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APDW Taipei, December 3, 2015

In What Asia-Pacific Populations is CRC Screening Justified?

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Outline

- ❖ CRC in the Asia-Pacific
- ❖ In which populations is screening justified?
- ❖ Risk- based algorithms for lower incidence countries
- ❖ Conclusion

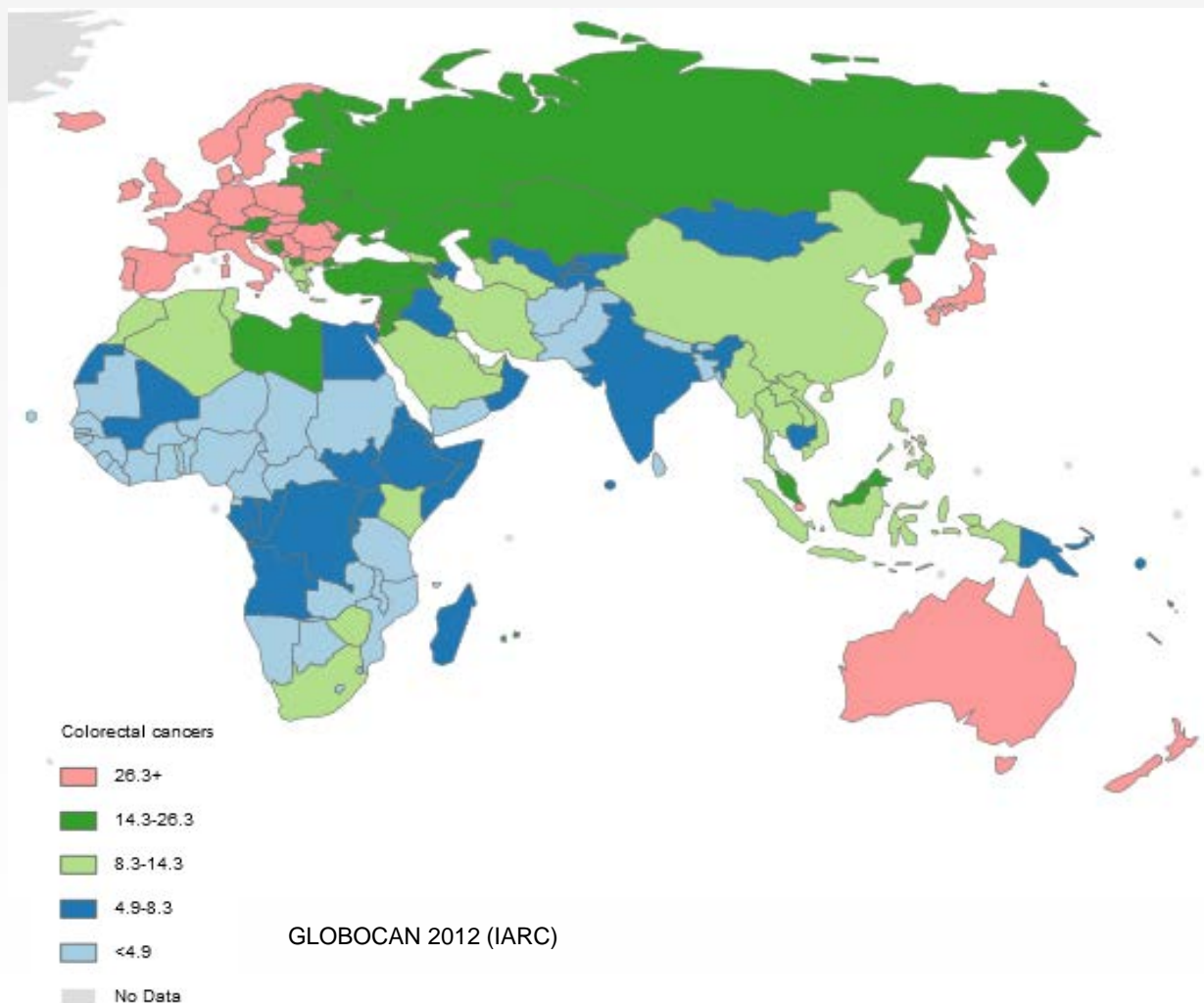


Outline

- ❖ **CRC in the Asia-Pacific**
- ❖ In which populations is screening justified?
- ❖ Risk- based algorithms for lower incidence countries
- ❖ Conclusion



Colorectal Cancer Incidence in the Asia-Pacific

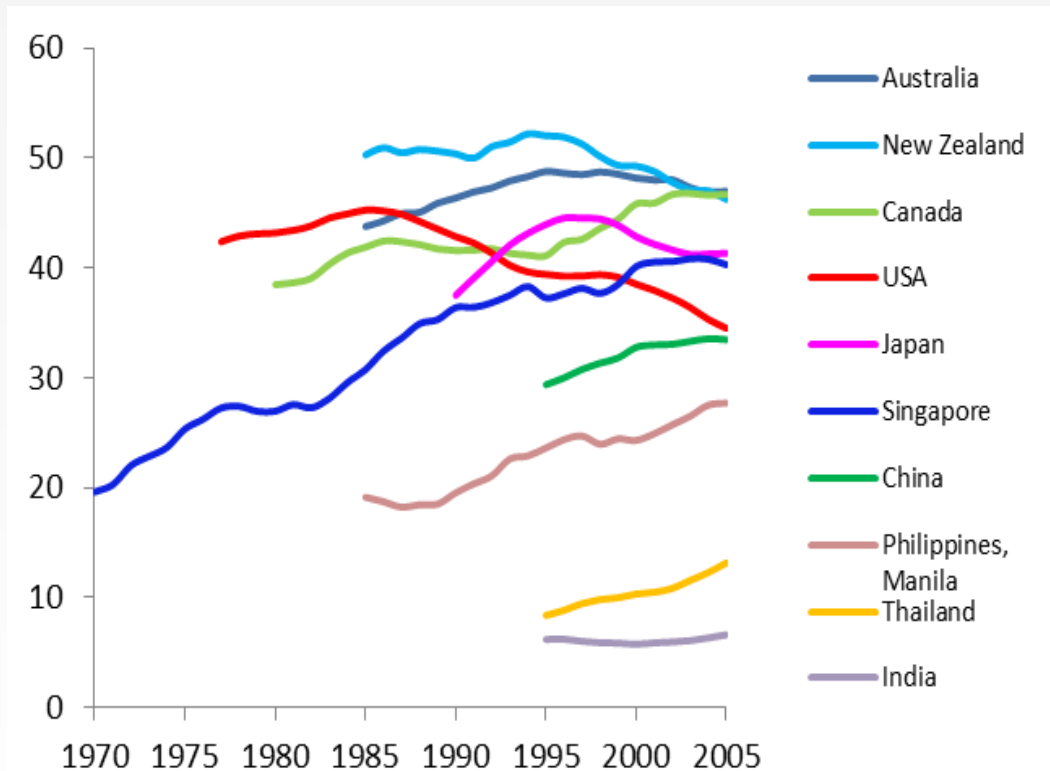


- **4th most common cancer in Asia, 600,000 new cases in 2012.**
- ~300,000 deaths annually
- Wide variation in incidence
- More in developed regions



Burden of Colorectal Cancer in the Asia-Pacific

Time Trend in CRC Incidence in Selected Asia-Pacific Countries (1970-2005)



