2018 IASGO, ICUR & KSGC Joint Symposium **Mar. 23th 2018 Seoul**
Cancer prevention and chemoprevention

Current status and new perspectives in chemoprevention of CRC

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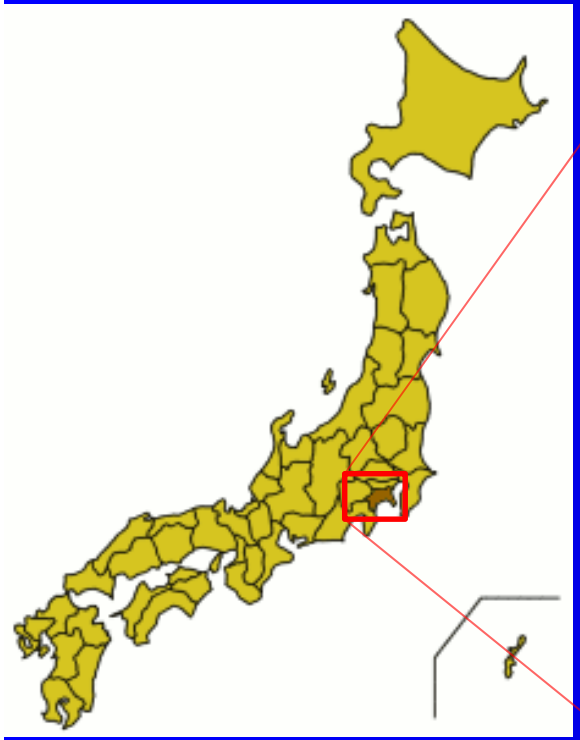
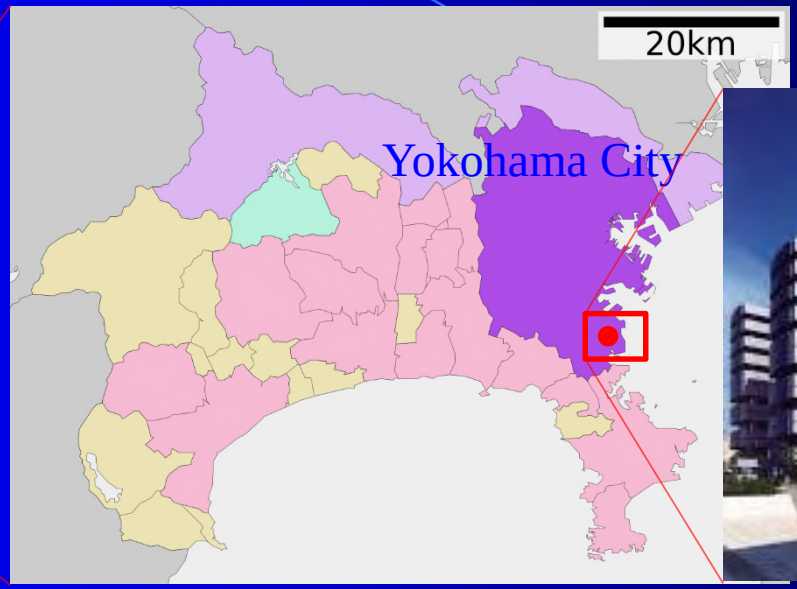
Yokohama city
area：437.4 km²
population：3.73 million（2016）





Yokohama City University Hospital
Beds：674
Beds for Gastrointestinal team：45 beds
EGD：4500/year
CS：2600/year
Upper ESD：168/year
Lower ESD：124/year

Topics

- Colorectal cancer(CRC), in a global view
- Current status in chemoprevention of CRC
- New perspectives in chemoprevention of CRC

  ~ our approach~

Cancer Statistics

WORLD	**Male**	**Female**	**Both sexes**
Population (thousands)	3,557,717	3,496,728	7,054,446
Number of new cancer cases (thousands)	7410.4	6657.5	14,067.9
Age-standardised rate (W)	204.9	165.2	182.0
Risk of getting cancer before age 75 (%)	21.0	16.4	18.5
Number of cancer deaths (thousands)	4653.4	3548.2	8,201.6
Age-standardised rate (W)	126.3	82.9	102.4
Risk of dying from cancer before age 75 (%)	12.7	8.4	10.5
5-year prevalent cases, adult population (thousands)	15296.1	17159.1	32455.2
Proportion (per 100,000)	589.4	660.5	625.0
5 most frequent cancers (ranking defined by total number of cases)			
	Lung	Breast	Lung
	Prostate	Colorectum	Breast
	Colorectum	Lung	Colorectum
	Stomach	Cervix uteri	Prostate
	Liver	Stomach	Stomach

International Agency for Research on Cancer
World Health Organization

GLOBOCAN 2012: Estimated Cancer Incidence Mortality and Prevalence Worldwide in 2012

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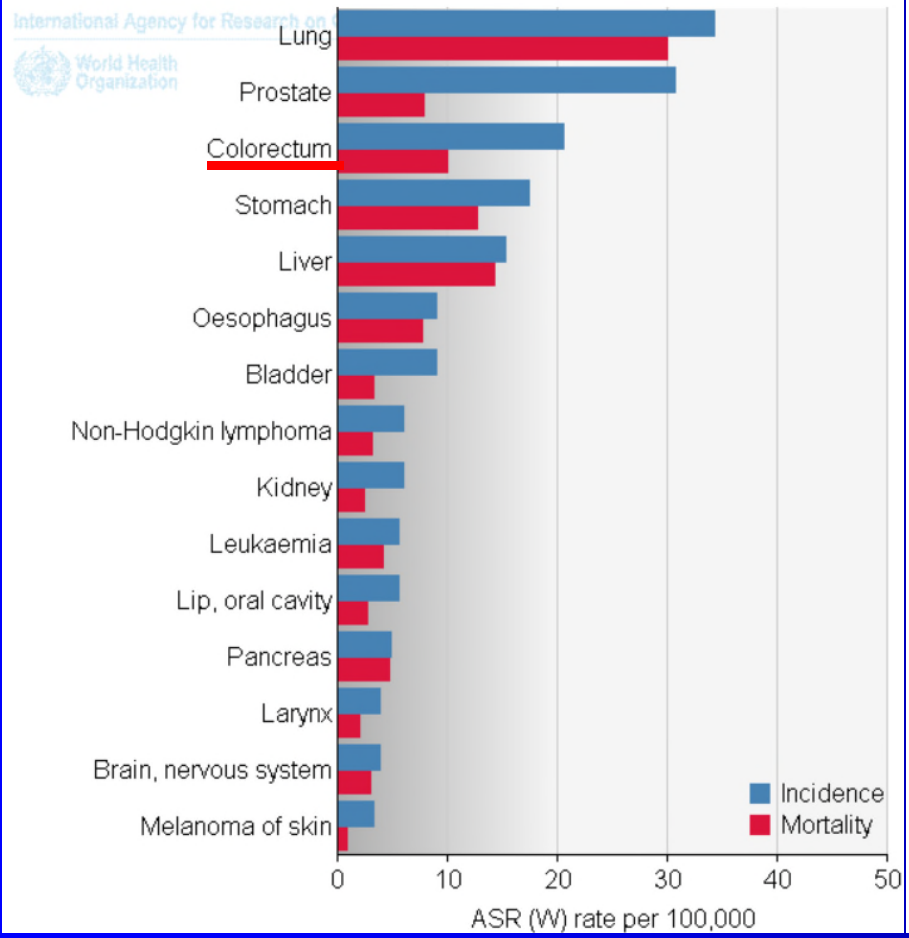
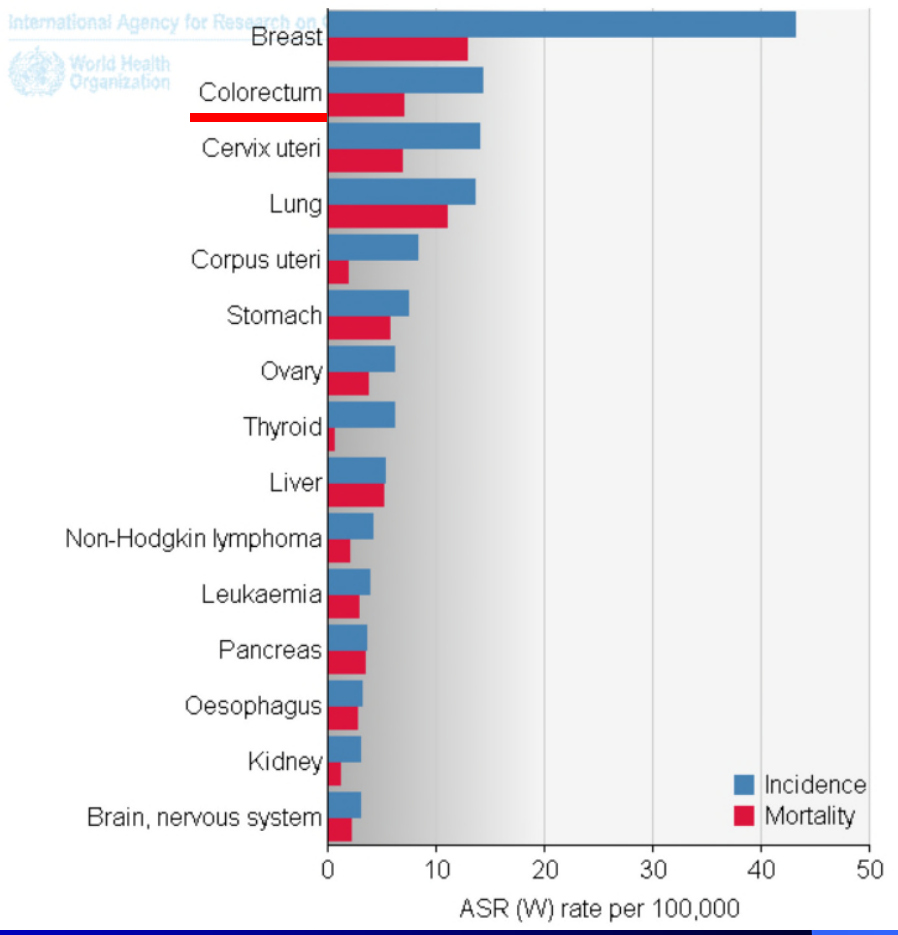
GLOBOCAN 2012: Estimated Cancer Incidence Mortality and Prevalence Worldwide in 2012

