Professor Ping Zhao
President  Cancer Foundation of China
Chair  Cancer Prevention & Control Committee
of Chinese Preventive Medicine Association
Oct 3 2018 Kuala Lumpur Malaysia
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

The Duty is weightier than Mount Tai
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

<table>
<thead>
<tr>
<th>Year</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>73%</td>
</tr>
<tr>
<td>1999</td>
<td>73%</td>
</tr>
<tr>
<td>2000</td>
<td>70%</td>
</tr>
<tr>
<td>2001</td>
<td>69%</td>
</tr>
<tr>
<td>2002</td>
<td>68%</td>
</tr>
<tr>
<td>2003</td>
<td>66%</td>
</tr>
<tr>
<td>2004</td>
<td>65%</td>
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<tr>
<td>2005</td>
<td>65%</td>
</tr>
<tr>
<td>2006</td>
<td>64%</td>
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<tr>
<td>2007</td>
<td>64%</td>
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<tr>
<td>2008</td>
<td>63%</td>
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<tr>
<td>2009</td>
<td>63%</td>
</tr>
<tr>
<td>2010</td>
<td>62%</td>
</tr>
<tr>
<td>2011</td>
<td>61%</td>
</tr>
<tr>
<td>2012</td>
<td>61%</td>
</tr>
<tr>
<td>2013</td>
<td>61%</td>
</tr>
<tr>
<td>2014</td>
<td>60%</td>
</tr>
</tbody>
</table>
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

- **Etiological Prevention**
  - Government Protection
  - Removing Carcinogens
  - Public Awareness

去除病因

政府保护

Government Protection

Removing Carcinogens

民众知晓

Public Awareness
What are factors inducing cancer

- Infection
- Lifestyle
- Environment

Genetic (internal)

多基因遗传易感性疾病
Multi-genetic susceptible diseases
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 disseminate health lifestyle
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.
attributable risks of cancer

One important attributable factor of cancer is smoking

Chronic Infection 25.9%

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

Helicobacter pylori - stomach cancer 11.83%

Hepatitis virus and liver cancer 9.9%

Hepatitis B virus (HBV)

Human papillomavirus (HPV)

Epstein-Barr virus (EBV)

Cervical cancer 2.63%

– 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 carrying rate in Chinese people over time

<table>
<thead>
<tr>
<th>Age Group (year)</th>
<th>1979</th>
<th>1992</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>1~4</td>
<td></td>
<td></td>
<td>0.96%</td>
</tr>
<tr>
<td>5~14</td>
<td></td>
<td></td>
<td>2.42%</td>
</tr>
<tr>
<td>15~59</td>
<td></td>
<td></td>
<td>8.57%</td>
</tr>
</tbody>
</table>

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

Historical comparison between Immunized and Unimmunized cohorts, baseline difference

Chiang et al. JAMA 2013, 310(9):974-6
Dr. Harald zur Hausen, a German Nobel 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 definite clinical effect in young women
- Vaccination among 18-26 yr women using HPV vaccine (3 shot) showed effective for preventing CIN3
- Research confirmed consistent response rates of the vaccine in the adolescents and adults
Chapter 1  Preface
Chapter 2  Harzards and influence of cancer
Chapter 3  Base and principle of cancer prevention and control
Chapter 4  Methods for cancer prevention and control
Chapter 5  Risk factors of cancer
Chapter 6  Carcinogenesis
Chapter 7  Strategies and measures for cancer control
Chapter 8  Prevention and control for common cancers
Global concerns for cancer prevention & treatment in China
亚洲国家癌症中心联盟
Government pays highly attention to cancer prevention.
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

Disclosure of interest: None declared
IARC: Cancer today 2018
IARC 2018: Lung cancer incidence and mortality by sex and region