IARC, CI5plus

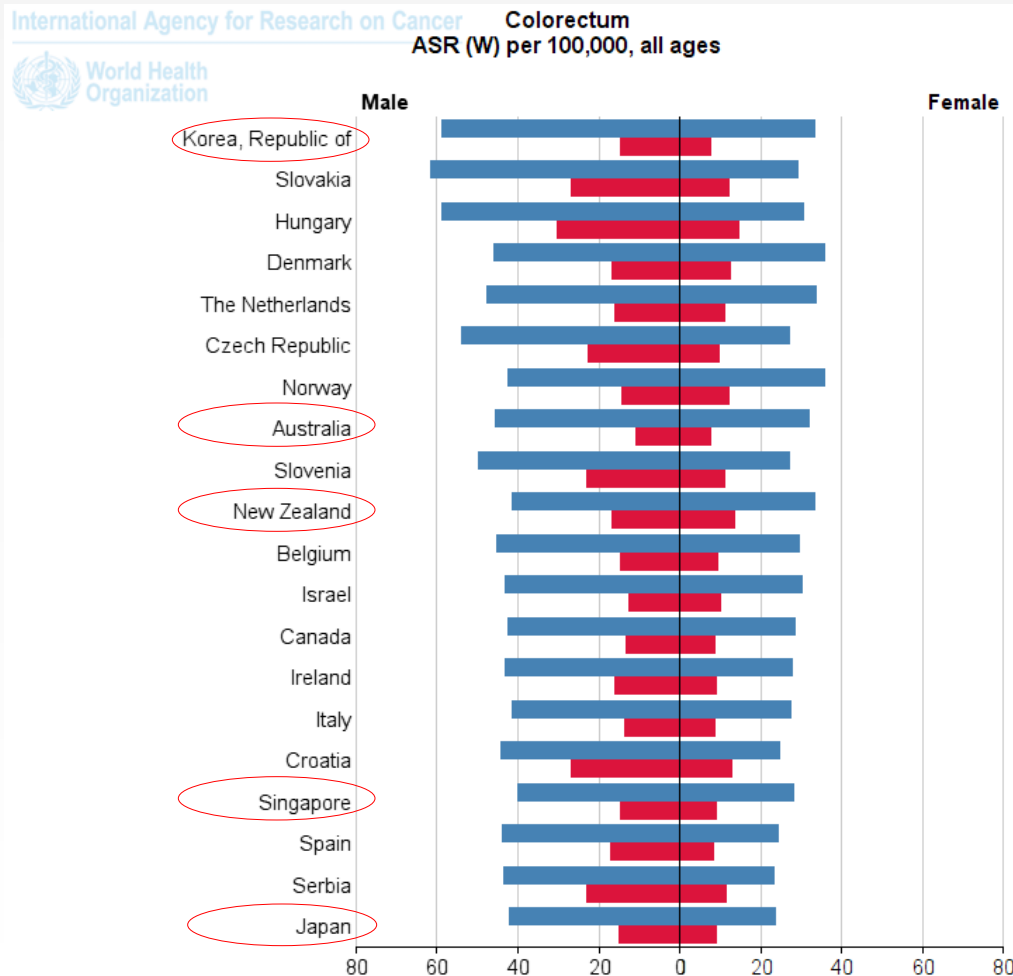
CRC incidence is increasing in many Asia-Pacific countries

- Aging population
- Change of life style, food
- Smoking
- Obesity



Burden of Colorectal Cancer in the Asia-Pacific

Top 20 in the world



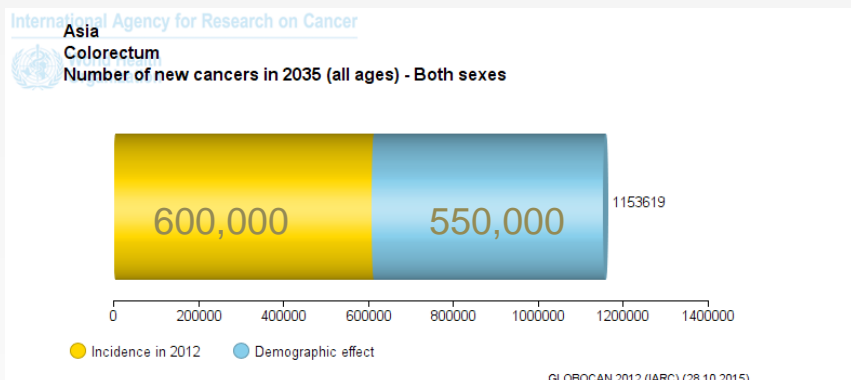
- 5 countries from Asia-Pacific are among the top 20 highest incidence rates in the world.



Burden of Colorectal Cancer in Asia

Future Burden of CRC in Asia : Prediction by Globocan

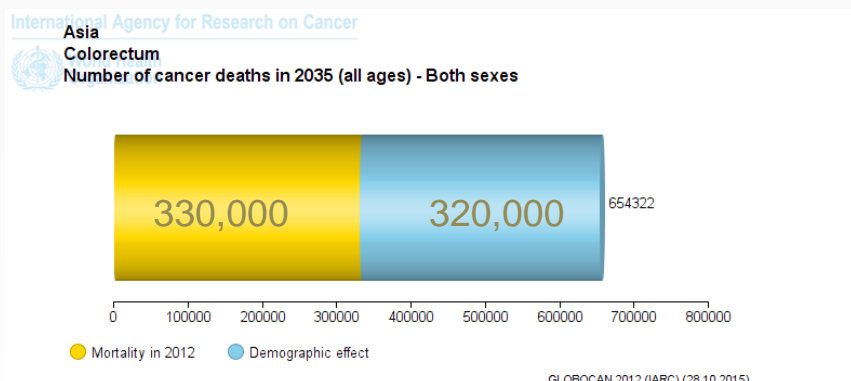
Incidence



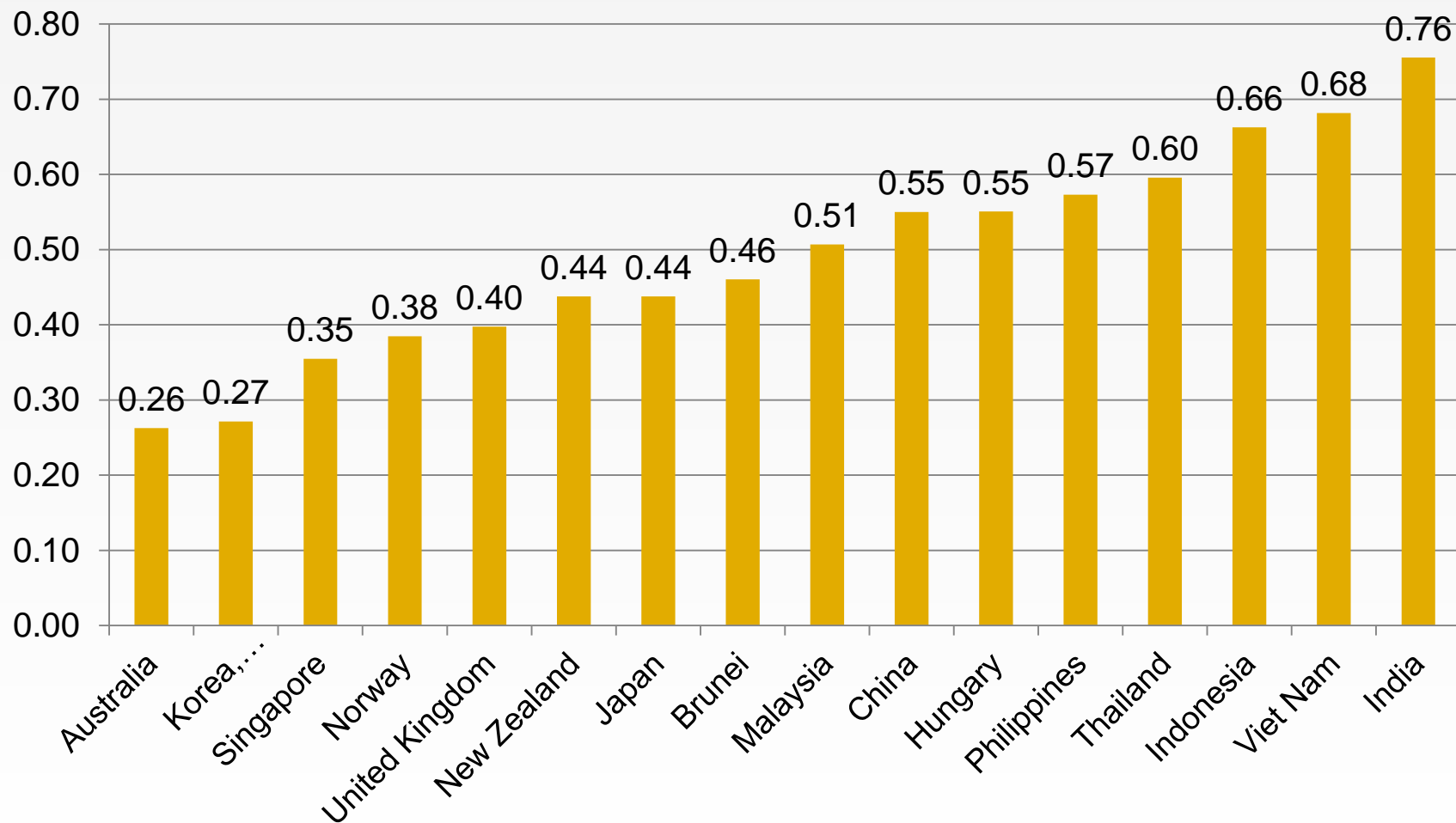
1,150,000

by 2035

Mortality



Ratio of CRC Mortality to Incidence (M:I)