Cancer in the world

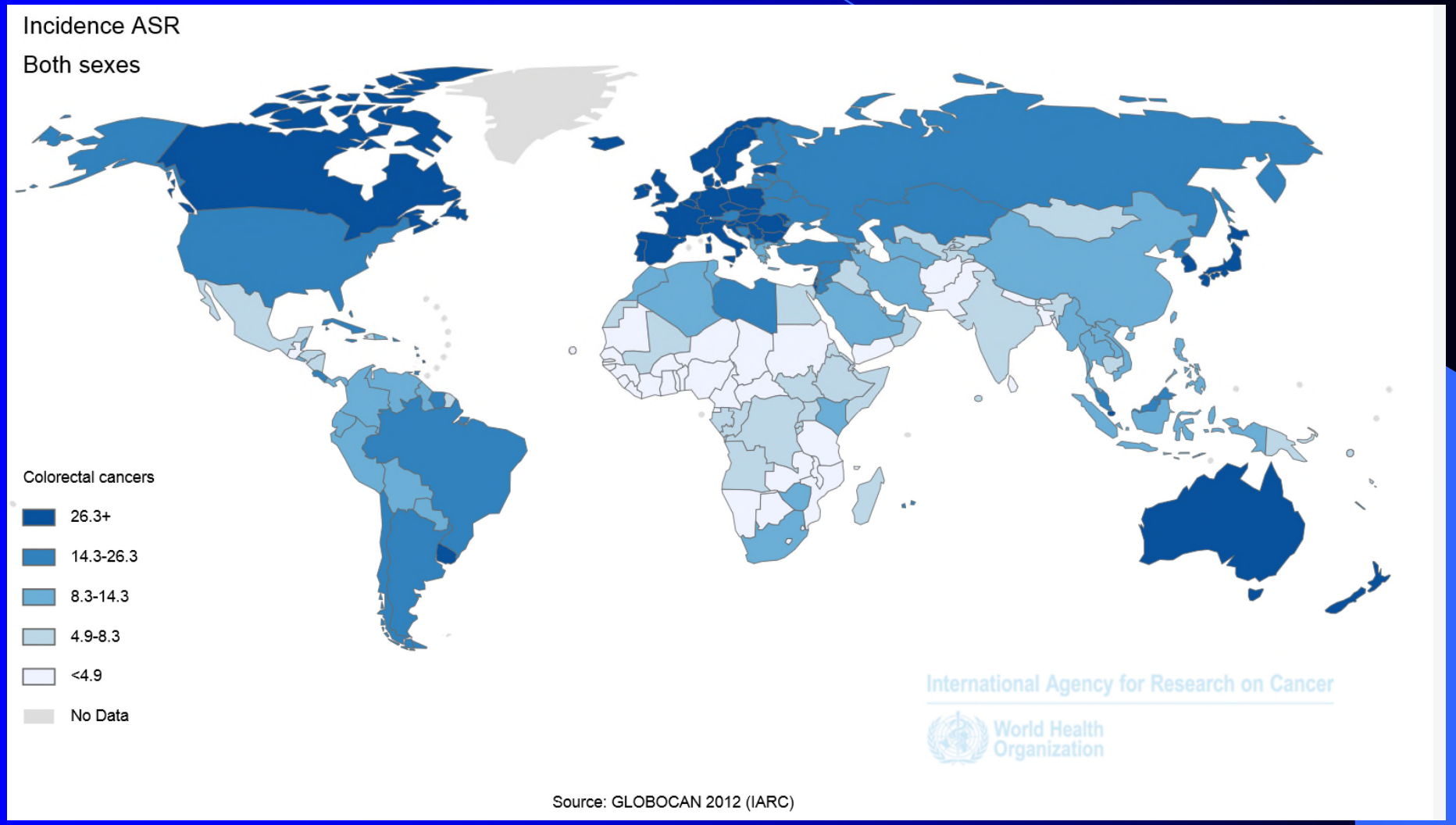
Estimated age-standardised incidence and mortality rates: men



Estimated age-standardised incidence and mortality rates: women

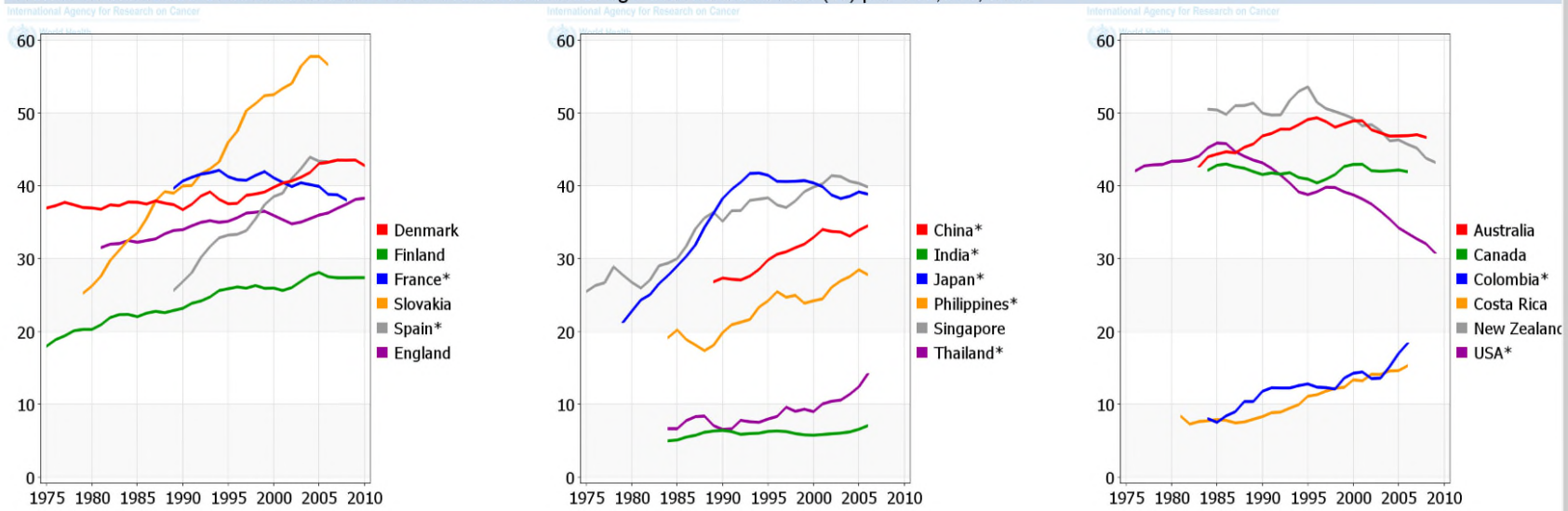


Colorectal Cancer (CRC) in the world

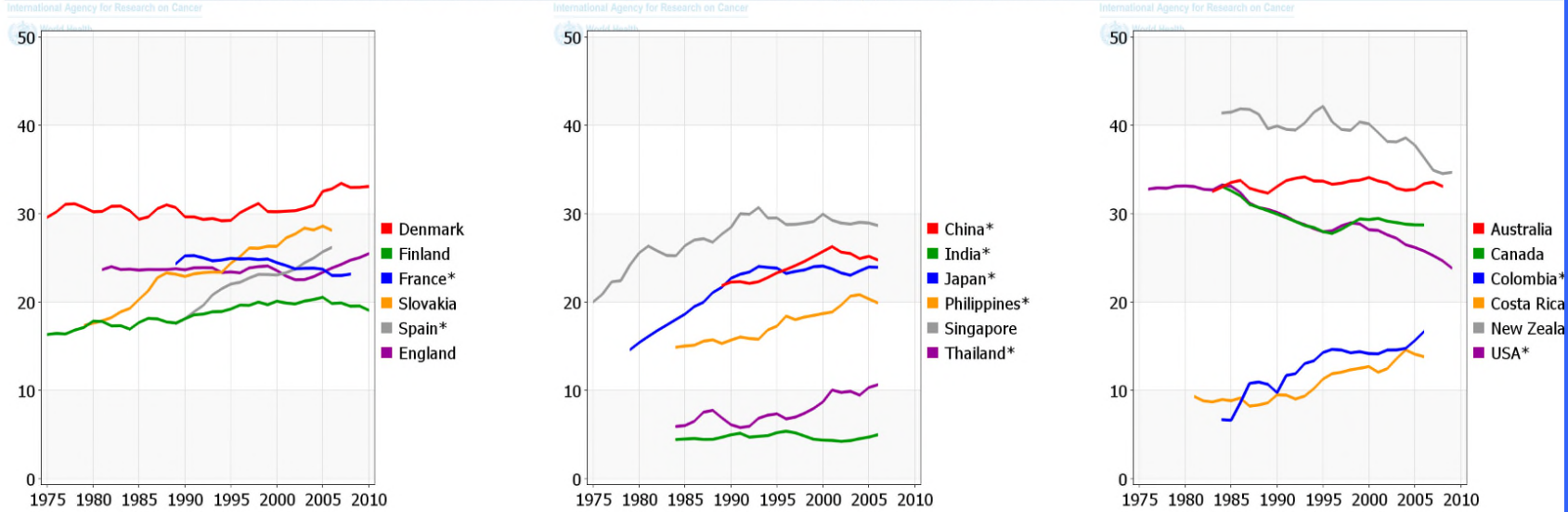


Trends in incidence of CRC

Trends in incidence of colorectal cancer in selected countries: age-standardised rate (W) per 100,000, men



