

GUILD

Gastroenterology Updates • IBD • Liver Disease

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Chemoprevention for GI Cancers: Is there a Role?

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Disclosures

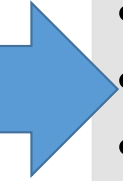
- Consultant for Freenome Inc and Iterative Scopes

Outline

- Principles of Chemoprevention
- Historical perspective
- Evidence review Supplemental agents for Cancer and CRC
- Best Practice Advice

Introduction

-Single cancer
-Too late or too difficult
- Diet vs. supplement



Approach
<ul style="list-style-type: none">• Anatomic• Public Health• Metabolic

Mechanism
<ul style="list-style-type: none">• Remove adenoma• Remove carcinogen• Chemoprevention

Examples
<ul style="list-style-type: none">• Colon adenomas• Smoking Cessation

Big Picture

WHAT:

- Safe
- Available
- Cheap



Who

- Average risk
- High Risk
- Prior Cancer

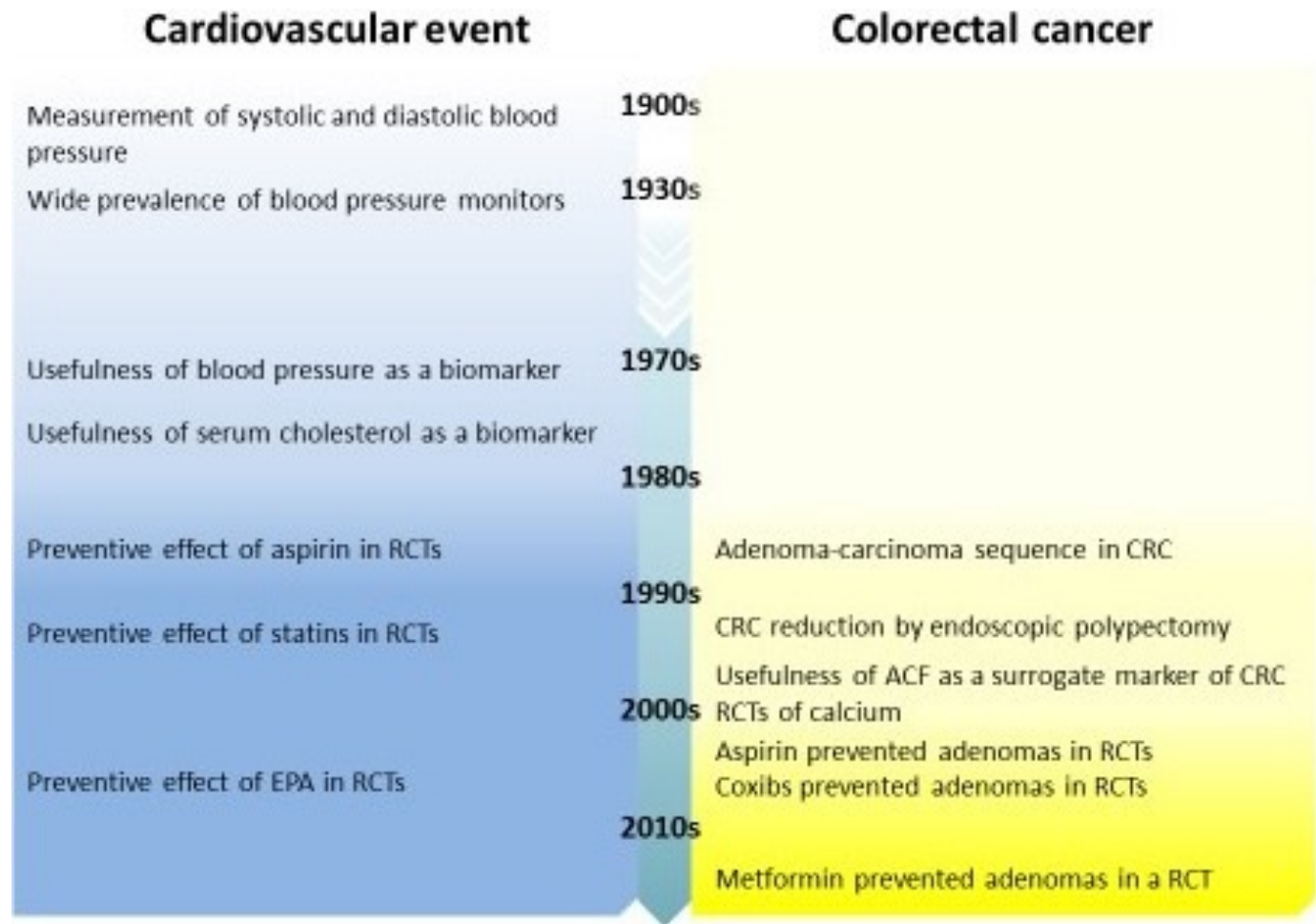
When

- Childhood
- Adult life
- Older age

How long

- Days
- Weeks
- Months
- Years
- Lifetime

Historical

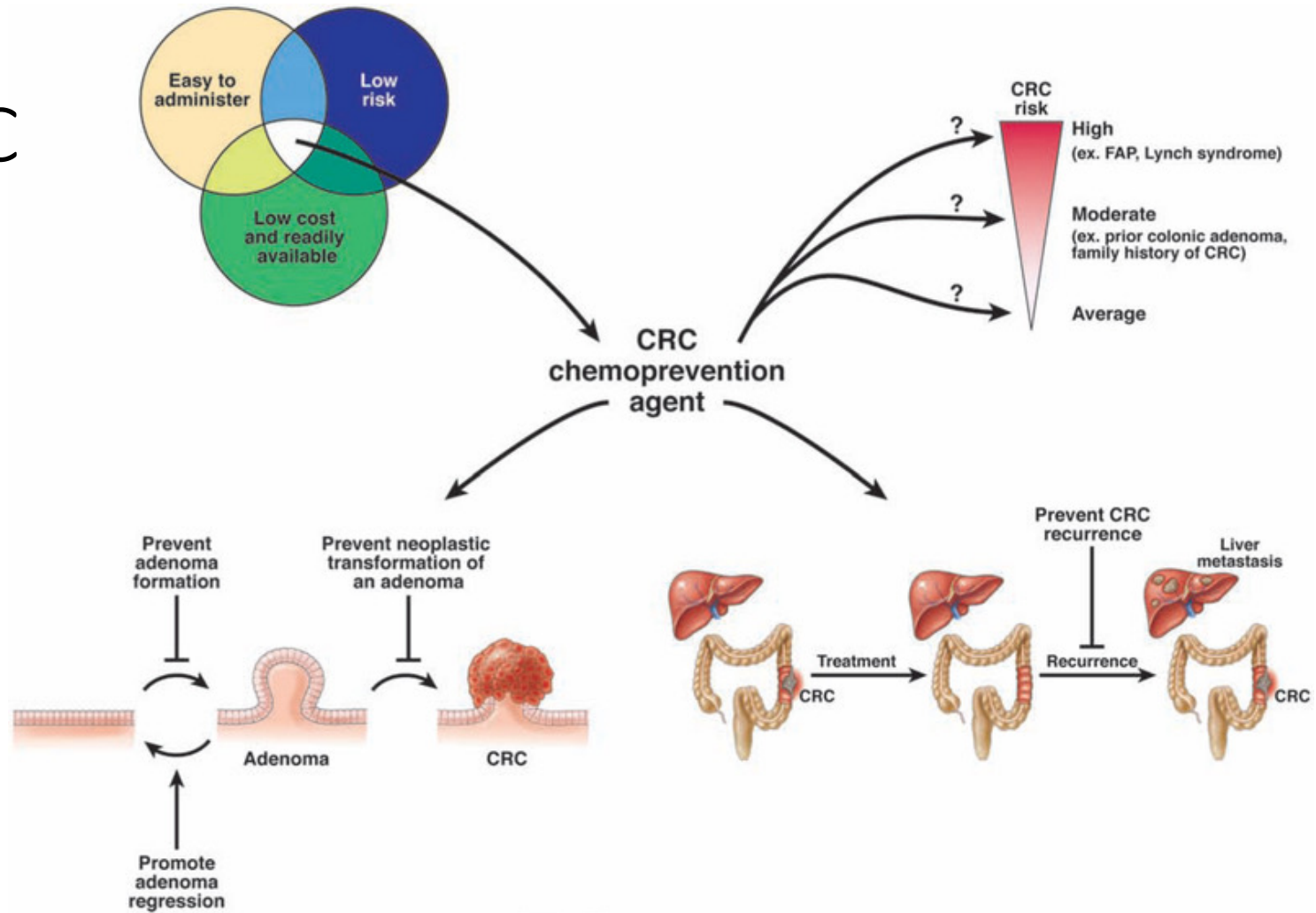


Umezawa S, Higurashi T, Komiya Y, et al. Chemoprevention of colorectal cancer: Past, present, and future. *Cancer Sci.* 2019;110(10):3018-3026.

Late 20th century Chemoprevention candidates

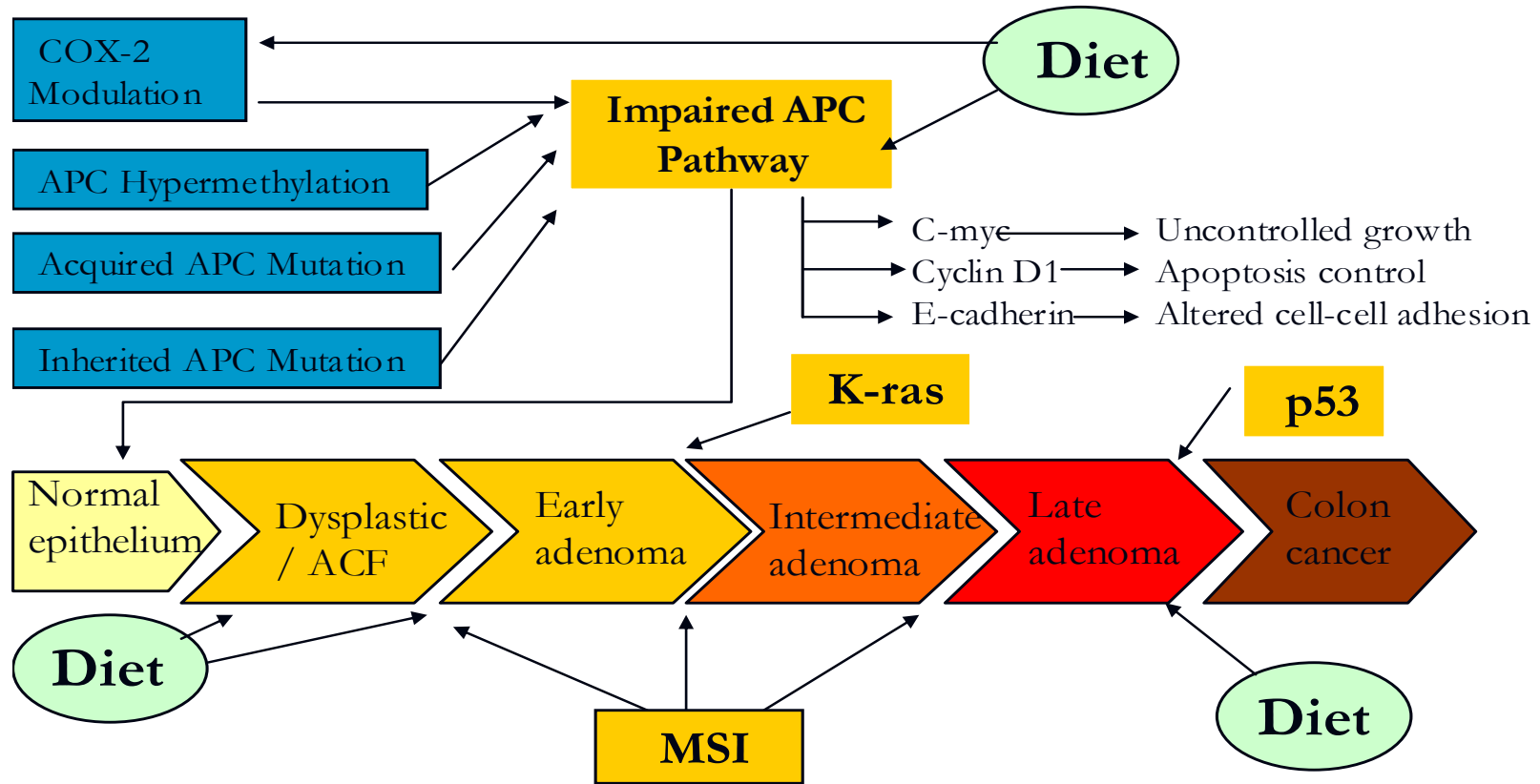
	CVD	Cancer
B-Carotene	Harmful	Harmful
Vitamin C and E	Didn't work	Didn't Work
Folic Acid	Didn't work	Didn't work
ASA	Beneficial	Beneficial

