肿瘤的一级预防

Strategies and long-term planning

Professor Ping Zhao

President Cancer Foundation of China

Chair Cancer Prevention & Control Committee

of Chinese Preventive Medicine Association

Oct 3 2018 Kuala Lumpur Malaysia

The Duty is weightier than Mount Tai

President Cancer Foundation of China

Chair Cancer Prevention & Control Committee of Chinese Preventive Medicine Association

Pre-director Cancer Hospital CAMS

Pre-Chairman National Office for Cancer Prevention & Control

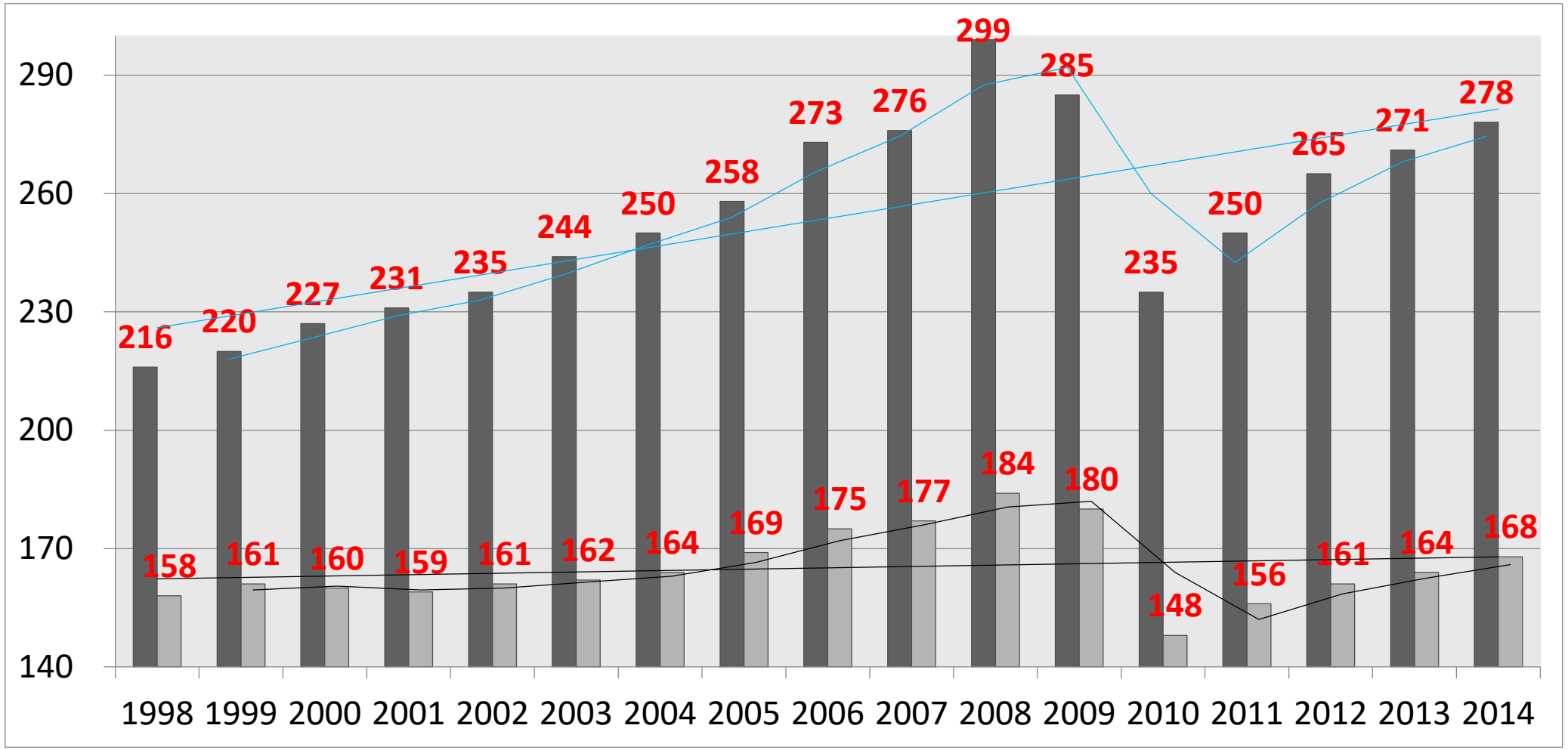
Pre-Chief National Central Cancer Registry

Pre-General Secretary of Asia National Cancer Center Alliance

Executive member Oncology committee Chinese Medical Association

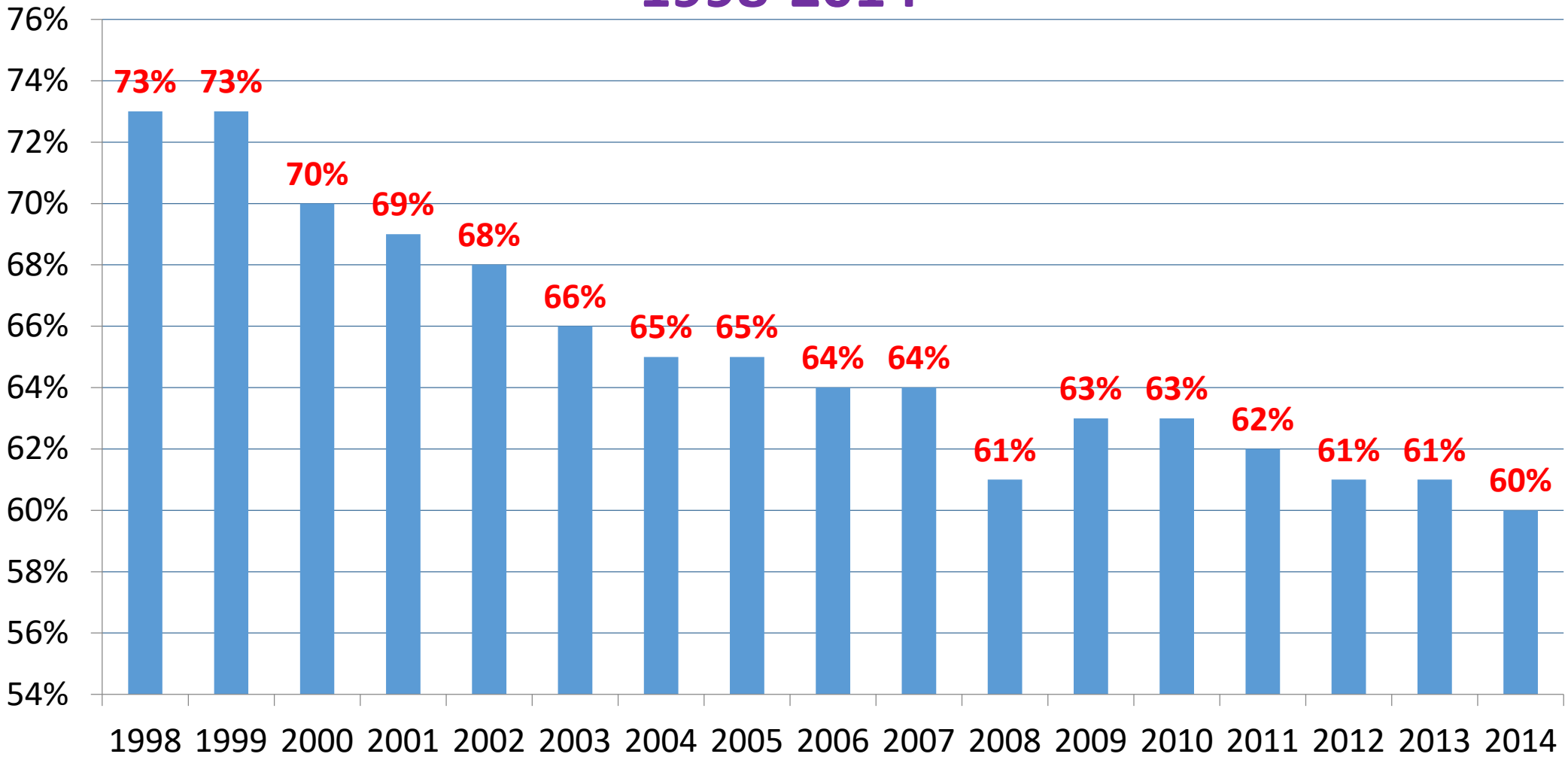
Chairman Oncology Specialized Committee Beijing Medical Association

Cancer Incidence and Mortality in China 1998-2014

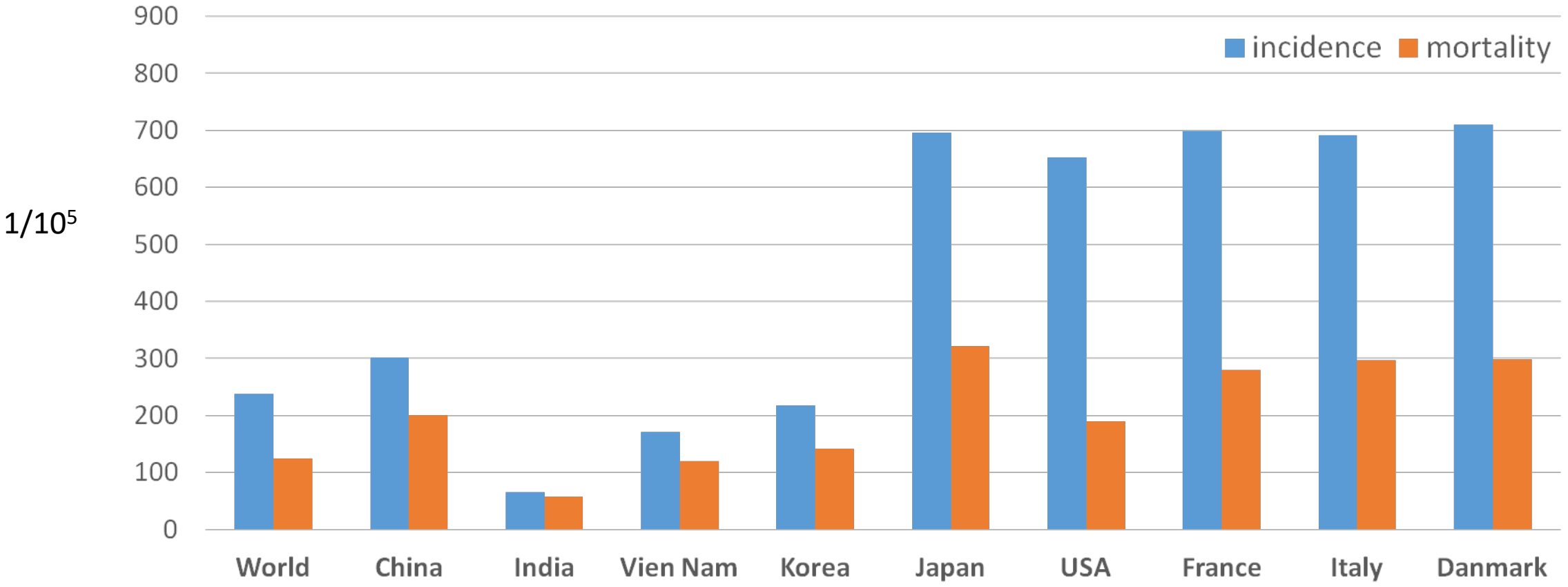


---------发病率 --------死亡率

The ratios of Cancer Mortality to Incidence in China 1998-2014



Cancer Incidence & mortality in the world 2018



Data source: IARC

Three-level Preventing Cancer

- *1/3* Cancer can be preventive (40%)
- *1/3* Cancer can be cured by early detected diagnosed and treated (40%)
- *1/3 the life can be prolonged*

WHO 1981

Strategies for cancer prevention

癌症是怎么生成的
What are factors inducing cancer

Genetic (internal)

cancer

external

Infection

Lifestyle

Environment

多基因遗传易感性疾病
Multi-genetic susceptible diseases

Etiological Prevention

通过行政命令和法律条文严格规定以保护个人和社会免遭致癌因素危害

Governmental law & regulations protect people and community from carcinogenic harms

利用媒体宣传癌症危害 普及防癌知识 建立安全健康的生活方式

Propaganda cancer hazard and disseminat health lifestyle

中华人民共和国中央人民政府
www.gov.cn

国务院 | 总理 | 新闻 | 政策 | 互动 | 服务 | 数据 | 国情

国务院办公厅关于成立京津冀及周边地区大气污染防治领导小组的通知 国办发〔2018〕54号

国务院办公厅关于完善国家基本药物制度的意见 国办发〔2018〕88号

国务院关于印发打赢蓝天保卫战三年行动计划的通知 国发〔2018〕22号

国务院办公厅关于印发中国防治慢性病中长期规划（2017—2025年）的通知 国办发〔2017〕12号

国务院办公厅关于进一步改革完善药品生产流通使用政策的若干意见 国办发〔2017〕13号

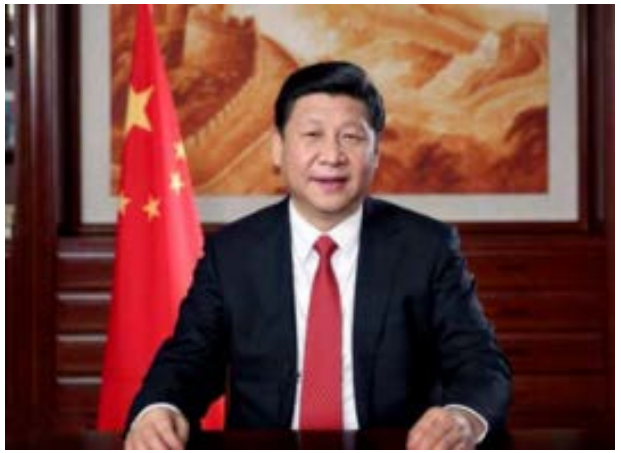
国务院关于印发“十三五”卫生与健康规划的通知 国发〔2016〕77号

国务院关于印发“十三五”深化医药卫生体制改革规划的通知 国发〔2016〕78号

国务院关于印发全民健身计划（2016—2020年）的通知 国发〔2016〕37号

国务院关于整合城乡居民基本医疗保险制度的意见 国发[2016]3号

Cancer Intervention Strategies



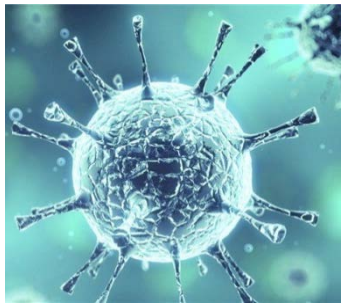
Vaccination

Smoke control regulation

By various media channels CFC introduces the knowledge to help people build up healthy lifestyle for cancer control

癌症的归因

Attributable risks of cancer



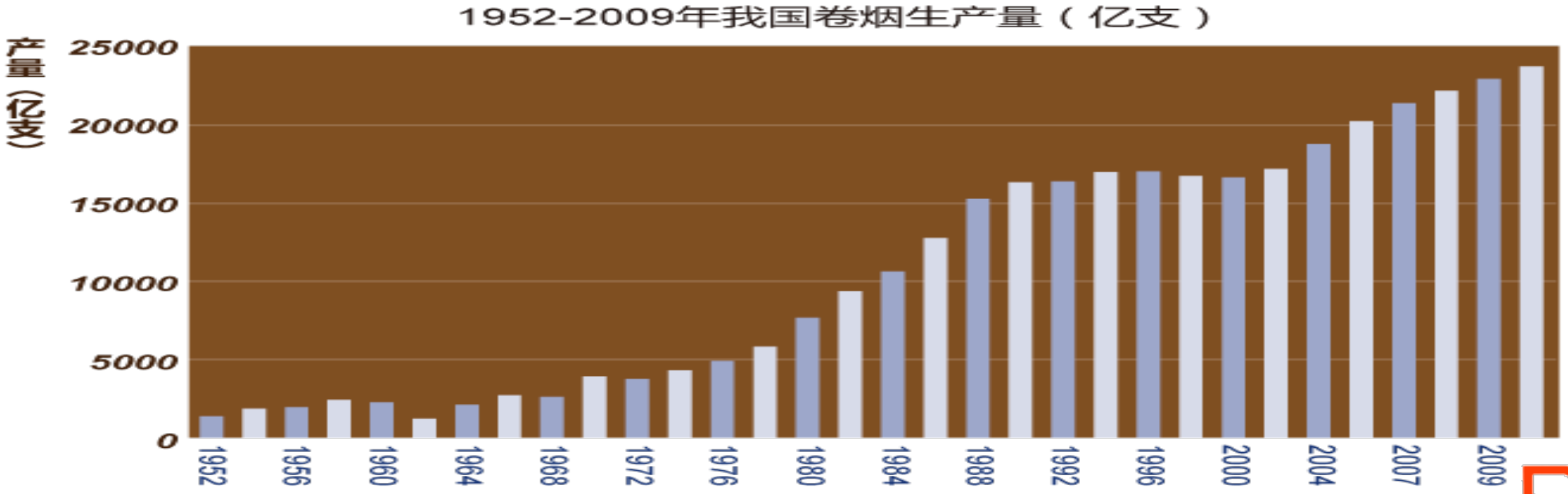
Chronic Infection
25.9%

One important attributable factor of cancer is smoking

Low intake of vegetables and fruits (<15.0%)

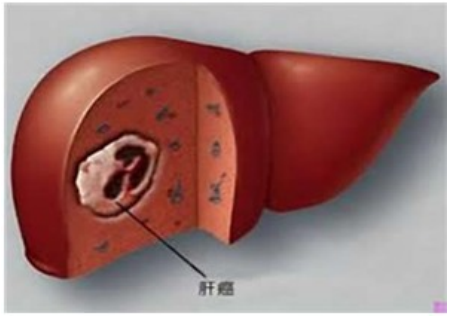
Smoking is chief culprit of cancer in China