**Age standardized (World) incidence rates, lung, by sex**

- Micronesia: 54.1 males, 24.0 females
- Polynesia: 52.0 males, 24.6 females
- Central and Eastern Europe: 49.3 males, 21.9 females
- Eastern Asia: 43.3 males, 15.7 females
- Western Europe: 43.1 males, 15.7 females
- Southern Europe: 39.1 males, 7.8 females
- North America: 38.8 males, 7.8 females
- Western Asia: 34.0 males, 14.6 females
- Northern Europe: 31.5 males, 14.6 females
- Australia/New Zealand: 28.4 males, 9.6 females
- South-Eastern Asia: 26.3 males, 8.9 females
- Southern Africa: 26.0 males, 8.9 females
- Caribbean: 23.5 males, 4.2 females
- Melanesia: 17.1 males, 4.2 females
- Northern Africa: 17.9 males, 4.5 females
- South America: 16.9 males, 4.5 females
- South-Central Asia: 16.8 males, 4.5 females
- Central America: 9.4 males, 4.0 females
- Middle Africa: 7.2 males, 4.0 females
- Eastern Africa: 3.8 males, 2.2 females
- Western Africa: 2.4 males, 1.2 females

**Age standardized (World) incidence and mortality rates, lung**

- Polynesia: Incidence 88.1, Mortality 30.2
- Micronesia: Incidence 79.9, Mortality 22.3
- North America: Incidence 74.5, Mortality 28.5
- Eastern Asia: Incidence 34.1, Mortality 24.6
- Western Europe: Incidence 33.9, Mortality 21.3
- Southern Europe: Incidence 30.1, Mortality 22.7
- Central and Eastern Europe: Incidence 28.3, Mortality 23.6
- Australia/New Zealand: Incidence 27.3, Mortality 17.0
- Western Asia: Incidence 26.0, Mortality 21.7
- Caribbean: Incidence 22.5, Mortality 18.6
- South-Eastern Asia: Incidence 18.5, Mortality 15.6
- Southern Africa: Incidence 17.2, Mortality 15.4
- South America: Incidence 15.6, Mortality 15.2
- Melanesia: Incidence 13.1, Mortality 11.9
- Northern Africa: Incidence 12.7, Mortality 12.2
- South-Central Asia: Incidence 9.9, Mortality 9.6
- Central America: Incidence 6.4, Mortality 6.0
- Middle Africa: Incidence 5.8, Mortality 5.9
- Eastern Africa: Incidence 2.9, Mortality 2.8
- Western Africa: Incidence 1.7, Mortality 1.7
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

The diagram illustrates the mortalities of lung cancer in China from 1973 to 2005, categorized by urban and rural areas, and three time periods: 1973-1975, 1990-1992, and 2004-2005. The mortalities are represented in the following ranges:

Area specific mortality of lung cancer in China

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.

<table>
<thead>
<tr>
<th>Year</th>
<th>Radon Concentration</th>
<th>Times VS National Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950-1959</td>
<td>10.43</td>
<td>8.03</td>
</tr>
<tr>
<td>1970-1974</td>
<td>9.29</td>
<td>5.75</td>
</tr>
<tr>
<td>1975-1979</td>
<td>6.07</td>
<td>3.25</td>
</tr>
<tr>
<td>1980-1984</td>
<td>2.92</td>
<td>1.67</td>
</tr>
<tr>
<td>1985-1989</td>
<td>2.18</td>
<td>1.07</td>
</tr>
<tr>
<td>1990-1994</td>
<td>2.63</td>
<td>1.04</td>
</tr>
<tr>
<td>1995-1999</td>
<td>2.89</td>
<td>1.02</td>
</tr>
</tbody>
</table>
Age-specific mortality in different regions 1973-1975

[Graph showing age-specific mortality rates for males and females from different regions (GJ, XW, SH, LN, GZ) per 100,000 people, with age groups ranging from 0-80+ years.]
lung cancer mortality correlated with using smoky coal in Xuanwei