Screening reduces incidence & mortality

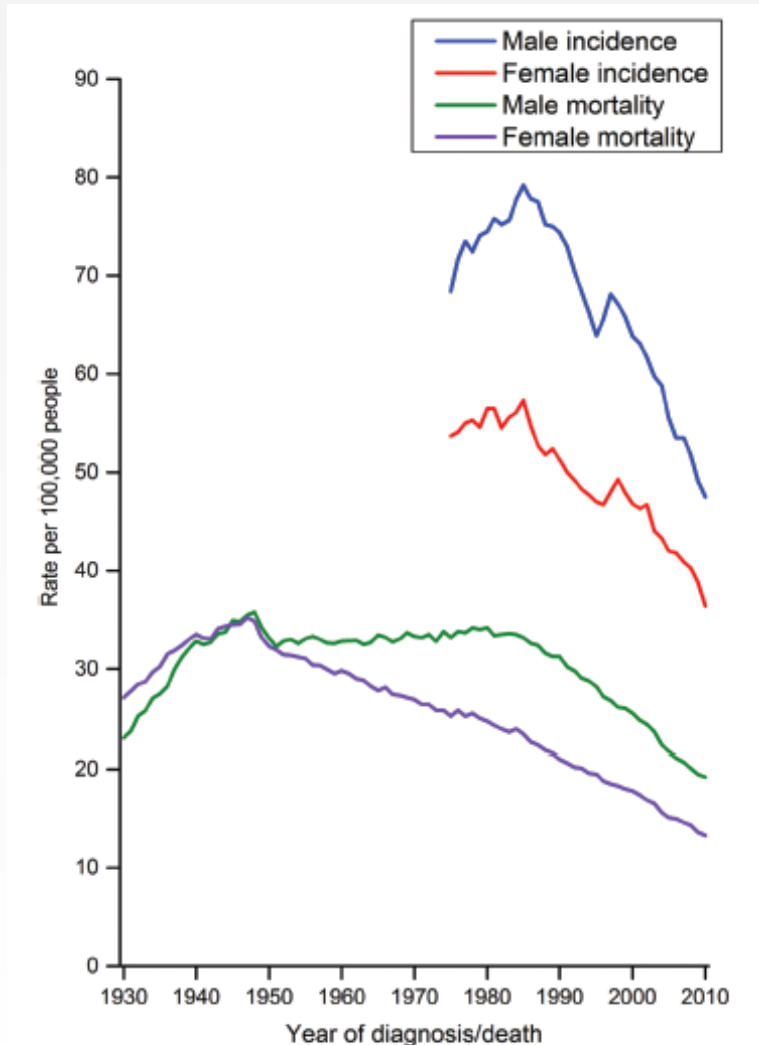


FIGURE 4. Long-Term Trends in Colorectal Cancer Incidence (1975-2010) and Mortality (1930-2010) Rates* by Sex, United States.

Decline in CRC incidence and mortality in the US.

Reasons

1. Effect of increased screening
2. Reduction of risk factors
3. Improved treatment

Cancer 2010;116:544-73

Siegel et al, CA Cancer J Clin. 2014; 64(2):104-17



Risk Factors for CRC

- Age
- Gender
- Ethnicity
- Smoking
- Heavy alcohol consumption
- Diet
- Obesity

- **Personal or family hx of CRC, polyps**
- **Genetic syndromes (FAP, Lynch)**
- **Inflammable bowel disease (Crohn's disease, or ulcerative colitis)**



Risk Factors for CRC – Red meat and processed meat

International Agency for Research on Cancer



PRESS RELEASE
N° 240

26 October 2015

IARC Monographs evaluate consumption of red meat and processed meat

Lyon, France, 26 October 2015 – The International Agency for Research on Cancer (IARC), the cancer agency of the World Health Organization, has evaluated the carcinogenicity of the consumption of red meat and processed meat.

Red meat

After thoroughly reviewing the accumulated scientific literature, a Working Group of 22 experts from 10 countries convened by the IARC Monographs Programme classified the consumption of red meat as *probably carcinogenic to humans* (Group 2A), based on *limited evidence* that the consumption of red meat causes cancer in humans and *strong* mechanistic evidence supporting a carcinogenic effect.

This association was observed mainly for colorectal cancer, but associations were also seen for pancreatic cancer and prostate cancer.

Processed meat

Processed meat was classified as *carcinogenic to humans* (Group 1), based on *sufficient evidence* in humans that the consumption of processed meat causes colorectal cancer.

Carcinogenic for CRC
recognized by IARC:

- Processed meat, Group
- Red meat, Group 2A



Risk Factors for CRC – Ethnicity

TABLE 4. Risk factors for colorectal neoplasm

	OR (95% CI)	P
Male sex	1.5 (1.1-2.2)	0.019
Age	1.05 (1.03-1.07)	0.001
Family History	2.5 (1.5-4.2)	0.001
Ethnicity		0.001
Chinese	Reference	
Japanese	4.2 (1.3—13.9)	0.019
Korean	2.0 (1.3-2.9)	0.001



Risk Factors for CRC – Ethnicity

- Chinese has the highest incidence of CRC compared with Malay and Indian in same environment in Singapore

Ethnic Group	No.	CIR (95%CI)	ASIR (95%CI)	RR (95%CI)	RR (95%CI)
Chinese	8,070	57.0 (55.7-58.2)	34.1 (33.3-34.8)	2.11 (2.34- 1.93)	1.31 (1.38 – 1.24)
Malay	776	30.4 (28.3-32.6)	26.1 (24.2-28.0)	-	Reference
Indian	307	17.5 (15.6-19.5)	16.1 (14.2-18.0)	Reference	-
Others	171	27.1 (23.1-31.2)	32.9 (27.5-38.3)	-	-
All	9324	48.8 (47.8-49.8)	32.1 (31.5-32.8)	-	-

p<0.001

Crude and Age-standardised Incidence Rate for CRC by Ethnic Group in Singapore (2010-2014)



Risk Factors for CRC

Statement 2: There are ethnic differences in CRC risk and screening programme should take this into account.

Accept completely (%)	Accept with some reservation (%)	Accept with major reservation (%)	Reject with reservation (%)	Reject completely (%)
69.4%	27.8%	2.8%	0%	0%

Quality of Evidence: II-3

Classification of Recommendations: B

An updated Asia Pacific Consensus Recommendations on colorectal cancer screening. Sung JJY, et al. **Gut** 2015; 64:121–132.

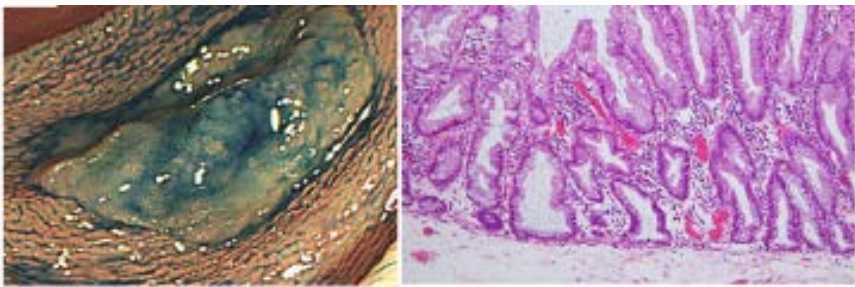


SSA in Asian Population

The Presence of Large Serrated Polyps Increases Risk for Colorectal Cancer

Sakiko Hiraoka et al, Gastroenterology 2010;139:1503–1510

	Subjects w/o advanced neoplasia (n =8626)	Subjects with advanced neoplasia (n =1573)	Univariate analysis, OR (95% CI)	Multivariate analysis, OR (95% CI)
Number of small adenomas				
0–3	8537	1470	1.00	1.00
≥4	89	103	6.72(5.03-8.97)	5.12 (3.80-6.88)
Large sessile polyps				
No	8548	1511	1.00	1.00
Yes	78	62	4.50 (3.21-6.30)	4.01 (2.83-5.69)