- 300 million smokers
- 700 million people exposed to secondhand smoking



Tobacco products in China ranked highest in the world

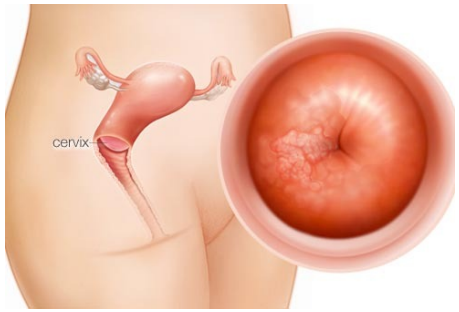
Infection and cancer



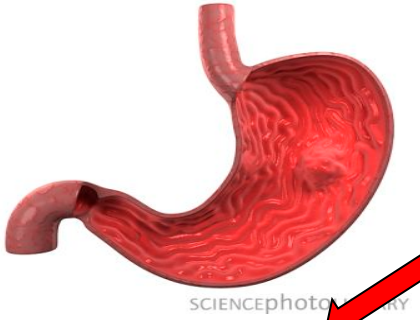
Hepatitis virus
and liver cancer
9.9%

HBV

HPV

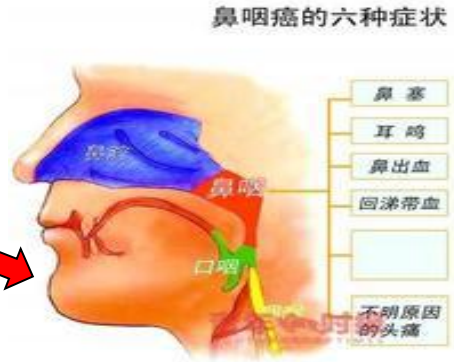


cervical cancer
2.63%



HP

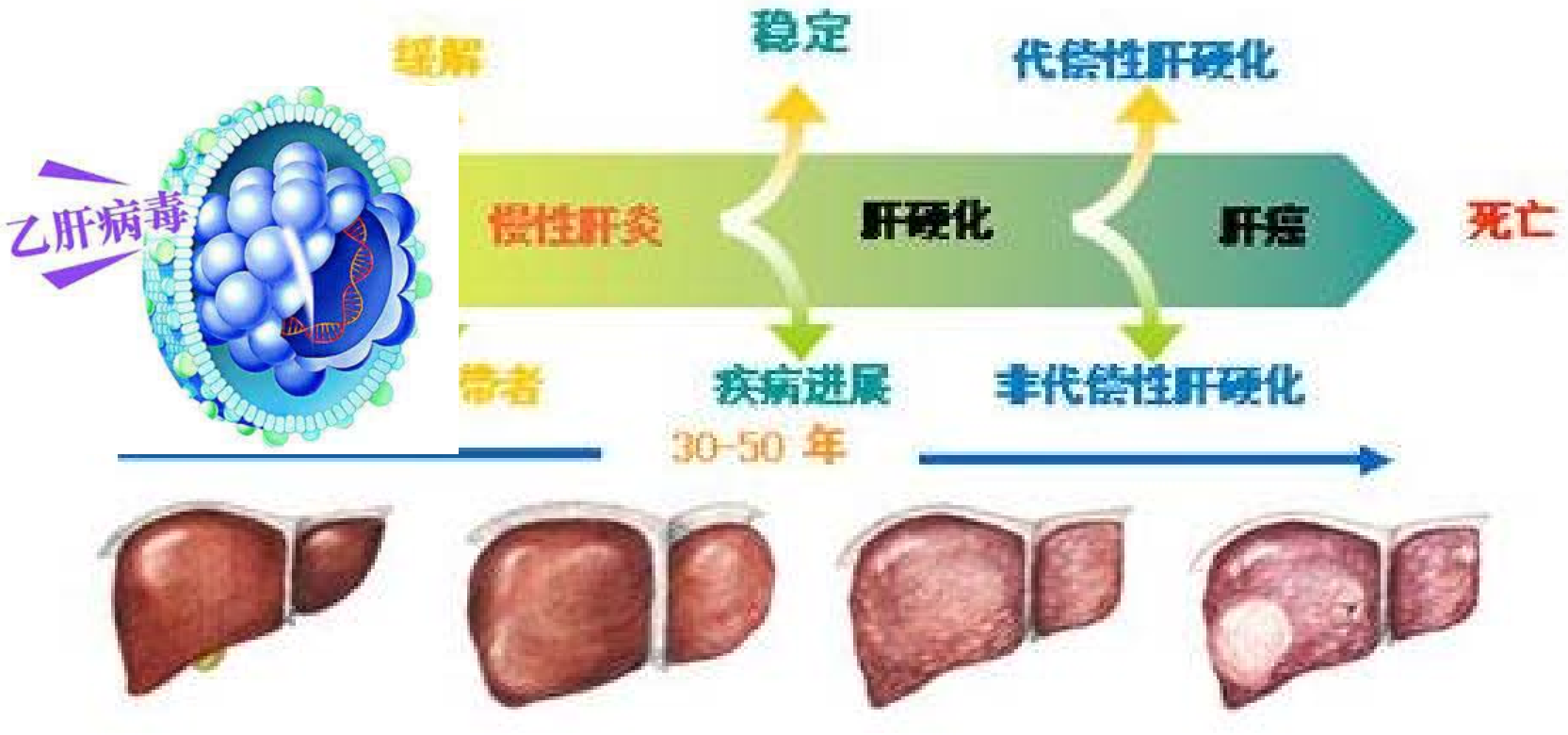
EBV



Helicobacter *pylori*-
stomach cancer 11.83%

– nasopharyngeal
Carcinoma 1.1%

HBV infection and liver cancer

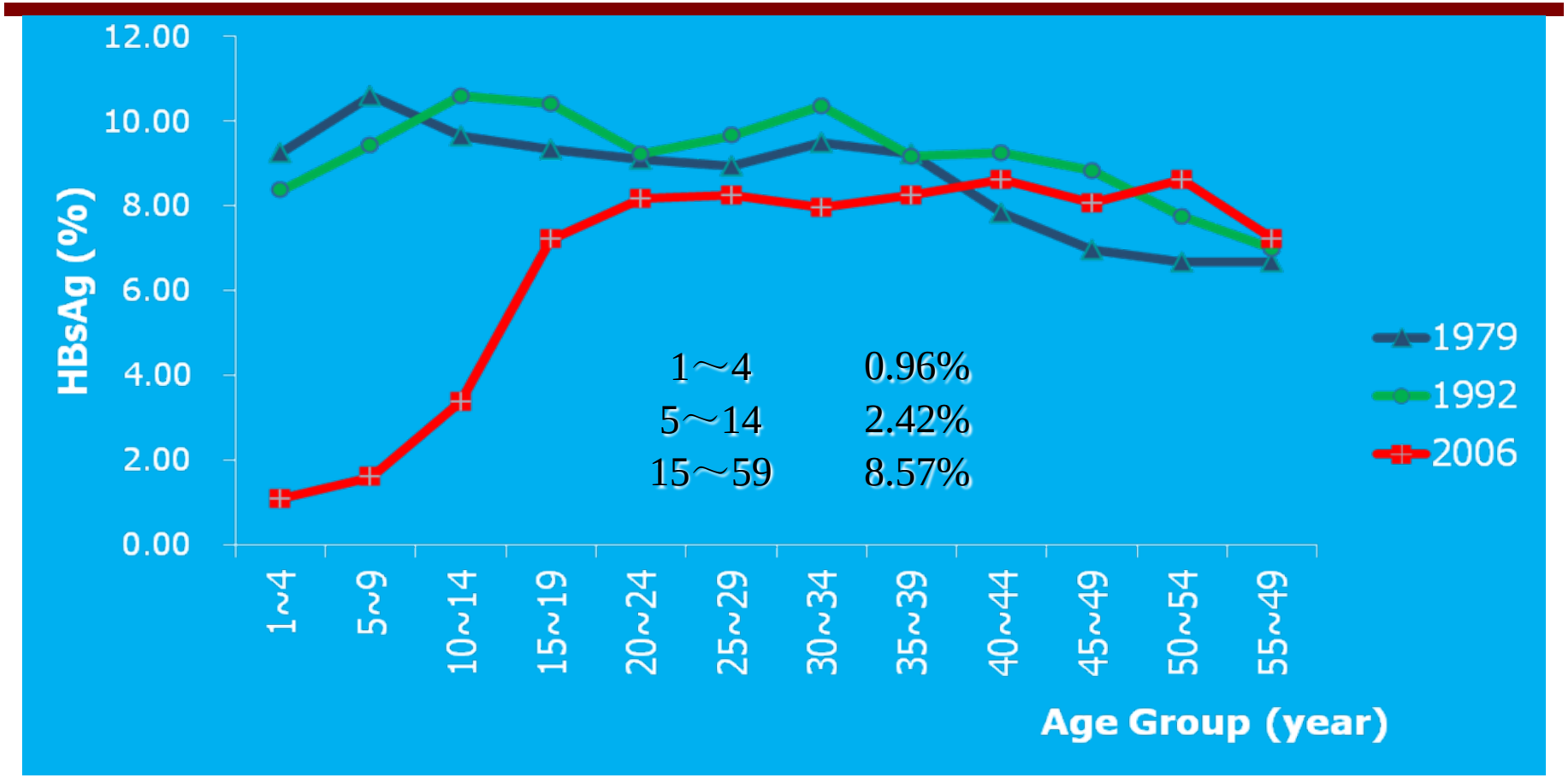


- HBV carrying rate was 9.75% in Chinese residents in 1992

HBV vaccine & liver cancer

- 1991 WHO brought HBV vaccine into planned immunity
- 1992 China brought HBV vaccine into planned immunity administration
- 2002 China brought HBV vaccine into official planned immunity administration

HBsAg carring rate in Chinese poeple over time

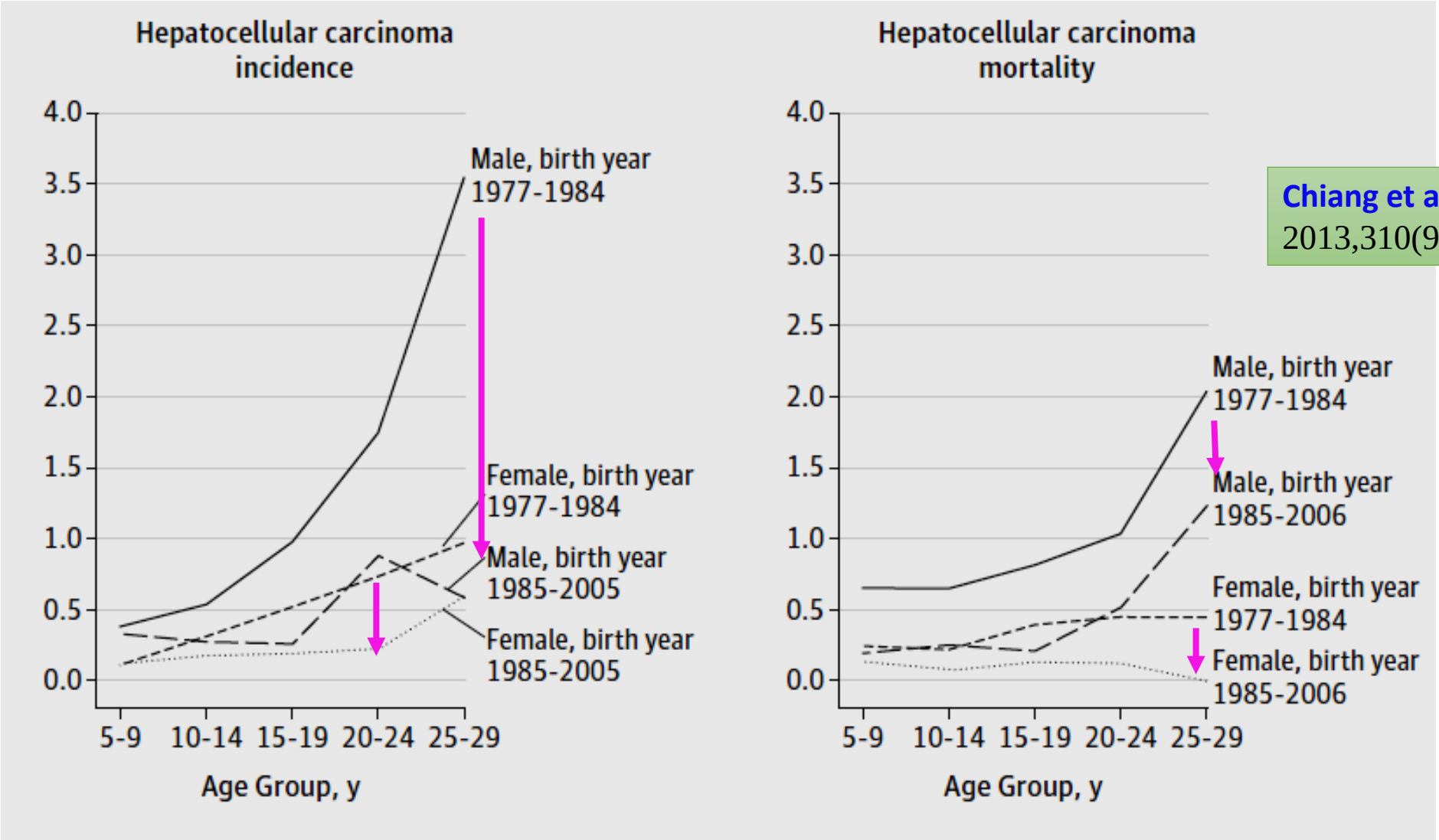


1.Qu Z. An epidemiological study on the distribution of HBsAg and anti-HBs in China. Chine Journal of Microbiogy Immunology. 1986; Suppl(20-40).

2.Dai ZC, G.M. Q. Seroepidemiological Survey in Chinese population (part one), 1992–1995. Beijing. Sci Tech Exp. 1996: 39-59.

3.Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Epidemiological serosurvey of hepatitis B in China--declining HBV prevalence due to hepatitis B vaccination. Vaccine. 2009; 27(47): 6550-7.

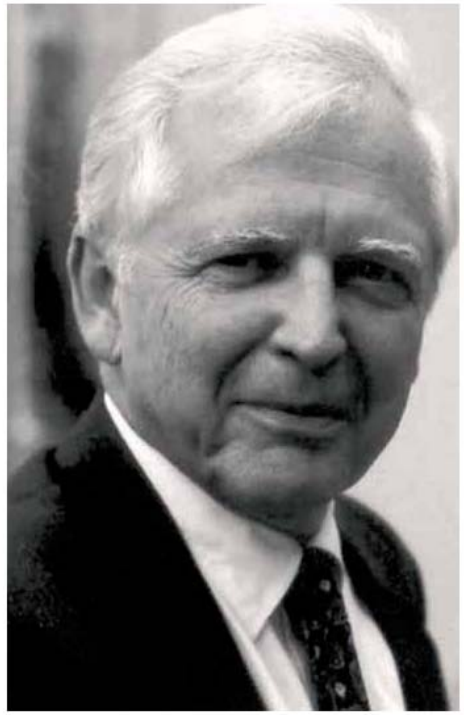
Hepatitis B immunization program launched in 1984 significantly reduced incidence and mortality of hepatocellular carcinoma in Taiwan

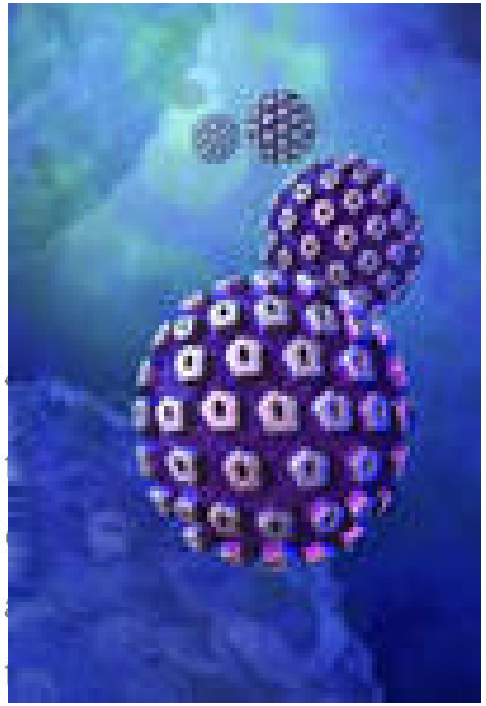


Chiang et al JAMA 2013,310(9):974-6

Historical comparison between Immunized and Unimmunized cohorts, baseline difference

Human Papilloma Virus (HPV) and cervical cancer



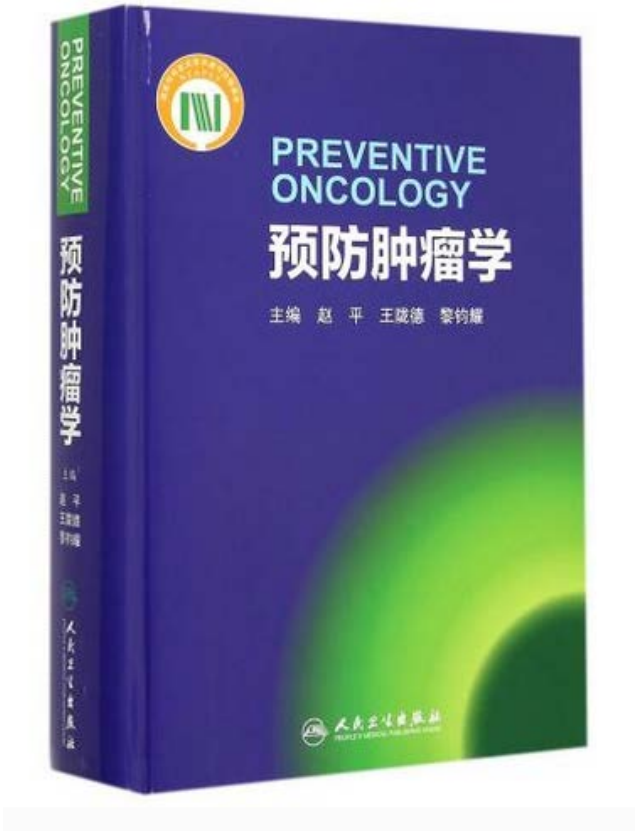


Dr. Harald zur Hausen, a Genman Noble prize-winner of physiology/medicine in 2008 discovered that the high risk type HPV（HR-HPV）induced cervical cancer. Soon fast-testing HPV methods and vaccines were developed to prevent cervical cancer effectively.

Effect of HPV vaccine （WHO document)

- HPV vaccine showed definit clinical effect in young women
- Vaccination among 18-26 yr women using HPV vaccine (3 shot) showed effective for preventing CIN3
- Research confirmed consistent reaponse rates of the vaccine in the adoscents and adults

Preventive oncology



Chapter1 Preface

Chapter 2 Harzards and influence of cancer

Chapter 3 Base and principle of cancer prevention and control

Chapter4 Methods for cancer prevention and control

Chapter5 Risk factors of cancer

Chapter6 Carcinogenesis

Chapter7 Strategies and measures for cancer control

Chapter8 Prevention and control for common cancers

Global concerns for cancer prevention & treatment in China

亚洲国家癌症中心联盟


THE FIRST MEETING OF
ASIAN NATIONAL CANCER CENTERS ALLIANCE
SEPTEMBER 6, 2005
NCC KOREA

Government pays highly attention to cancer prevention


Thank You

Lung cancer prevention in the residents of Xuan Wei and Ge Jiu in southwest China

Prof. Xiao Nong Zou

Deputy Chair, Tobacco Control and Lung Cancer Control Branch, Cancer Foundation of China

Office of Cancer Registry, National Cancer Center - Cancer Hospital, Chinese Academy of Medical Sciences

Oct 3, 2018 Kuala Lumpur, Malaysia

World Cancer Congress
Kuala Lumpur, Malaysia
1—4 Oct 2018

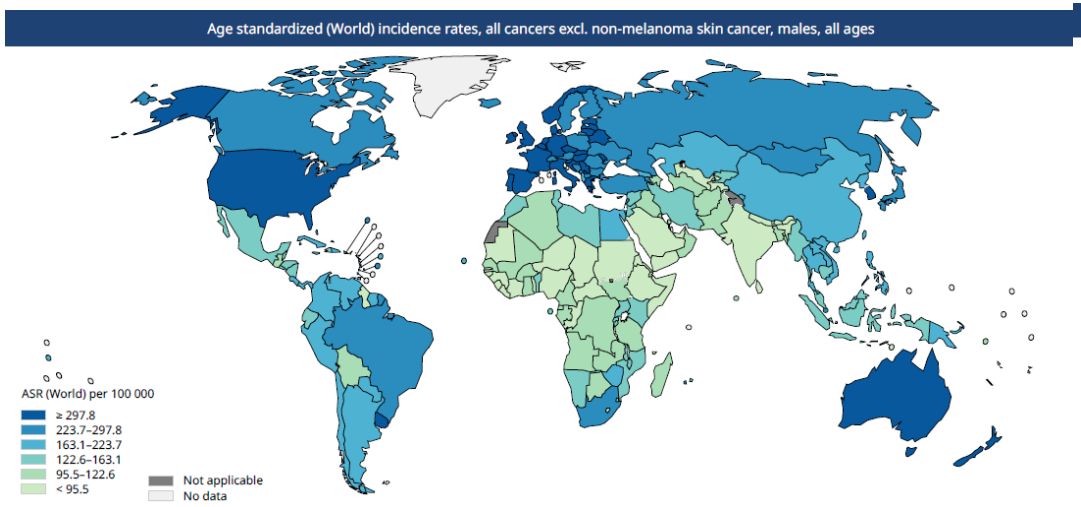
Strengthen
Inspire
Deliver

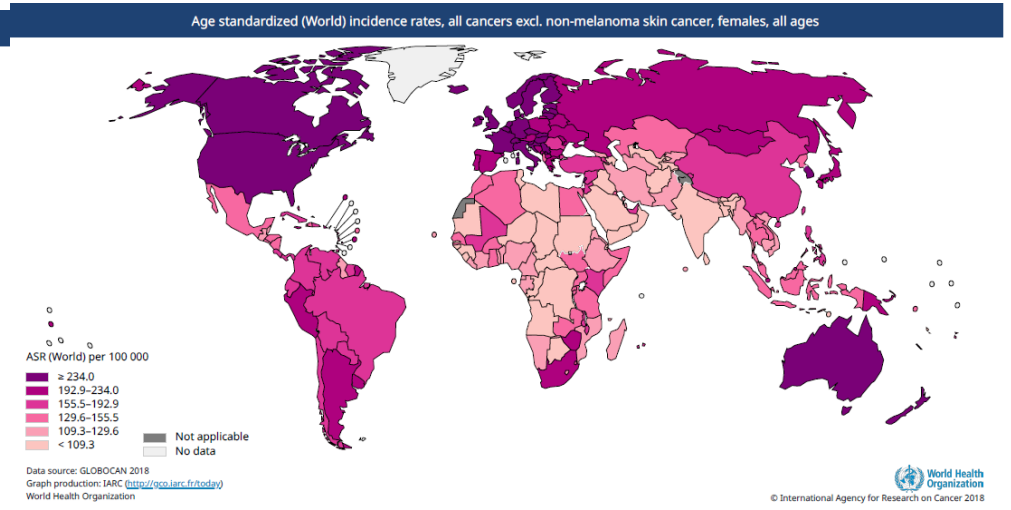
uicc global cancer control WORLD CANCER CONGRESS