<table>
<thead>
<tr>
<th>Commune</th>
<th>Use smoky coal (%) before 1958</th>
<th>Use firewood (%)</th>
<th>Use smokeless coal (%)</th>
<th>Lung cancer mortality (1/10⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng-guan</td>
<td>100.0</td>
<td>0.0</td>
<td>0.0</td>
<td>174.2</td>
</tr>
<tr>
<td>Lai-bin</td>
<td>89.7</td>
<td>8.7</td>
<td>1.6</td>
<td>128.3</td>
</tr>
<tr>
<td>Rong-cheng</td>
<td>81.9</td>
<td>18.1</td>
<td>0.0</td>
<td>104.1</td>
</tr>
<tr>
<td>Long-chang</td>
<td>76.1</td>
<td>17.9</td>
<td>6.0</td>
<td>39.5</td>
</tr>
<tr>
<td>Long-tan</td>
<td>78.0</td>
<td>22.0</td>
<td>0.0</td>
<td>32.5</td>
</tr>
<tr>
<td>Ban-qiao</td>
<td>34.0</td>
<td>16.4</td>
<td>49.8</td>
<td>22.1</td>
</tr>
<tr>
<td>Hai-fa</td>
<td>49.7</td>
<td>22.5</td>
<td>27.8</td>
<td>19.1</td>
</tr>
<tr>
<td>Luo-shui</td>
<td>2.7</td>
<td>39.0</td>
<td>58.3</td>
<td>13.5</td>
</tr>
<tr>
<td>Pu-li</td>
<td>35.2</td>
<td>52.0</td>
<td>12.8</td>
<td>7.5</td>
</tr>
<tr>
<td>Xi-ze</td>
<td>0.0</td>
<td>90.9</td>
<td>9.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Re-shui</td>
<td>0.0</td>
<td>66.6</td>
<td>33.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

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

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,
Deputy Chief, Tobacco Control and Lung Cancer Control Branch, Cancer Foundation of China
Professor, Office of Cancer Registry, National Caner Center - Cancer Hospital of Chinese Academy of Medical Sciences, Beijing 100021, People’s Republic of China

xnzou@cicams.ac.cn
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

Le Tran Ngoan, MD., PhD.

DEPT. OF OCCUPATIONAL HEALTH, INSTITUTE OF PREVENTIVE MEDICINE AND PUBLIC HEALTH, HANOI MEDICAL UNIVERSITY, VIET NAM.

DEPT. OF GLOBAL HEALTH, SCHOOL OF MEDICINE, INTERNATIONAL UNIVERSITY OF HEALTH AND WELFARE, JAPAN
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.
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.


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.
### Study populations: Colorectal Cancer

<table>
<thead>
<tr>
<th>Colorectal cancer (CRC)</th>
<th>Participants</th>
<th>CRC</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurses' Health Study</td>
<td>65,785</td>
<td>418</td>
<td>14-Y</td>
</tr>
<tr>
<td>Health Professional Follow-up Study</td>
<td>29,615</td>
<td>790</td>
<td>14-Y</td>
</tr>
<tr>
<td>NIH-AARP Diet and Health Study</td>
<td>300,948</td>
<td>2,719</td>
<td>7.2-Y</td>
</tr>
<tr>
<td>The Multiethnic Cohort Study</td>
<td>131,763</td>
<td>1,757</td>
<td>8.1-Y</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>528,111</strong></td>
<td><strong>5,684</strong></td>
<td><strong>Y: Year</strong></td>
</tr>
</tbody>
</table>
### Study populations: Colorectal Adenoma