Outline

- ❖ CRC in the Asia-Pacific
- ❖ **In which populations is screening justified?**
- ❖ Risk- based algorithms for lower incidence countries
- ❖ Conclusion



Asia Pacific Working Group for Colorectal Ca

An updated Asia Pacific Consensus
Recommendations on colorectal cancer
screening

Gut

J J Y Sung,¹ S C Ng,^{1,2} F K L Chan,^{1,2} H M Chiu,³ H S Kim,⁴ T Matsuda,⁵ S S M Ng,⁶
J Y W Lau,⁶ S Zheng,⁷ S Adler,⁸ N Reddy,⁹ K G Yeoh,¹⁰ K K F Tsoi,¹¹ J Y L Ching,²
E J Kuipers,¹² L Rabeneck,¹³ G P Young,¹⁴ R J Steele,¹⁵ D Lieberman,¹⁶ K L Goh¹⁷

- Modified Delphi process ((literature review, individual statement review, consensus meeting, voting and final consensus statement)
- Vote based on review of the literature on a Likert scale anchored by 1–5
- Consensus was achieved when >80% of the voting members indicated ‘accept completely’ or ‘accept with some reservation’
- Hong Kong, 9 - 10 June 2013
- Key opinion leaders, 14 countries



Screening Guidelines

2015 Asia Pacific Consensus Recommendations for CRC screening

An updated Asia Pacific Consensus Recommendations on colorectal cancer screening. Sung JJY, et al. **Gut** 2015; 64:121–132.

- Age range for CRC screening is defined as 50–75 years.
- Quantitative FIT, but not gFOBT, is preferred for average-risk subjects.
- A risk-stratified scoring system is recommended to select high-risk patients for early colonoscopy.
- Quality control measures should be included in CRC screening programmes.



2015 Asia Pacific Consensus Recommendations

Statement 1: Population screening for CRC is recommended in those Asia-Pacific regions where the incidence of CRC is high. In both genders, subjects aged 50 to 75 years are the target for CRC screening.

Level of agreement: A 69.4%, B=30.6%, C=0%, D=0%, E=0%.

Quality of evidence: II-2

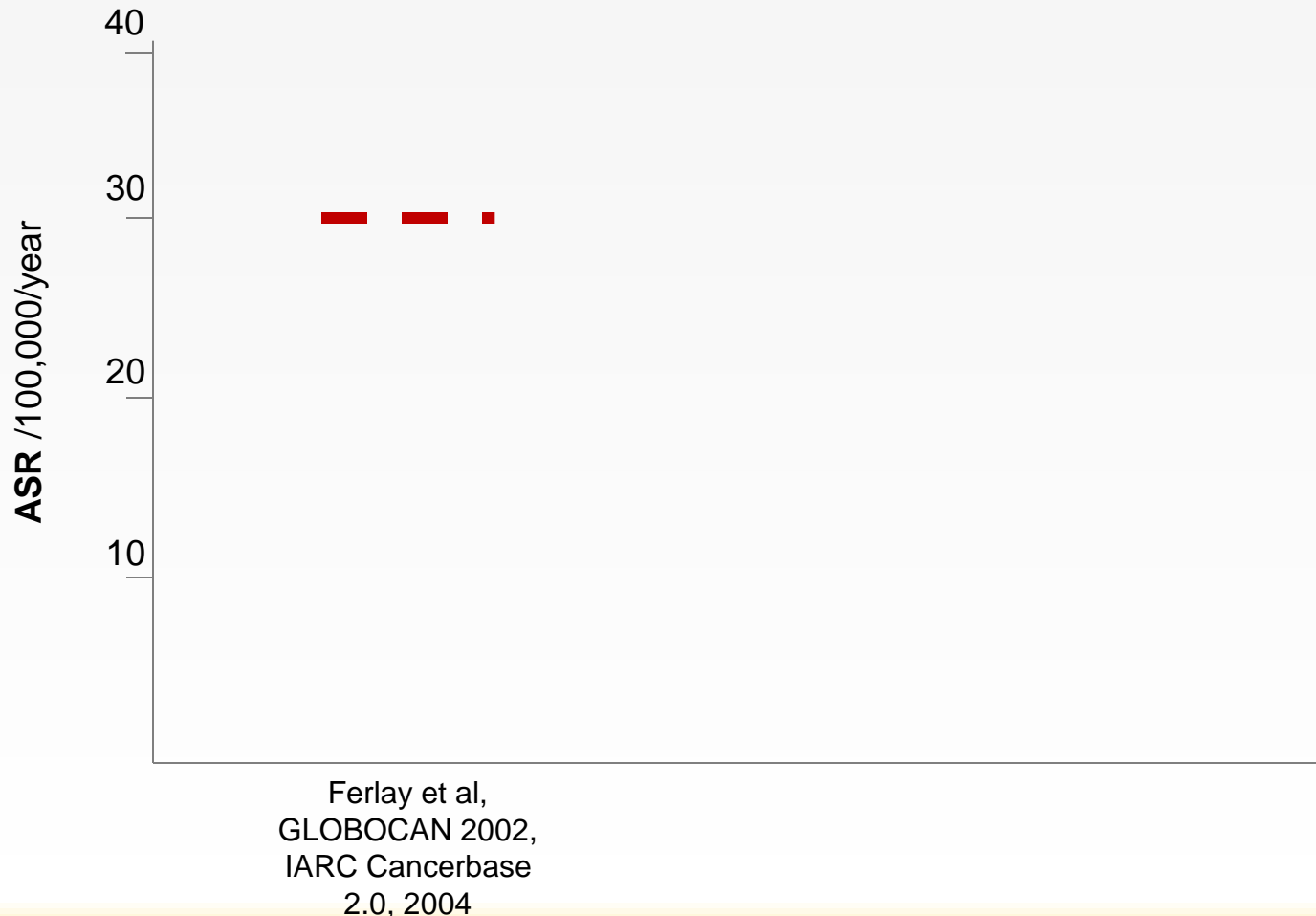
Classification of recommendation: B

An updated Asia Pacific Consensus Recommendations on colorectal cancer screening. Sung JJY, et al. **Gut** 2015; 64:121–132.

