KMCC

Korean Multi-center Cancer Cohort Study

Keun-Young Yoo, MD, PhD

Professor	**Seoul National University College of Medicine**
President	**Korean Society for Genome Epidemiology**
Co-Chair	**Asia Cohort Consortium (2005~2008)**

Incredible Changes in Korean Society from Agricultural to Highly Advanced Industrial Country

Cause of death = infections
Life expectancy < 45 yrs
Per capita GNI < US$20
Traditional medicine

1911

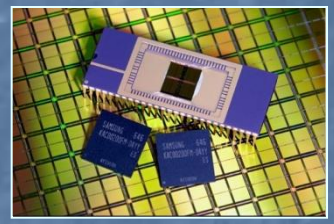
Korea

Cause of death = cancer
Life expectancy = 78 yrs
Per capita GNI = US$20,000
Universal health insurance

2009

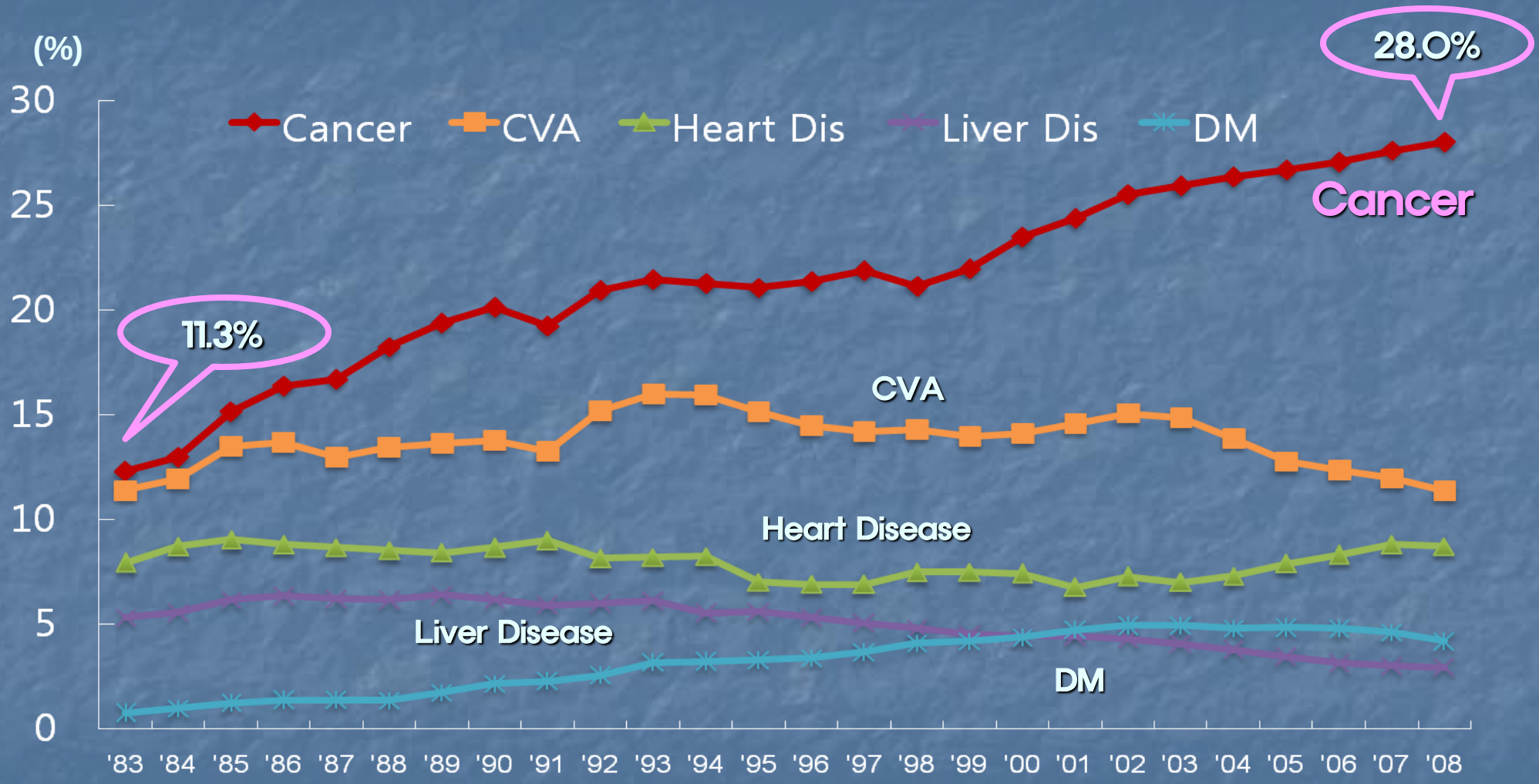
Health and Welfare Statistics
Republic of Korea

population: (ranked 18th in the world)	49 M (south) 23 M (north) as of 2007
life expectancy:	75.7 yrs (M) / 82.4 yrs (F)
aging (65+):	9.0% (2005) 20.0% (2026)
population IR:	0.33% (2007)
health insurance:	universal coverage
per capita GNI:	USD 20,045 (2007)
major industries:	semiconductors, automobiles, ships, mobile telecoms, chemicals, steels, consumer electronics




◇ 삼성전자와 일본 소니가 합작으로 세운 S-LCD의 생산라인 모습. [사진=삼성전자]