CRC



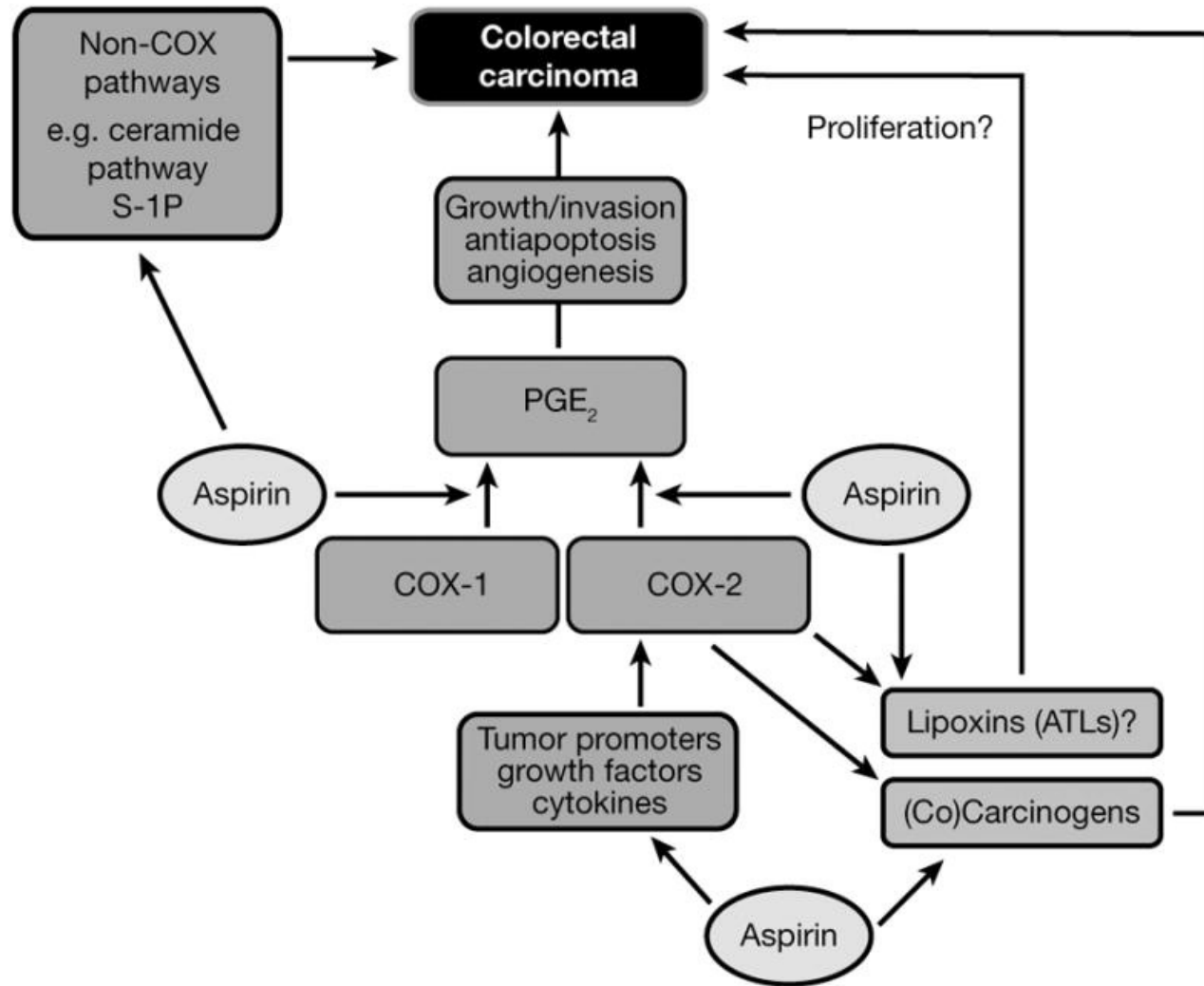
Katona BW, Weiss JM. Chemoprevention of Colorectal Cancer. *Gastroenterology*. 2020 ;158(2):368-388

Molecular Basis of Colon Carcinogenesis



Modified from Vogelstein B, Knizler KW. The multi-step nature of cancer. Trends Genet 1993; 9:138-141.