<table>
<thead>
<tr>
<th>Colorectal adenoma (CRA)</th>
<th>Participants</th>
<th>CRA</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Professional Follow-up Study</td>
<td>14,032</td>
<td>581</td>
<td>6-Y</td>
</tr>
<tr>
<td>The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial</td>
<td>17,072</td>
<td>1008</td>
<td>3.5-Y</td>
</tr>
<tr>
<td>The ursodeoxycholic acid (UDCA)</td>
<td>869</td>
<td>379</td>
<td>31-M</td>
</tr>
<tr>
<td>EPIC study</td>
<td>21,452</td>
<td>516</td>
<td>6_y</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>53,425</strong></td>
<td><strong>2,484</strong></td>
<td></td>
</tr>
</tbody>
</table>
d) Convert HR (95%CI) into “lnhr”, “sehr”

<table>
<thead>
<tr>
<th>HR (95%CI)</th>
<th>hr</th>
<th>lci</th>
<th>uci</th>
<th>lnhr</th>
<th>varlnhr</th>
<th>sehr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.15 (0.84, 1.57)</td>
<td>1.15</td>
<td>0.84</td>
<td>1.57</td>
<td>0.1398</td>
<td>0.0255</td>
<td>0.1595</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Method</th>
<th>Pooled</th>
<th>95% CI</th>
<th>Asymptotic</th>
<th>No. of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Est</td>
<td>Lower</td>
<td>Upper</td>
<td>z_value</td>
</tr>
<tr>
<td>Fixed</td>
<td>1.107</td>
<td>0.999</td>
<td>1.226</td>
<td>1.945</td>
</tr>
<tr>
<td>Random</td>
<td>1.107</td>
<td>0.999</td>
<td>1.226</td>
<td>1.945</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Weights</th>
<th>Study</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fixed</td>
<td>Random</td>
<td>Est</td>
</tr>
<tr>
<td>HPFS</td>
<td>35.47</td>
<td>35.47</td>
<td>1.02</td>
</tr>
<tr>
<td>NHS</td>
<td>76.28</td>
<td>76.28</td>
<td>1.04</td>
</tr>
<tr>
<td>NIH-AARP</td>
<td>256.82</td>
<td>256.82</td>
<td>1.14</td>
</tr>
</tbody>
</table>
\( f \) Quintile exposure

### COLORECTAL CANCER

<table>
<thead>
<tr>
<th>Quintile levels</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>META analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
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<td>5</td>
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<tr>
<td>4</td>
<td>4</td>
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<td>3</td>
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<td>3</td>
<td>a</td>
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<tr>
<td>2</td>
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<td>2</td>
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<td>2</td>
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</tr>
<tr>
<td>1</td>
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<td>1</td>
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<td></td>
</tr>
</tbody>
</table>

- **a**: Quintile-5 versus Quintile-1

### COLORECTAL ADENOMA

<table>
<thead>
<tr>
<th>Quintile levels</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>META analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
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<td>5</td>
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</tr>
<tr>
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<td>4</td>
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<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>b</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

- **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

<table>
<thead>
<tr>
<th>HCAs</th>
<th>Method (Q-5 vs Q-1)</th>
<th>HR (95%CI)</th>
<th>p_value</th>
<th>Heterogeneity (p_value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDM</td>
<td>Fixed</td>
<td>1.11 (1.00, 1.23)</td>
<td>0.052</td>
<td>0.685</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.11 (1.00, 1.23)</td>
<td>0.052</td>
<td></td>
</tr>
<tr>
<td>PhIP</td>
<td>Fixed</td>
<td>1.00 (0.91, 1.09)</td>
<td>0.958</td>
<td>0.661</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.00 (0.91, 1.09)</td>
<td>0.958</td>
<td></td>
</tr>
<tr>
<td>MeIQx</td>
<td>Fixed</td>
<td>1.12 (1.03, 1.22)</td>
<td>0.009</td>
<td>0.400</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.12 (1.03, 1.22)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>DiMeIQx</td>
<td>Fixed</td>
<td>1.07 (0.99, 1.16)</td>
<td>0.084</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.03 (0.87, 1.22)</td>
<td>0.763</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Pooled multivariable adjusted HR (95%CI) for colorectal adenoma, (Q-3 vs Q-1)