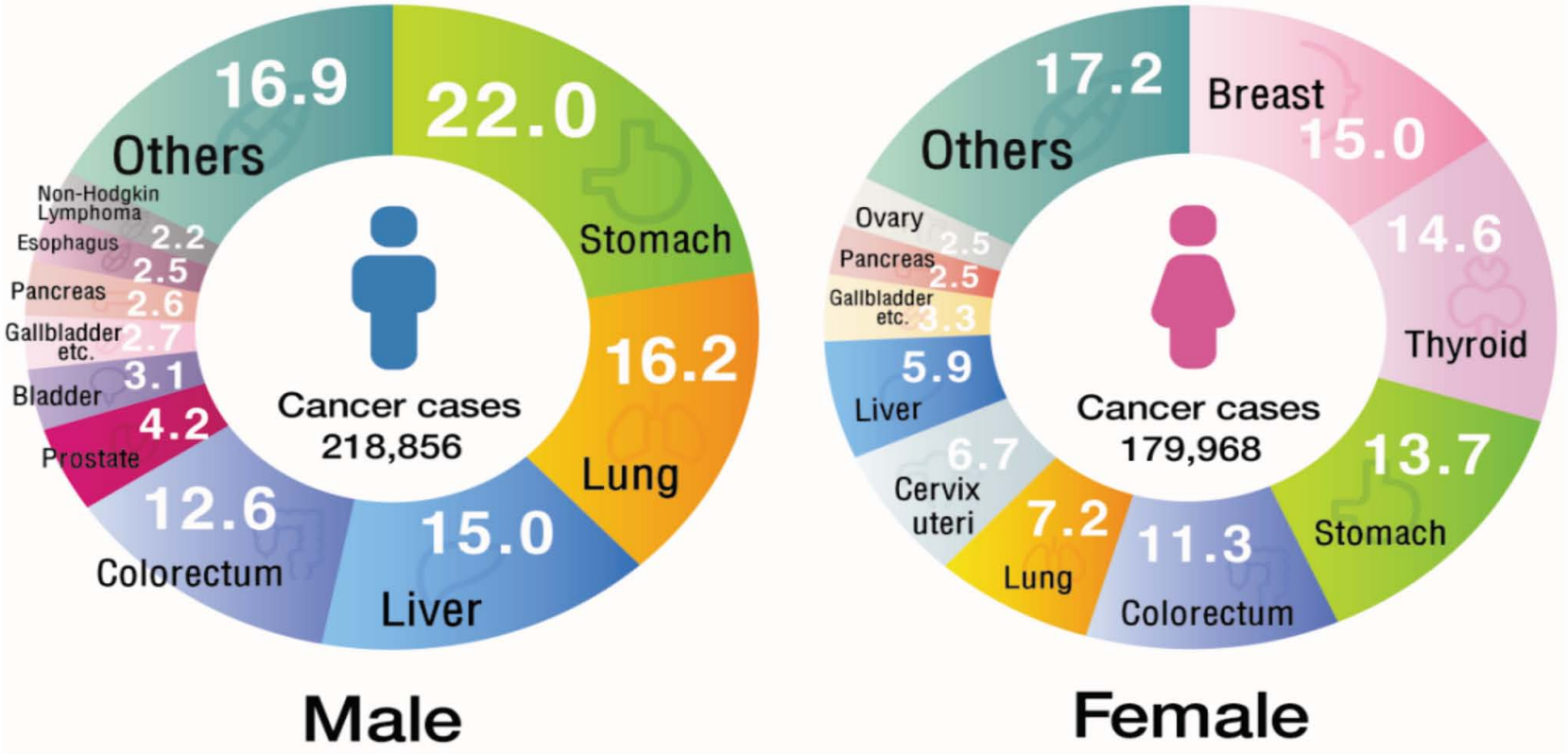
Causes of Deaths in Korea



Source: Korea National Statistical Office, 2008

Relative Frequency of Incident Cancer Cases in Korea 2003~2005

Unit : %

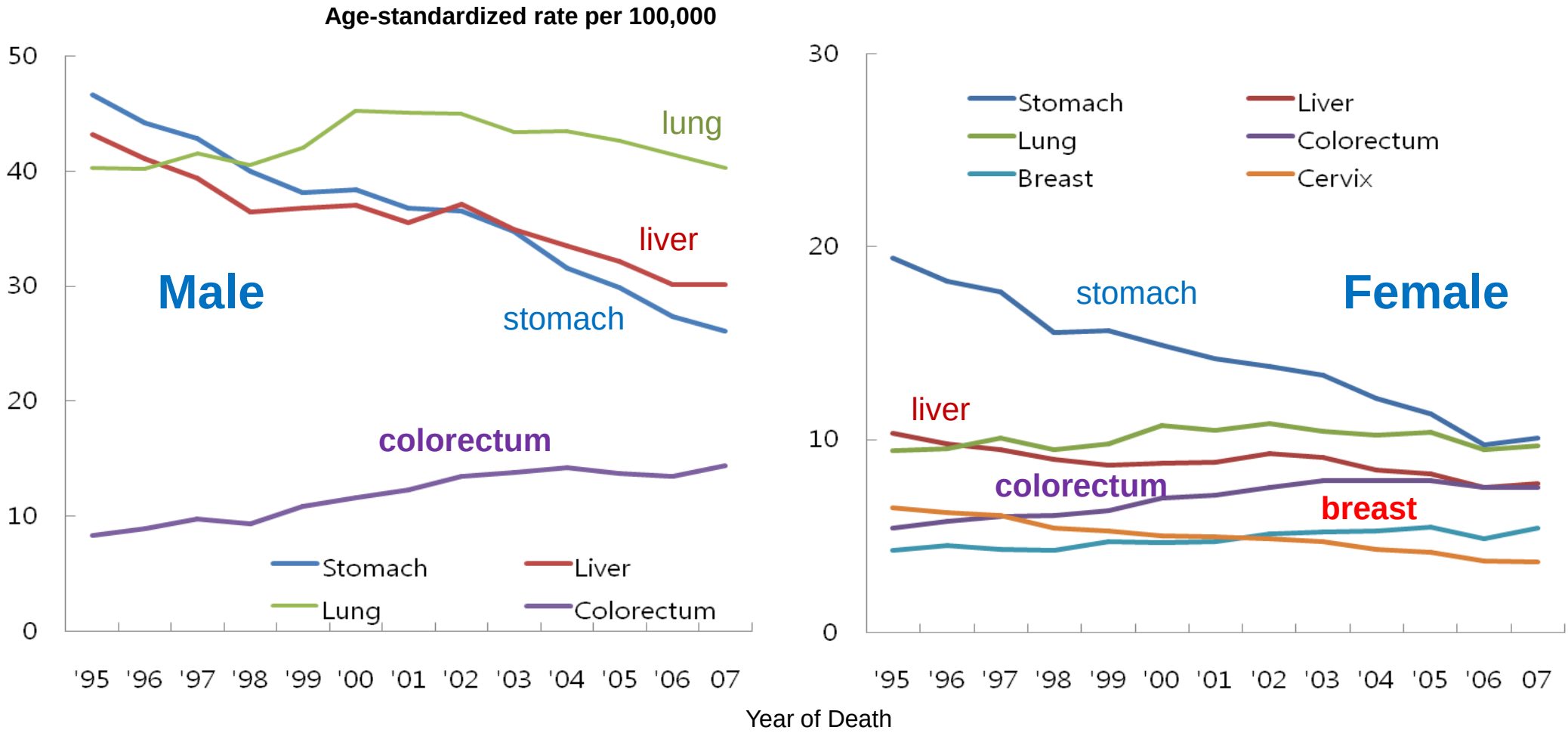


Source: Korea Central Cancer Registry, 2008

보건복지가족부
MINISTRY FOR HEALTH, WELFARE AND FAMILY AFFAIRS

국립암센터

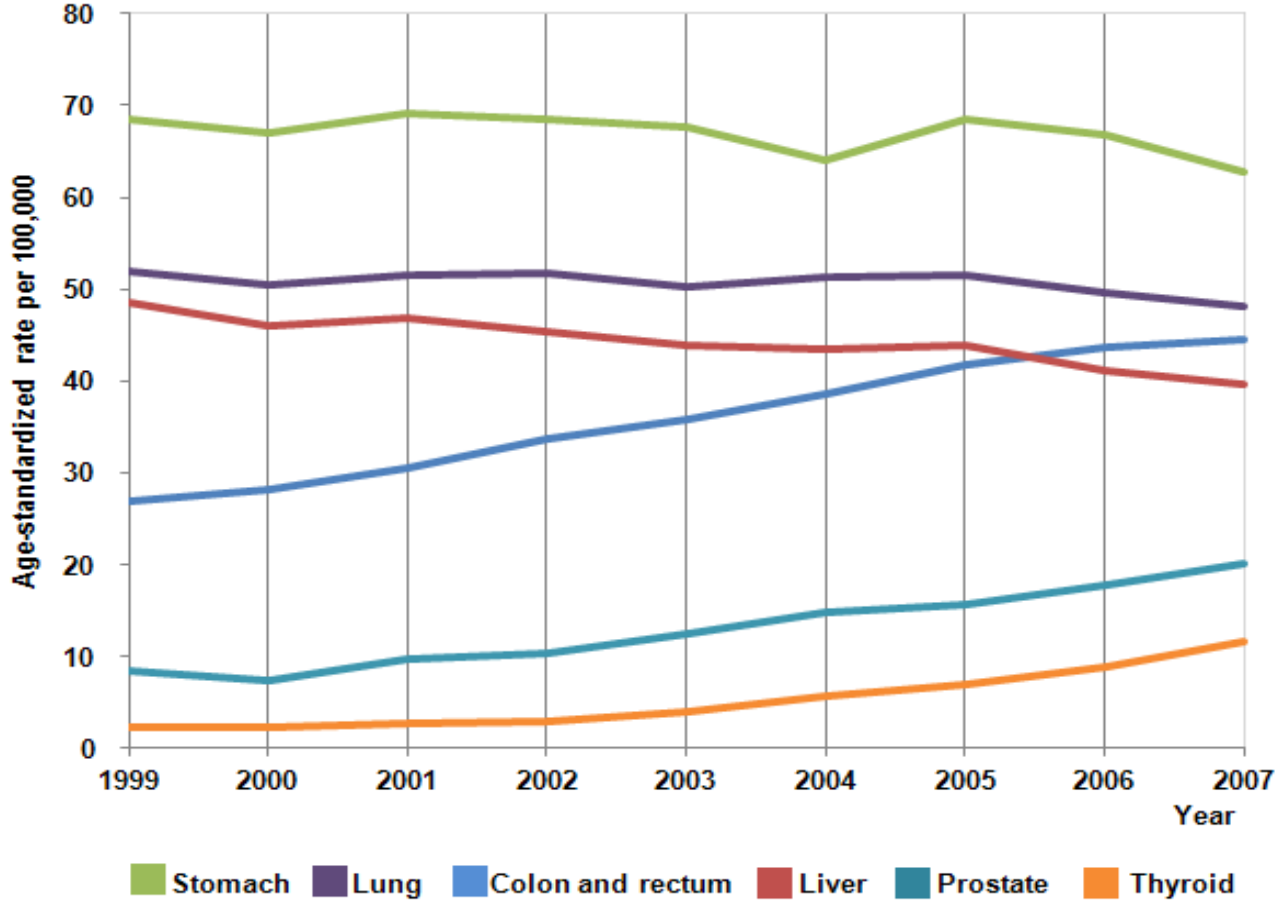
Trend in Major Cancer Mortality Rates



Source: Annual Report of Causes of Death, Korea National Statistical Office
(age-standardized rates on the 2000 Korea registration population)