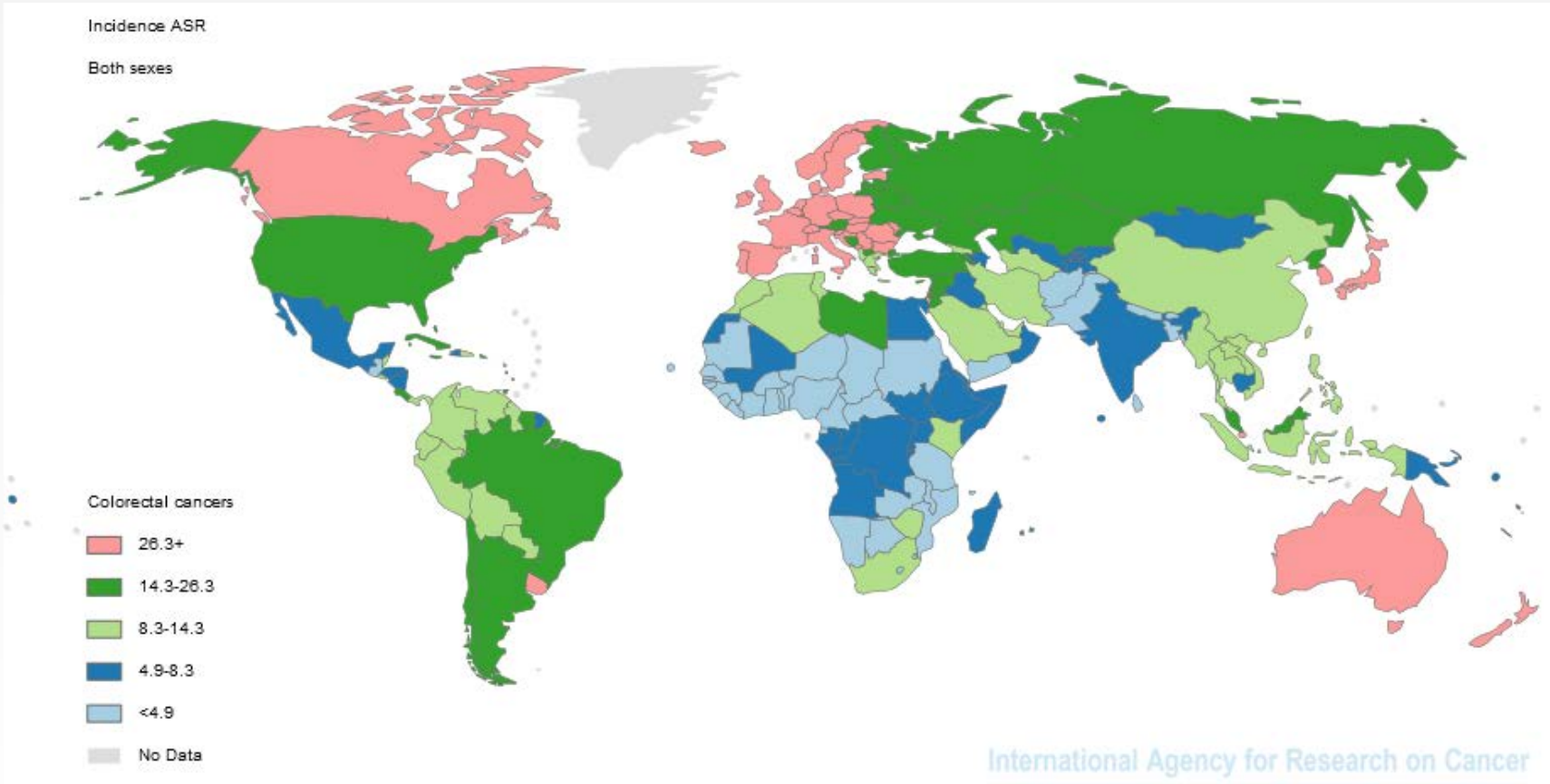


2015 Asia Pacific Consensus Recommendations

Statement 1: Population screening for CRC is recommended in those Asia-Pacific regions where the incidence of CRC is **high**.



Colorectal Cancer Incidence



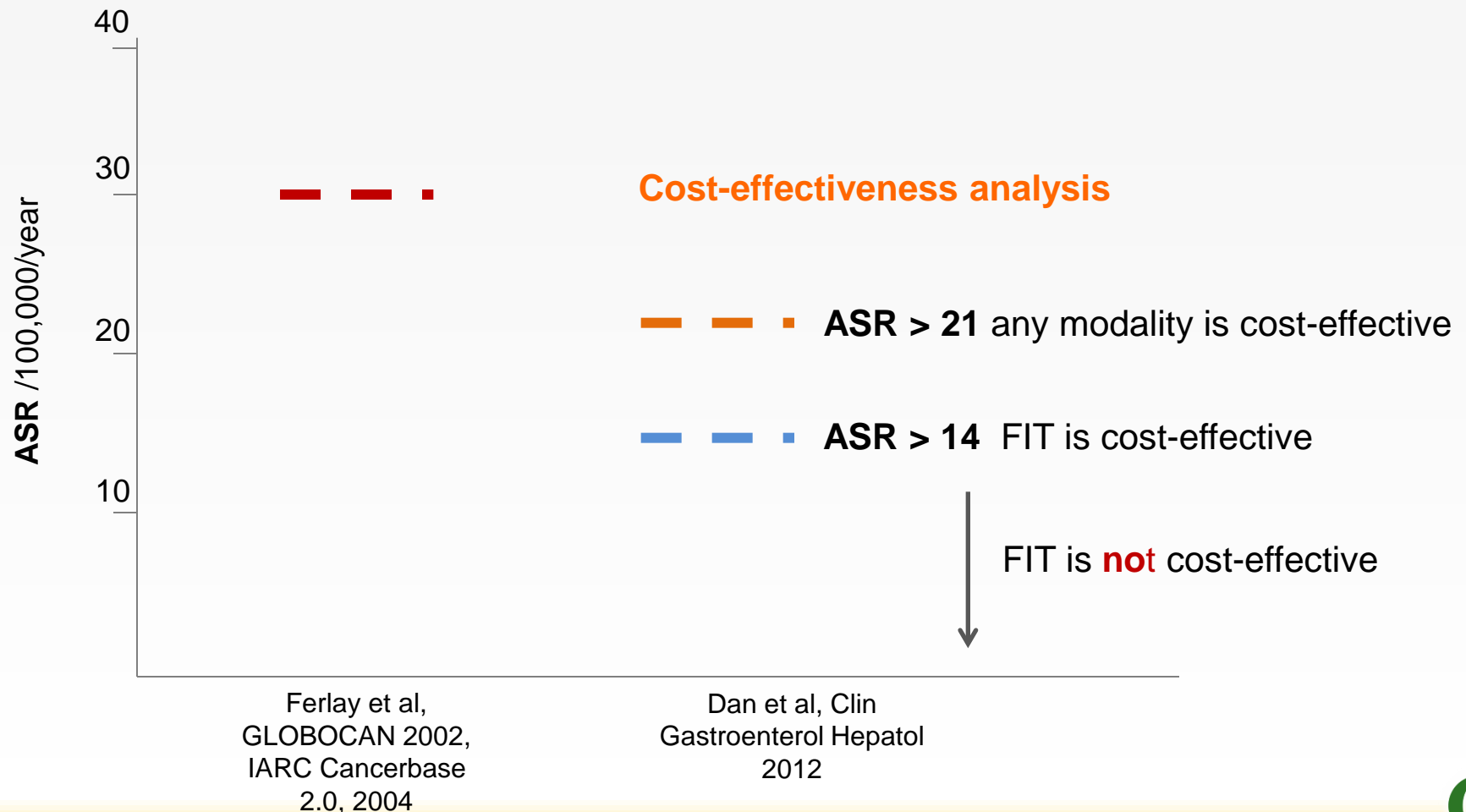
Source: GLOBOCAN 2012 (IARC)

International Agency for Research on Cancer



Population Screening for CRC in Asia

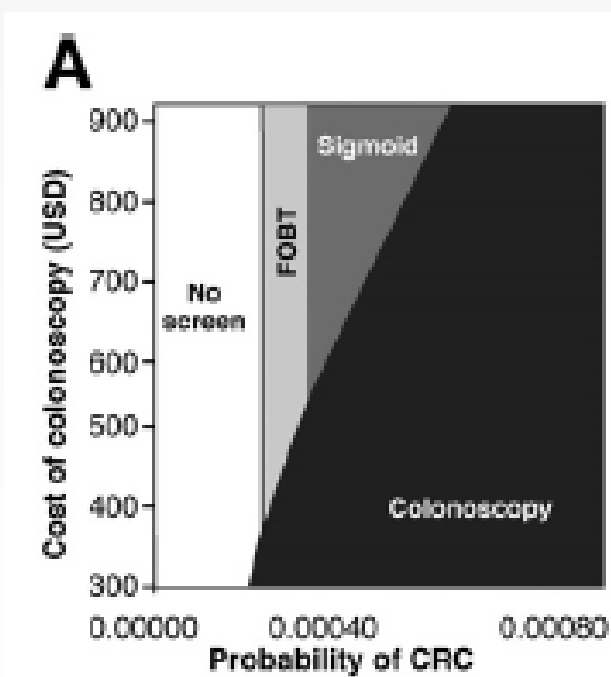
Statement 1: Population screening for CRC is recommended in those Asia-Pacific regions where the incidence of CRC is **high**.



Cost-Effectiveness of CRC Screening

Cost-effectiveness of Screening is related to the Incidence (ASR) of CRC

Cost-effectiveness analysis:



- ASR for CRC $> 21/100,000$, any screening modality is cost-effective.
- ASR for CRC $< 14/100,000$, FIT is not cost-effective.
- ASR for CRC $< 21.7/100,000$, colonoscopy once in 10 years is not cost-effective (ICER $>$ USD 50,000/ QALY)
- When cost of colonoscopy $<$ USD300, colonoscopy is the most cost-effective option.

Dan YY, ...Yeoh KG. Screening based on risk for colorectal cancer is the most cost-effective approach. Clin Gastroenterol Hepatol 2012; 10(3):266-71.