ASA



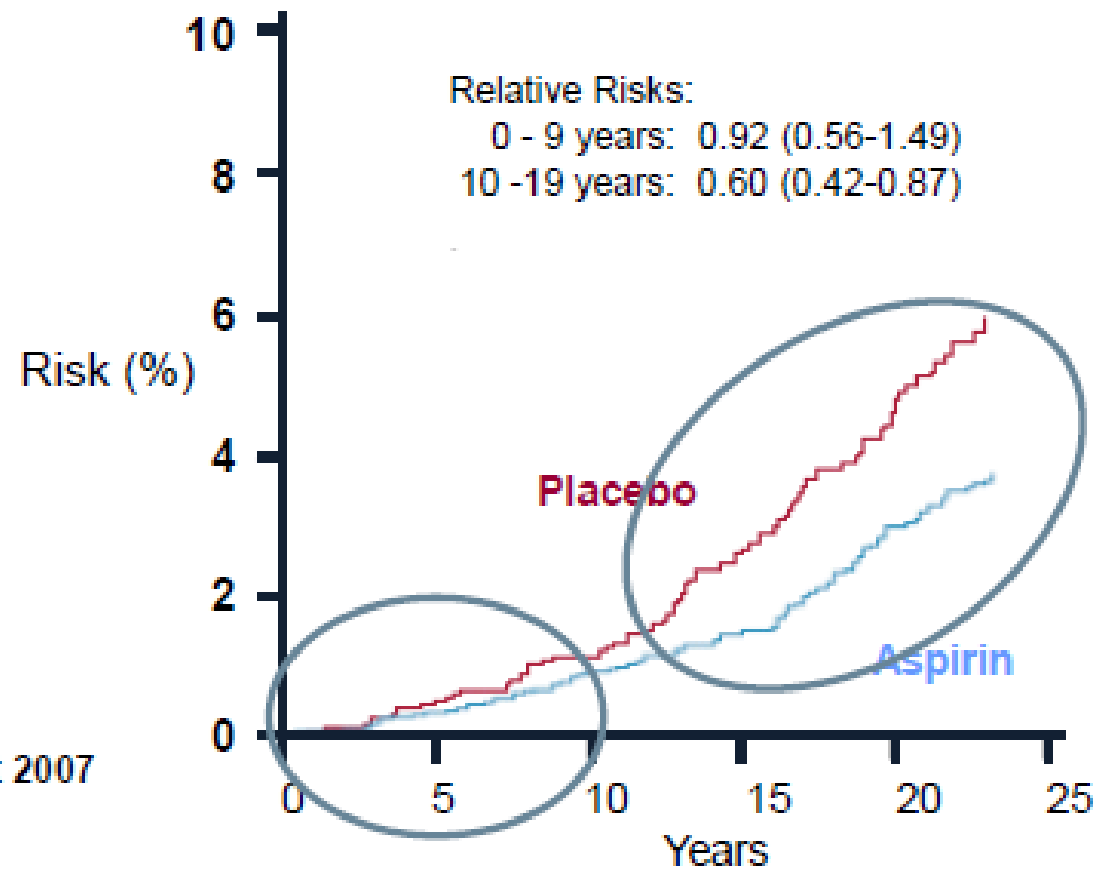
Aspirin for CRC

Pooled Analysis

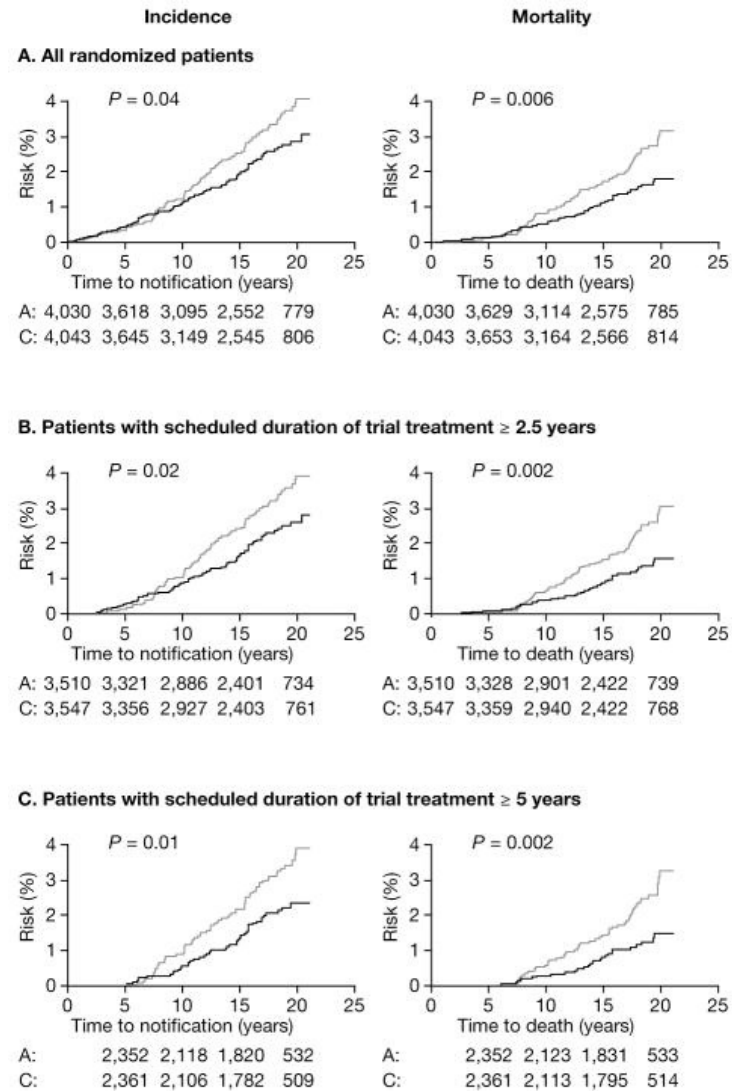
British Doctors:
500 mg qday
(5 years)

UK-TIA:
300 mg q day or
1200 mg q day
(1-7 years)

Flossmann et al, Lancet 2007



ASA and CRC Risk



Chan AT, et al. Aspirin in the chemoprevention of colorectal neoplasia: an overview. *Cancer Prev Res (Phila)*. 2012 Feb;5(2):164-78.

Risk Benefit Ratio

Hypothetical Example: Population of 100,000

*Risk=1.5 per 1000 cases/year**

*Colorectal cancer risk in
US males, aged 65-69 years

- Effective agent: ↓ 50% of CRC after 5 years
- Safe: annual risks of 0.01% stroke, 0.1% GI bleed
- Other benefit: prevents MI 0.1% per year
- Over 10 years:
 - 375 CRC
 - 1000 MI's
 - +100 strokes
 - +1000 GI bleeds
 - Net: ???

Off target effects matter

- Toxicity can negate an “effective” agent.
- Non-colorectal benefits may be needed for effectiveness

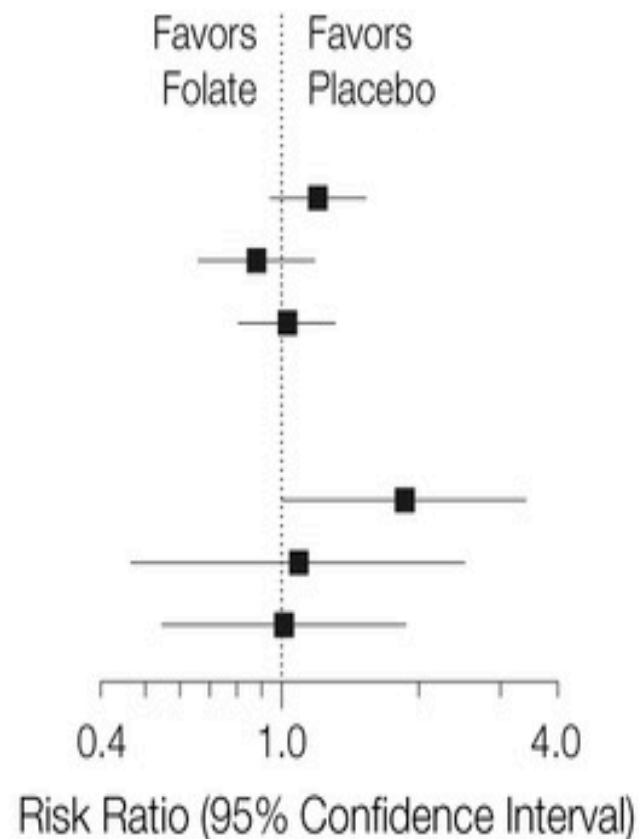
Population	Adults aged 50 to 59 y with a $\geq 10\%$ 10-y CVD risk	Adults aged 60 to 69 y with a $\geq 10\%$ 10-y CVD risk	Adults younger than 50 y	Adults aged 70 y or older
Recommendation	Initiate low-dose aspirin use. Grade: B	The decision to initiate low-dose aspirin use is an individual one. Grade: C	No recommendation. Grade: I (insufficient evidence)	No recommendation. Grade: I (insufficient evidence)