Trend in Age-standardized Incidence Rates of Cancer

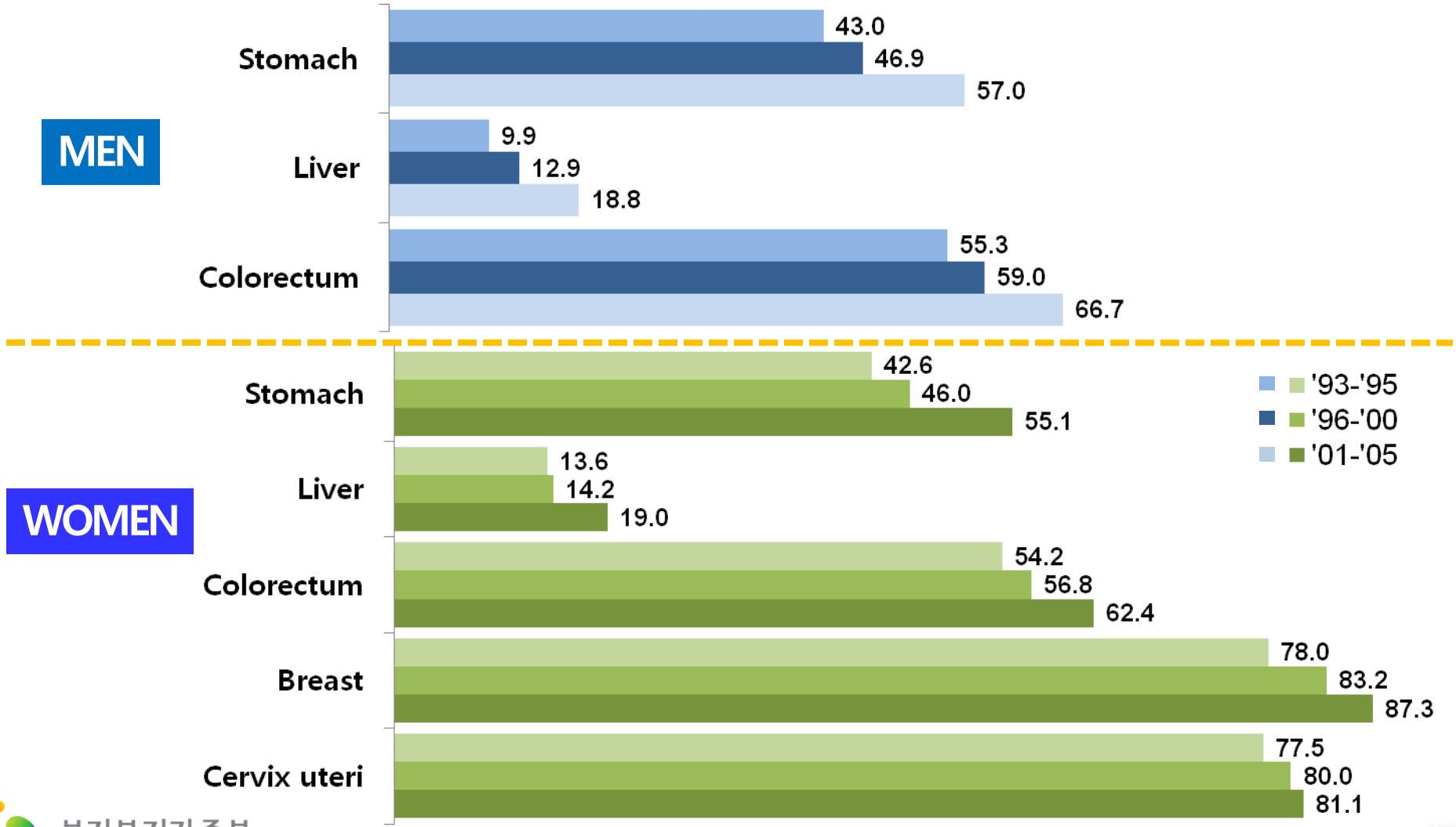
Male, Korea Central Cancer Registry, 1999-2007



Site	Year		Annual percent change (%)
	1999	2007	
Stomach	68.4	62.8	-0.7
Lung	51.9	48.1	-0.6
Colon and rectum	27.0	44.5	7.0 *
Liver	48.5	39.6	-2.2 *
Prostate	8.5	20.1	13.2 *
Thyroid	2.3	11.6	24.5 *

* P < .05

Five Year Survival of Cancer Sites of National Screening Program



보건복지가족부
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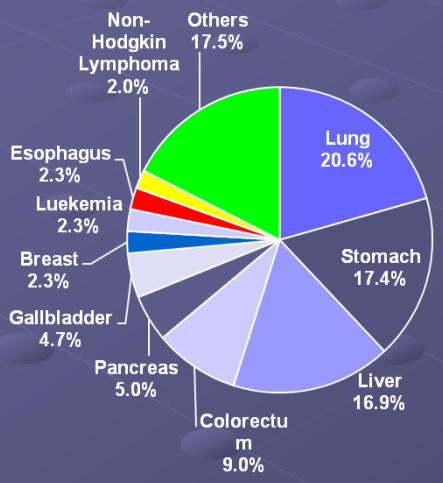
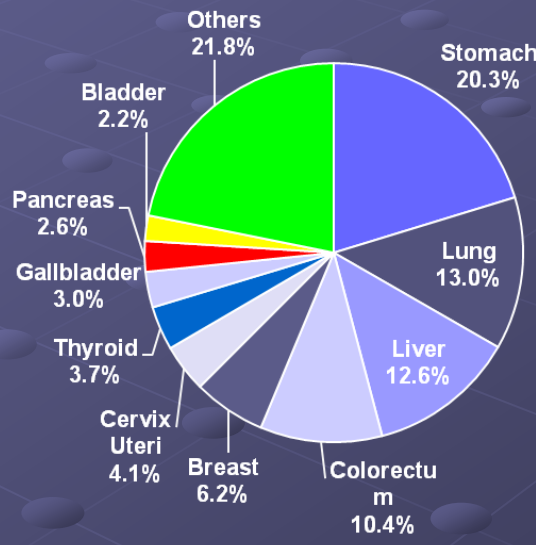
Increase in Cancer Survival *ultimately induces* Increase in Cancer Prevalence

Mortality (2007)



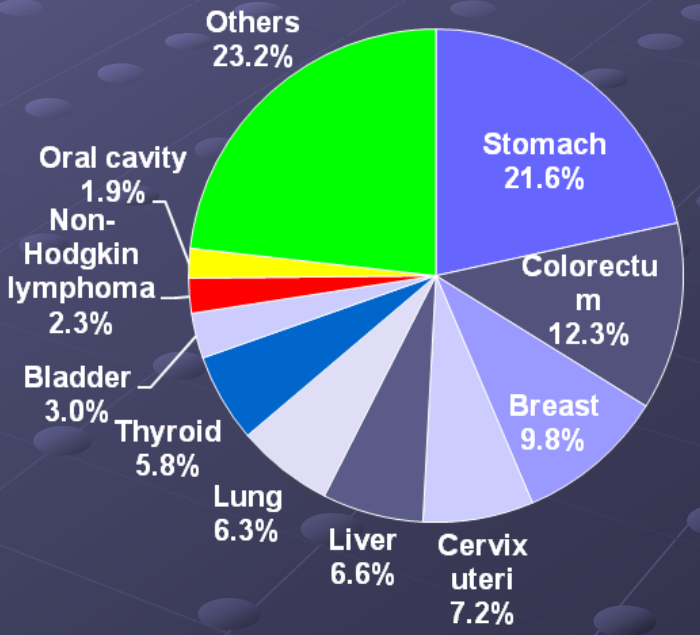
67,559 deaths

Incidence (2007)



161,920 cases

Prevalence (2007)