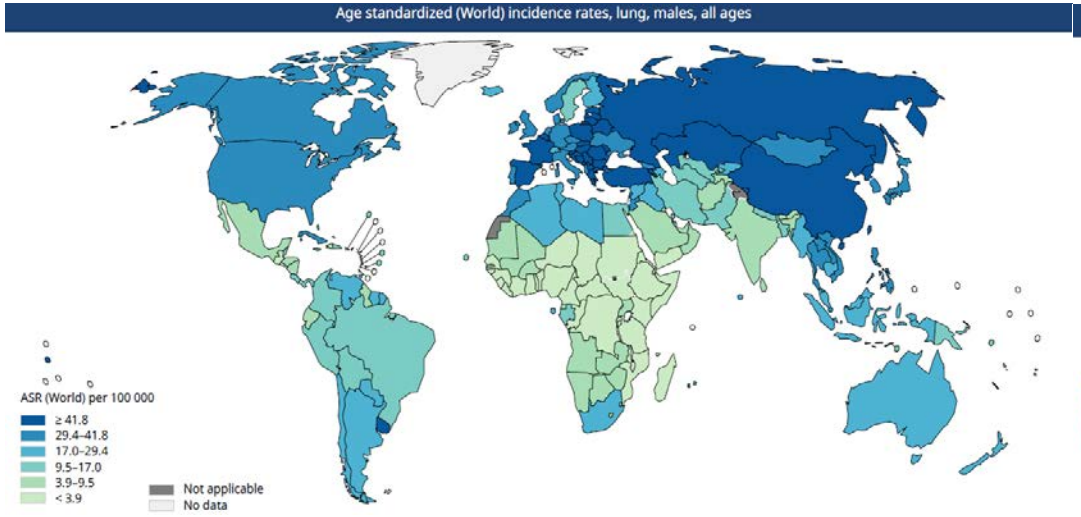
Track1 :Motivating prevention and healthy behaviour

