.46-0.79)	Trend 0.82 (0.64-1.06)	Trend 0.69 (0.43-1.1)**	40-50%	30%	Highly likely
Pancreatic	No 0.97 (0.73-1.30)	No 0.97 (0.87-1.07)	No 0.81 (0.51-1.26)**	-	-	No effect, insufficient evidence
Lung	Yes 0.74 (0.56-0.97)	No 1.00 (0.94-1.06)	Equivocal† 0.78 (0.59-1.03)	10%	0%	Probable benefit
Prostate	Yes 0.88 (0.75-1.04)	Yes 0.94 (0.87-1.00)	Trend 0.81 (0.61-1.06)	10%	0%	Probable benefit
Breast	Yes 0.83 (0.77-0.91)	Yes 0.91 (0.85-0.98)	No 0.98 (0.87-1.09)	10%	0%	Probable benefit

CRC-Chemoprevention: Ready for General Use? Summary and Outlook for Aspirin and NSAIDs

- Moderately effective chemoprevention of CRC is possible with Aspirin and NSAID‘s. Risks + benefits have long been discussed. So – why not doing it, esp. in „higher-risk“ individuals?
- Certainly, questions still remain regarding ideal age, as well as dose and duration of the preventive application of Aspirin and NSAIDs, and further research will continue.
- An extensive review about „Long-term effects of Aspirin on CRC incidence and mortality“ by P. Rothwell in Lancet 2010 closes as follows, and i.m.o. deserves implementation:
- „Aspirin taken for several years at doses of 75-100 mg daily reduced long-term incidence + mortality due to CRC. Benefit was greatest for cancers in the proximal colon, where they cannot easily be otherwise prevented by screening“.

„Silvertower“ in St.Gallen: Home of Tumor- and Breast-Center ZeTuP and St.Gallen Oncology Conferences