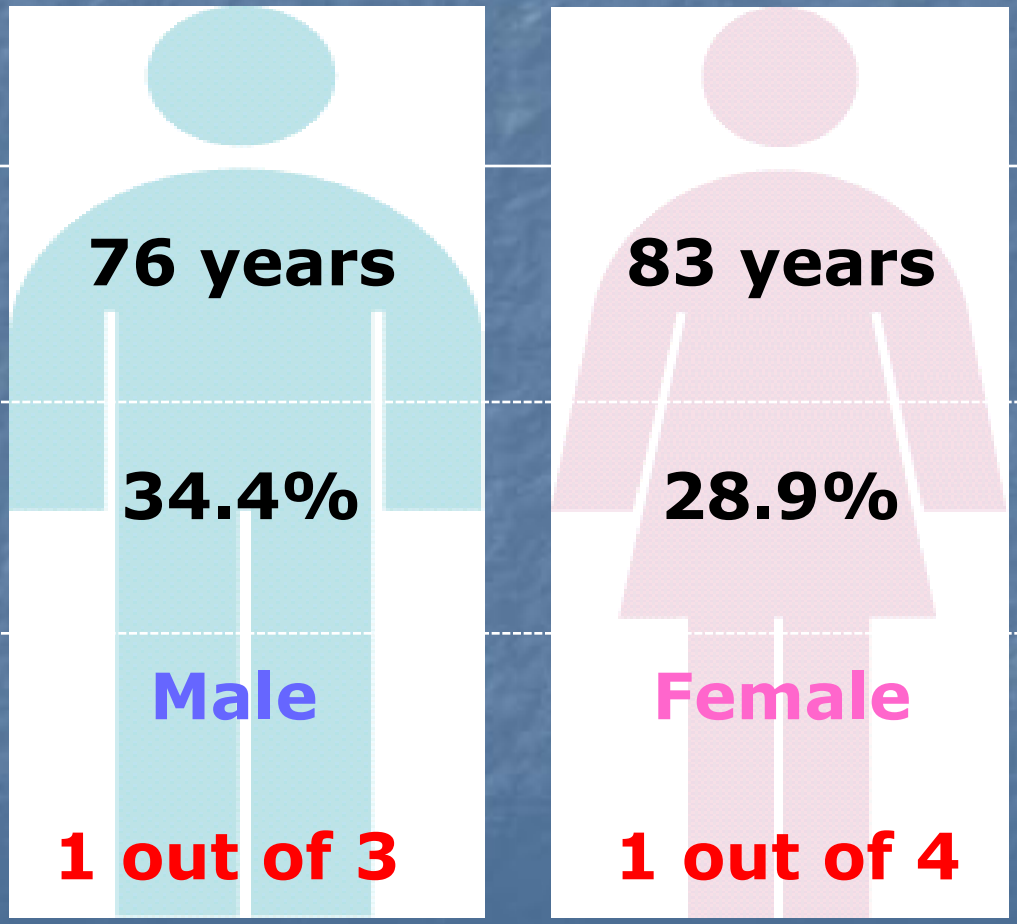


606,804 persons

NATIONAL CANCER CENTER

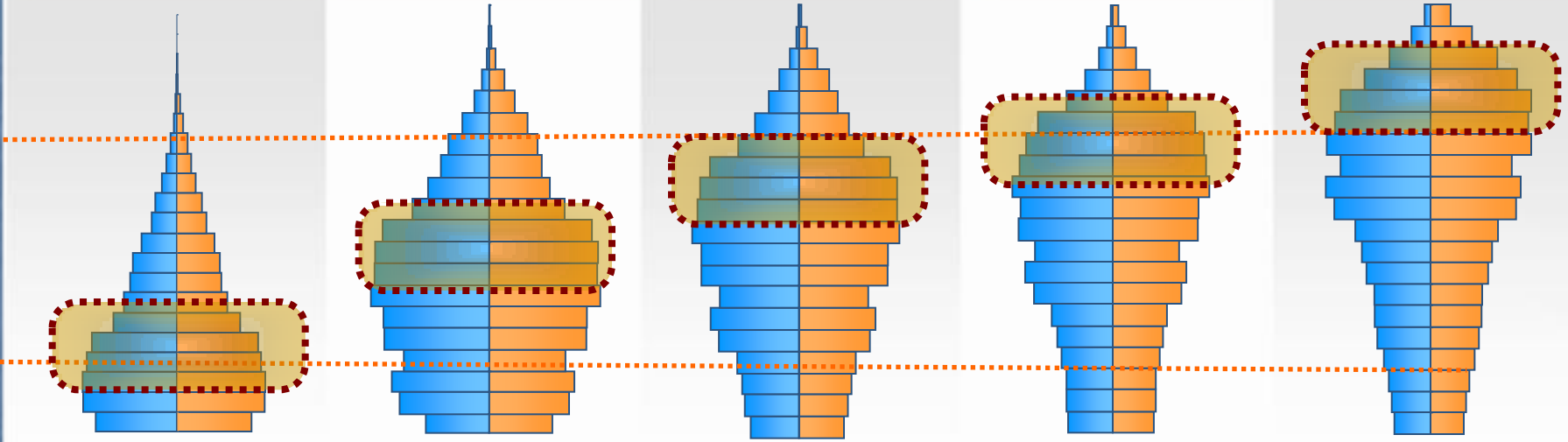
Cumulative Risk of Cancer in Korea

	Male	Female
Life expectancy (2007)	76 years	83 years
Cumulative risk	34.4%	28.9%
	Male	Female
	1 out of 3	1 out of 4



Source: Korea National Statistical Office, 2009

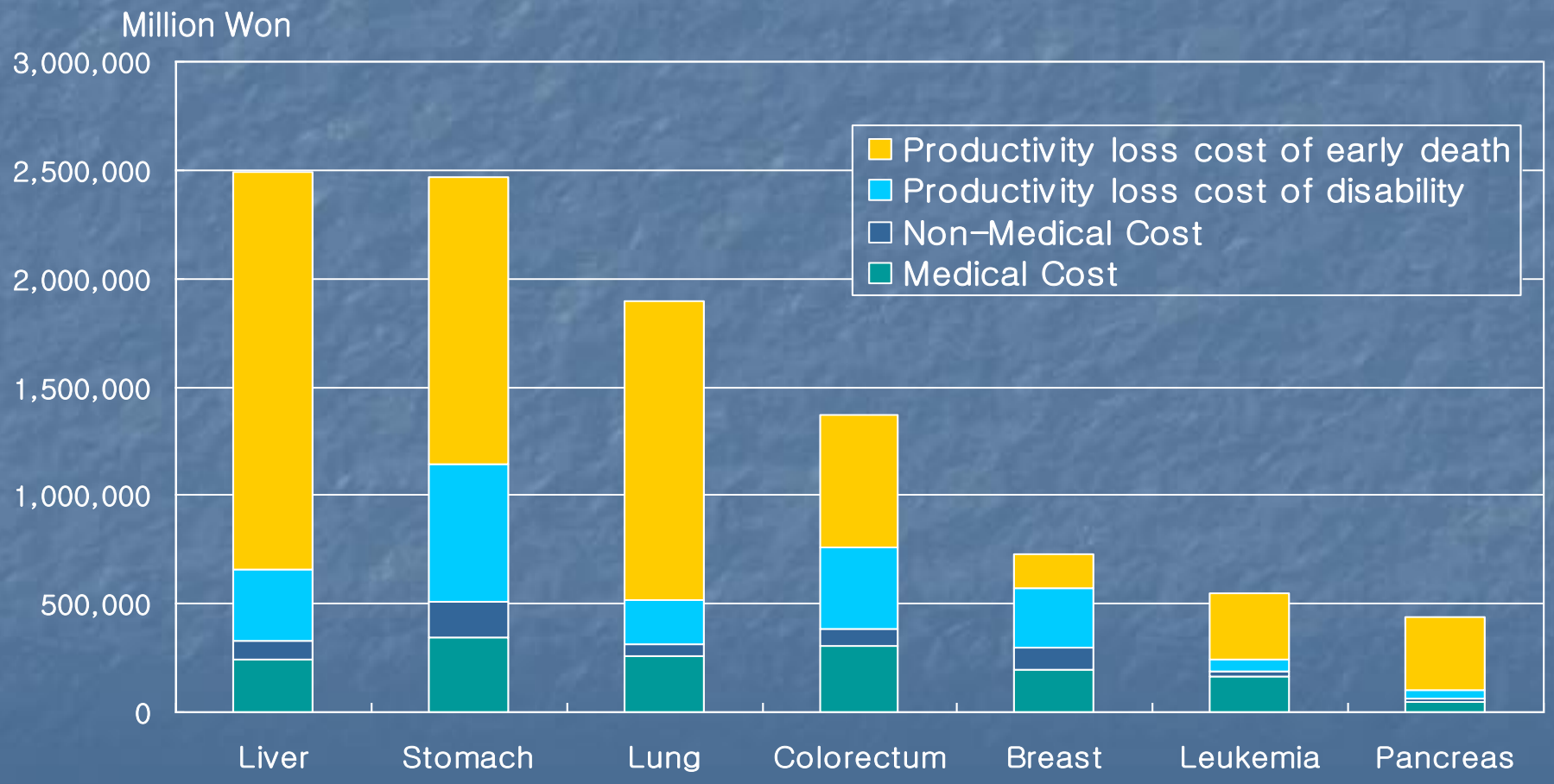
Age Tsunami: Baby Boomer born 1953-1958



	1980	2005	2018	2030	2050
Total (10,000 persons)	3,812	4,814	4,934	4,863	4,234
15~64 years (10,000 persons)	2,372	3,453	3,598	3,123	2,242
65+ years (10,000 persons)	146	437	707	1,181	1,616
Old Dependency Ratio	6.2	12.7	19.6	37.8	72.1