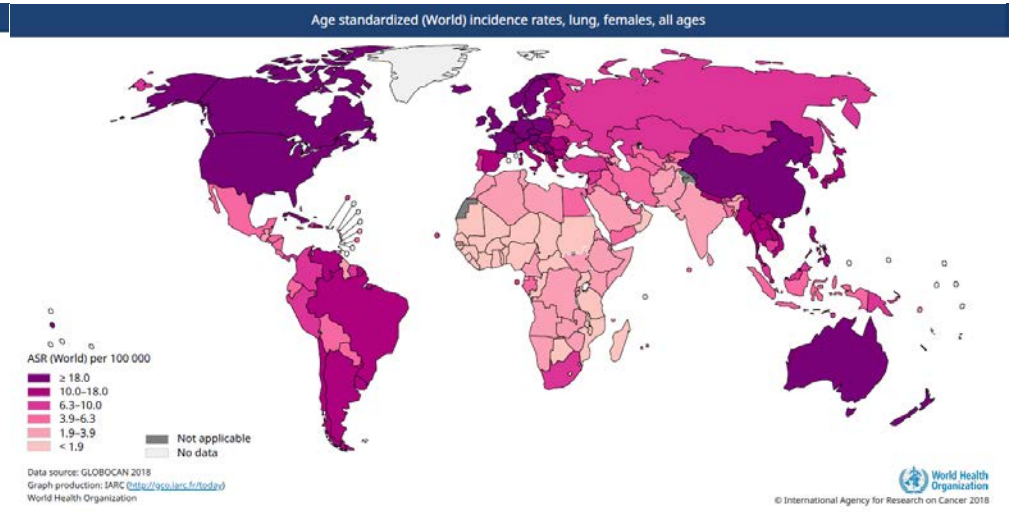
Disclosure of interest: None declared

IARC: Cancer today 2018

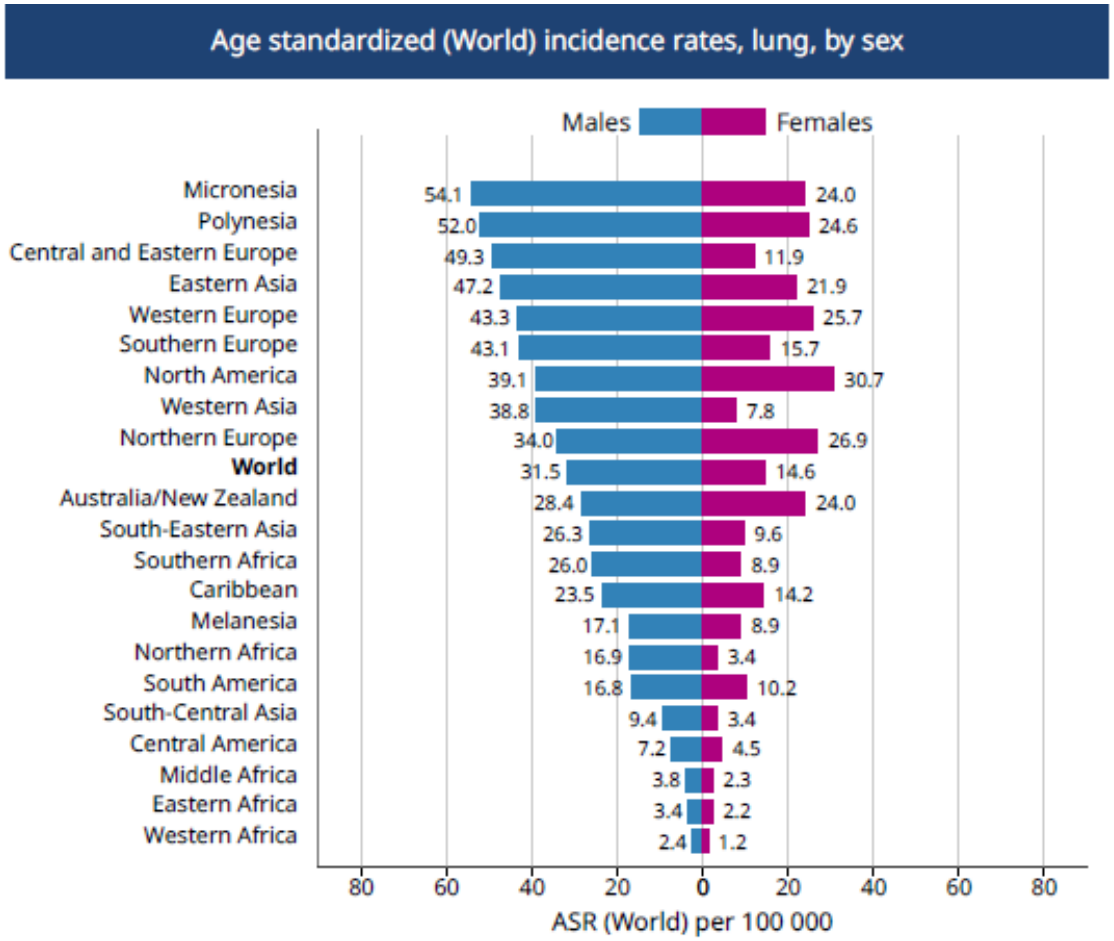


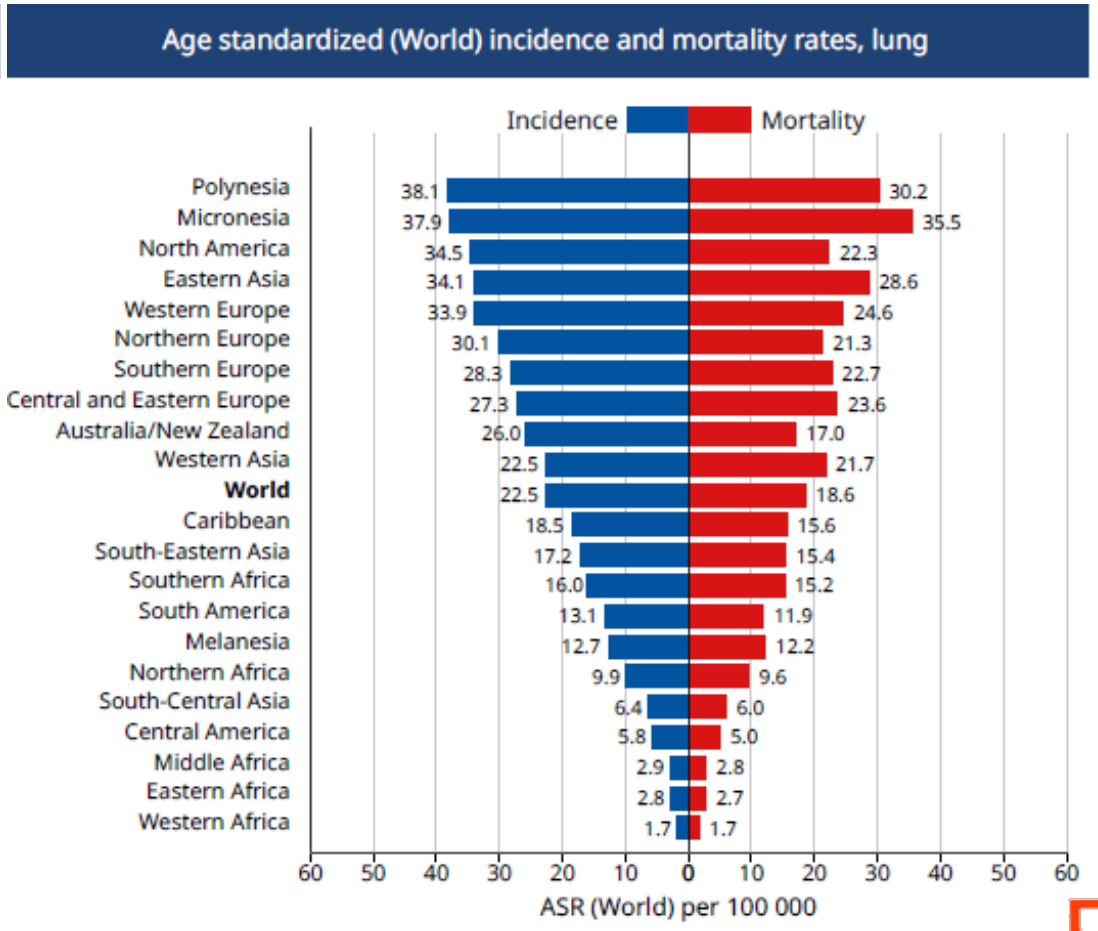




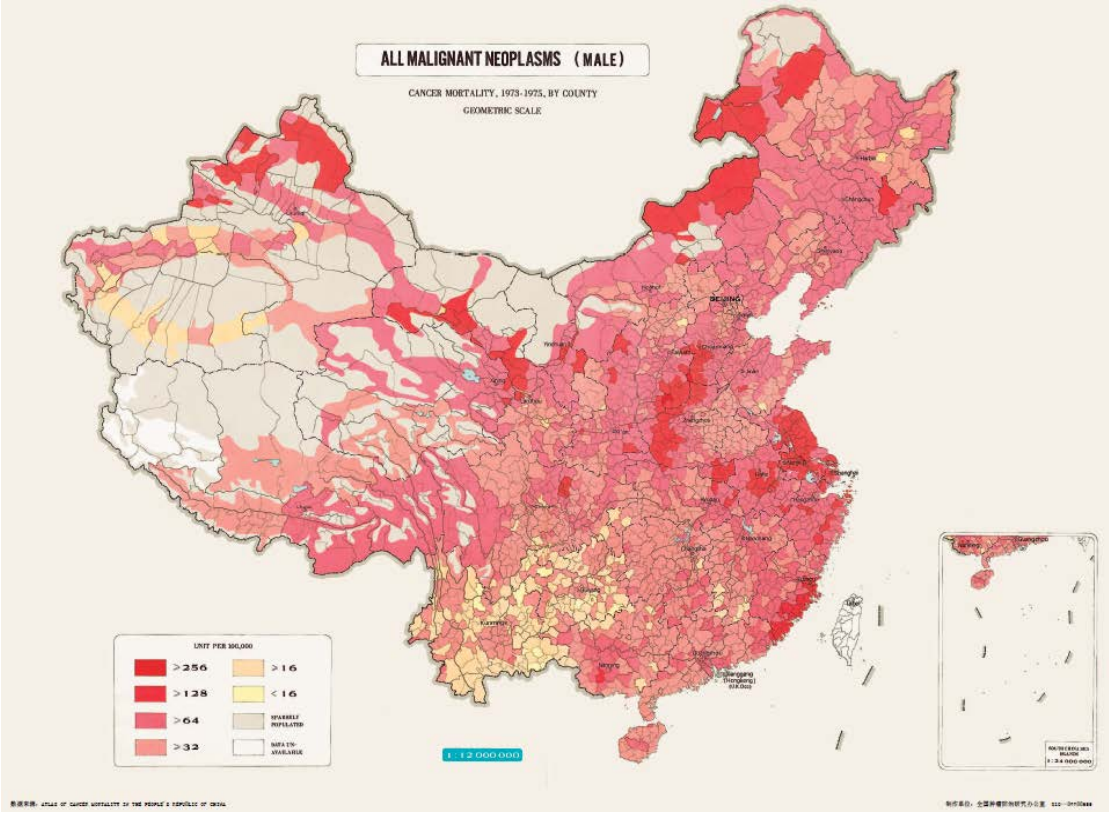


IARC 2018: Lung cancer incidence and mortality by sex and region

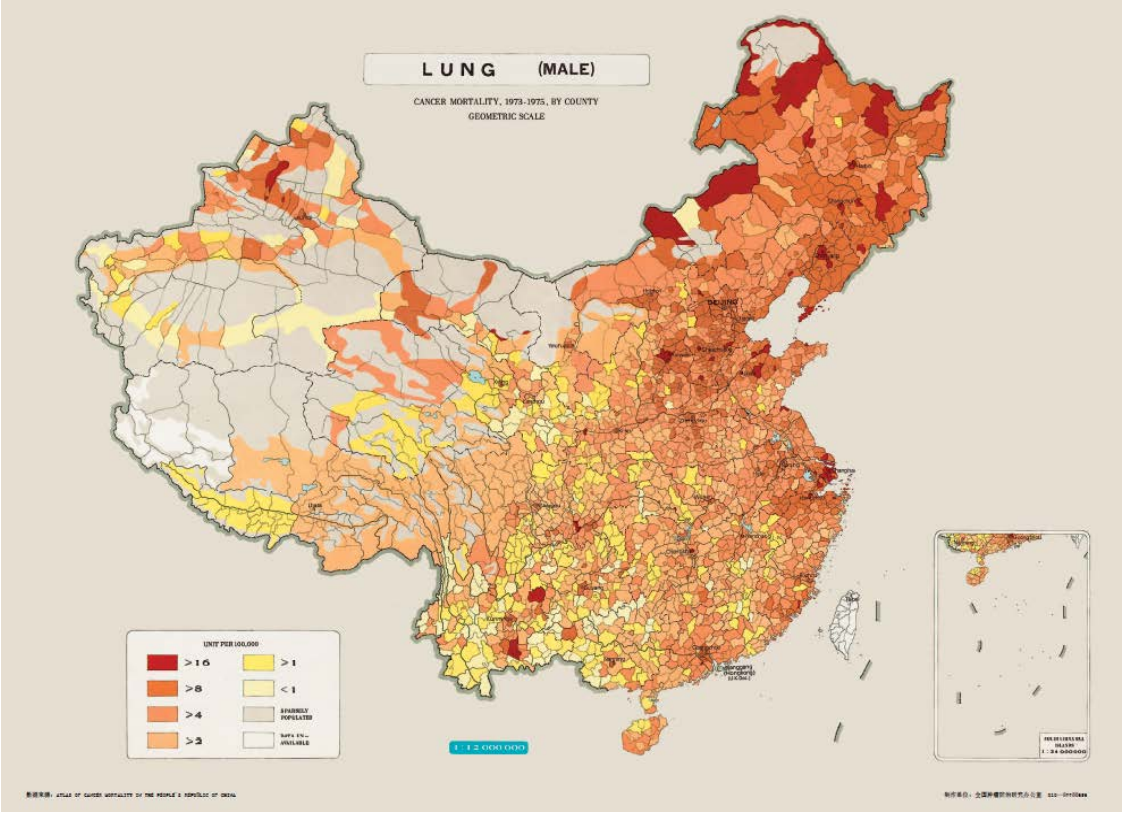




Cancer Mortality for men in china 1973-1975

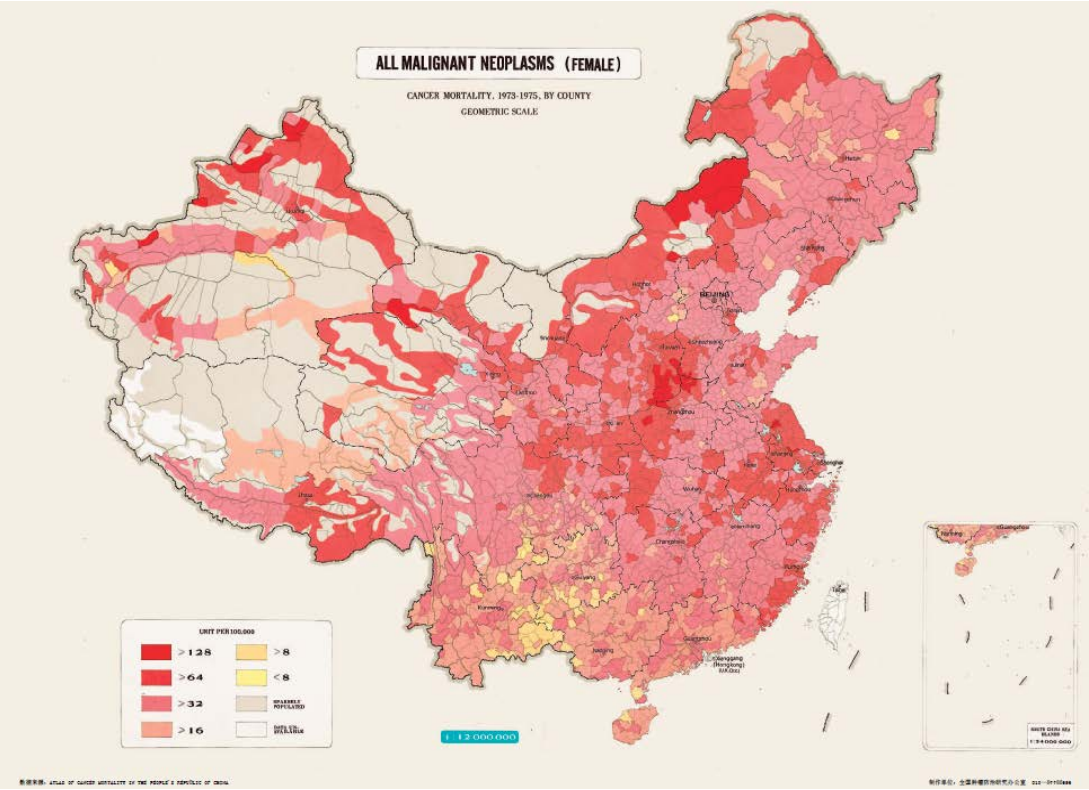


All cancer

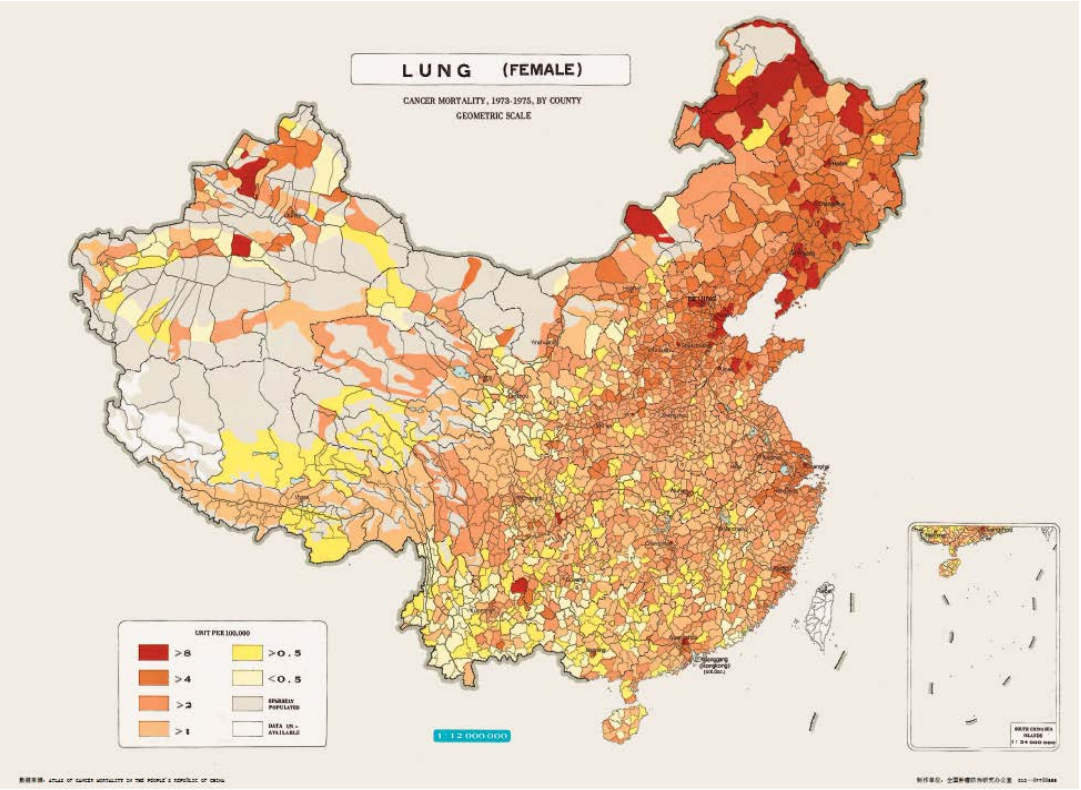


Lung cancer

Cancer Mortality for women in china 1973-1975

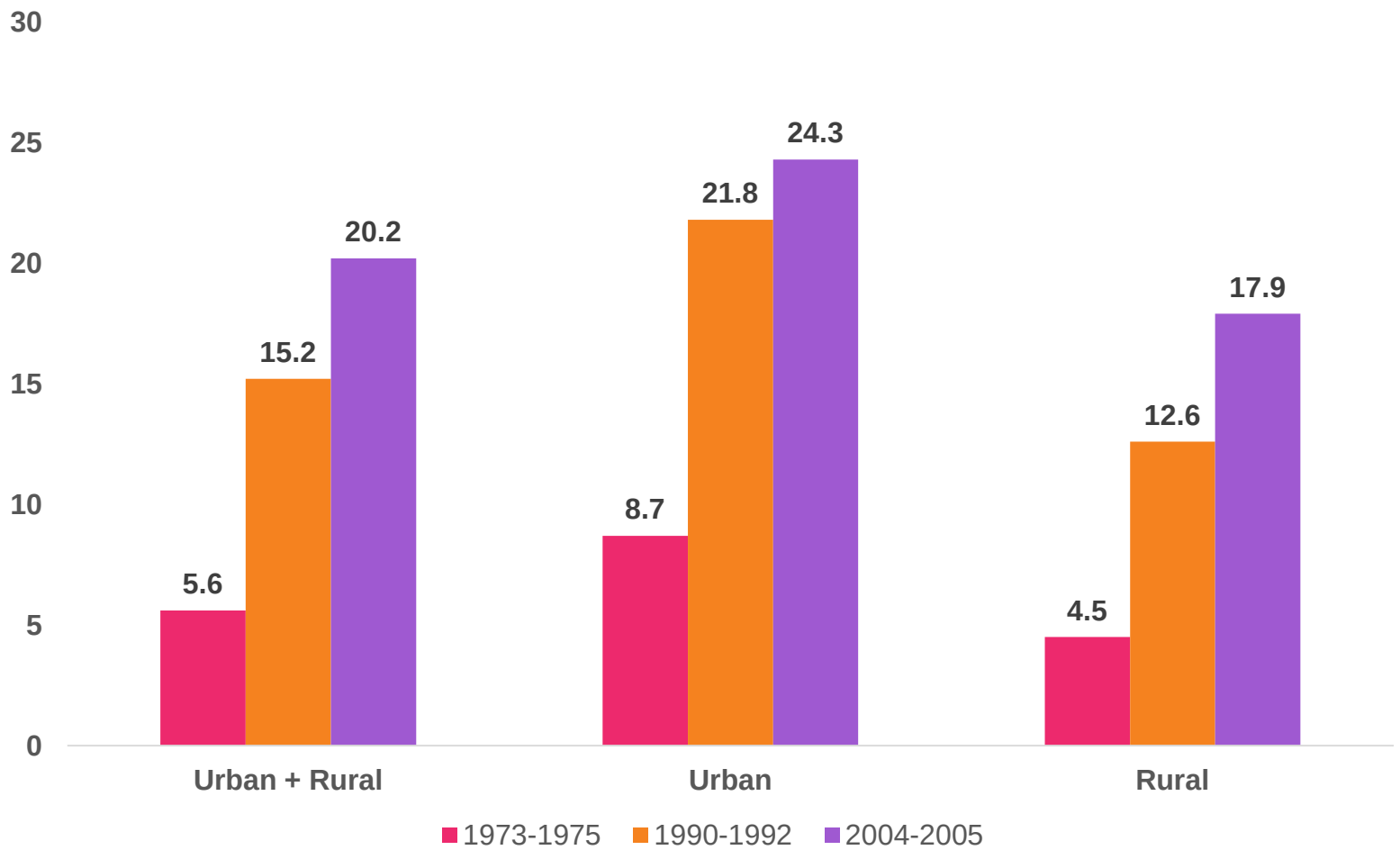


All cancer:

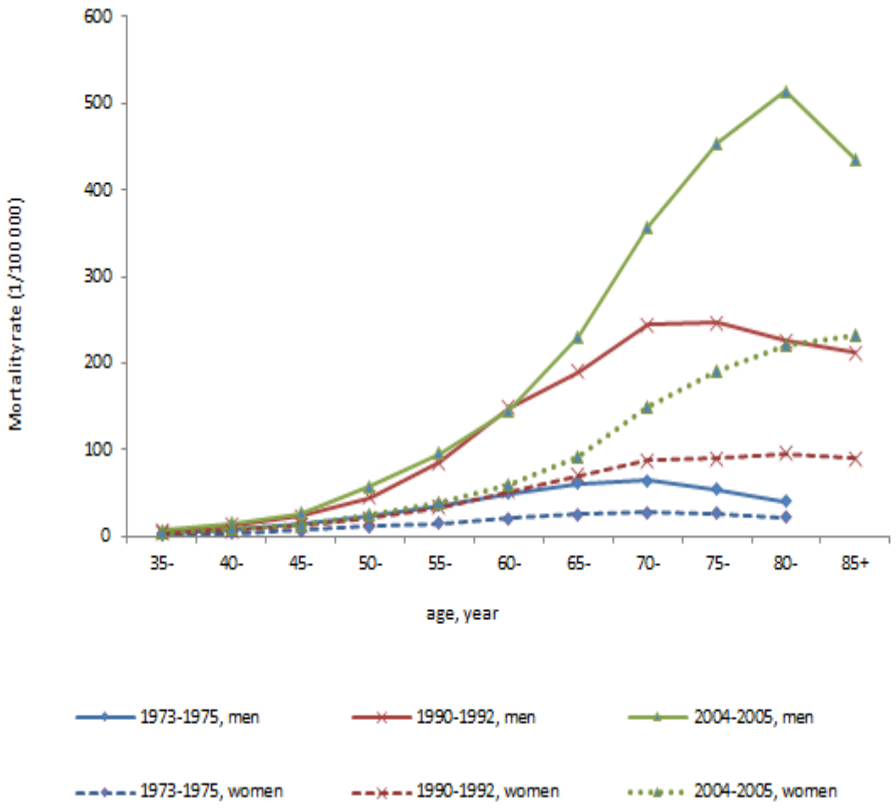


Lung cancer:

Mortalities of lung cancer in China 1973-2005



Area specific mortality of lung cancer in China

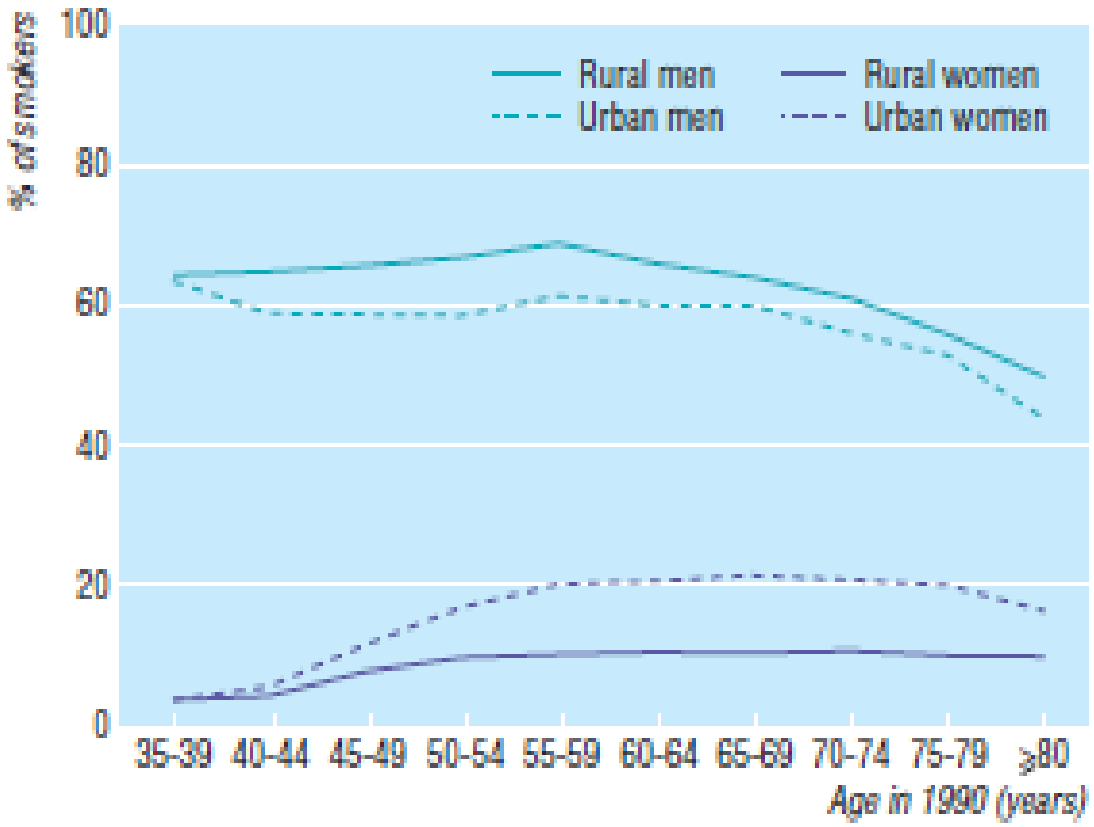


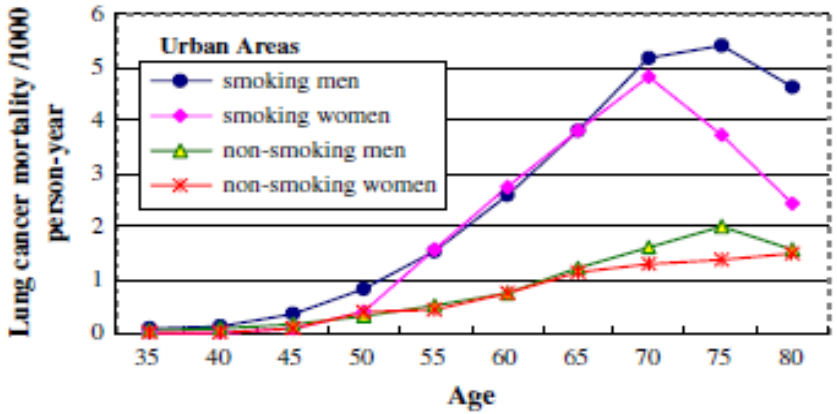
1973-1975 Blue
1990-1992 Red
2004-2005 Green

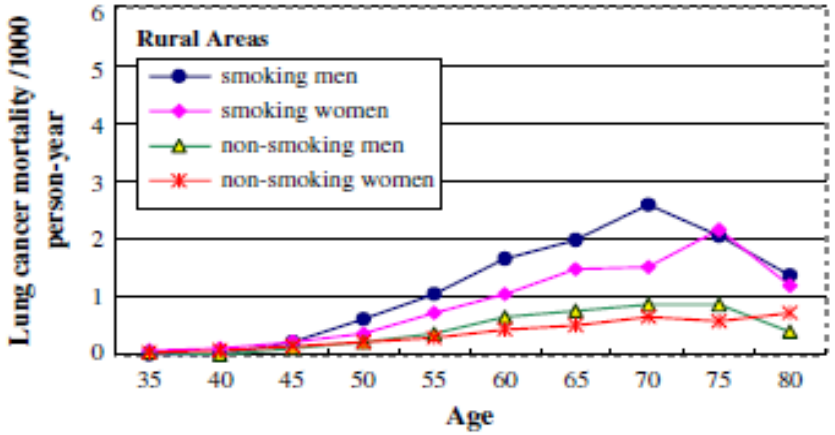
Male ——
female ……

Source: Cancer 2015

Smoking and lung cancer risks

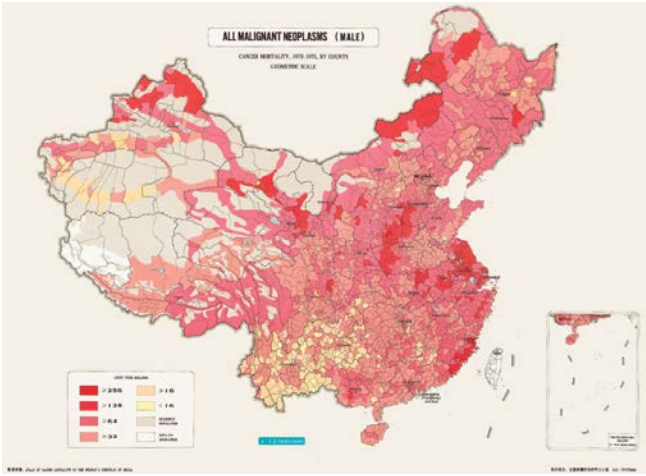


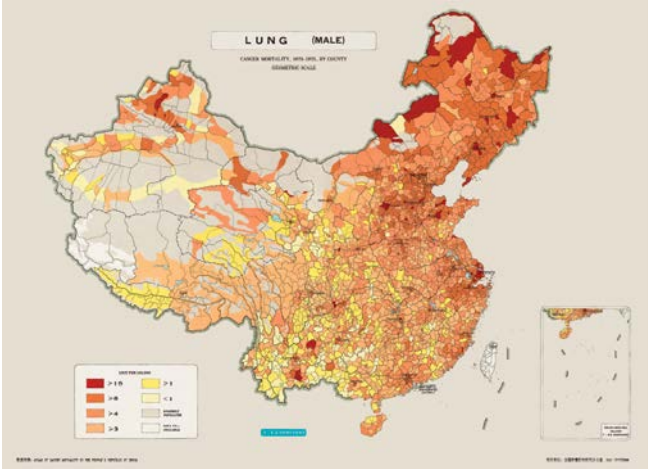




National survey on death & smoking
Source: BMJ 1998; AEP 2008

Xuanwei and Gejiu, Yunnan Province





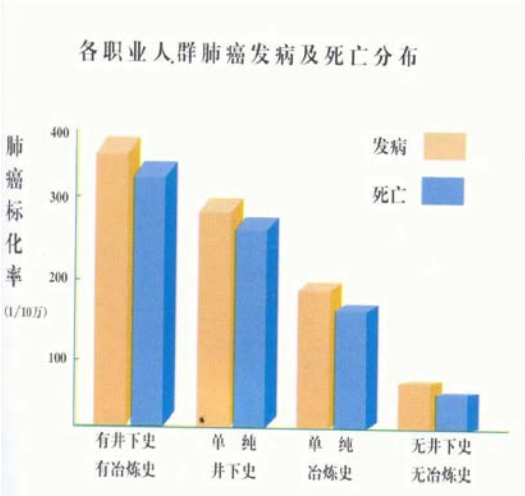
Xuanwei city, northeast of Yunnan, 6 069.88 km²

Gejiu city, south of Yunnan, 1 587 km²

Yunan Province, Southeast China

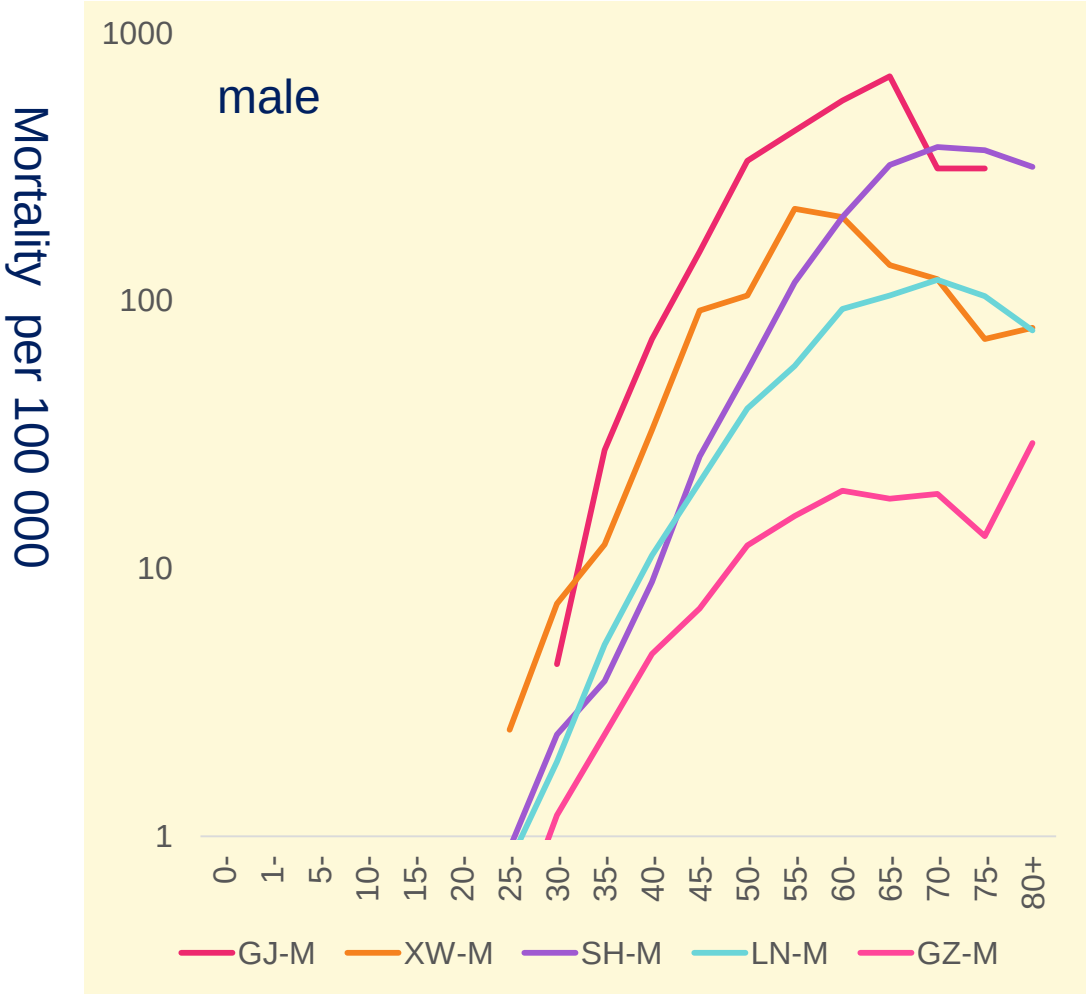
Occupational environmental pollution-lung cancer