Population	Recommendation 2021	Grade
Adults ages 40 to 59 years with a 10% or greater 10-year cardiovascular disease (CVD) risk	Individualize decision	C
Adults age 60 years or older	The USPSTF recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults age 60 years or older.	D

ASA and Folic Acid for CRC Precursor lesions: RCT

- N=1409

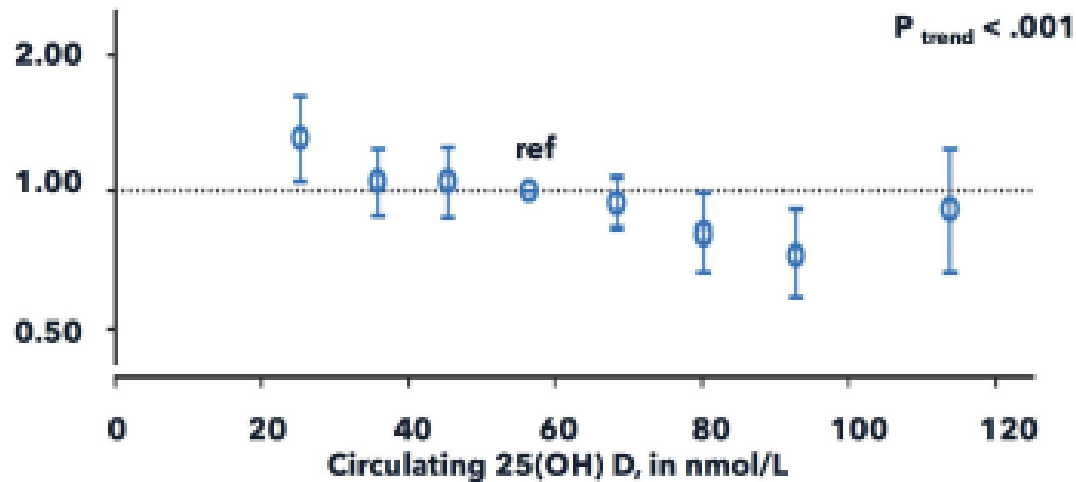
	Adenomas, No./Total No. (%) of Patients	
	Folate	Placebo
Any Adenoma		
Aspirin Placebo	87/168 (51.8)	70/162 (43.2)
Aspirin 81 mg/d	58/168 (34.5)	65/166 (39.2)
Aspirin 325 mg/d	76/165 (46.1)	71/158 (44.9)
Advanced Lesion		
Aspirin Placebo	27/168 (16.1)	14/162 (8.6)
Aspirin 81 mg/d	11/168 (6.5)	10/166 (6.0)
Aspirin 325 mg/d	19/165 (11.5)	18/158 (11.4)



Calcium and Vitamin D

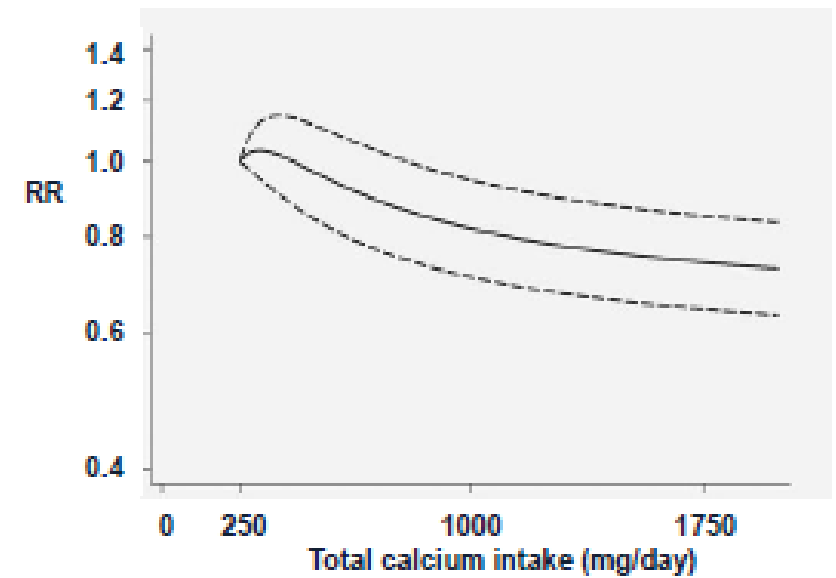
Vitamin D

Serum 25-(OH)D & Colorectal Cancer Risk



Calcium

Total Calcium Intake & Colorectal Cancer Risk



McCullough et al. JNCI 2019
Keum et al, Int J Cancer 2014

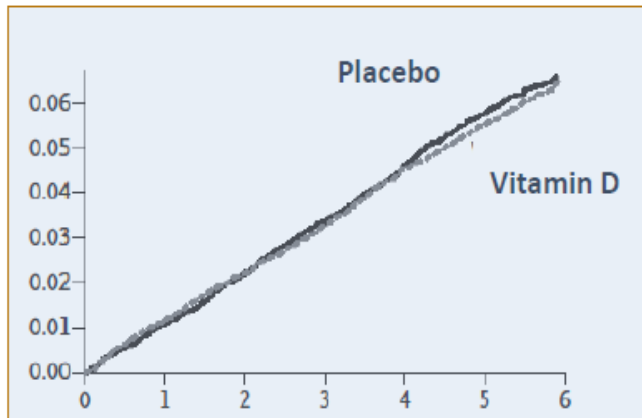
Supplemental Vitamin D and Calcium for Cancer and CRC