Economic Burden of Cancer Korea, 2005

Total : 14 billion USD (1.7% of GDP)



Source: Kim et al. Eu J Cancer Care 2007

Cohort 16

KMCC: Korean Multi-center Cancer Cohort

Lead study investigator(s), institution(s), and contact information

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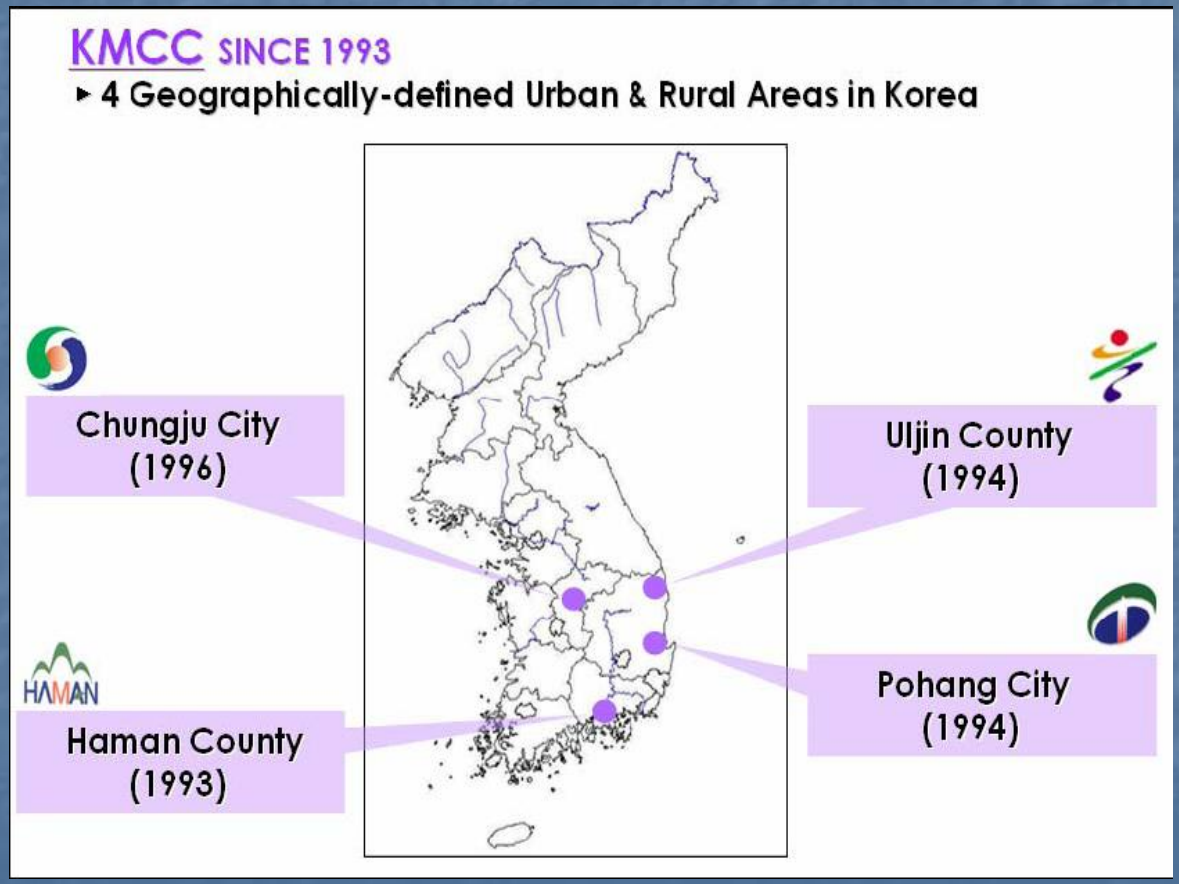
Seoul National University College of Medicine[1]; National Cancer Center[2]; Konkuk University College of Medicine[3] and Kosin Univesity College of Medicine[4]

Contact Information : Department of Preventive Medicine, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-799, Korea
Tel : 82-2-740-8324 Fax : 82-2-747-4830 Email: kyyoo@snu.ac.kr

KMCC: Basic Facts/Framework/Core Elements

Geographic location of the population



The study areas of the KMCC are consisted of Haman County in Kyungnam Province, Chungju City in Chungbuk Province, Uljin County in Kyungbuk Province and Pohang City in Kyungbuk Province

which represent both urban and rural communities in Korea.

KMCC: Basic Facts/Framework/Core Elements

Selection of cohort from base population

Eligible subjects were adults, male and female, who were voluntary participants in a cancer screening survey in each area.

Men and women aged over 35, in the geographically defined areas, have been invited through cross-sectional surveys for cancer screening since 1993.

Voluntary participants in the screening for cancer detection were eligible as members of the study population for this multi-center cohort.

KMCC Study Group

Since 1993

Yoo KY	Cancer Epidemiology-breast
Shin HR	Cancer Epidemiology-liver
Chang SH	Environ. Epidemiology
Kang D	Molecular Epidemiology
Lee KS	Health Policy/Education
Lee DH	Cancer Epidemiology-colon
Ha M	Radiation Epidemiology
Park SK	Cancer Epidemiology-female
Yang MH	Environ. Toxicology
Kim JH	Bioinformatics
Choi YH	Biostatistics
Kim CS	Toxicology
Shin AS	Cancer Epidemiology-stomach
Jun JG	Cancer Epidemiology-colon
Kim YJ	Cancer Epidemiology-breast
Gwak J	Cancer Epidemiology-stomach

KMCC: Korean Multi-Center Cancer Cohort
韓國人多機關癌코호트研究 (since 1993)

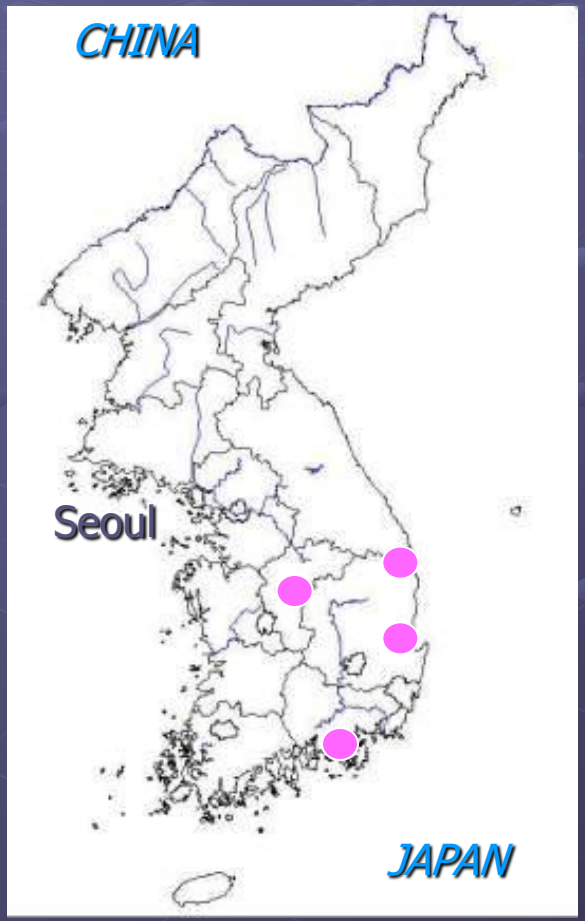
- KMCC

1993-2004
4 sites : urban & rural

Haman(1993)
Choongju(1996)
Uljin(1994)
Pohang(1994)