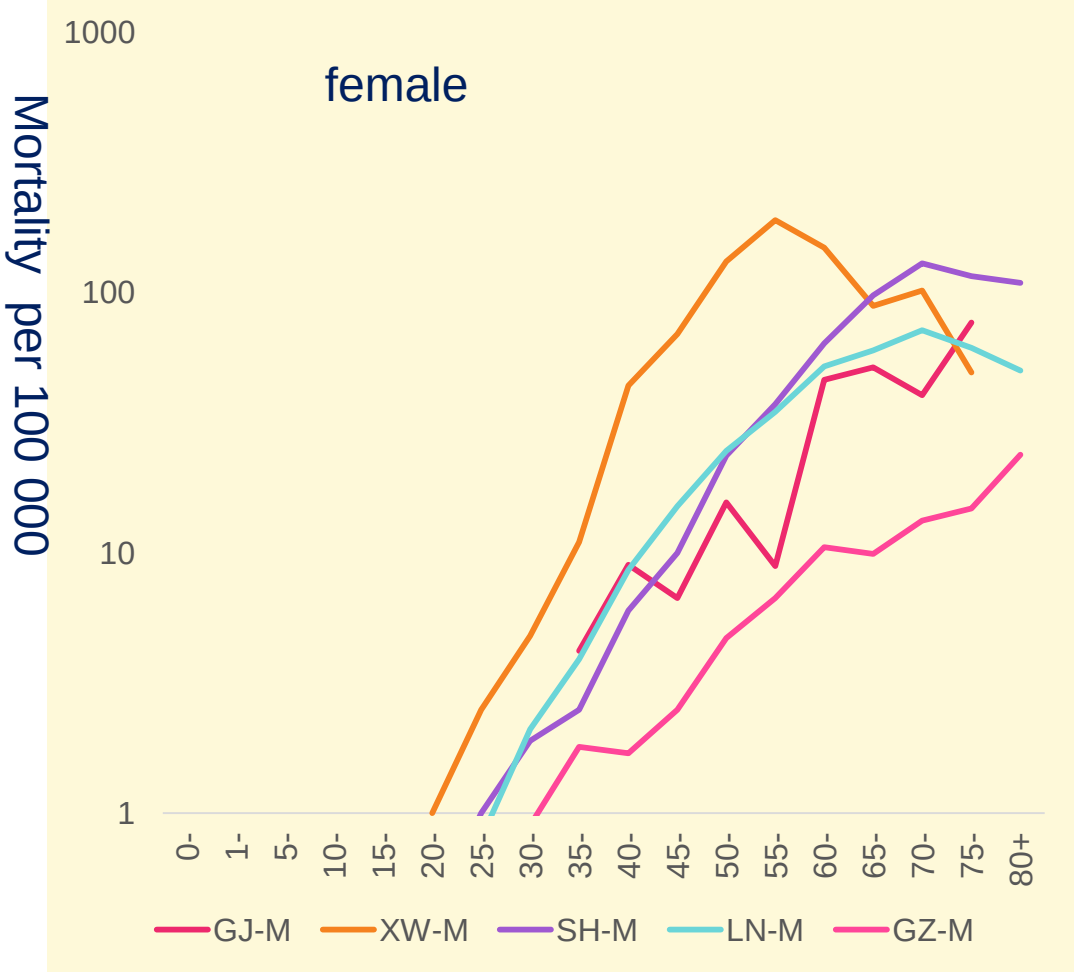
Occupational Exposure to Radon, arsenic were reported the main contributors to lung cancer among tin miners in Gejiu city, Yunnan province.



Year	Radon Concentration	Times VS National Criteria
1950-1959	10.43	8.03
1960-1969	9.62	6.31
1970-1974	9.29	5.75
1975-1979	6.07	3.25
1980-1984	2.92	1.67
1985-1989	2.18	1.07
1990-1994	2.63	1.04
1995-1999	2.89	1.02

Age-specific mortality in different regions 1973-1975



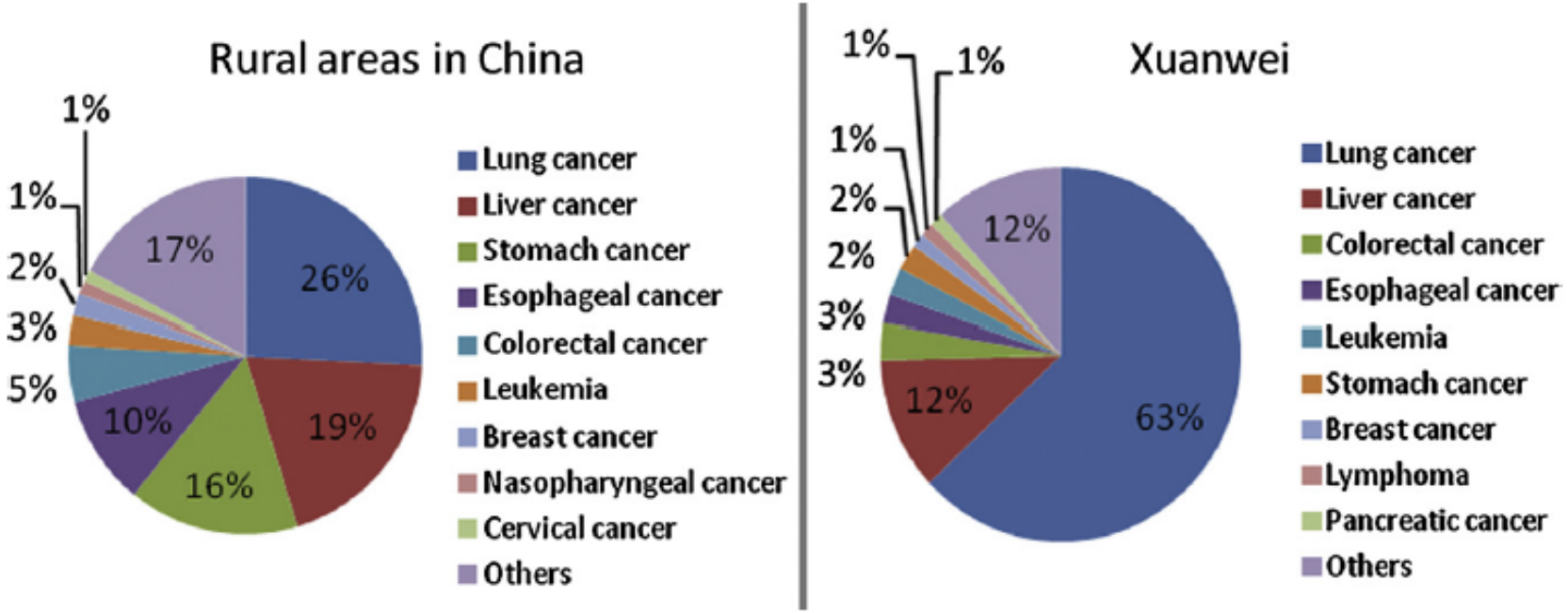


lung cancer mortality correlated with using smoky coal in Xuanwei

Commune	Use smoky coal (%) before 1958	Use firewood (%)	Use smokeless coal (%)	Lung cancer mortality ($1/10^5$)
Cheng-guan	100.0	0.0	0.0	174.2
Lai-bin	89.7	8.7	1.6	128.3
Rong-cheng	81.9	18.1	0.0	104.1
Long-chang	76.1	17.9	6.0	39.5
Long-tan	78.0	22.0	0.0	32.5
Ban-qiao	34.0	16.4	49.8	22.1
Hai-fa	49.7	22.5	27.8	19.1
Luo-shui	2.7	39.0	58.3	13.5
Pu-li	35.2	52.0	12.8	7.5
Xi-ze	0.0	90.9	9.1	3.8
Re-shui	0.0	66.6	33.4	2.1

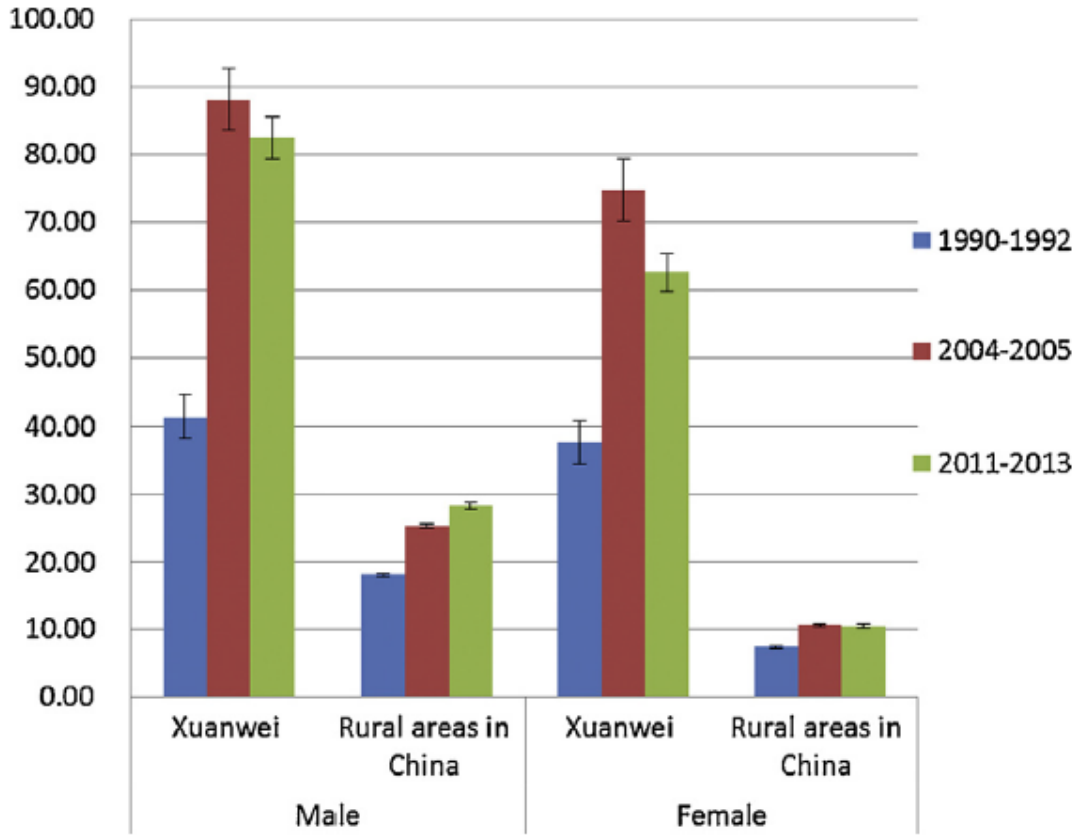
Source: Health Research 1994

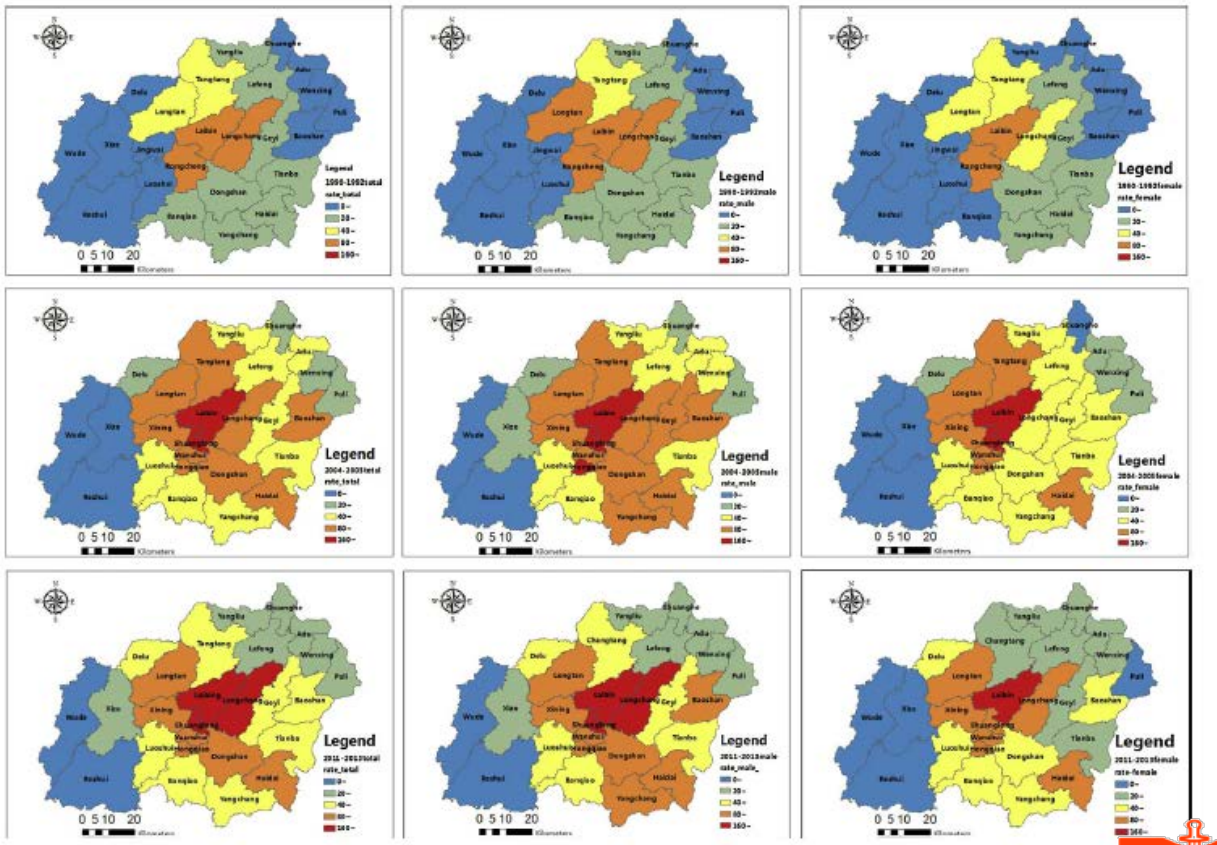
Constituent of deaths due to cancers in Xuanwei, 2011-2013



Chen GB, lung cancer 2015

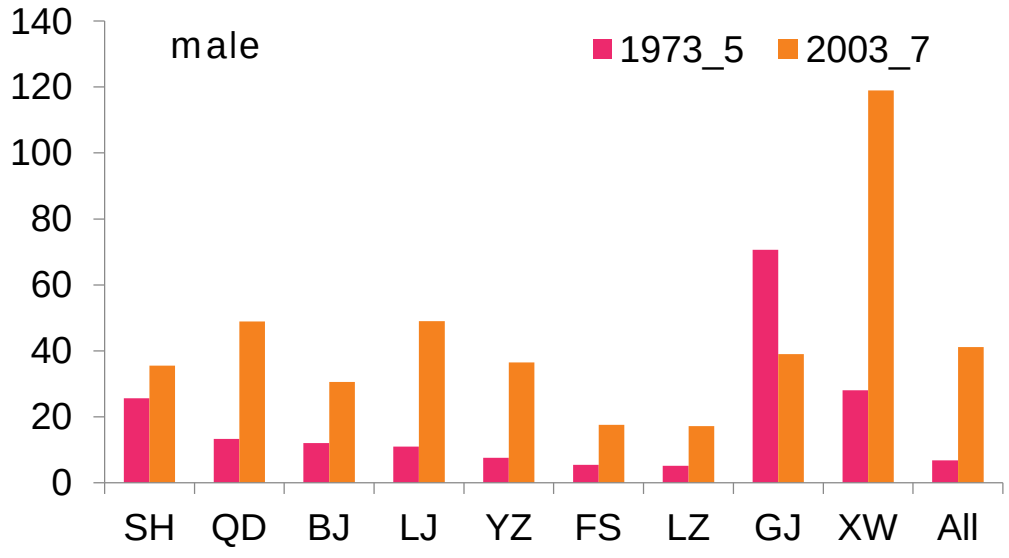
LUNG CANCER MORTALITY IN XUANWEI 1990-2013

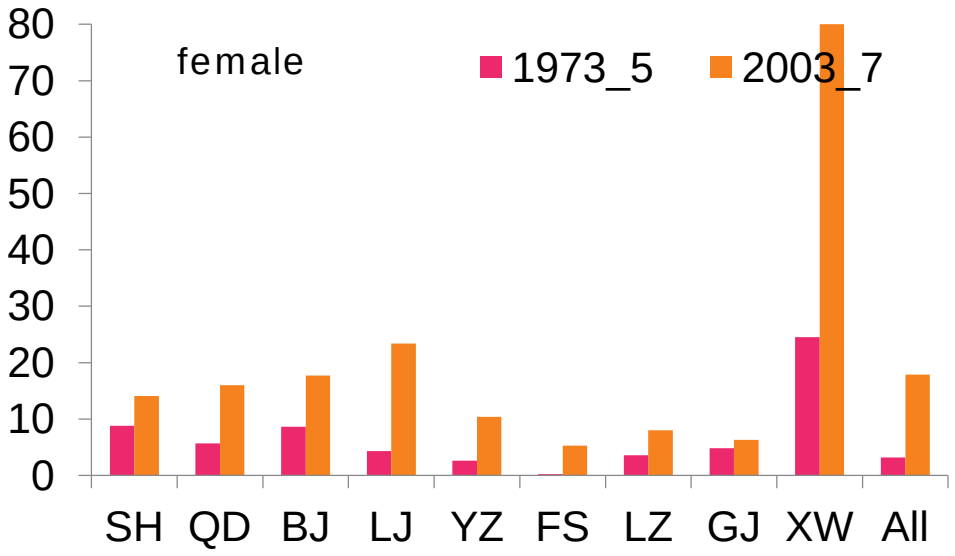




Source: lung cancer 2015

Lung cancer mortality in selected counties 1973-1975 and 2003-2007





Source: National Death survey, National cancer registry annual report

Experiences from lung cancer prevention in Gejiu and Xuanwei

Experience for prevention of Lung cancer in Gejiu and Xuanwei, southeast of China disclosed that different etiological factors had been contributing to that preventable disease. It is important to search and change the general and specific contributing un-health lifestyles and living conditions, improve the occupational environment to reduce the risks of lung cancer.

Thanks!

Prof. Xiao Nong Zou,

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Current Achievement and Challenges of Food, Cooking Methods and Cancer Control,

A Pooled Multivariable-Adjusted Analysis for the Association between Meat Mutagens Intake and Colorectal Adenoma and Cancer

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1. Objective

Heterocyclic amines (HCAs) as a heated-food-borne carcinogens might be associated to risk of colorectal adenoma and cancer?

2. Backgrounds: Landmark of HCAs

- HCAs were first detected in 1977; A group of more than 20 types;
- HCAs in food are mainly produced from sugar and amino acids during heating meat at high temperatures “Maillard Reaction”;
- Exposures to HCAs 2-amino-3,8-dimethylimidazo(4,5-j)quinoxaline (**MeIQx**), 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (**PhIP**), 2-amino-3,4,8-trimethylimidazo(4,5-f)quinoxaline (**DiMeIQx**), meat-derived mutagenicity (**MDM**), and the risk of cancer have been examined by number of studies.