Trends in incidence of colorectal cancer in selected countries: age-standardised rate (W) per 100,000, women



*Regional data

NORDCAN (www.ancr.nu)
ECO (eco.iarc.fr)
England: www.ons.gov.uk

*Regional data

CI5.iarc.fr

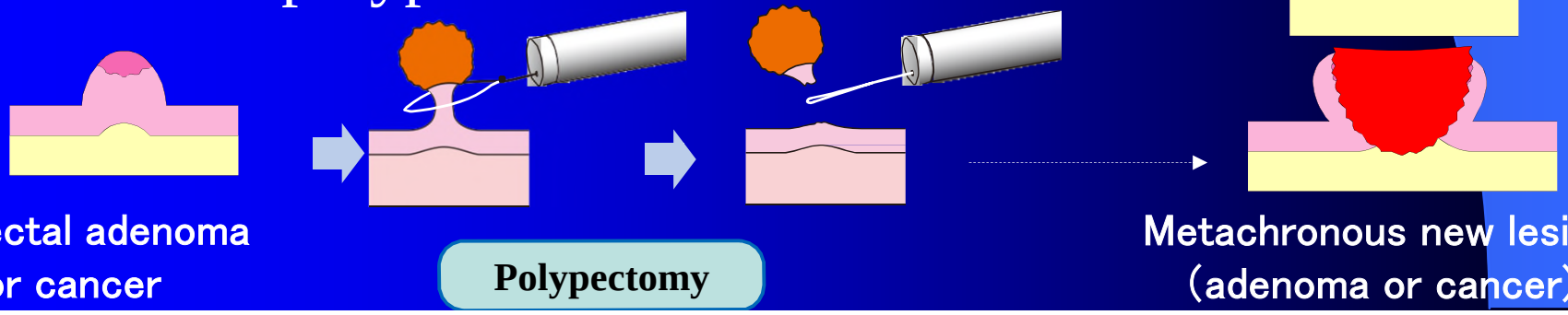
*Regional data

CI5.iarc.fr
Australia: www.aihw.gov.au
New Zealand: www.health.govt.nz
USA: seer.cancer.gov

Current status in chemoprevention of CRC

Background

- Colorectal cancer (CRC) is one of the most commonly occurring neoplasms and a leading cause of cancer death worldwide.
- New strategies for prevention is needed to lower the burden of this disease.
- CRC death, however, patients with polyps constitute a high-risk group for the development of metachronous colorectal polyps and/or CRC.



Prevention of CRC

1. Primary Prevention

   Health Promotion

   Prevention of disease

Improvement of living habits

Chemoprevention

2. Secondly Prevention

   Early Detection & Diagnosis

   Early Therapy

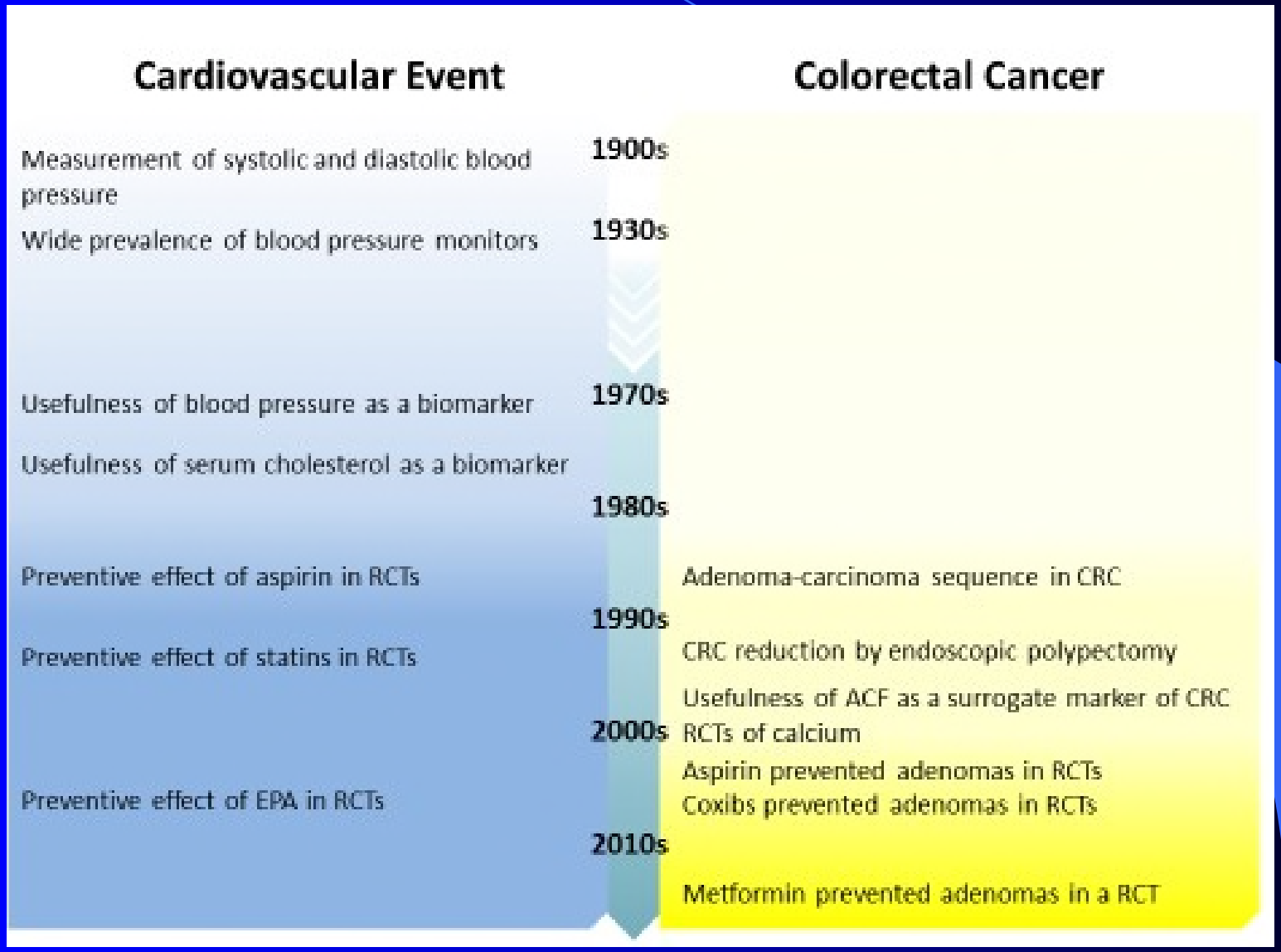
- Colonoscopy
- CT
- Resection

(Polypectomy or OPE)

Chemoprevention

- This method is intake specific nutrition or medical product for prevention of cancer.
- In the Cardiovascular Disease, chemoprevention of the Myocardial infraction is very popular.

The History of Chemoprevention in Cardiovascular event and colorectal cancer



Candidate substance of chemoprevention for CRC

NSAIDs
- **Aspirin**
- **Sulinduc**
- **Indometacine**
- **Piroxicam**
- **Celecoxib**

Vitamin Group
- **Folic Acid**
- **Vitamin C**
- **Vitamin D**
- **Vitamin E**

Carotenoid
- **A-carotene**
- **B-carotene**
- **Lycopene**

Dietary Fiber
- **Hemicellose**
- **Pectine**
- **Resistant starch**
- **oligosaccharide**

Minor elements
- **Selenium**
- **Calcium**
- **Phytic acid**

polyunsaturated fatty acid
- **Docosahexaenoic acid :DHA**
- **Eicosapentaenoic acid :EPA**
- **α-linolenic acid**

5aminosalicylic acid
- **Salazosulfapyridine**
- **Mesalazine**

Other therapeutic drug
- **Pioglitazone**
- **α-glucosidase inhibitor**
- **Metformin**
- **Statin**
- **5-FU**
- **Probiotic product**
- **UDCA**
- **Estrogen**

Others
- **Curcumin**
- **Lactoferrin**

CRC chemoprevention with Aspirin

Aspirin use reduces 47% CRC risk:

First description of a relationship between aspirin use and the risk of CRC

Kune, et al. Cancer Res 1988; 48: 4399-404.

Placebo-controlled trials of chemoprevention of colorectal adenoma

Author（year）	Period	Number	results	RR（95％CI）	Adverse events
Baron（2003）	3y	1121	Positive※	0.81（0.69-0.96）	-
Sandler（2003）	3y	635	Positive	0.65（0.46-0.91）	-
Logan（2008）	3y	939	Positive	0.79（0.63-0.99）	-
Benamouzig（2012）	4y	272	Negative	0.96（0.75-1.22）	-
Ishikawa（2014）	2y	311	Positive	0.60（0.36-0.98）	-

※only aspirin 81㎎ group was positive

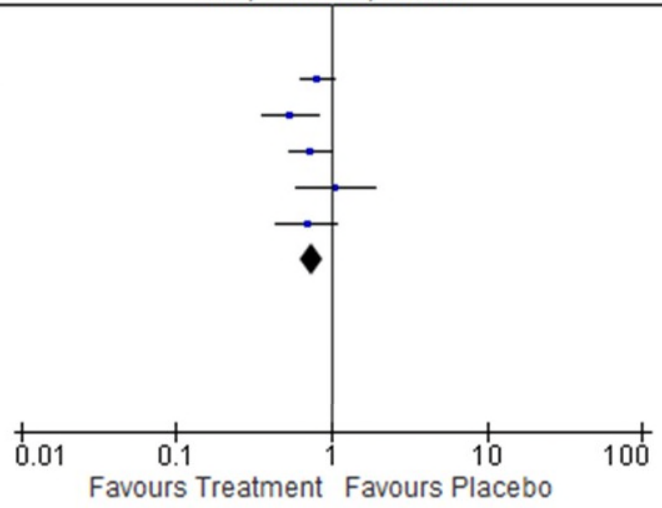
Baron, et al. N Engl J Med 2003; 348: 891-9
Sandler, et al. N Engl J Med 2003; 348: 883-90
Logan, et al. Gastroenterology 2008; 134: 29-38
Benamouzig, et al. Gut 2012; 61: 255-61
Ishikawa, et al. Gut 2014; 63: 1755-9

CRC chemoprevention with Aspirin

Study or Subgroup	Treatment Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.1.3 Aspirin							
Baron 2003	300	721	171	363	9.0%	0.80 [0.62, 1.03]	2003
Sandler 2003	43	259	70	258	7.1%	0.53 [0.35, 0.82]	2003
Logan 2008	99	434	121	419	8.4%	0.73 [0.53, 0.99]	2008
Benamouzig 2012	42	102	33	83	5.5%	1.06 [0.59, 1.91]	2012
Ishikawa 2014	56	152	73	159	6.8%	0.69 [0.44, 1.08]	2014
Subtotal (95% CI)		**1668**		**1282**	**36.8%**	**0.74 [0.63, 0.87]**	
Total events	540		468				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.13$, $df = 4$ ($P = 0.39$); $I^2 = 3\%$

Test for overall effect: $Z = 3.65$ ($P = 0.0003$)



The draft guideline of the United States Preventive Service Task Force published in 2015 provides a Grade B recommendation ("high or moderate certainty that the net benefit is moderate to substantial.") for the use of aspirin for chronic prophylaxis against diseases, including CRC, in certain select populations.