questionnaires = 20,000
biospecimen = 20,000

100,000 person-years



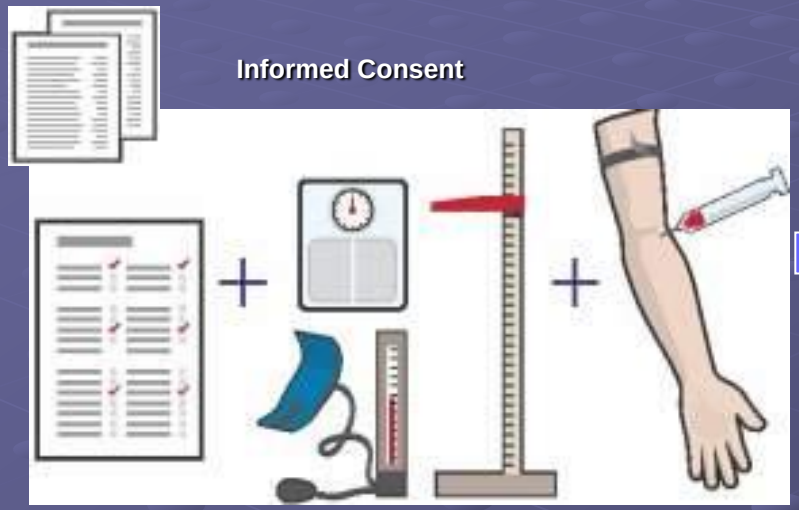
Baseline information
- cancer-free cohort
- interviewer-administered questionnaire (SQFFQ)
- anthropometry
- clinical lab test

Biologic materials bank
- serum/plasma
- buffy coat
- packed RBC
- urine (spot)

Cancer surveillance

Source : Yoo et al. Asian Pacific J Cancer Prev 2002

Cohort Study Design: KMCC



F/U

Health Insurance DB
National Death Certificate

Central Cancer Registry
Regional Cancer Registry

Outcomes
CV diseases, DM, Metabolic syndrome
Incident Cancer Cases
Death (all causes)

Laboratory data

Plasma Serum

DNA

Urine

KMCC: Factors

Categories of agricultural exposures and assessment techniques

agricultural exposure: pesticides
assessment technique: questionnaires

Other disease factor information

demographic characteristics
past medical history / family history of cancer
dietary habit / smoking and alcohol drinking habits / physical activity
occupational history / medication history
exposure history to hazardous chemicals including pesticides
exposure to electro-magnetic fields
reproductive history for female
other factors related to cancer development.

Interviewer-administered

- standardized questionnaire
- web-based data warehouse with multi-sites registries

by medical students and nursing school students

Direct measurement

- height, weight
- waist & hip circumference
- body fat composition
- bone density

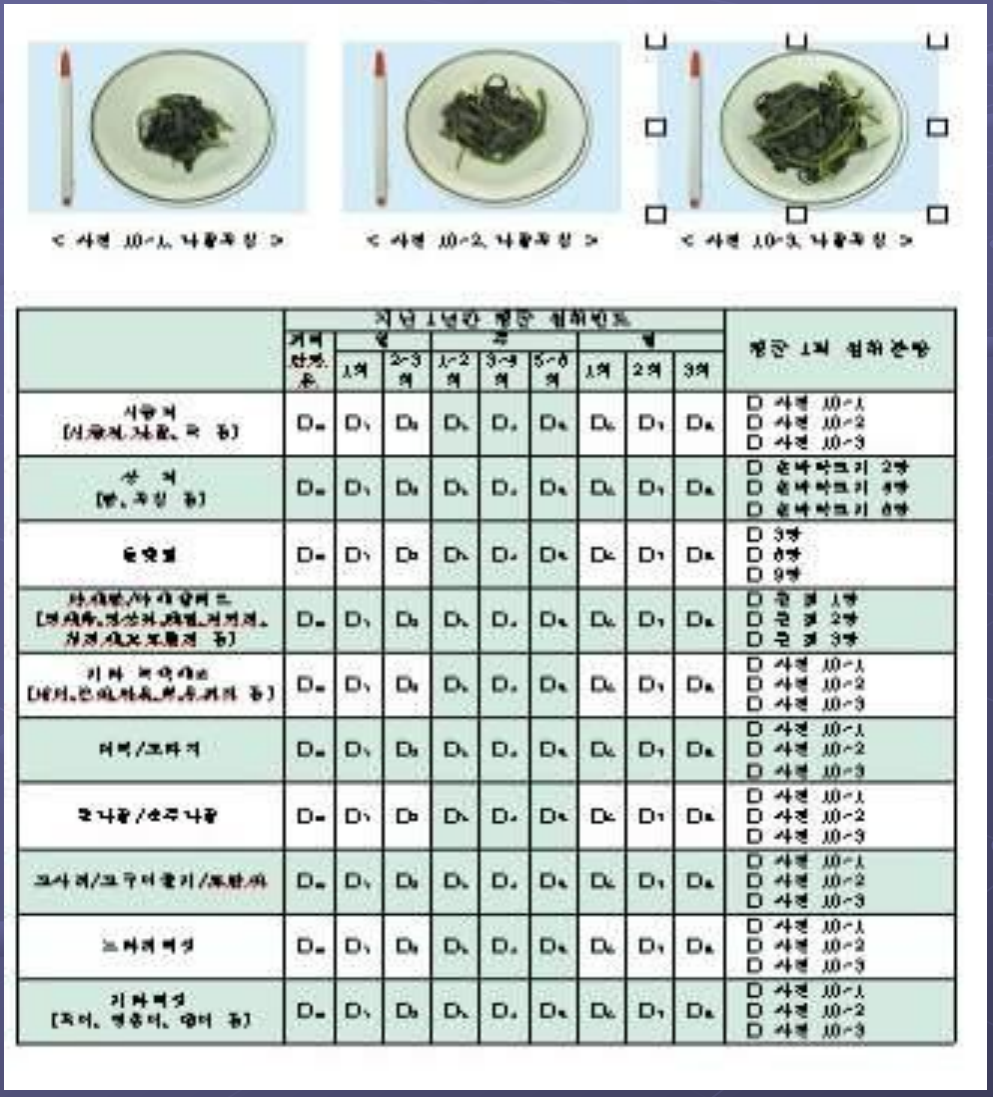
Questionnaire: KoGES

Interviewer-administered

- demographic characteristics
- past medical history
- family history of cancer
- job / residential history
- dietary habit
- smoking and alcohol drinking habit
- physical activity
- supplements / medication history
- psychosocial factors
- reproductive history (women)
- other factors related to target diseases

FFQ

Food Frequency Questionnaire



- 9 response categories
- 3 portion size
- depending on the median value of each food from the 24-hr recall data
- validation

Biologic Samples: blood and urine

whole blood

spot urine

Protocol for Sample Handling: KoGES

Blood Drawing (20 cc)

Blood test → Lab

DNA extraction → ~100 ug DNA

Plasma (2cc) Serum (2cc) → microtube1, microtube2, microtube3, microtube4, ... (cryovials)