Population Risk for CRC & Cost Effectiveness

COUNTRY	ASR (W)
Korea	45.0
Taiwan	43.8
Australia/ NZ	38.2
Singapore	33.7
Japan	32.2
Brunei	25.0
Malaysia	18.3
China	14.2
Philippines	13.1
Indonesia	12.8
Thailand	12.4
Viet Nam	10.1
India	6.1
Mongolia	6.0
Pakistan	4.0

ASR > 21
any modality is cost-effective

FIT is cost-effective

ASR < 14
FIT is **not** cost-effective

Source: GLOBOCAN 2012, IARC;
Taiwan Cancer Registry, 2011

Dan YY, Yeoh KG. Screening based on risk for colorectal cancer is the most cost-effective approach. Clin Gastroenterol Hepatol 2012; 10(3):266-71.



Burden of Health in Developing Countries

- **CRC incidence is low in developing countries**
- **Communicable disease has heavier weight as the cause of death compared with cancer**
- **Among cancers, CRC is less common compared to liver and cervical cancer**

TABLE I – WORLDWIDE ESTIMATION IN 2005 OF THE CRUDE AND ASR OF INCIDENCE FOR CRC IN DEVELOPED AND DEVELOPING COUNTRIES FOR MEN AND WOMEN

CRC incidence/100,000	Men		Women	
	Crude rate/100,000	ASR/100,000	Crude rate/100,000	ASR/100,000
Developed countries	60.8	40.0	50.9	26.6
Developing countries	7.7	10.2	6.5	10.7

Source: Globocan 2002, IARC database.¹
ASR, age-standardized rate; CRC, colorectal cancer.

TABLE IV – RESPECTIVE IMPACT OF MORTALITY BY CANCER ALL CAUSES (BOTH SEXES) AND BY COMMUNICABLE DISEASES IN THE GENERAL MORTALITY IN PERSONS UNDER AGE 70, IN VARIOUS COUNTRIES, WITH PREVISIONS FOR 2005 AND 2030 (BASED ON 2002 WHO BURDEN OF DISEASE ESTIMATES)

Countries	% Global mortality in 2005		% Global mortality in 2030	
	Cancer	Communicable diseases	Cancer	Communicable diseases
Japan	31.7	11.7	29.9	10.2
France	28.3	6.1	27.9	4.3
Slovakia	23.4	3.4	25.2	2.7
USA	23.2	5.9	22.4	4.7
China	20.2	9.3	23.6	5.8
India	8.0	36.2	11.9	21.9
South Africa	5.3	67.7	5.9	66.4
Kenya	4.7	68.2	8.0	55.1
Nigeria	4.4	68.9	6.8	57.8

Source: World Health Organization-Global InfoBase—Impact cancer.¹⁵

TABLE V – ESTIMATION OF THE NUMBER OF INCIDENT CASES OF CANCER OCCURRING IN 2005 IN DEVELOPED AND IN DEVELOPING COUNTRIES

Site of cancer	World no. of cases	Developed countries no. of cases	Developing countries no. cases and % Total
Colorectal (both sexes)	972,350	665,700	306,850 (31.6%)
Liver (both sexes)	623,400	110,400	513,000 (82.3%)
Breast (women)	1,150,200	636,100	514,100 (44.7%)
Cervix (women)	492,800	83,400	409,400 (83.1%)

Source: Globocan 2002, IARC database.¹

Outline

- ❖ CRC in the Asia-Pacific
- ❖ In which populations is screening justified?
- ❖ **Risk- based algorithms for lower incidence countries**
- ❖ Conclusion

2015 Asia Pacific Consensus Recommendations

Statement 4: The Asia Pacific Risk Score is useful to identify subjects with a high risk of colorectal advanced neoplasia

Level of agreement: A= 55.6%, B=38.9%, C=5.5%, D=0%, E=0%

Quality of evidence: II-2

Classification of recommendation: B

An updated Asia Pacific Consensus Recommendations on colorectal cancer screening. Sung JJY, et al. **Gut** 2015; 64:121–132.



Asia Pac Risk Score (APCS) Identifies High Risk Group

Risk Stratification Tool

Gut 2011; 60(9):1236-41

The Asia-Pacific Colorectal Screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects

Khay-Guan Yeoh,¹ Khek-Yu Ho,¹ Han-Mo Chiu,² Feng Zhu,¹ Jessica Y L Ching,³ Deng-Chyang Wu,⁴ Takahisa Matsuda,⁵ Jeong-Sik Byeon,⁶ Sang-Kil Lee,⁷ Khean-Lee Goh,⁸ Jose Sollano,⁹ Rungsun Rerknimitr,¹⁰ Rupert Leong,¹¹ Kelvin Tsoi,³ Jaw-Town Lin,² Joseph J Y Sung,³ for the Asia-Pacific Working Group on Colorectal Cancer

Risk Factor	Criteria	Points
Age	50-69	2
	≥70 yrs	3
Sex	Male	1
Family History	1 st degree	2
Smoking	Current / Ex	1

Score 0 to 7

Asia Pacific CRC Screening Score (APCS)

Prevalence and relative risk of colorectal adv neoplasia by Risk score

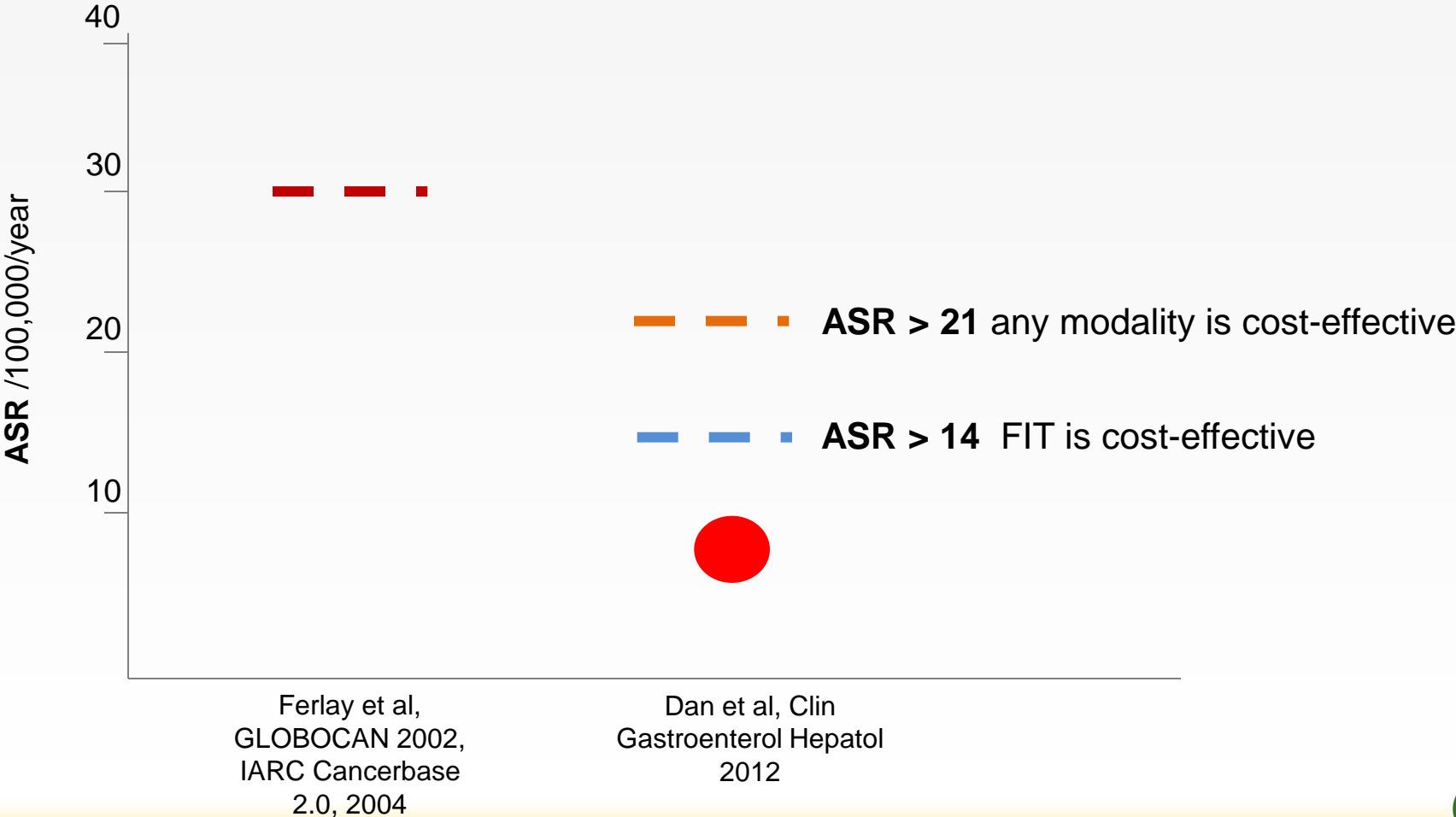
Risk Tier	Risk Score	No. of subjects (%)	Colorectal Adv neoplasm (%)	RR (95% CI)
Low risk	0 – 1	559 (29.5)	7 (1.3)	Reference
Intermediate	2 – 3	966 (51.1)	31 (3.2)	2.6 (1.1-6.0)
High risk	4 – 7	367 (19.4)	19 (5.2)	4.3 (1.8-10.3)
Total		1892 (100)	57 (3.0)	

The high risk group has 4.3 x more advanced neoplasm vs low-risk group.