CRC chemoprevention with COX-2 inhibitor

Trial	Author（year）	Agents	Period	N	Results	RR（95%CI）
①	Arber（2006）	Celecoxib	3y	1561	Positive	0.64（0.56-0.72）
②	Baron（2006）	Rofecoxib	3y	2587	Positive	0.76（0.57-0.83）
③	Bertagnolli（2006）	Celecoxib	3y	1541	Positive	200mg: 0.67（0.59-0.77） 400mg: 0.55（0.48-0.64）

Arber et al. N Engl J Med 2006 355: 885–95
Baron, et al. Gastroenterology 2006; 131: 1674–82
Bertagnolli, et al. N Engl J Med 2006; 355: 873–84

COX-2 inhibitor revealed strong preventive effects for adenoma recurrence

CRC chemoprevention with COX-2 inhibitor

Trial	Author（year）	Increase of CV events	HR（95%CI）
①	Arber（2006）	+	1.30（0.65-2.62）
②	Bresalier（2005）	+	1.92（1.19-3.11）
③	Solomon（2005）	+	Celecoxib 200mg: 2.3（0.9-5.5） Celecoxib 400mg: 3.4（1.4-7.8）

However, after that serious cardiovascular toxicity were proved.

Bresalier, et al. N Engl J Med 2005; 352: 1092-102
Solomon, et al. N Engl J Med 2005; 352: 1071-80

Other Chemoprevention RCT

Trial (year)	Agents	period	Number	Results	RR（95%CI）
Baron（1999）	Calcium	4y	930	Positive	0.85（0.74-0.98）
Bonithron（2000）	Calcium	3y	665	Negative	0.66（0.38-1.17）
Wactawski-Wende（2006）	Calcium, Vitamin D	7y	36,282	Negative	1.08（0.86-1.34）
Baron（2015）	Calcium	3-5y	2259	Negative	0.95（0.85-1.06）
	Vitamin D			Negative	0.99（0.89-1.09）
Pommergaard（2016）	Calcium, Vitamin D, Aspirin	3y	427	Negative	0.95（0.61-1.48）

Calcium and Vitamin D may not reduce the risk of colorectal adenoma.

Baron, et al. N Engl J Med 1999; 340: 101-7
Bonithron et al. lancet 2000; 356: 1300-6
Wactawski-Wende, et al. N Engl J Med 2006; 354: 684-96
Baron, et al. N Engl J Med 2015; 373: 1519-30
Pommergaard, et al. Gastroenterology 20016; 150: 114-122

Current status in chemoprevention of CRC
Short summary

- Aspirin is most convinced chemoprevention agents, however, the effect is not strong and have some adverse events such as bleeding.
- COX-2 inhibitor has strong chemopreventive effect, but has serious cardiovascular toxicity.
- Other chemprevention agents are also evaluated, however there is not established for chemoprevention for CRC.

New perspectives in chemoprevention of CRC ~our approach to prevent CRC~

NSAIDs

- •Aspirin
- •S
- •I
- •P
- •C

Dietary Fiber

- •Hemicellose
- •Phytic acid

5aminosalicylic acid

- •Salazosulfapyridine

Therefore, investigation to identify novel "post-aspirin" agents for CRC chemoprevention is needed.

- •P
- •V
- •Vitamin D
- •Vitamin E

- •Probiotic product
- •UDCA
- •Estrogen

Carotenoid

- •A-carotene
- •B-carotene
- •Lycopene

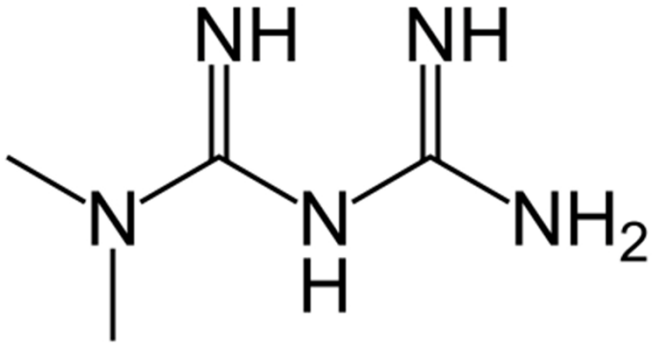
polyunsaturated fatty acid

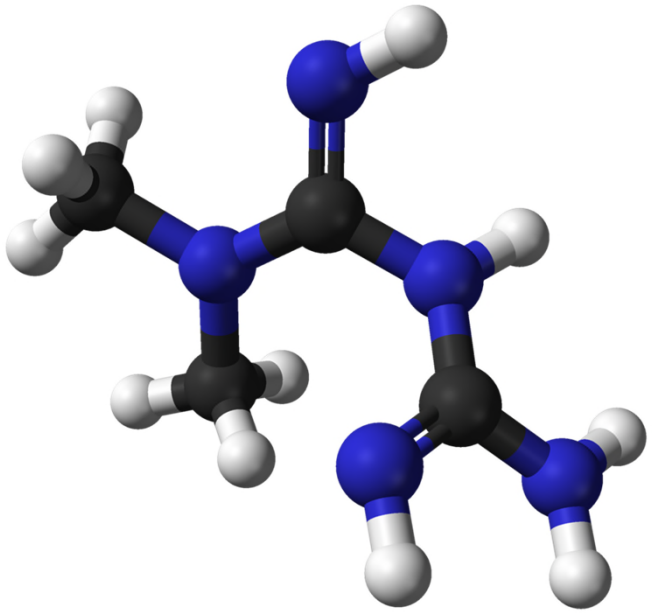
- •Docosahexaenoic acid :DHA
- •Eicosapentaenoic acid :EPA
- •α-linolenic acid

Others

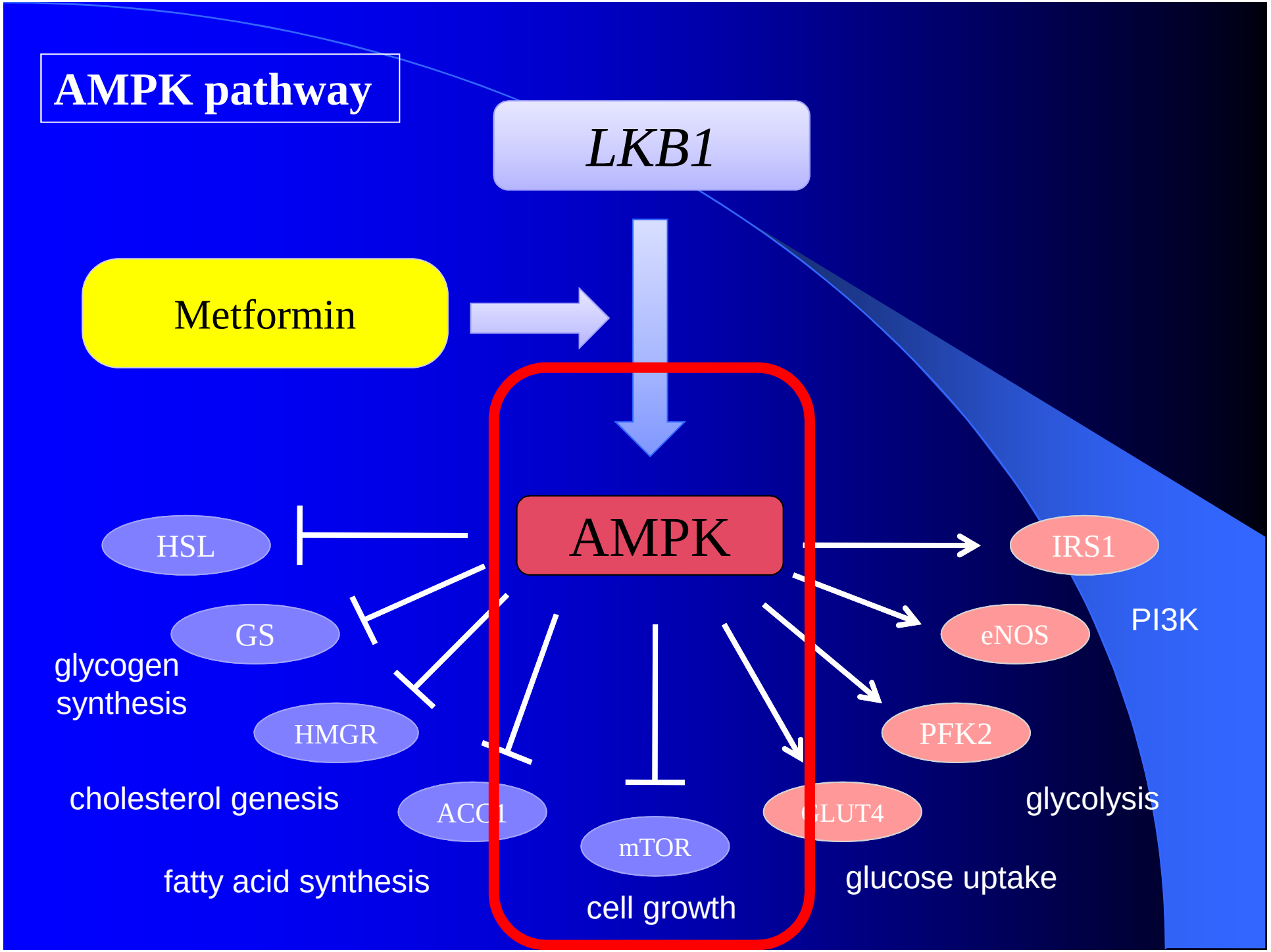
- •Curcumin
- •Lactoferrin

What is a metformin?