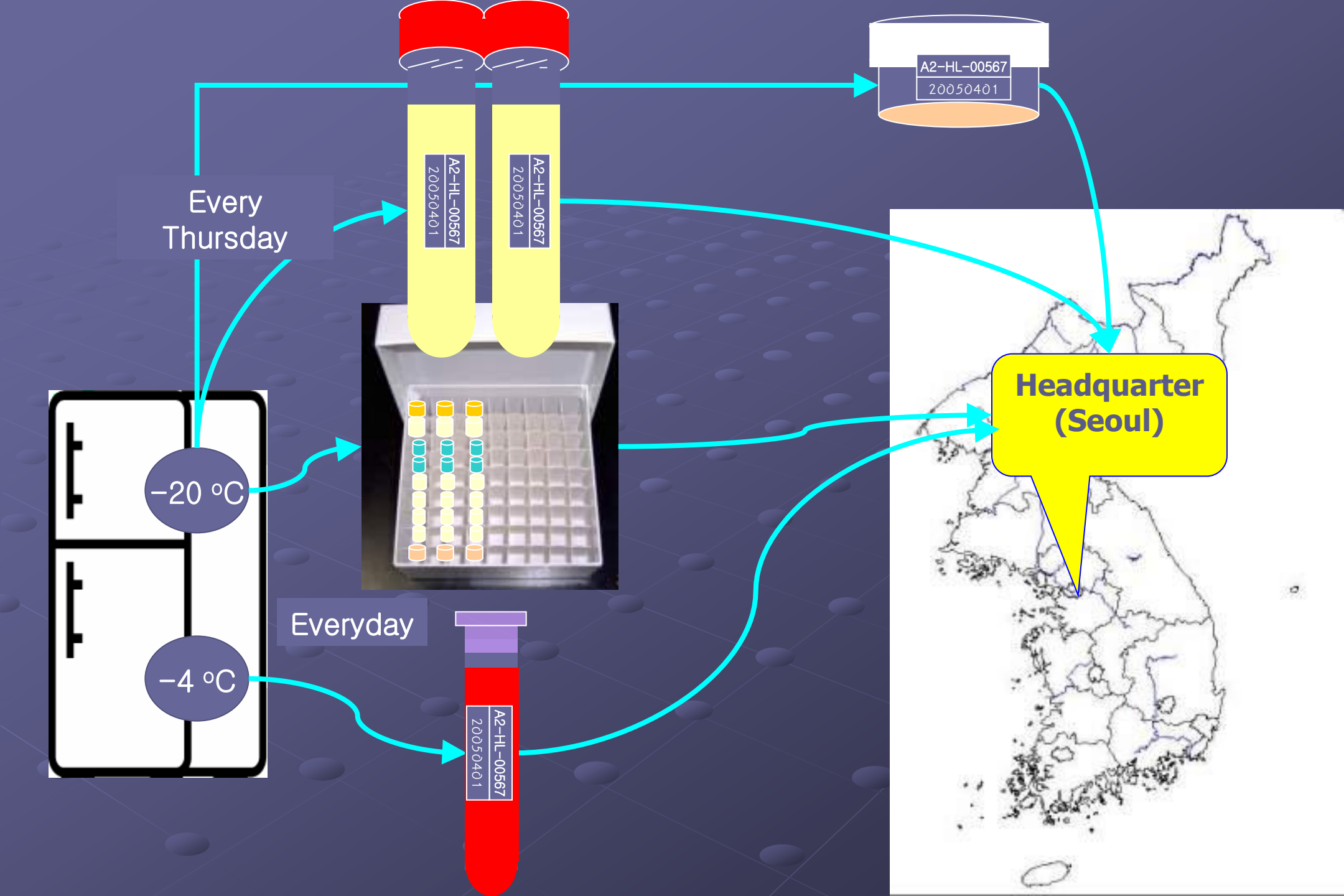
-70 ℃ Deep freezer → Center → KCDC

Central/backup biorepository

Urine (10cc) → Conical tube (cryovial)

Informed consent

approved by IRB of SNUH


A2-HL-00567
20050401
A2-HL-00567
20050401
A2-HL-00567
20050401
Every
Thursday
−20 °C
−4 °C
Everyday
A2-HL-00567
20050401
Headquarter
(Seoul)

Biospecimen Bank

K-NCC

K-CDC

Biobanking: KMCC

	Serum	Plasma	Buffy	RBC	Urine
Haman	4,159	6,274	5,315	5,626	4,173
Chungju	-	8,942	8,950	8,955	8,992
Uljin	792	-	-	-	-
YYoungil	311	-	-	-	-
Total	5,262	15,216	14,265	14,581	13,165

KMCC: Basic Facts/Framework/Core Elements

Number of participants with questionnaires and biomaterials

Study area	Year began	Questionnaire	Serum	Plasma	Buffy	RBC	Urine
Haman	1993	8,554	4,159	6,274	5,315	5,626	4,173
Chungju	1996	8,594	–	8,942	8,950	8,955	8,992
Uljin	1994	1,539	792	–	–	–	–
Youngil	1994	1,001	311	–	–	–	–
Total		19,688	5,262	15,216	14,265	14,581	13,165

Mean age of the subjects: 54.9 for men, 55.0 for women
Male to female ratio: 0.67
Time period of enrollment: 1993-2004

DNA Yield Study: KMCC

DNA stability test (1)

frozen buffy coats (n=100)

stored in 1995, 1996, 1997, 1998, 2001

overall success rate for PCR products : 98%

Source : Yang et al. (2003)

central / regional biorepository

DNA stability test (2)

urine (n=26, healthy volunteers)

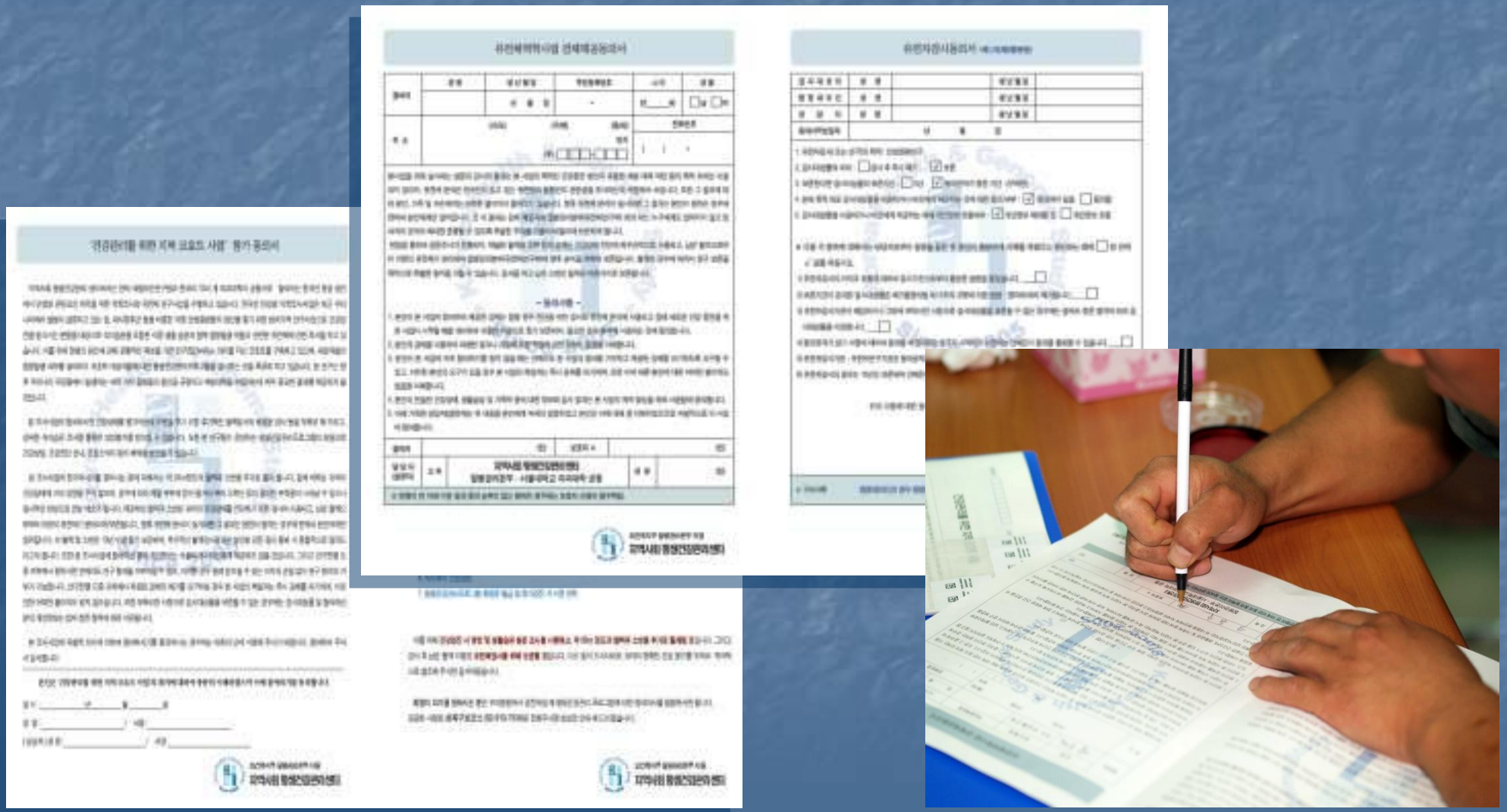
yield: MTHFR gene : 100%

β-globin gene : 100%

NAT2 gene : 88.5 %

Source : Kim et al. (2006)

Informed Consent



Informed Consent

informed consent form

1. providing questionnaire data and biological samples
2. use of biological materials for research in the future without additional notice
3. possible future contact to the subject for follow-up or getting further information
4. access and use of the secondary data of the participants for research purpose without further notice, including medical record, health insurance record, cancer registry data, etc.

consent form for future genetic test

Follow-up: KMCC

Endpoint : incidence / mortality of
CV diseases, DM, Cancers, etc.