HCAs categorized as Group 2B

- In 1993, the IARC (International Agency for Research on Cancer) concluded that HCAs of **PhIP, MeIQx, DiMeIQx** may possibly be carcinogenic to humans (Group 2B)
- In 2014, the National Institute of Health concluded that **PhIP and MeIQx** is "reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting genotoxicity data.

HCAs and Colorectal Cancer: “2016 Environ Health Perspective”

A Prospective Analysis of Meat Mutagens and Colorectal Cancer in the Nurses’ Health Study and Health Professionals Follow-up Study.

Le NT, et al. 2016 Environ Health Perspect DOI: 10.1289/EHP238.

Conclusions: Estimated intakes of meat mutagens were not significantly associated with CRC risk over 14 years of follow-up in the NHS and HPFS cohorts. Results for PhIP from red but not from white meat warrant further investigation !

3. Methods

a) Data sources:

- By 2017, our database of published articles included 40 studies (Consensus), of which 6 studies were repeated examination that were excluded.
- Among 34 published articles, 6 papers are prospective cohort studies; 28 papers are case-control study.

b) Study populations: Colorectal Cancer

Colorectal cancer (CRC)	Participants	CRC	Follow-up
Nurses' Health Study	65,785	418	14-Y
Health Professional Follow-up Study	29,615	790	14-Y
NIH-AARP Diet and Health Study	300,948	2,719	7.2-Y
The Multiethnic Cohort Study	131,763	1,757	8.1-Y
Total	**528,111**	**5,684**	**Y: Year**

c) Study populations: Colorectal Adenoma

Colorectal adenoma (CRA)	Participants	CRA	Follow-up
Health Professional Follow-up Study	14,032	581	6-Y
The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	17,072	1008	3.5-Y
The ursodeoxycholic acid (UDCA)	869	379	31-M
EPIC study	21,452	516	6_y
Total	**53,425**	**2,484**	

d) Convert HR (95%CI) into “lnhr”, “sehr”

HR (95%CI)	hr	lci	uci	lnhr	varlnhr	sehr
1.15 (0.84, 1.57)	1.15	0.84	1.57	0.1398	0.0255	0.1595

The Fix and random pooled HR, 95%CI was analyzed using ln(HR) and se(ln(HR)) by STATA-10.

The number of data pooled to estimate the risk of CRA and CRC was four for PhIP, MeIQx, DiMeIQx and three for MDM.

e) Performed STATA

```
meta lnhr sehr if  hcacode==1 & adcode==2, eform graph(f) cline xline(1) ///
> xlab(.5,1,1.75) id(name) b2title(Hazard Ratio) print
```

```
Meta-analysis (exponential form)

       |  Pooled      95% CI          Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-------------------------------------------------------
Fixed  |   1.107   0.999   1.226    1.945    0.052      3
Random |   1.107   0.999   1.226    1.945    0.052

Test for heterogeneity: Q=  0.756 on 2 degrees of freedom (p= 0.685)
Moment-based estimate of between studies variance =  0.000

           |      Weights      Study       95% CI
     Study |   Fixed  Random     Est   Lower   Upper
-----------+-------------------------------------------
      HPFS |   35.47   35.47    1.02    0.73    1.42
       NHS |   76.28   76.28    1.04    0.83    1.30
  NIH-AARP |  256.82  256.82    1.14    1.01    1.29
```

f) Quintile exposure

COLORECTAL CANCER

Quintile levels						
P1	P2	P3	P4		META analysis	
5	5	5	5		5	
4	4	4	4		4	
3	3	3	3	a	3	
2	2	2	2		2	
1	1	1	1		1	
a: Quintile-5 versus Quintile-1						

COLORECTAL ADENOMA

Quintile levels						
P1	P2	P3	P4		META analysis	
		5	5		5	
	4	4	4		4	
3	3	3	3	b	3	
2	2	2	2		2	c
1	1	1	1		1	
b: Quintile-high versus Quintile-1 C: Quintile-3 versus Quintile-1						

4. Results

A Prospective Pooled Analysis of Meat Mutagens and Colorectal Adenoma and Cancer in the US and EPIC Studies

Table 1. Pooled multivariable adjusted HR (95%CI) for colorectal cancer

HCAs	Method (Q-5 vs Q-1)	HR (95%CI)	*p*_value	Heterogeneity (*p*_value)
MDM	Fixed	1.11 (1.00, 1.23)	0.052	0.685
	Random	1.11 (1.00, 1.23)	0.052	
PhIP	Fixed	1.00 (0.91, 1.09)	0.958	0.661
	Random	1.00 (0.91, 1.09)	0.958	
MeIQx	Fixed	1.12 (1.03, 1.22)	0.009	0.400
	Random	1.12 (1.03, 1.22)	0.009	
DiMeIQx	Fixed	1.07 (0.99, 1.16)	0.084	0.013
	Random	1.03 (0.87, 1.22)	0.763	

Table 2. Pooled multivariable adjusted HR (95%CI) for colorectal adenoma, (Q-3 vs Q-1)

HCAs	Method (Q-3 vs Q-1)	HR (95%CI)	*p*_value	Heterogeneity (*p*_value)
MDM	Fixed	1.11 (0.95, 1.28)	0.190	0.178
	Random	1.13 (0.92, 1.39)	0.237	
PhIP	Fixed	1.12 (0.98, 1.27)	0.096	0.285
	Random	1.11 (0.96, 1.29)	0.169	
MeIQx	Fixed	1.14 (1.00, 1.30)	0.048	0.634
	Random	1.14 (1.00, 1.30)	0.048	
DiMeIQx	Fixed	0.99 (0.88, 1.12)	0.918	0.296
	Random	1.00 (0.87, 1.15)	0.999	

Table 3. Pooled multivariable adjusted HR (95%CI) for colorectal adenoma, (Q-h vs Q-1)

HCAs	Method (Q-h vs Q-1)	HR (95%CI)	*p*_value	Heterogeneity (*p*_value)
MDM	Fixed	1.15 (0.99, 1.34)	0.069	0.514
	Random	1.15 (0.99, 1.34)	0.069	
PhIP	Fixed	1.19 (1.05, 1.36)	0.008	0.272
	Random	1.19 (1.02, 1.39)	0.024	
MeIQx	Fixed	1.16 (1.01, 1.33)	0.033	0.327
	Random	1.17 (1.01, 1.35)	0.040	
DiMeIQx	Fixed	1.09 (0.97, 1.23)	0.142	0.394
	Random	1.09 (0.97, 1.23)	0.142	

Figure 1. Pooled multivariable adjusted HR (95%CI) for colorectal cancer of individual study populations and overall risk of cancer

Q5 vs Q1: Quintile-5 versus Quintile-1;

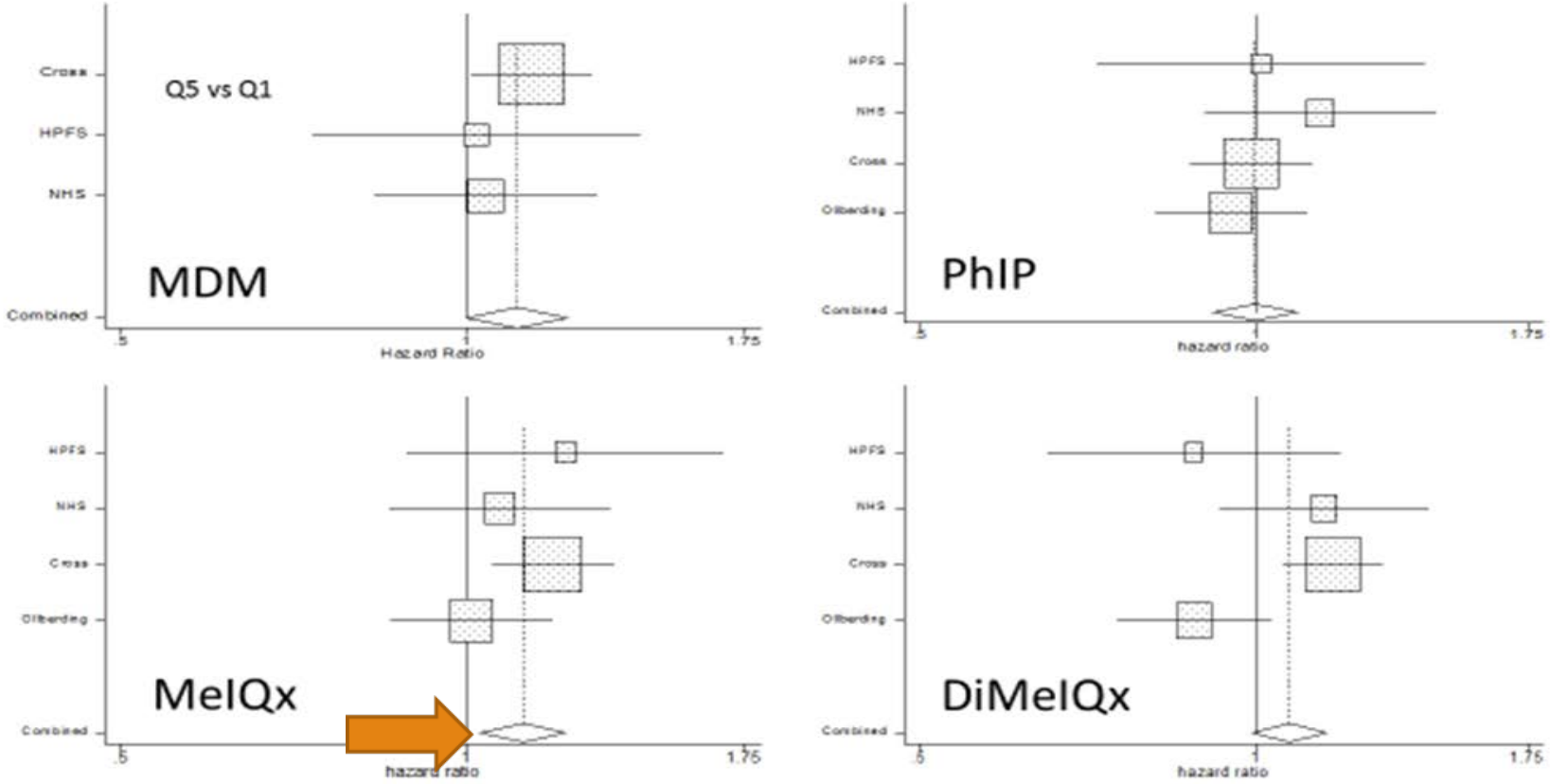


Figure 2. Pooled multivariable adjusted HR (95%CI) for colorectal adenoma of individual study populations and overall risk of adenoma (Q3 vs Q1).

Q3 vs Q1: Quintile-3 versus Quintile-1

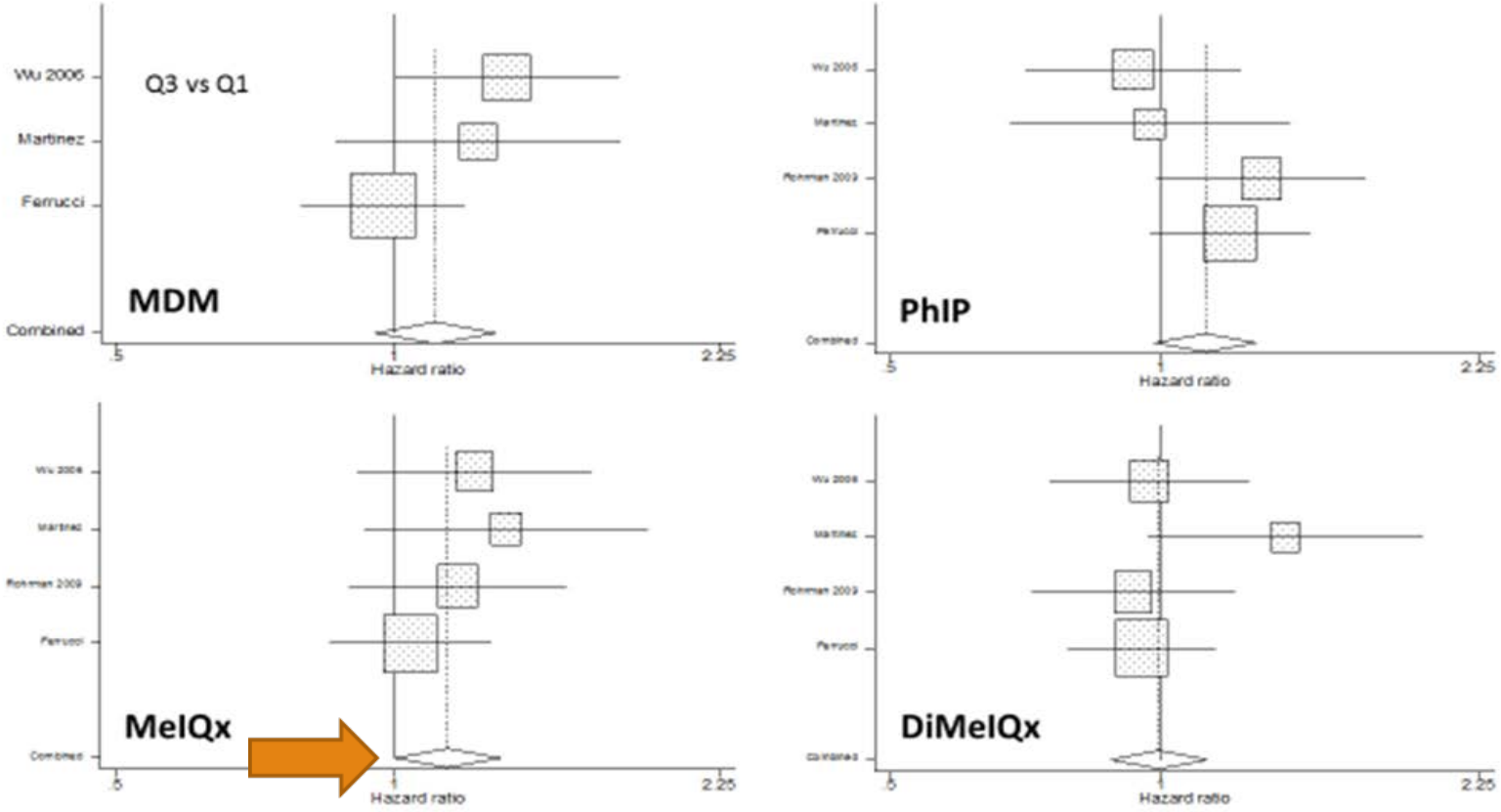
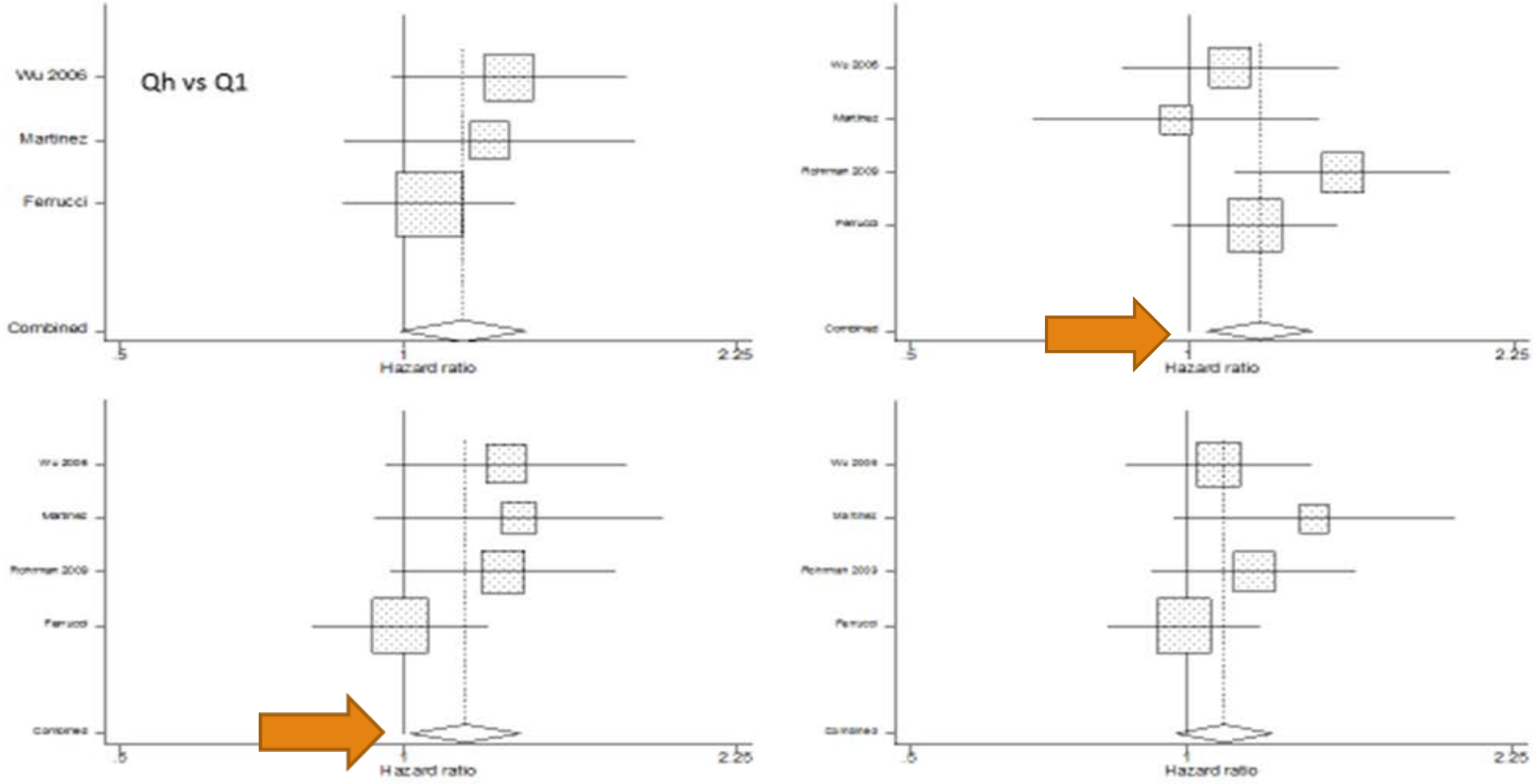


Figure 3. Pooled multivariable adjusted HR (95%CI) for colorectal adenoma of individual study populations and overall risk of adenoma (Qh vs Q1).

Qh vs Q1: Quintile-highest versus Quintile-1



5. Conclusions

We observed a positive association between exposures to MeIQx and the risk of both CRC and CRA that supports to the hypothesis of the role of HCAs in developing CRC. MeIQx might be the underlying mechanisms of red meat induced CRC.

6. Perspectives

- **HCAs now is about 40 years old**,
  - Observational findings with a consideration of methodology
- **Enhance quality of HCAs measurement**,
  - Population-based cooking methods to produce meat mutagens
- **Findings are generated**,
  - To Label the content of HCAs in Cooked meat to promote cancer prevention by meat mutagens control?

Dietary carcinogens and cancer risk: findings from Japanese studies

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Disclosure of conflict of interest: Not declared.

Red meat / processed meat and colorectal cancer

- Red meat
  - Probably carcinogenic to humans (Group 2A, vol.114) by IARC
  - Probable risk factor by WCRF 2017 report
- Processed meat
  - Carcinogenic to humans (Group 1, vol.114) by IARC
  - Convincing risk factor by WCRF 2017 report
- Possible mechanisms
  - Heterocyclic aromatic amines (HAAs)
  - Polycyclic aromatic hydrocarbons (PAHs)
  - N-nitroso compounds
  - Heme iron

Heterocyclic aromatic amines and colorectal cancer

- Heterocyclic aromatic amines (HAAs) are mutagenic and carcinogenic compounds that are formed in meats cooked at high temperature for long duration
- PhIP as possibly carcinogenic to humans (Group 2B, vol. 56) by IARC
  - Findings of epidemiological studies that have specifically examined the association between HAA intake and colorectal cancer risk have been inconsistent.
- HAAs requires N-oxidation by CYP1A2, followed by O-acetylation by NAT2 before they can exert their genotoxicity.
  - Interaction between HAA intake and NAT2 on colorectal cancer has been hypothesized.