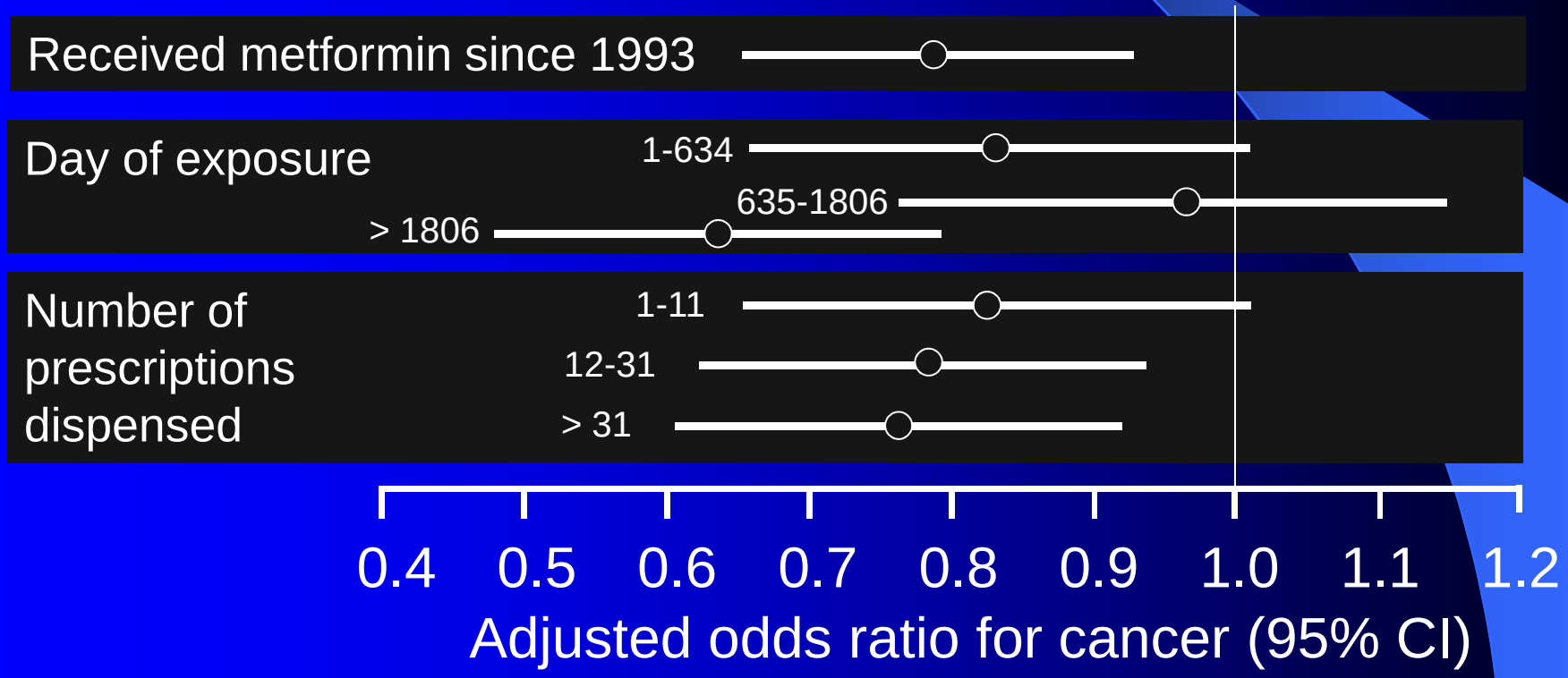
- Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide derivative that is widely used for treating diabetes mellitus.
- 1950s Metformin was discovered and widely used until today.
- It decreases basal glucose output by suppressing gluconeogenesis and glycogenolysis in the liver and increasing glucose uptake by muscle.


AMPK pathway
LKB1
Metformin
AMPK
HSL
GS
glycogen synthesis
HMGR
cholesterol genesis
ACC1
fatty acid synthesis
mTOR
cell growth
GLUT4
glucose uptake
PFK2
glycolysis
eNOS
IRS1
PI3K

Receipt of metformin was associate with a reduced risk of cancer

The Diabetes Audit Research in Tayside / Medicines Monitoring Unit (DARTS/MEMO) 1993~2001

11876 patients with newly-diagnosed type 2 diabetes



Evans et al. BMJ 2005;330:1304-5

The potential of metformin for the prevention of colorectal cancer

We investigated the chemopreventive effect of metformin in two rodent models of colorectal carcinogenesis.

- APC $^{Min/+}$ mice
- Chemical carcinogen–induced murine model

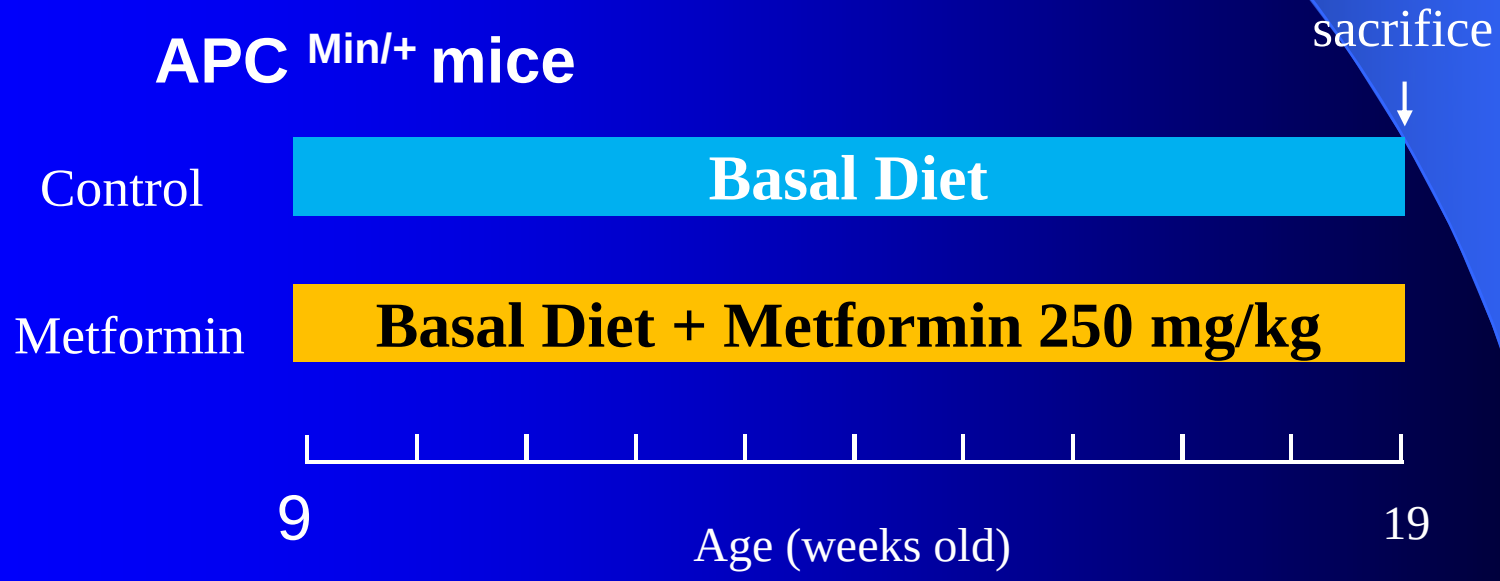
Metformin suppresses intestinal polyp growth in *Apc*$^{Min/+}$ mice

Ayako Tomimoto,[1,7] Hiroki Endo,[1,7] Michiko Sugiyama,[1] Toshio Fujisawa,[1] Kunihiro Hosono,[1] Hirokazu Takahashi,[1] Noriko Nakajima,[2] Yoji Nagashima,[3] Koichiro Wada,[4] Hitoshi Nakagama[5] and Atsushi Nakajima[1,6]

[1]Division of Gastroenterology, [3]Department of Molecular Pathology, Yokohama City University School of Medicine, 3-9 Fuku-ura, Kanazawa-ku, Yokohama 236-0004; [2]Department of Pathology, National Institute of Infectious Diseases, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8640; [4]Department of Pharmacology, Graduate School of Dentistry, Osaka University, 1-8 Yamadaoka, Suita, Osaka 565-0871; [5]Biochemistry Division, National Cancer Center Research Institute, 1-1 Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan

Cancer Sci | 2008

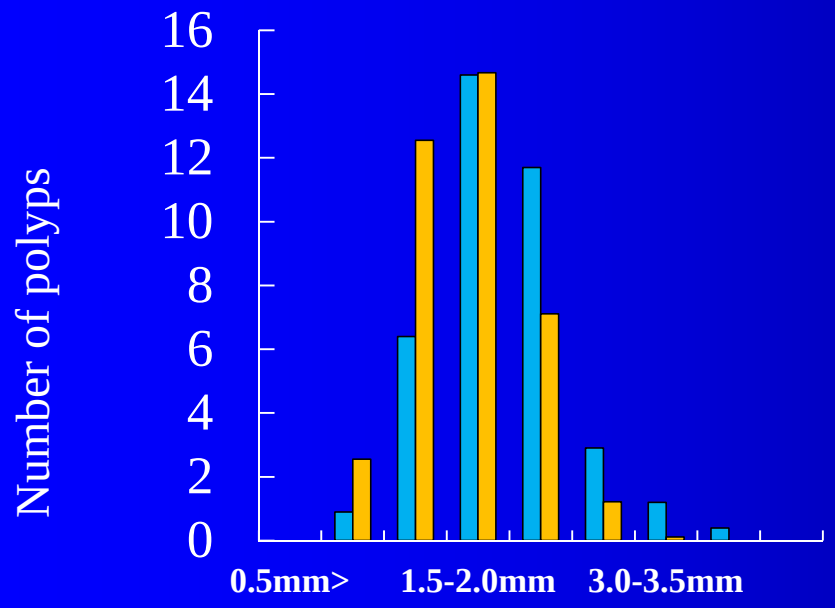
(Received June 6, 2008/Revised July 10, 2008/Accepted July 16, 2008)

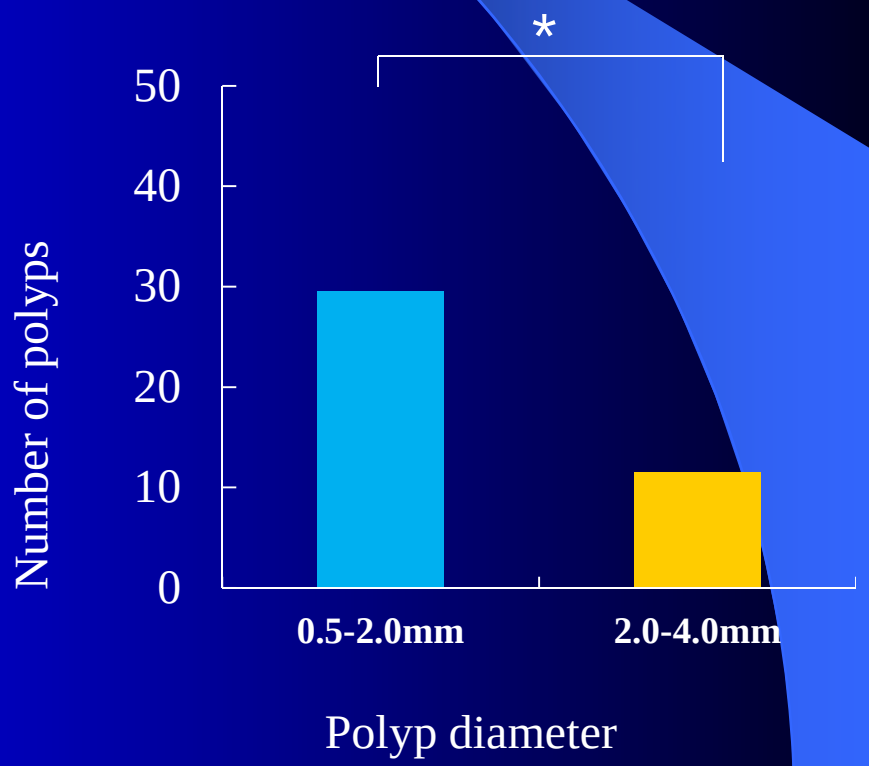


The effect of metformin on the suppression of intestinal polyp formation

Diet	No. of mice	No. of polyp	No. of polyps > 2mm
Control	10	42.1 ± 4.76	19.4 ± 3.87
Metformin	10	38.2 ± 4.53	8.4 ± 2.38*

Mean ±SE * $P < 0.05$



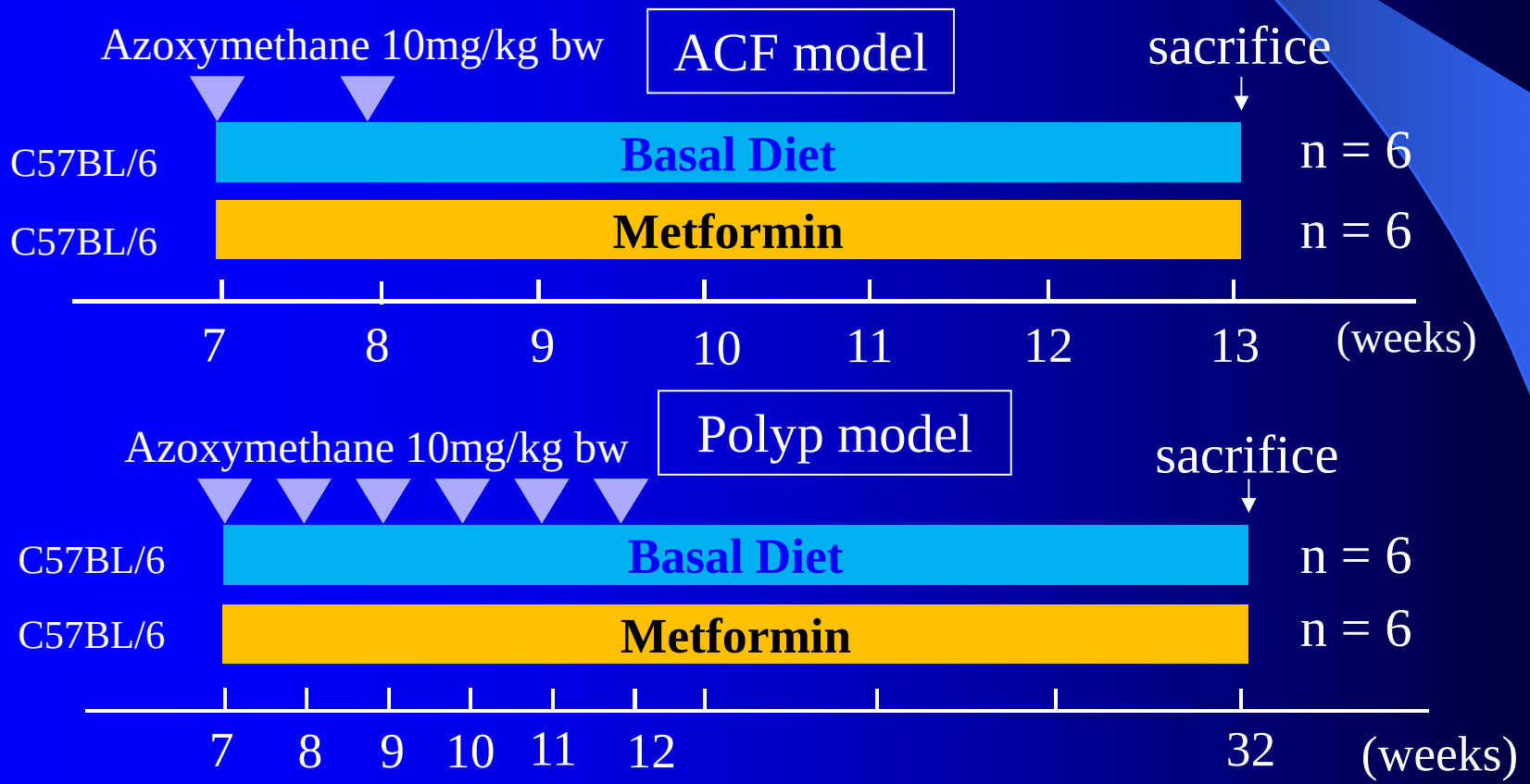


MOLECULAR CARCINOGENESIS 49:662–671 (2010)

Metformin Suppresses Azoxymethane-Induced Colorectal Aberrant Crypt Foci by Activating AMP-Activated Protein Kinase

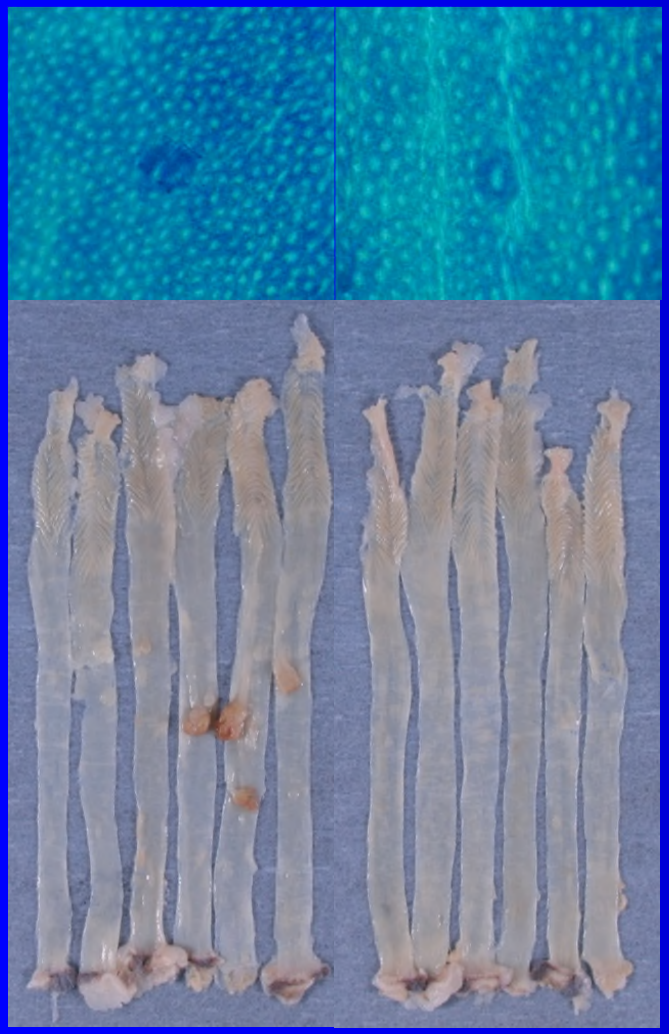
Kunihiro Hosono,[1] Hiroki Endo,[1] Hirokazu Takahashi,[1] Michiko Sugiyama,[1] Takashi Uchiyama,[1] Kaori Suzuki,[1] Yuichi Nozaki,[1] Kyoko Yoneda,[1] Koji Fujita,[1] Masato Yoneda,[1] Masahiko Inamori,[1] Akiko Tomatsu,[2] Takeshi Chihara,[2] Kan Shimpo,[2] Hitoshi Nakagama,[3] and Atsushi Nakajima[1]*