Vitamin D Trial (VITAL)

25871 subjects
2000 IU Vitamin D₃ vs placebo

All Cancer
HR=0.96 (0.88-1.06)

Colorectal Cancer
HR=1.09 (0.73-1.62)
(98 events)

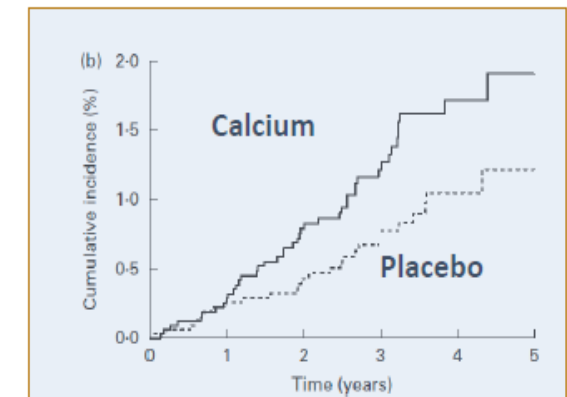
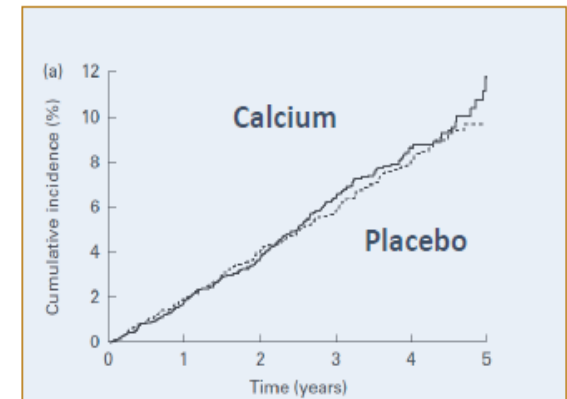


Calcium Trial Combined Analysis:

5 trials
7221 subjects
0.6 – 1.0 gm Ca⁺⁺

All Cancer
HR=1.07 (0.89, 1.28)
448 cases

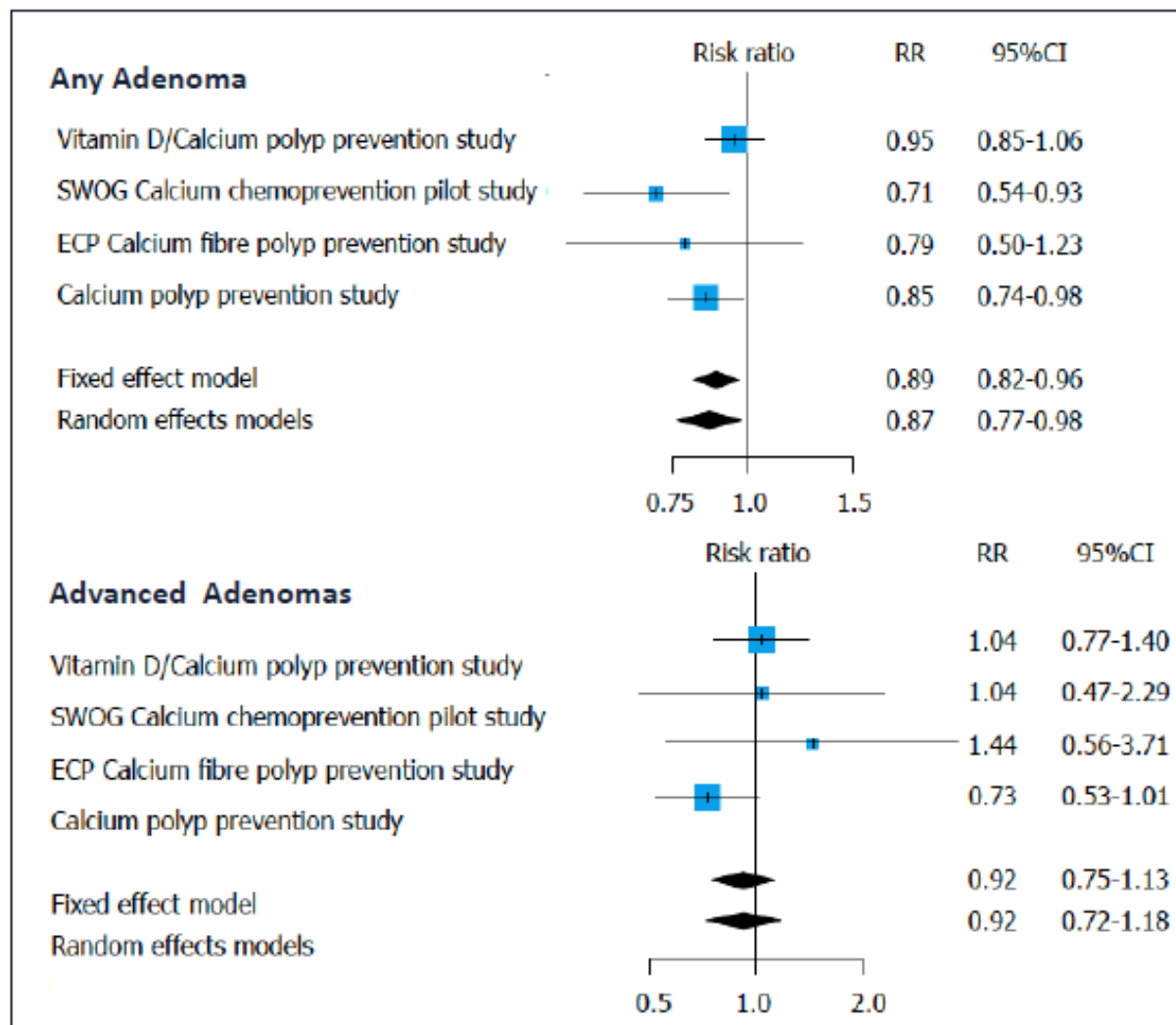
Colorectal Cancer
HR=1.63 (1.01, 2.64)
70 cases



Manson et al. NEJM 2019 3;380(1):33-44
Bristow et al Br J Nutr 2013;110(8):1384-93

Calcium
Supplementation for
Adenoma recurrence

Calcium



Shaukat A et al. AJG 2005;100(2):390-4.