Dietary factor assessments (FFQ)

過去１年間の食事を思い出して、平均的な頻度や量を記入してください。

食品名	食べない	月に1～3回	週に1～2回	週に3～4回	週に5～6回	毎日1回	毎日2～3回	毎日4～6回	毎日7回以上	一回あたりの目安量	目安量より 少ない(半分以下)	同じ	多い(1.5倍以上)
まぐろ缶詰（シーチキン･フレーク）	○	○	○	○	○	○	○	○	○	４分の１缶（20ｇ位）	○	○	○
さけ・ます	○	○	○	○	○	○	○	○	○	切り身１きれ（70ｇ位）	○	○	○

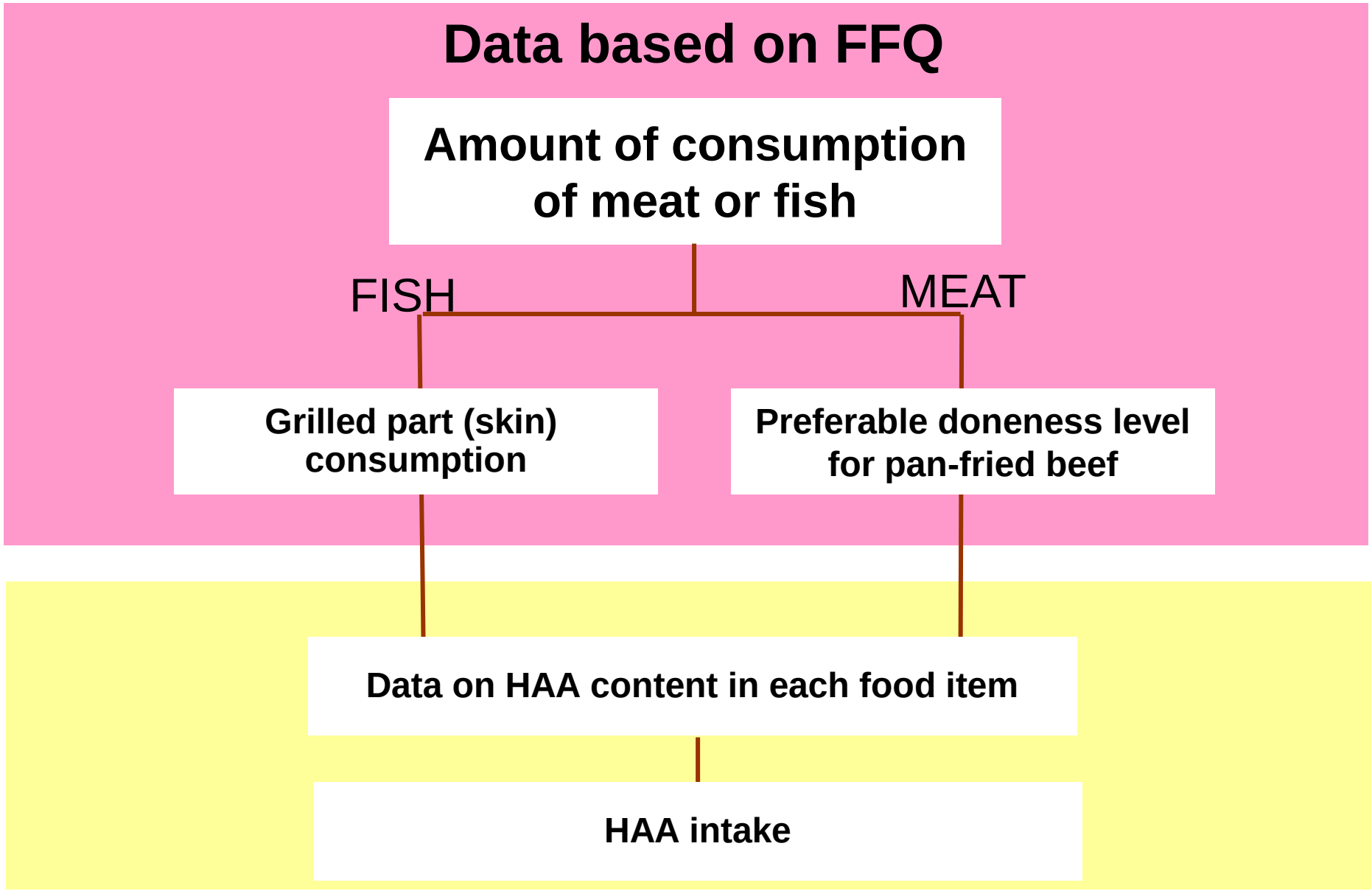
Nine-frequency categories and three relative portion sizes

Meat, fish and HAA exposure assessment

	Fish	**Meats**
Foods listed in FFQ	**19 fish items/groups**	**18 meat items**
	↓ **6 items/groups**	↓ **7 meat items**
Foods used to calculate HAA	Salted fish, semi-dried split fish, salmon, horse mackerel or sardines, Pacific saury or mackerel, and eel of six groups (usually grilled items)	pan-fired and grilled beef, stir-fried pork and pork liver, grilled chicken and chicken liver, and bacon

Kobayashi M et al. *Mutat Res* 2002;506-507:233-41

Estimation of HAA Intake from FFQ



Kobayashi M et al. *Mutat Res* 2002;506-507:233-41

Validation of the exposure assessments

4-day diet records (DR) of 144 sub-sample

Correlation coefficient between FFQ and DR

	Men	Women
Fish and shellfish	0.69	0.57
Processed Meat	0.63	0.47
Red Meat	0.74	0.53
Poultry	0.38	0.36

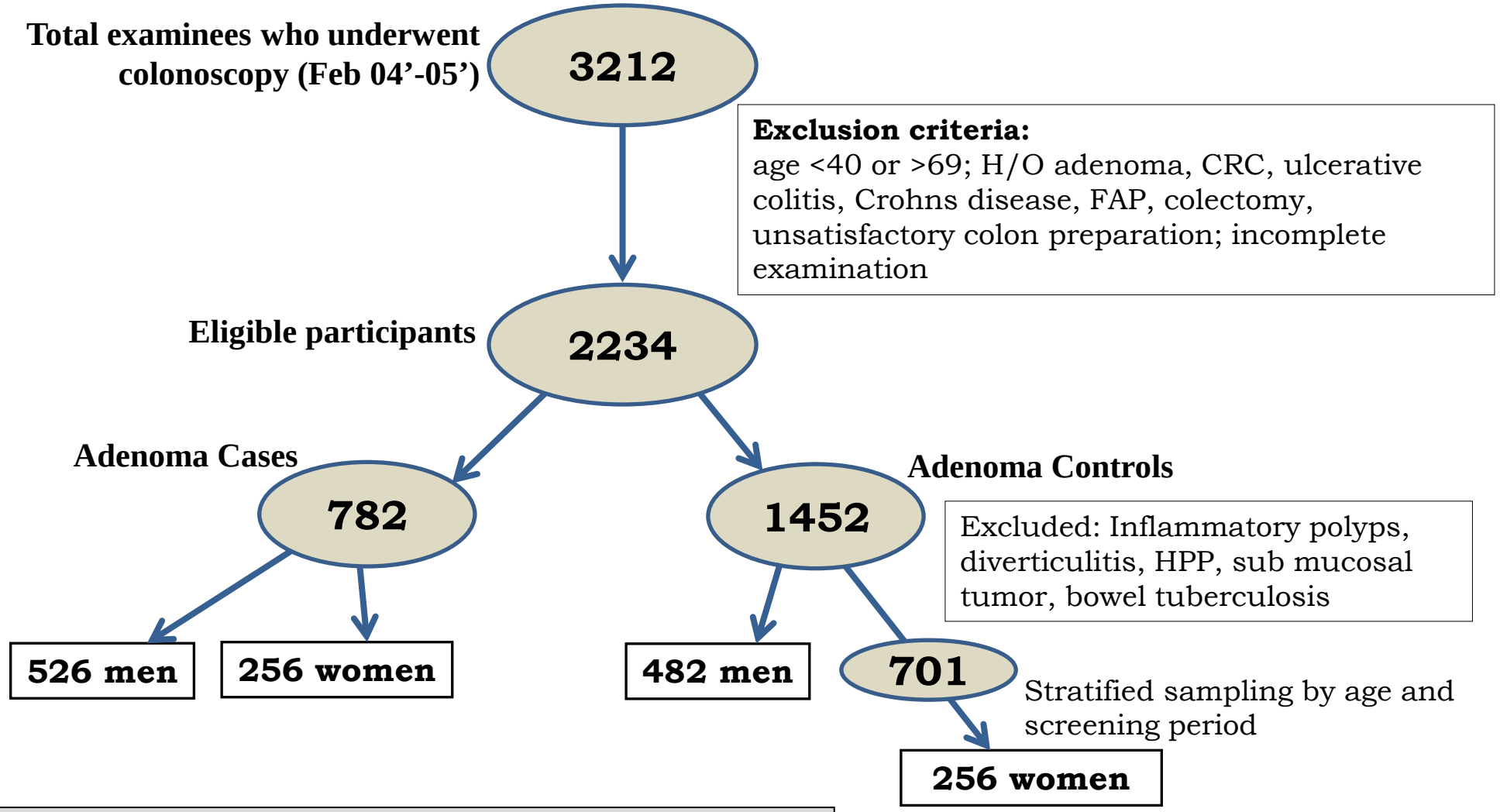
Hair samples from 65 sub-sample

Correlation coefficient between PhIP in hair and HAA from FFQ

	Men	Women
PhIP	0.33	0.37
MeIQ	0.33	0.55
MeIQx	0.31	0.41
Total HAA	0.32	0.42

Takachi R et al. J Epidemiol 2011;21:447-58
Iwasaki M et al. Cancer Causes and Control 2014;25:1015-28

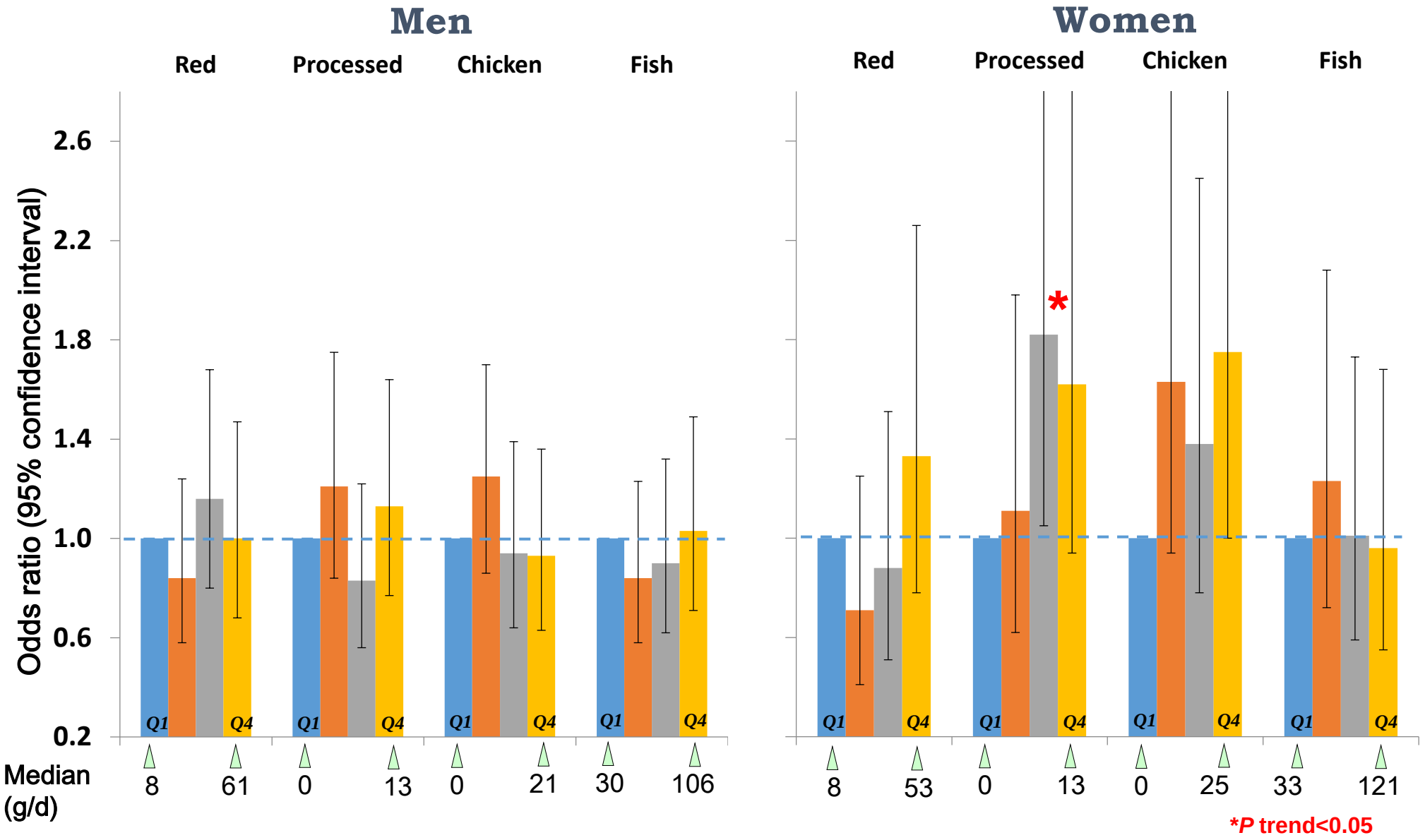
Colorectal adenoma study in Tokyo



Excluded top or bottom 2.5% of total energy intake by sex & age stratum and with missing values on covariates (44 cases, 41controls)

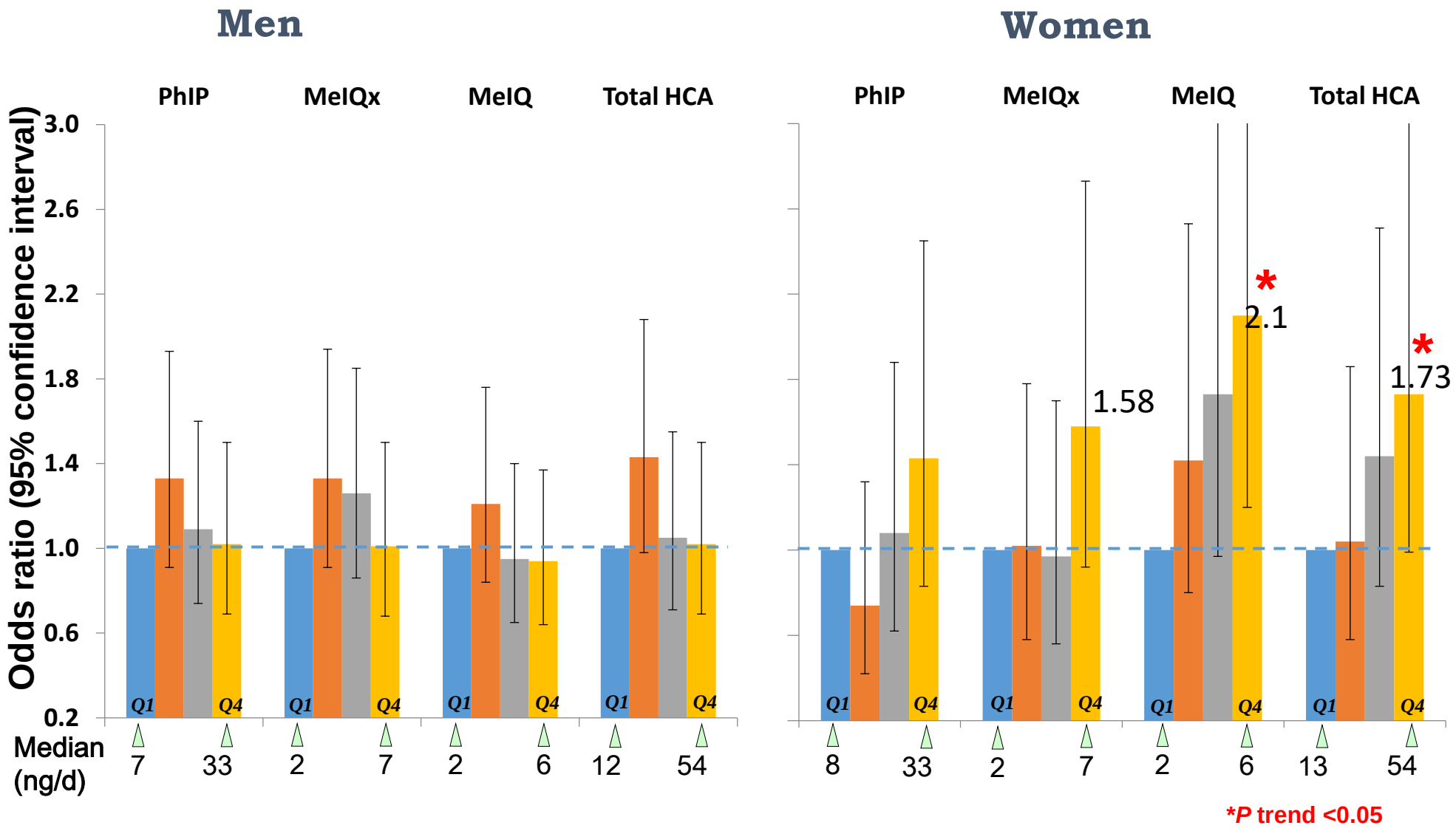
738 cases and 697 controls

Meat and fish intake and colorectal adenoma risk in Tokyo Adenoma Study



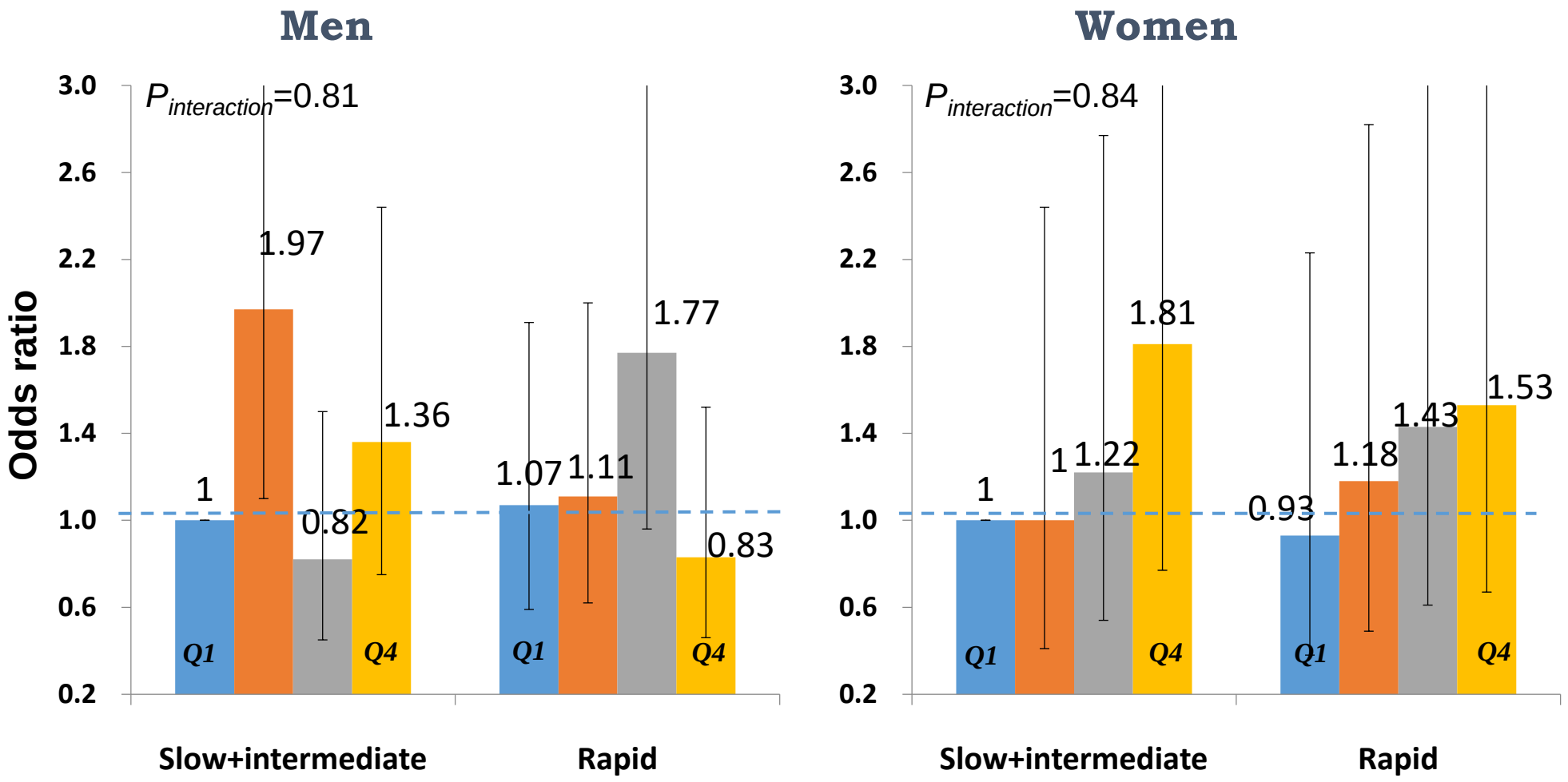
Budhathoki S, et al. Cancer Epidemiol Biomarkers Prev. 2015;24:613-20.