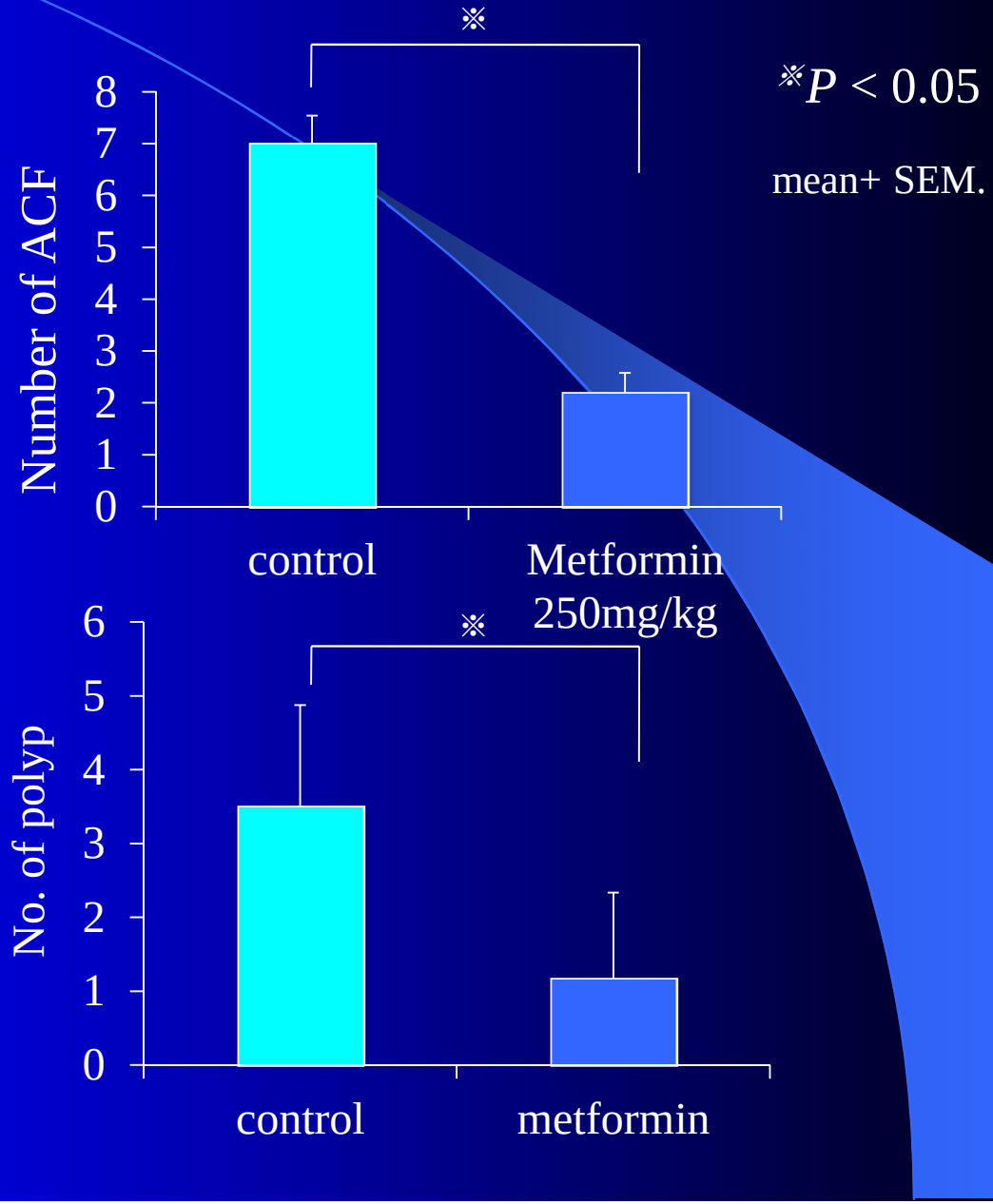
[1]*Division of Gastroenterology, Yokohama City University School of Medicine, Yokohama, Japan*
[2]*Division of Biochemistry, Fujita Memorial Nanakuri Institute, Fujita Health University, Mie, Japan*
[3]*Biochemistry Division, National Cancer Center Research Institute, Chuo-ku, Tokyo, Japan*



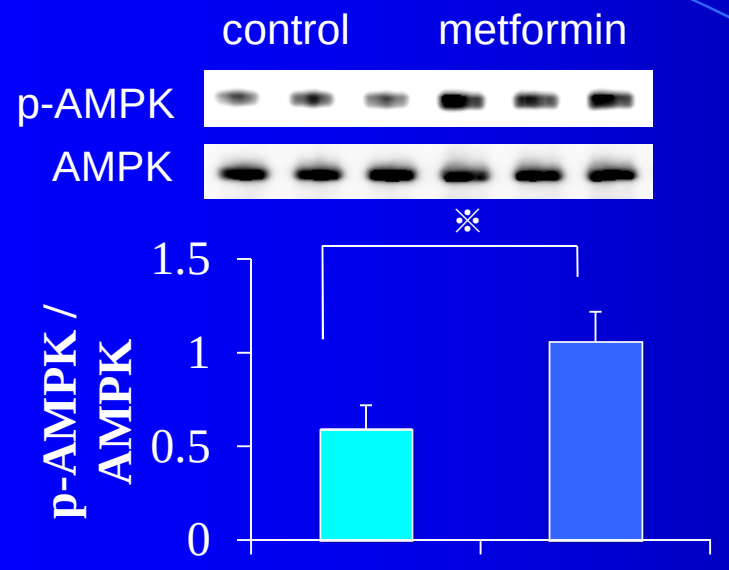
Effects on the formation of ACF and polyp

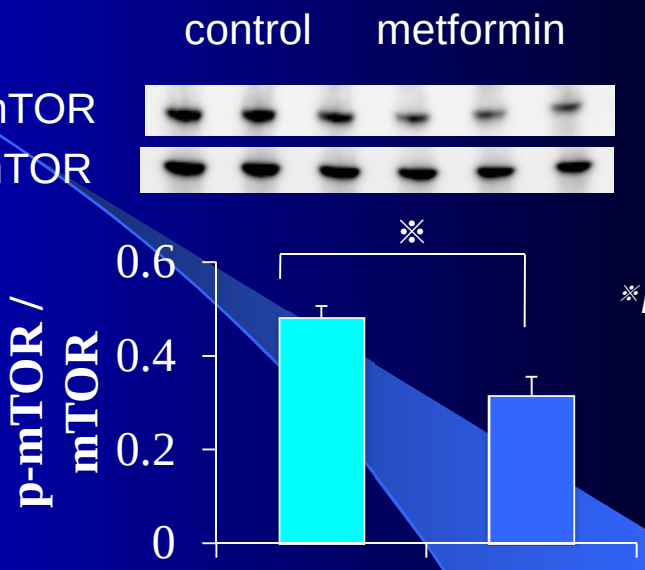
control metformin



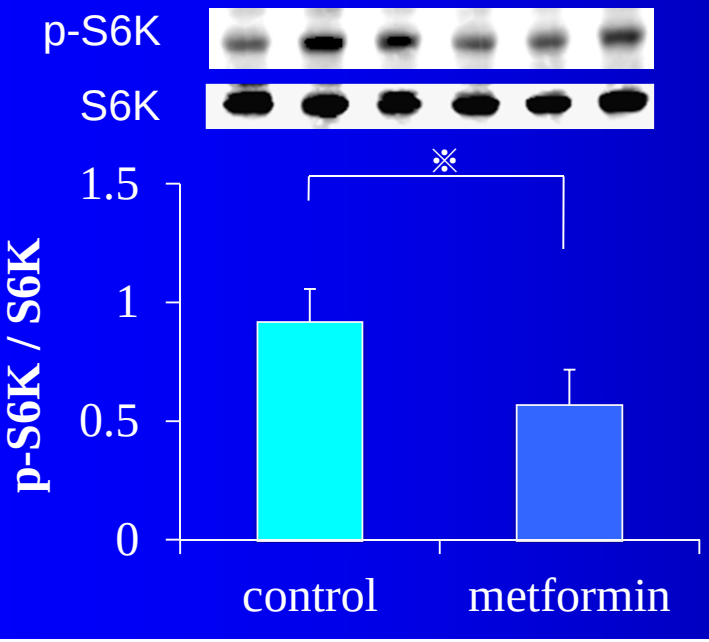


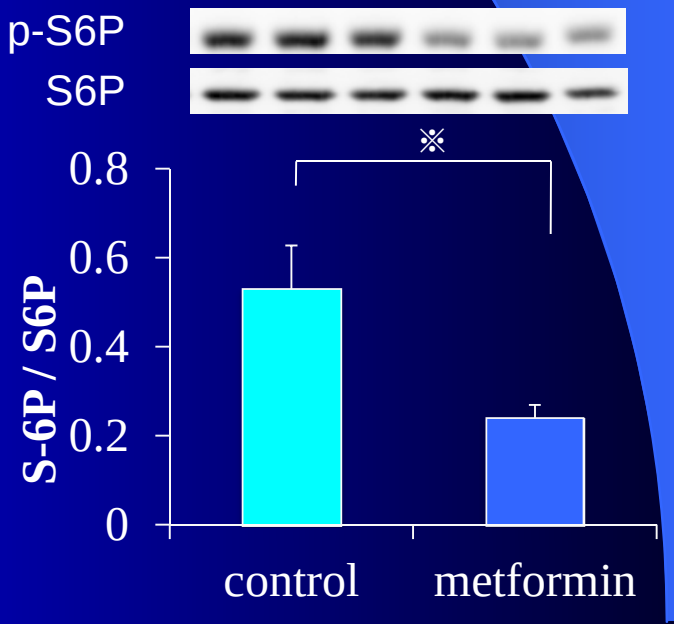
AMPK – mTOR pathway





※$P < 0.05$





Short Summary

- In epidemiologic study, Metformin use decrease CRC risk
- Metformin suggested to have a chemopreventive effect in both colorectal cancer model mice

(genetic or chemical induced).