<table>
<thead>
<tr>
<th>HCAs</th>
<th>Method (Q-3 vs Q-1)</th>
<th>HR (95%CI)</th>
<th>p_value</th>
<th>Heterogeneity (p_value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDM</td>
<td>Fixed</td>
<td>1.11 (0.95, 1.28)</td>
<td>0.190</td>
<td>0.178</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.13 (0.92, 1.39)</td>
<td>0.237</td>
<td></td>
</tr>
<tr>
<td>PhIP</td>
<td>Fixed</td>
<td>1.12 (0.98, 1.27)</td>
<td>0.096</td>
<td>0.285</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.11 (0.96, 1.29)</td>
<td>0.169</td>
<td></td>
</tr>
<tr>
<td>MeIQx</td>
<td>Fixed</td>
<td>1.14 (1.00, 1.30)</td>
<td>0.048</td>
<td>0.634</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.14 (1.00, 1.30)</td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td>DiMeIQx</td>
<td>Fixed</td>
<td>0.99 (0.88, 1.12)</td>
<td>0.918</td>
<td>0.296</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.00 (0.87, 1.15)</td>
<td>0.999</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Pooled multivariable adjusted HR (95%CI) for colorectal adenoma, (Q-h vs Q-1)

<table>
<thead>
<tr>
<th>HCAs</th>
<th>Method</th>
<th>HR (95%CI)</th>
<th>p_value</th>
<th>Heterogeneity (p_value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDM</td>
<td>Fixed</td>
<td>1.15 (0.99, 1.34)</td>
<td>0.069</td>
<td>0.514</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.15 (0.99, 1.34)</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>PhIP</td>
<td>Fixed</td>
<td>1.19 (1.05, 1.36)</td>
<td>0.008</td>
<td>0.272</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.19 (1.02, 1.39)</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>MelIQx</td>
<td>Fixed</td>
<td>1.16 (1.01, 1.33)</td>
<td>0.033</td>
<td>0.327</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.17 (1.01, 1.35)</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>DiMelQx</td>
<td>Fixed</td>
<td>1.09 (0.97, 1.23)</td>
<td>0.142</td>
<td>0.394</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>1.09 (0.97, 1.23)</td>
<td>0.142</td>
<td></td>
</tr>
</tbody>
</table>
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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Division of Epidemiology
Center for Public Health Sciences
National Cancer Center, Japan

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)

<table>
<thead>
<tr>
<th>食 品 名</th>
<th>食べない</th>
<th>月に1-3回</th>
<th>週に1-2回</th>
<th>週に3-4回</th>
<th>頻に5-6回</th>
<th>毎日1回</th>
<th>毎日2-3回</th>
<th>毎日4-6回</th>
<th>毎日7回以上</th>
<th>一回あたりの目安量</th>
<th>目安量より</th>
</tr>
</thead>
<tbody>
<tr>
<td>まぐろ焼鰤（シーチキン・フレーク）</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4分の1缶（20g位）</td>
<td></td>
</tr>
<tr>
<td>さけ・ます</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nine-frequency categories and three relative portion sizes

Meat, fish and HAA exposure assessment

**Foods listed in FFQ**

- **Fish**: 19 fish items/groups
  - 6 items/groups
  - Salted fish, semi-dried split fish, salmon, horse mackerel or sardines, Pacific saury or mackerel, and eel of six groups (usually grilled items)

- **Meats**: 18 meat items
  - 7 meat items
  - Pan-fired and grilled beef, stir-fried pork and pork liver, grilled chicken and chicken liver, and bacon