Can Calcium Chemoprevention of Adenoma Recurrence Substitute for Colonoscopic Surveillance or Extend Surveillance Intervals?

Cost Effectiveness Analysis



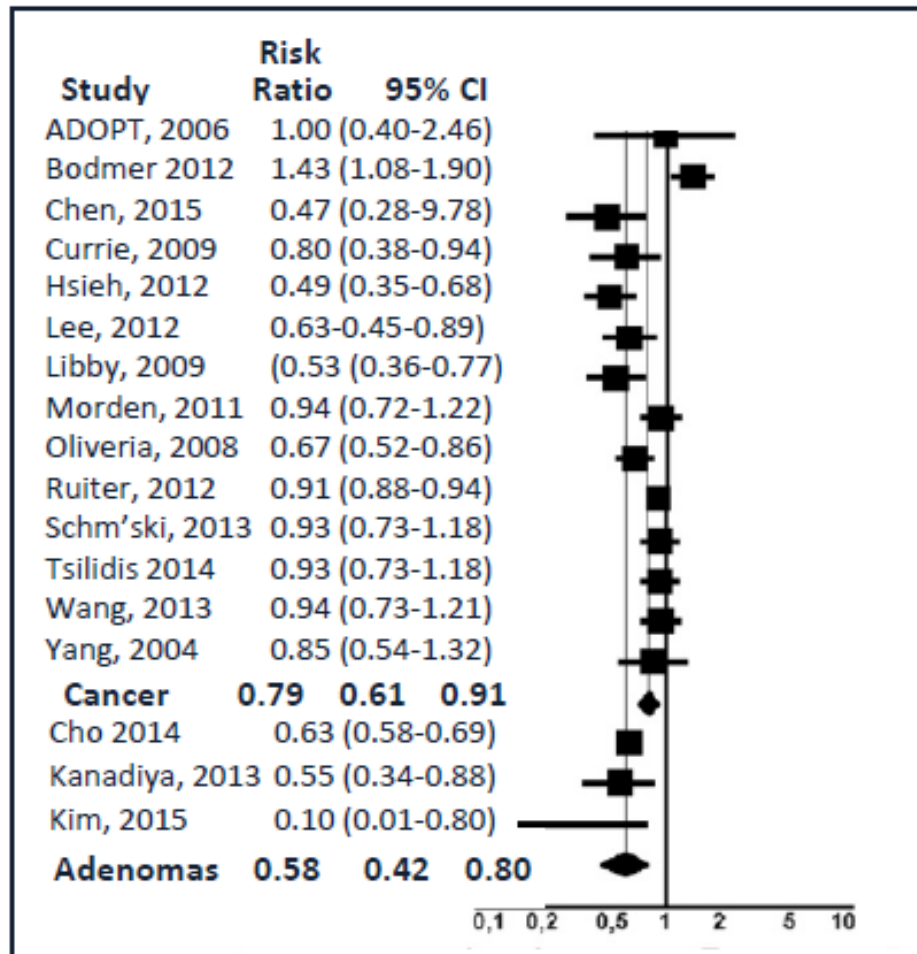
Shaukat A, Parekh M, Lipscomb J, Ladabaum U. Can calcium chemoprevention of adenoma recurrence substitute or serve as an adjunct for colonoscopic surveillance? *Int J Technol Assess Health Care*. 2009;25(2):222-31

Cost effectiveness of Calcium supplementation

	Life years per person	Cost per person	Life years gained in a cohort of 1000 people (vs. NH)
Natural History (NH)	18.6424	\$2,450	0.0
Calcium	18.6543	\$2,350	11.9
Surveillance	18.7289	\$4,003	86.5
Calcium + Surveillance	18.7292	\$4,118	86.8

Shaukat A, Parekh M, Lipscomb J, Ladabaum U. Can calcium chemoprevention of adenoma recurrence substitute or serve as an adjunct for colonoscopic surveillance? *Int J Technol Assess Health Care*. 2009;25(2):222-31