⇒Next step

To evaluate the chemopreventive effect of metformin against metachronous colorectal adenoma/cancer, we devised a phase 3 randomized controlled trial in post-polypectomy patients.

Metformin chemoprevention trial for metachronous colorectal adenoma/polyps in non-diabetic, post-polypectomy subjects: a multi-centre phase 3 randomised controlled trial

Takuma Higurashi[1], Kunihiro Hosono[1], Hirokazu Takahashi[1], Yasuhiko Komiya[1], Shotaro Umezawa[1], Eiji Sakai[1], Takashi Uchiyama[2], Leo Taniguchi[2], Yasuo Hata[2], Shiori Uchiyama[3], Akiko Hattori[3], Hajime Nagase[3], Takaomi Kessoku[4], Jun Arimoto[4], Nobuyuki Matsuhashi[5], Yoshiaki Inayama[6], Shoji Yamanaka[6], Masataka Taguri[7], Atsushi Nakajima[1]

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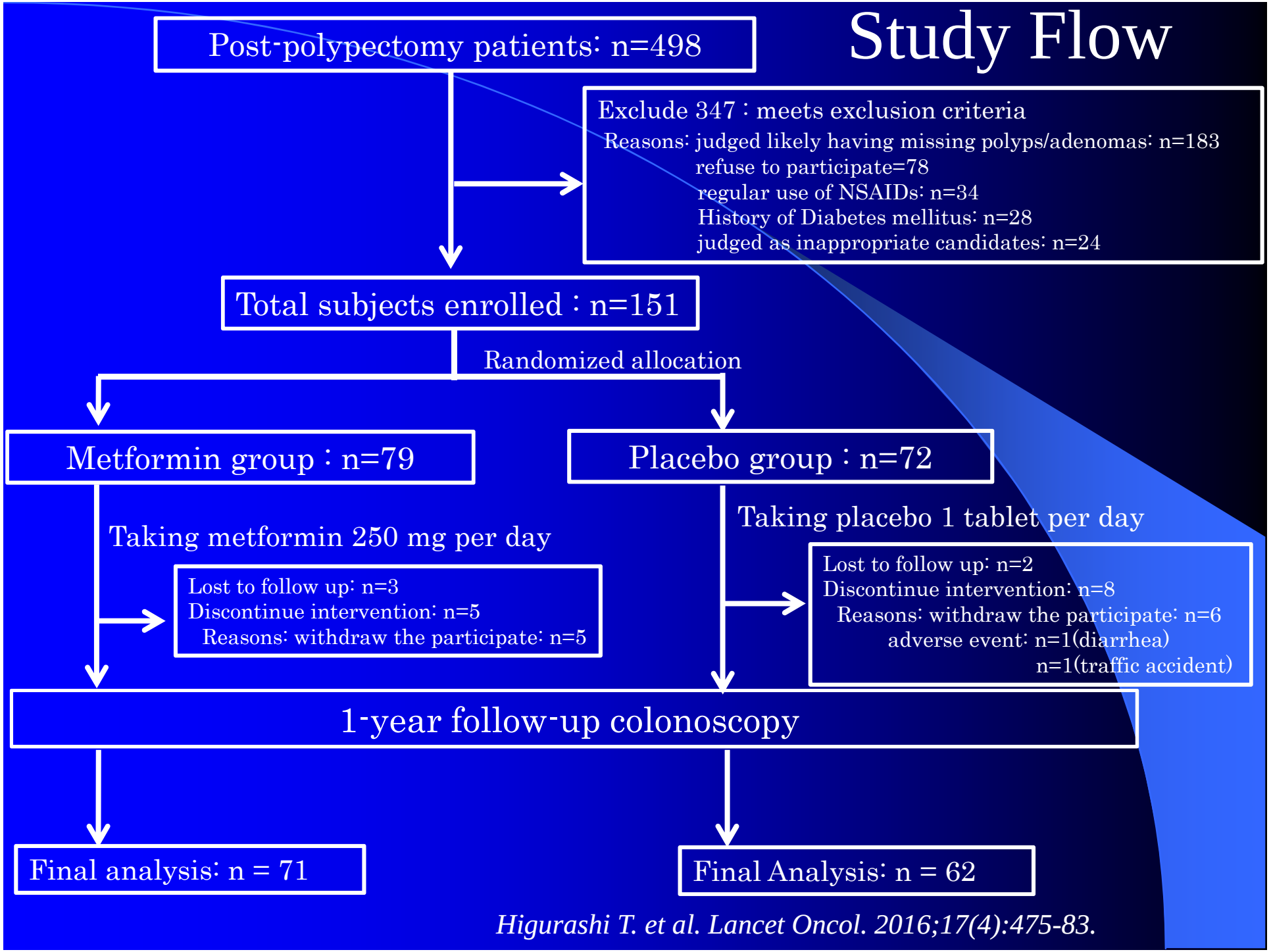
Higurashi T. et al. Lancet Oncol. 2016;17(4):475-83.

Study protocol was submitted on BMC Cancer 2012;12:118.
and registered in the University Hospital Medical Information Network as UMIN000006254.

Study Flow



Higurashi T. et al. Lancet Oncol. 2016;17(4):475-83.

Results

Table 1: **Baseline characteristics of the subjects**

	metformin	Placebo	p-value
No of subject	71	62	
Age, (mean ± SD), y	63.1±8.5	63.5±10.2	n.s
Sex (M/F)	54/17	49/13	n.s
Family history of CRC	8	10	n.s
Current smoker	23	25	n.s
History of Diabetes	0	0	n.s
History of Hyperlipidemia	15	7	n.s
History of Hypertension	20	20	n.s
Finding of baseline CS			
Multiple & Advanced adenoma + early carcinoma	51 (72%)	43 (69%)	n.s

CS = colonoscopy; Multiple = more than three adenomas;
advanced adenomas = high grade dysplasia, large size (>10 mm), or villous features.

Higurashi T. et al. Lancet Oncol. 2016;17(4):475-83.

Results

Table 2: **Incidence of total polyps and incidence of adenomas at 1 year after colonoscopy**

	metformin	placebo	p-value
Incidence of total polyp	27/71 (38%)	35/62 (56%)	0.034
Risk ratio (95%CI)	0.674 (0.466-0.974)	1(reference)	
Incidence of total adenomas	22/71 (31%)	32/62 (52%)	0.016
Risk ratio (95%CI)	0.600 (0.393-0.916)	1(reference)	
Number of total polyps			
mean ± SD	0.62±0.98	1.06±1.46	0.039
median (range)	0 (0-4)	1 (0-8)	
Number of adenomas			
mean ± SD	0.52±0.91	0.95±1.42	0.037
median (range)	0(0-4)	0 (0-8)	

Higurashi T. et al. Lancet Oncol. 2016;17(4):475-83.

Results

Table 4: **Adverse events in the metformin group and the placebo group**

Adverse events	metformin	placebo
Abdominal pain	0	1
Diarrhea	1	4
rash	2	0
constipation	3	3
alopecia	0	1
Total	6	9

All adverse events were NCI-CTCAE grade 1

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Summary

- Low-dose metformin is safe and effective in reducing the prevalence of metachronous adenomas and polyps in non-diabetic patients after polypectomy

Discussion

- This is first randomized control trial to show the effect of metformin for human colorectal metachronous adenoma.
- These results were suggested the possibility to establish the CRC chemoprevention by metformin

Discussion

Requirement for chemopreventive material

- Low risk of adverse effect
- Good drug compliance
- Low cost
- Evident action mechanism

⇒metformin meets these criteria

Ongoing clinical trials for cancer using Metformin

Trial number	Title	Target
NCT00897884	Clinical and Biologic Effects of Metformin in Early Stage Breast Cancer	Brest cancer
NCT01087983	Lapatinib With Sirolimus or Metformin	Various cancer
NCT0098449	Metformin Hydrochloride in Treating Women With Stage I or Stage II Breast Cancer That Can Be Removed By Surgery	Brest cancer
NCT00881725	A Study of Pre-operative Metformin in Prostate Cancer (ANIMATE)	Prostate cancer
NCT01101438	Metformin Hydrochloride in Treating Patients With Early-Stage Breast Cancer	Brest cancer
NCT00909506	Efficacy and Safety of Adjuvant Metformin for Operable Breast Cancer Patients	Brest cancer
NCT00930579	Metformin Pre-Surgical Pilot Study	Brest cancer

Referred from http://clinicaltrials.gov

Discussion

Limitation

- We did not plan to conduct a dose–response study of the effect of metformin on colorectal polyp formation.
- Repeat colonoscopy at 1 year may be too soon to allow reliable detection of differences between the groups.

⇒ We are now planning to conduct further large sample, long term, metformin chemoprevention trial.

Take home massage

- Colorectal cancer (CRC) is increasing all over the world and new strategies for prevention such as chemoprevention is needed to lower the burden of this disease
- Aspirin is most convinced chemoprevention agents, however, the effect is not strong and have some adverse events such as bleeding.

Take home massage

- Metformin has a potential role in the chemoprevention of CRC.

- To establish the chemoprevention for CRC, further analysis is needed