HAA intake and colorectal adenoma risk in Tokyo Adenoma Study



Budhathoki S, et al. Cancer Epidemiol Biomarkers Prev. 2015;24:613-20.

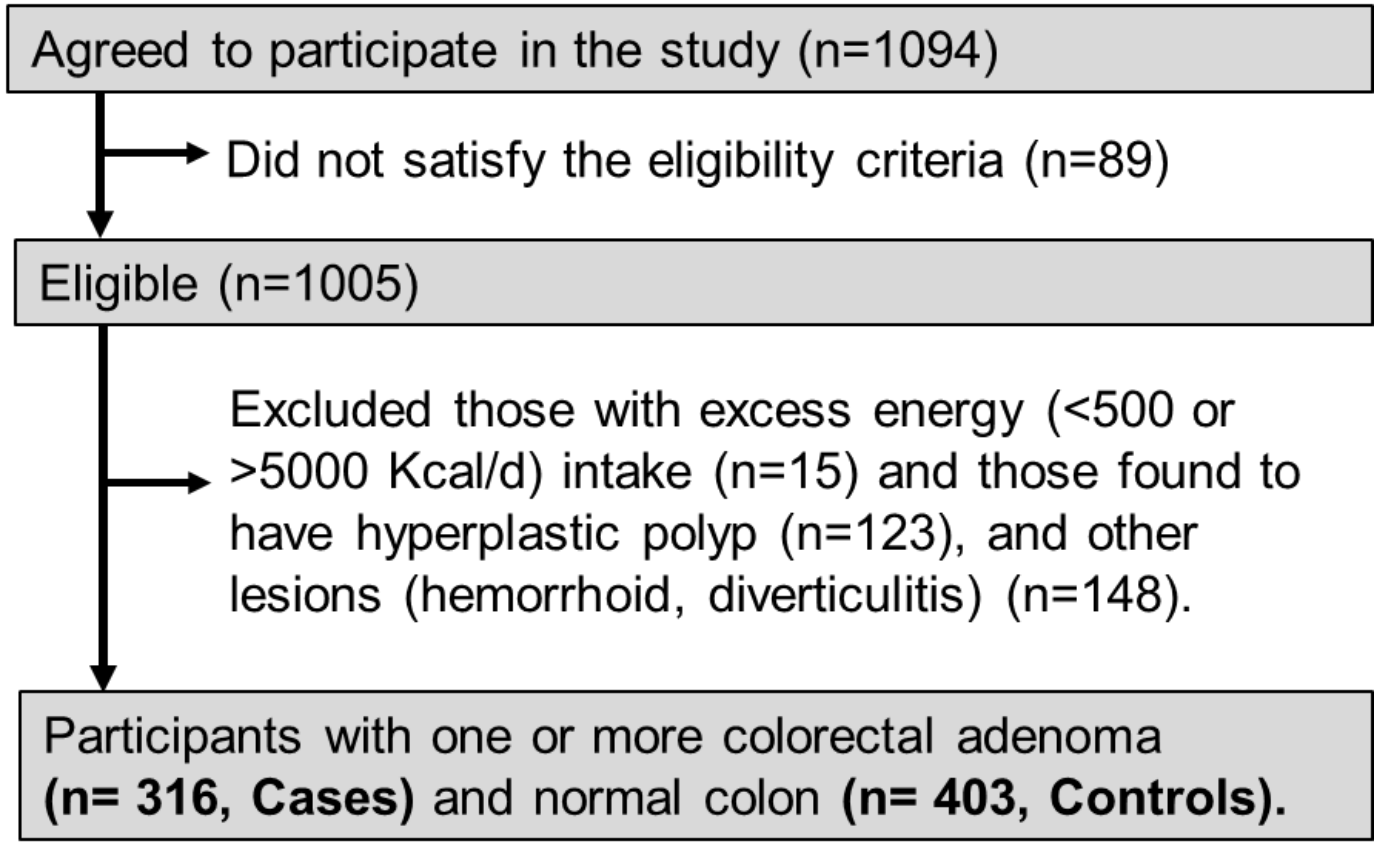
HAA intake and colorectal adenoma risk by *NAT2*-acetylation genotype in Tokyo Adenoma Study



Budhathoki S, et al. Cancer Epidemiol Biomarkers Prev. 2015;24:613-20.

Colorectal adenoma study in Brazil

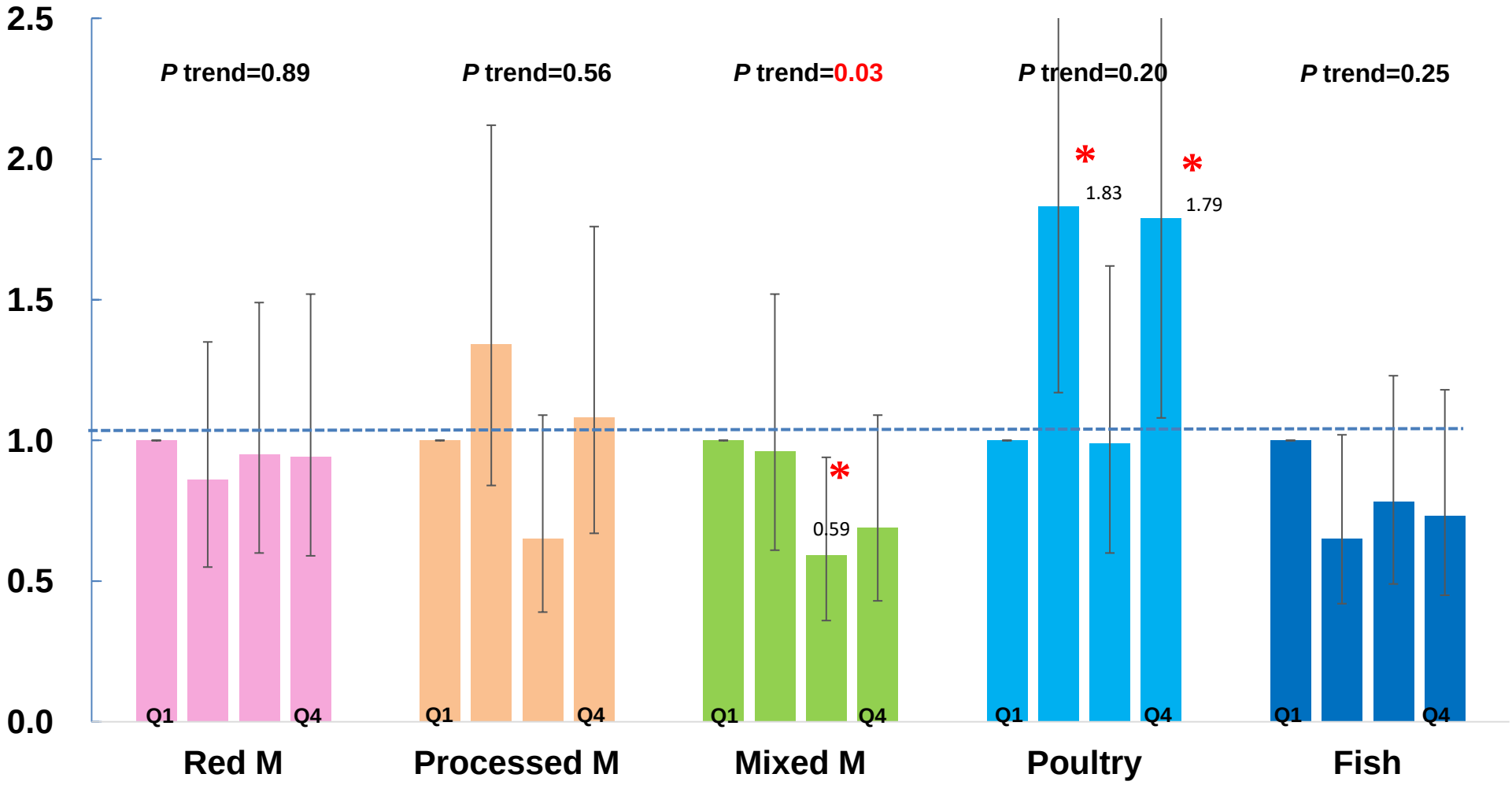
- Study participants were recruited from among patients who underwent colonoscopy in two hospitals in São Paulo, Brazil, between May 2007 and August 2013.
- Patients were eligible to participate if they were aged 40–79 years; had at least three grandparents of pure Japanese ancestry and had lived in São Paulo for at least 6 months prior to recruitment.



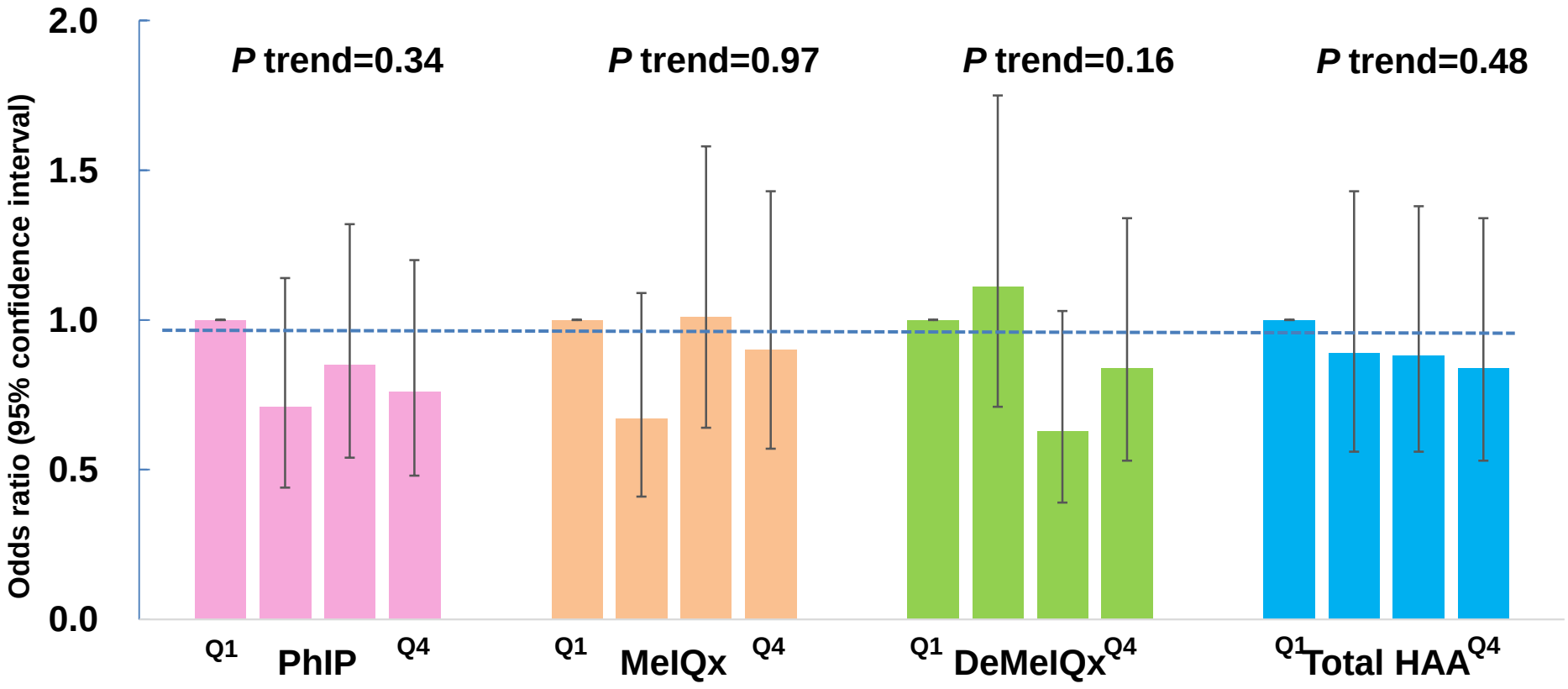
Dietary intake assessment

- Dietary assessment was performed using food frequency questionnaire (FFQ); daily food intake was calculated by multiplying frequency of intake by standard portion size for each food item in the FFQ (161 food items).
- The questionnaire included 21 meat or meat dishes, 13 chicken or poultry dishes, 12 fish or fish dishes and 2 meat alternatives
- Additional questions asked about the ‘doneness’ levels (rare, medium rare, medium, well cooked, very well cooked) of 14 grilled, churrasco or pan-fried meat items (4 beef items, 1 pork item, 6 chicken items and 3 fish items).
- The FFQ data, along with an HAA database we previously developed for meat and fish items cooked by Brazilian methods, were used to estimate the intake of MeIQx, DiMeIQx, and PhIP.

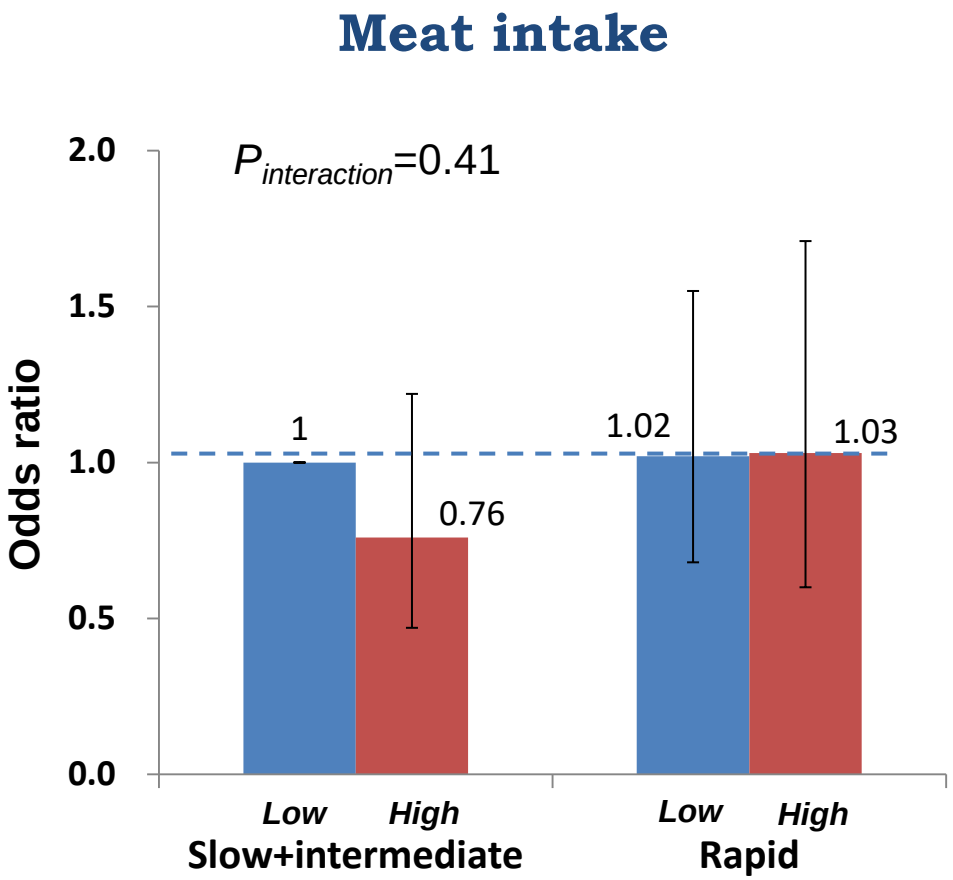
Meat and fish intake and colorectal adenoma risk in Brazil Adenoma Study

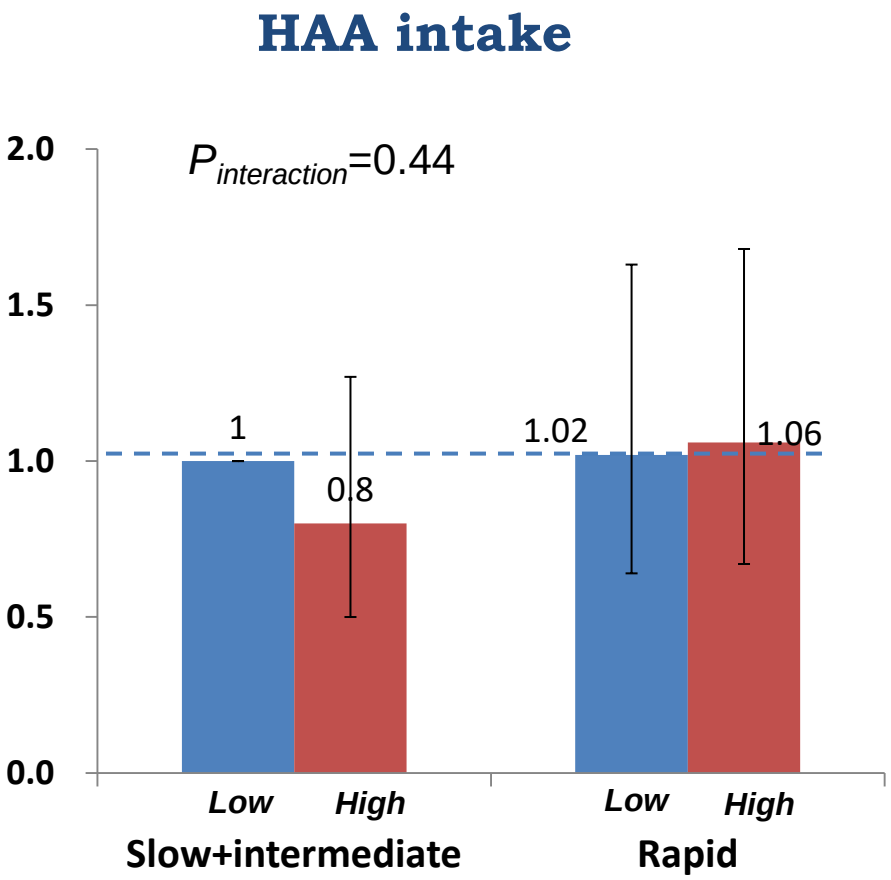


HAA intake and colorectal adenoma risk in Brazil Adenoma Study



Meat and HAA intake and colorectal adenoma risk by *NAT2*-acetylation genotype in Brazil Adenoma Study





Discussion

- Tokyo adenoma study showed positive association for MeIQ in women and not in men.
  - Although MeIQ is less abundant in food than PhIP, it is a more potent mutagen.
  - Correlation coefficient for validity of MeIQ intake was lower in men (0.33) than in women (0.55).
- No clear association with PhIP or MeIQx intakes and no effect modification by NAT2 genotype was observed.
  - Intake of PhIP and MeIQx in the present study was lower than in previous studies (median PhIP= 18 ng/d vs. 38-55 ng/d)
- Brazil adenoma study found no association for HAAs and no effect modification by NAT2 genotype.

Conclusion

- Tokyo adenoma study suggests HAA may play a role in colorectal carcinogenesis in humans although Brazil adenoma study failed to observe positive associations.

Thank you for your attention.