Gut 2011; 60(9):1236-41

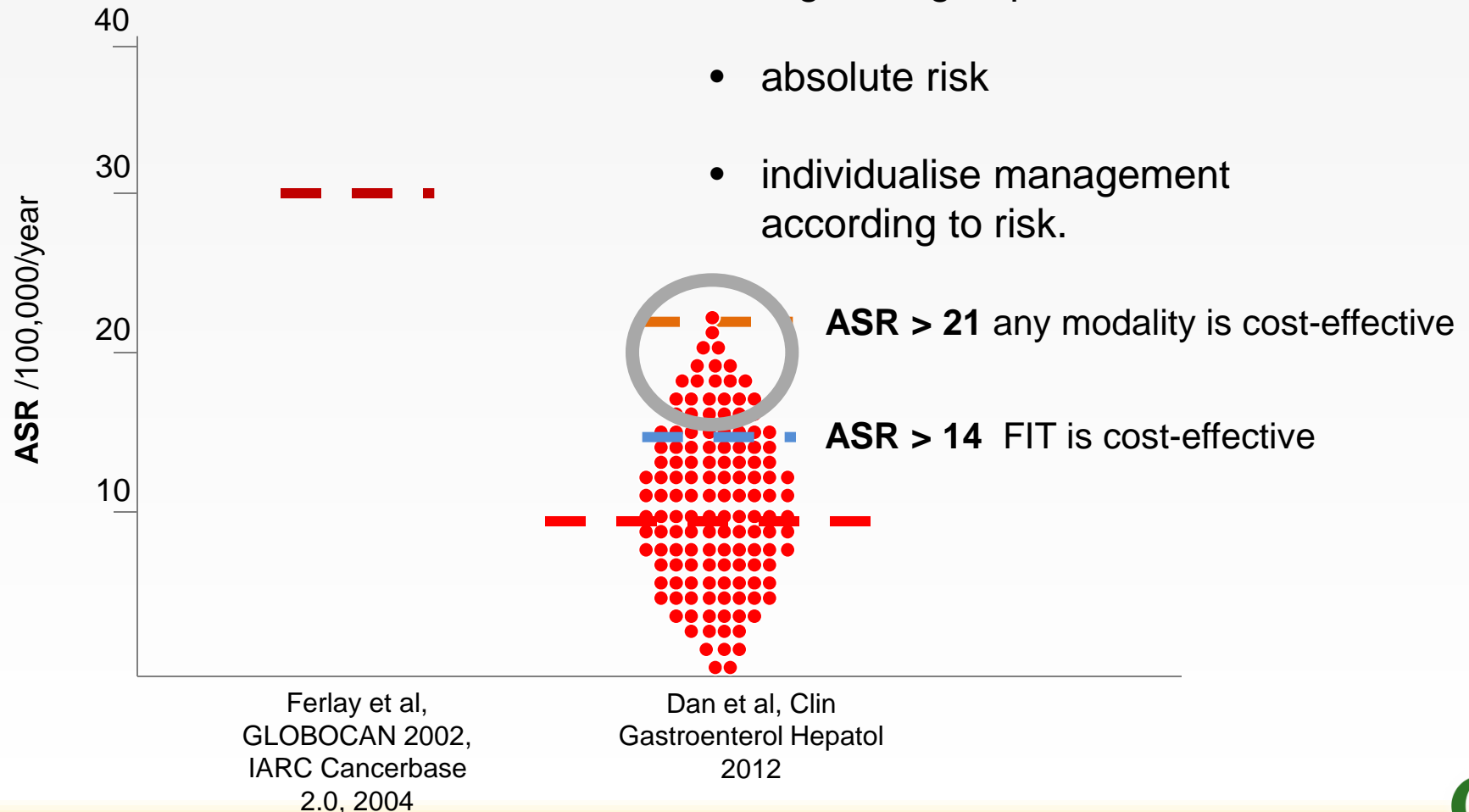


Countries with a low incidence rate for CRC



Using APCS Risk Score to Select High Risk Individuals, in countries with low incidence.

- Using the APCS risk score, the high risk group has 4x risk vs AR.
- absolute risk
- individualise management according to risk.



Asia Pacific CRC Screening Score (APCS)

Prevalence and relative risk of colorectal adv neoplasia by Risk score

Risk Tier	Risk Score	No. of subjects (%)	Colorectal Adv neoplasm (%)	RR (95% CI)
Low risk	0 – 1	559 (29.5)	7 (1.3)	Reference
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Total		1892 (100)	57 (3.0)	

The high risk group has 4.3 x more advanced neoplasm vs low-risk group.

Gut 2011; 60(9):1236-41



Screening Guidelines

CRC screening guidelines USA 2012

Ann Intern Med. 2012



Guidance Statement 1: ACP recommends that clinicians perform **individualized assessment of risk** for colorectal cancer in all adults.

Guidance Statement 2: ACP recommends that clinicians screen for colorectal cancer in average-risk adults starting at the age of 50 years and in high-risk adults starting at the age of 40 years or 10 years younger than the age at which the youngest affected relative was diagnosed with colorectal cancer.

Guidance Statement 3: ACP recommends using a stool-based test, flexible sigmoidoscopy, or optical colonoscopy as a screening test in patients who are at average risk. **ACP recommends using optical colonoscopy as a screening test in patients who are at high risk.** Clinicians should select the test based on the benefits and harms of the screening test, availability of the screening test, and patient preferences.

Guidance Statement 4: ACP recommends that clinicians stop screening for colorectal cancer in adults over the age of 75 years or in adults with a life expectancy of less than 10 years.

Asia Pacific CRC Screening Score (APCS)

- Include important risk factors in the population
- Able to differentiate risk groups
- Easy to use
- Can be replicated

APCS score

- ✓ Age
- ✓ Gender
- ✓ Family Hx
- ✓ Smoking
- + BMI

Modified APCS risk score

Modified Asia-Pacific Colorectal Screening (APCS) Score to Stratify Risk for Colorectal Advanced Neoplasia in Asymptomatic Population in Asian subjects

Joseph J. Y. Sung, Martin C. Wong, Kelvin K. Tsoi

Risk category	No. of subjects (%)	Colorectal Adv neoplasm (%)	RR (95% CI)
Low risk (0)	110 (2.0)	1 (0.9)	1.00
Intermediate (1-3)	4148 (75.9)	169 (4.1)	4.48 (0.63-31.7)
High risk (4-6)	1205 (22.1)	126 (10.5)	11.5 (1.62-81.5)
Total	5463 (100)	296 (5.4)	

Modified APCS score

- ✓ Age
- ✓ Gender
- ✓ Family Hx
- ✓ Smoking
- ✓ BMI

Scoring Systems Published Recently

Study, Yr	Population	Risk Factors	Scores	Risk for Adv Neo	% of adv neo (100%)
Yeoh et al, 2011	Asian 860 1892	Age, sex, first-degree relative with CRC, Smoking (4)	0 - 7 0, 1 = average 2, 3 = moderate 3 to 7 = high	1.3% 4.4% 7.9%	12% 55% 33%
Cai et al. 2012	Chinese 5229 2312	Age,sex,diabetes,smoking,green vegetables, pickled food, fried food, white meat (7)	0 - 13 0 to 3 = low >3 = high	2.6% 10.2%	20% 80%
Tao et al, 2014	German 7891 3519	Age, sex, FHx,smoking, ethanol,NSAID use, prior colono, polyp history, red meat consumption (8)	Risk quintiles: very low, low, Intermediate, high, very high	4.9%, 9.2%, 10.1%, 14.6%, 18.9%	10% 18% 20% 25% 27%
Kaminski et al, 2014	Poland 17979 17939	Age, sex, FHx, smoking, BMI (5)	0 – 8 0 = low 7-8 = high	1.32% 19.1%	0.2% 2%
Kim et al, 2015	Korean 3561 1316	Age, sex, first-degree relative with CRC, smoking, BMI (5)	0 – 8 0, 1 = average 2, 3 = moderate 3 to 8 = high	2.0% 3.7% 10.9%	14% 46% 40%
Imperiale et al, 2015	US, 94% white 2993 1467	Age, sex, first-degree relative with CRC, smoking, waist circumference (5)	0 - 12 0 = very low 1 to 3 = low 4 to 6 = intermediate >6 = high risk	1.7% 3.3% 11% 22%	2% 18% 41% 39%

Other Risk Scores

T. F. Imperiale et al, Derivation and Validation of a Scoring System to Stratify Risk for Advanced Colorectal Neoplasia in Asymptomatic Adults, *Ann Intern Med* 2015;163:339-346.