Estimation of HAA Intake from FFQ

Data based on FFQ

Amount of consumption of meat or fish

FISH

Grilled part (skin) consumption

MEAT

Preferable doneness level for pan-fried beef

Data on HAA content in each food item

HAA intake

## Validation of the exposure assessments

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

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish and shellfish</td>
<td>0.69</td>
<td>0.57</td>
</tr>
<tr>
<td>Processed Meat</td>
<td>0.63</td>
<td>0.47</td>
</tr>
<tr>
<td>Red Meat</td>
<td>0.74</td>
<td>0.53</td>
</tr>
<tr>
<td>Poultry</td>
<td>0.38</td>
<td>0.36</td>
</tr>
</tbody>
</table>

**Correlation coefficient between FFQ and DR**

**Hair samples from 65 sub-sample**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhIP</td>
<td>0.33</td>
<td>0.37</td>
</tr>
<tr>
<td>MeIQ</td>
<td>0.33</td>
<td>0.55</td>
</tr>
<tr>
<td>MeIQx</td>
<td>0.31</td>
<td>0.41</td>
</tr>
<tr>
<td>Total HAA</td>
<td>0.32</td>
<td>0.42</td>
</tr>
</tbody>
</table>

**Correlation coefficient between PhIP in hair and HAA from FFQ**

Excluded: Inflammatory polyps, diverticulitis, HPP, sub mucosal tumor, bowel tuberculosis

Exclusion criteria:
age <40 or >69; H/O adenoma, CRC, ulcerative colitis, Crohn's disease, FAP, colectomy, unsatisfactory colon preparation; incomplete examination

738 cases and 697 controls

Colorectal adenoma study in Tokyo

Total examinees who underwent colonoscopy (Feb 04’-05’)

3212

Eligible participants

2234

Adenoma Cases

782

526 men 256 women

Adenoma Controls

1452

482 men 701

701

256 women

Stratified sampling by age and screening period

Excluded top or bottom 2.5% of total energy intake by sex & age stratum and with missing values on covariates (44 cases, 41 controls)
Meat and fish intake and colorectal adenoma risk in Tokyo Adenoma Study

Men

Red

Processed

Chicken

Fish

Women

Red

Processed

Chicken

Fish

Odds ratio (95% confidence interval)


*P trend<0.05
HAA intake and colorectal adenoma risk in Tokyo Adenoma Study

HAA intake and colorectal adenoma risk by \textit{NAT2}-acetylation genotype in Tokyo Adenoma Study

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.

```
Agreed to participate in the study (n=1094)  

Did not satisfy the eligibility criteria (n=89)  

Eligible (n=1005)  

Excluded those with excess energy (<500 or >5000 Kcal/d) intake (n=15) and those found to have hyperplastic polyp (n=123), and other lesions (hemorrhoid, diverticulitis) (n=148).

Participants with one or more colorectal adenoma (n=316, Cases) and normal colon (n=403, Controls).
```
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

- Red M: $P_{\text{trend}} = 0.89$
- Processed M: $P_{\text{trend}} = 0.56$
- Mixed M: $P_{\text{trend}} = 0.03$
- Poultry: $P_{\text{trend}} = 0.20$
- Fish: $P_{\text{trend}} = 0.25$
## HAA intake and colorectal adenoma risk in Brazil Adenoma Study

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% confidence interval)</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 PhIP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 MelIQx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 DeMelIQx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 Total HAA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PhIP, MeIQx, DeMeIQx, Total HAA are representative of specific high-activity amines (HAA).*
Meat and HAA intake and colorectal adenoma risk by \( NAT2 \)-acetylation genotype in Brazil Adenoma Study

**Meat intake**

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow+intermediate</td>
<td>1.00</td>
<td>0.76</td>
</tr>
<tr>
<td>Rapid</td>
<td>1.02</td>
<td>1.03</td>
</tr>
</tbody>
</table>

\( P_{\text{interaction}} = 0.41 \)

**HAA intake**

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow+intermediate</td>
<td>1.00</td>
<td>0.80</td>
</tr>
<tr>
<td>Rapid</td>
<td>1.02</td>
<td>1.06</td>
</tr>
</tbody>
</table>

\( P_{\text{interaction}} = 0.44 \)
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.