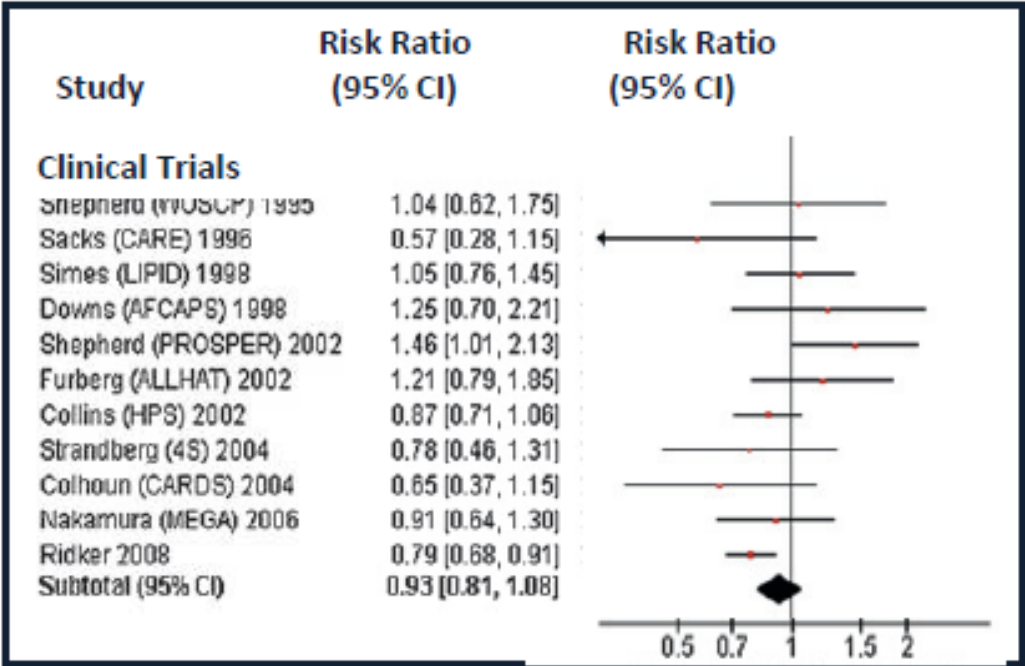
Metformin



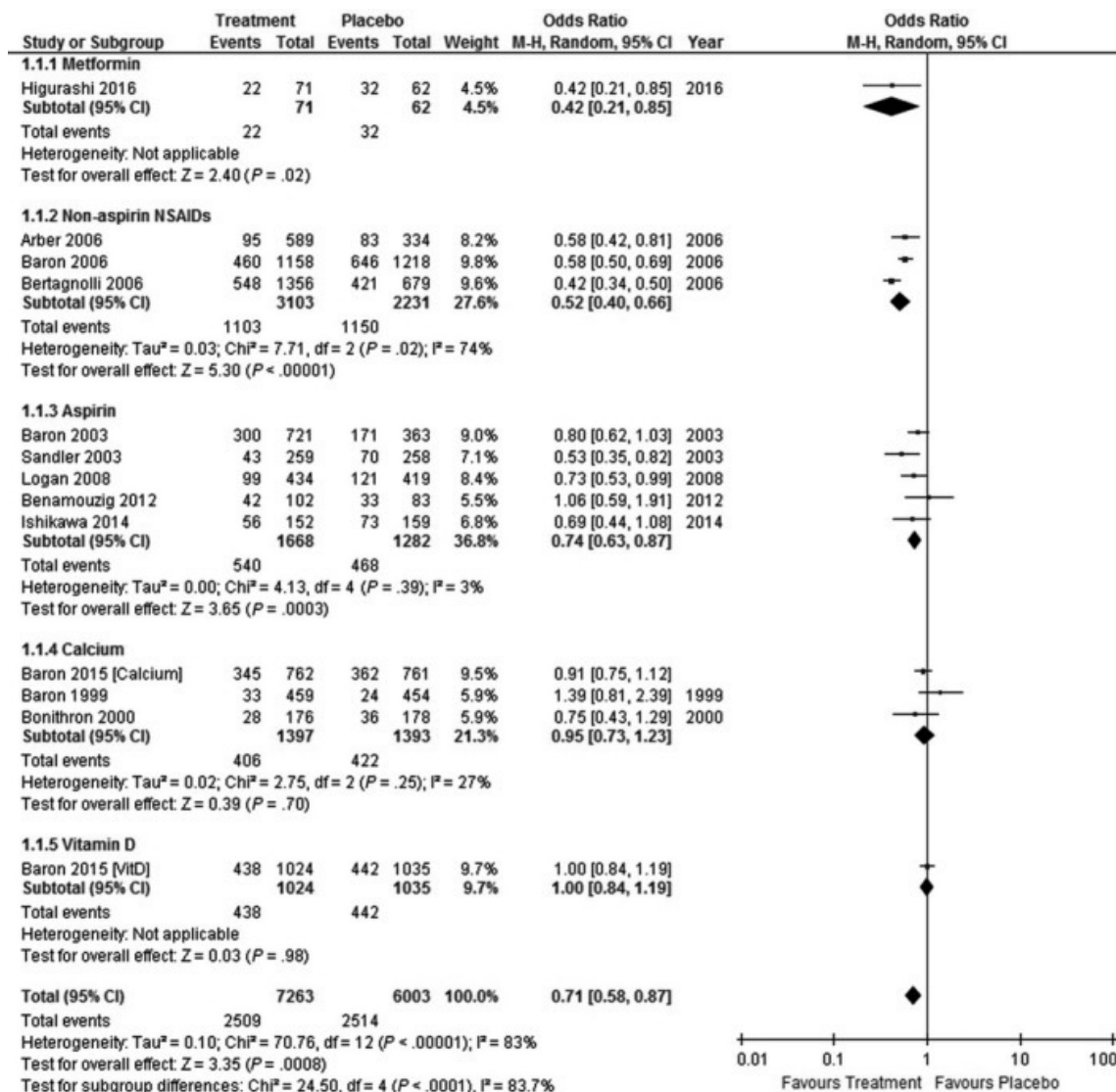
Rokkas et al.
 Eur J Int Med
 2016

Statins and CRC Risk

Bardou et al Gut 2010



All together



Chapelle N, Martel M, Toes-Zoutendijk E, *et al*
 Recent advances in clinical practice: colorectal cancer chemoprevention in the average-risk population
Gut 2020;**69**:2244-2255.

Medication	CRC mortality	CRC incidence	Adenoma/SSL incidence	Safety
Aspirin	Pooled RCT data: 33% lower mortality over 20 yrs	Pooled RCT data: 24% lower incidence over 20 yrs	Meta-analysis of RCTs: 17% lower adenoma recurrence in those with prior adenoma / RCT: 35% lower adenoma recurrence in those with prior CRC	Meta-analysis of RCTs: 59% higher risk of major GI bleeding, 34% higher risk of intracranial bleeding
Non-aspirin NSAIDs	RCT: no effect on mortality in those with CRC	Meta-analysis of observational studies: 26% lower incidence	RCTs: 34-45% lower adenoma recurrence in those with prior adenoma	Substantial cardiovascular (COX-2 inhibitors) and GI bleeding (non-selective NSAIDs) risks
Metformin	Meta-analysis of observational studies: 25% lower mortality in those with CRC and diabetes	Meta-analysis of observational studies: 27% lower incidence in those with diabetes	RCT: 40% lower adenoma recurrence in non-diabetics / Meta-analysis of observational studies: 20% lower adenoma incidence in those with diabetes	Relatively safe, but mild GI side effects are common
Calcium	--	Prospective cohort: 22% lower incidence	RCTs: mixed results	Relatively safe
Vitamin D	--	RCT (vit D + calcium): no effect / Observational studies: mixed results	RCT: no effect on adenoma recurrence or SSL incidence	Relatively safe
Folic acid	--	Meta-analysis of RCTs: no effect	Meta-analysis of RCTs: no effect on adenoma recurrence	Relatively safe
Statins	Observational studies: mixed results	MA observational and RCT: Mixed results	Observational studies: mixed results	Relatively safe

Liang PS, Shaukat A. CGH 2021;19:1327-36

Best Practice Advice

Agent	Recommendation
ASA	1) younger than 70 years with a life expectancy of at least 10 years, 2) have a 10-year cardiovascular disease risk of at least 10% ^a , and 3) not at high risk for bleeding 
Metformin	Type 2 Diabetics 
NSAIDs	
Calcium	
Vitamin D	
Statins	
Folic acid	

Future Directions

- Combination?
- Food fortification?
- Tailored to age, sex and risk?