Variable	Odds Ratio (95% CI)	Log-Odds Coefficient	Score
Age (per 1-y increase)	1.06 (1.04-1.08)	0.0592	0-4†
Sex			
Female	Reference	-	0
Male	1.69 (1.30-2.20)	0.5225	1
≥1 first-degree relative with CRC	1.39 (0.94-2.04)	0.3259	1
Waist circumference			
Small‡	Reference	-	0
Medium§	1.41 (1.08-1.84)	0.3426	1
Large	1.88 (1.14-3.09)	0.6313	2
Cigarette smoking			
0 pack-years	Reference	-	-
0 to <30 pack-years	2.07 (1.52-1.84)	0.7250	2
≥30 pack-years	3.33 (2.43-4.58)	1.2042	4

- Caucasian population in US, split-sample validation
- Five risk factors with 0-12 points
- Four risk categories with highest risk of 22% of advanced neoplasia, compared with lowest one of 1.7%
- Use different screening method in different risk categories
- Save resources

Table 4. Risk for Advanced Neoplasia and Likelihood Ratios in Each Risk Group Within Derivation and Validation Sets

Risk Group	Score*	Derivation Set (n = 2993)			Validation Set (n = 1467)		
		Participants, n (%)	Risk (95% CI), %	Likelihood Ratio (95% CI)†	Participants, n (%)	Risk (95% CI), %	Likelihood Ratio (95% CI)†
Very low	0	260 (8.7)	1.92 (0.63-4.43)	0.19 (0.08-0.46)	121 (8.2)	1.65 (0.20-5.84)	0.18 (0.05-0.73)
Low	1-3	1331 (44.5)	4.88 (3.79-6.18)	0.50 (0.40-0.62)	665 (45.3)	3.31 (2.08-4.97)	0.37 (0.25-0.55)
Intermediate	4-6	937 (31.3)	9.93 (8.09-12.0)	1.07 (0.90-1.28)	466 (31.7)	10.9 (8.26-14.1)	1.34 (1.07-1.68)
High	>6	465 (15.5)	24.9 (21.1-29.1)	3.23 (2.73-3.83)	215 (14.7)	22.3 (16.9-28.5)	3.14 (2.42-4.08)

Outline

- ❖ CRC in the Asia-Pacific
- ❖ In which populations is screening justified?
- ❖ Risk- based algorithms for lower incidence countries
- ❖ **Conclusion**

Conclusions (1)

1. CRC screening unequivocally improves survival and reduces mortality from colorectal cancer. **(Saquib et al. Int. J. Epidemiol 2015: 44 (1): 264-277)**
1. Encouraging decline in CRC incidence and mortality in the US, due to screening, improved treatment and control of risk factors. **(Cancer 2010;116:544–73).**
2. Consensus recommendations for the Asia Pacific region **(Sung JJY, et al. Gut 2015)**
 - Age range for CRC screening is defined as 50–75 years.
 - Quantitative FIT, but not gFOBT, is preferred for average-risk subjects.
 - A risk-stratified scoring system is recommended to select high-risk patients for early colonoscopy



Conclusions (2)

4. *In What Asia-Pacific Populations is CRC Screening Justified?*

Population screening is recommended for communities where the incidence of CRC is high. **(Sung JJY, et al. Gut 2015)**

5. In countries with low incidence of CRC, where population screening is not cost-effective, a risk-based algorithm may be helpful on identifying high-risk individuals for screening.

6. The Asia Pacific CRC Risk Score (APCS) is useful in identifying subjects with a high risk of colorectal advanced neoplasia. **(Gut 2015)**



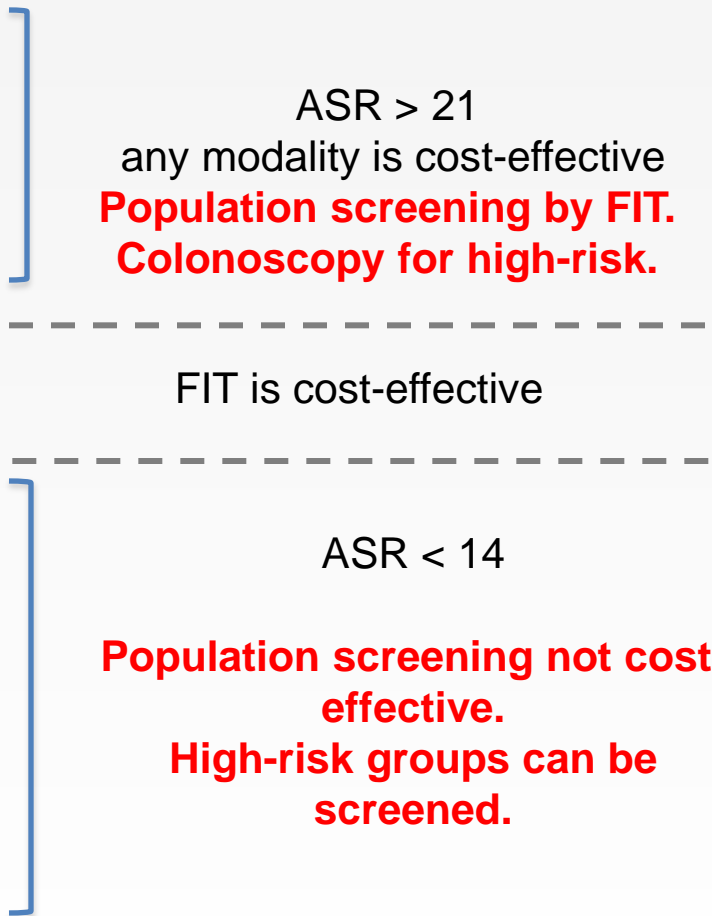
Conclusions (3)

7. **The Asia Pacific CRC Risk Score (APCS)** enables an individualized assessment of risk for advanced neoplasia, it is simple & easy to use, and modelling suggests this approach is cost-effective.
 - In low incidence countries, it can be used to identify high-risk individuals for screening.
 - In high incidence countries, prioritise high risk individuals for colonoscopy (**Gastroenterol 2015, in press**).



Population Risk for CRC & Cost Effectiveness

COUNTRY	ASR (W)
Korea	45.0
Taiwan	43.8
Australia/ NZ	38.2
Singapore	33.7
Japan	32.2
Brunei	25.0
Malaysia	18.3
China	14.2
Philippines	13.1
Indonesia	12.8
Thailand	12.4
Viet Nam	10.1
India	6.1
Mongolia	6.0
Pakistan	4.0



Source: GLOBOCAN 2012, IARC;
Taiwan Cancer Registry, 2011



Using APCS to select HR group for Early Colonoscopy

Gastroenterology

Article in Press

A Risk-scoring System Combined with a Fecal Immunochemical Test Is Effective in Screening High-risk Subjects for Early Colonoscopy to Detect Advanced Colorectal Neoplasms

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- Total 5657 subject from 12 AP regions
- LR, MR – FIT while HR – early colonoscopy
- Advanced neoplasia in LR, MR and HR were 1.5%, 5.1% and 10.9% respectively
- 70.6% of advanced neoplasia were in HR and asked to go for early colonoscopy
- Use of the APCS score-based algorithm in triaging subjects for FIT or colonoscopy can substantially reduce colonoscopy workload