Passive surveillance

- National Cancer Registries
- National Death Certificate
- Health Insurance Database

Active surveillance

- District health workers

⇒ *record-linkage using* ***Korean ID***

Birth(6)
YYMMDD
—
Regist(7)
Sex-Place-Order-hidden

Cancer Registry System in Korea

Hospital Cancer Registries

hospital-based

since 1980

headquarter : NCC

coverage:
95% of all cancers

Regional Cancer Registries

population-based

Seoul / Busan
Daegu / Gwangju
Incheon / Daejeon
Ulsan / Jeju

coverage :
50% of population

Site-specific Cancer Registries

Academic Societies: breast, uterine, cervix etc.

KMCC: Outcomes/Results/Conclusions

Major disease outcomes and current numbers specific outcomes

Table. Major cause of death (as of December, 2007)

Major outcomes	Male	Female	Both
Cancer	403	174	577
Stomach	81	22	103
Liver	71	32	103
Lung	110	30	140
DM	25	17	42
Circulatory system	106	114	220
Ischaemic heart disease	22	24	46
Cerebrovascular disease	68	65	133
Respiratory system	44	20	64
COPD	31	14	45
Digestive system	42	9	51
Liver disease	31	8	39
Total	1,078	720	1,798

Frequency of outcome determination: annually

KMCC: Outcomes/Results/Conclusions

Major disease outcomes and current numbers specific outcomes

Sites	Male	Female	Both
Stomach	220	109	329
Lung	163	45	208
Liver	121	51	172
Colorectal	58	71	129
Biliary tract	48	32	80
Esophagus	21	0	21
Bladder	28	2	30
Pancreas	22	24	46
Breast	1	43	44
Thyroid	4	44	48
Uterine cervix	0	34	34
Prostate	26	0	26
Others	48	61	109
Total	760	516	1,276

Leading sites of cancer incidence (as of December, 2007)

The KMCC uses two surveillance systems to ascertain cancer occurrence. The first one is an active surveillance system in each project area, which encompasses a mailed morbidity questionnaire survey, a direct telephone interview by health personnel, and a cancer diagnosis by physicians at hospitals. The second is a passive surveillance system through record linkages between the national cancer registry, the national death certificate system, and health insurance medical records databases.

National Programs for Health Promotion

- Health Screening Program (國民健康保險公團 健康檢診事業)
  - 40 years and older
  - every 2 years
  - 23 items at 1st step, and 28 items at 2nd step

- National Cancer Screening Program (國家癌早期檢診事業)

- Physical Examinations at Life-Cycle Transitional Periods
  (生涯轉換期 健康檢診事業)
  - started in 2007
  - at 16, 40, and 66 years old
  - personalized health risk assessment
  - consultation for healthy life styles including nutrition, physical activity, obesity, quitting smoking

Repeated Survey

Repeated collection of

- biospecimen
- questionnaire survey
- anthropometric measurements

***every two years** for health examinee module*

***every five years** for community module*

KMCC: Outcomes/Results/Conclusions

Short description for up to five important findings

Stomach cancer, one of the leading cancers in South Korea, was evaluated through a nested case-control study using the KMCC data (Shin et al, 2005). In this study, 86 cases of gastric adenocarcinoma and their matched controls were evaluated for clarifying the association between *Helicobactor pylori* and gastric adenocarcinoma. By using their stored biospecimens, *Helicobactor pylori* IgG antibody was tested. This study suggested that there might be no direct association between *Helicobactor pylori* and gastric adenocarcinoma risk.

Citation of a published paper that best describes the cohort

Yoo et al. Korean Multi-center Cancer Cohort Study including a Biological Materials Bank (KMCC-I). *Asian Pac J Cancer Prev* 2002;3:85-92

Yoo et al. Genomic Epidemiology Cohorts in Korea: Present and the Future. *Asian Pac J Cancer Prev* 2005;6:238-43

KMCC: Outcomes/Results/Conclusions

List of major published papers

Shin et al. A nested case-control study of the association of Helicobacter pylori infection with gastric adenocarcinoma in Korea. *Brit J Cancer* 2005;92:1273-5

Gwack et al. CagA-producing Helicobacter pylori and increased risk of gastric cancer: A nested case-control study in Korea. *Brit J Cancer* 2006;95:639-41

Ko et al. Association between interleukin-10 genetic polymorphisms and gastric cancer risk. *J Nutr* 2009;139:1008-12

Kim et al. Epstein-Barr virus antibody level and gastric adenocarcinoma risk in Korea: A nested case-control study. *Brit J Cancer* 2009;101:526-9

Yang et al. The role of TNF genetic variants and the interaction with cigarette smoking for gastric cancer risk: a nested case-control study. *BMC Cancer* 2009;9:238

Ko et al. Isoflavones of phytoestrogens and gastric cancer risk: a nested case-control study within the Korean Multi-Center Cancer Cohort. *Cancer Epidemiol Biomarkers Prev* 2010;19(5):1292-300

Publications, Consortium - KMCC

[Consortia – Asia Cohort Consortium]

◇ Boffetta et al. Priorities and challenges for cohort studies and consortia. Cancer Epidemiol Biomarkers Prev 2010 (in submission)

◇ Boffetta et al. Body mass index and diabetes in Asia: A cross-sectional pooled analysis of 900,000 individuals in the Asia Cohort Consortium. Brit J Med 2010 (submitted)

◇ Zheng et al. Body mass index and mortality in Asia: Analysis of one million individuals in the Asia Cohort Consortium. NEJM 2010 (submitted)

[Consortia – P3G]

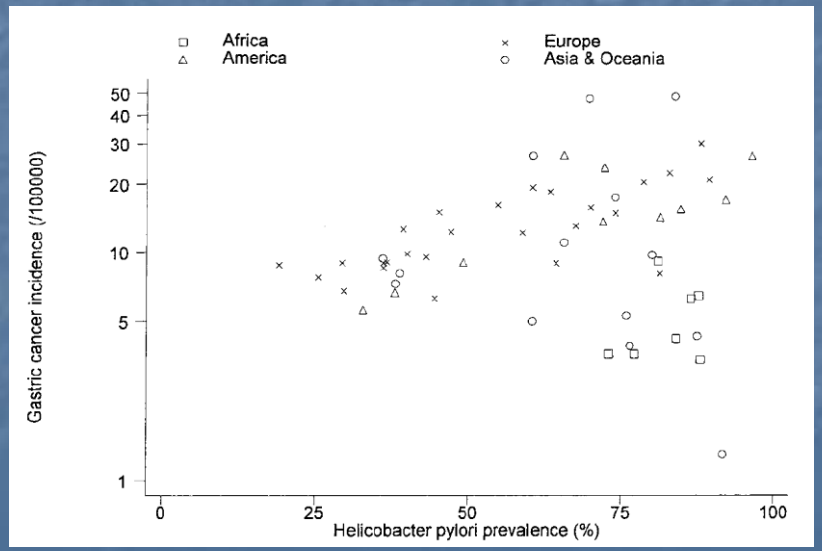
◇ P3G. Isabel Fortier. Is rigorous harmonization possible? Application of the DataSHaPER approach across 52 large bioclinical studies. (in preparation)

A Nested Case-Control Study on Helicobacter pylori Infection and Gastric Cancer Risk within the KMCC Cohort

- 86 cases
  - incident gastric cancer
- 344 controls
  - matched for age, gender, recruitment site & year
- *H. pylori*
  - detected by ELISA
- Further Studies
  - *H.p.* subtype
  - Polymorphisms: *IL1b, TNG-b*
  - *Effect modification by dietary component*

Overall results

	Hp(+)	Hp(−)	seropositivity	OR (95% CI)
cases	78	14	83.7%	1.06 (0.80−1.40)
controls	278	66	80.8%	



Shin et al. Brit J Cancer 2005

CagA-producing Helicobacter pylori Increased Risk of Stomach Cancer in Korea

British Journal of Cancer (2006) 95, 639–641

www.bjcancer.com

Short Communication

CagA-producing *Helicobacter pylori* and increased risk of gastric cancer: a nested case–control study in Korea

J Gwack[1], A Shin[2], C-S Kim[1], K-P Ko[1], Y Kim[1], JK Jun[1], J Bae[1], SK Park[1], Y-C Hong[1], D Kang[1], S-H Chang[3], H-R Shin[4] and K-Y Yoo[*,1,5]

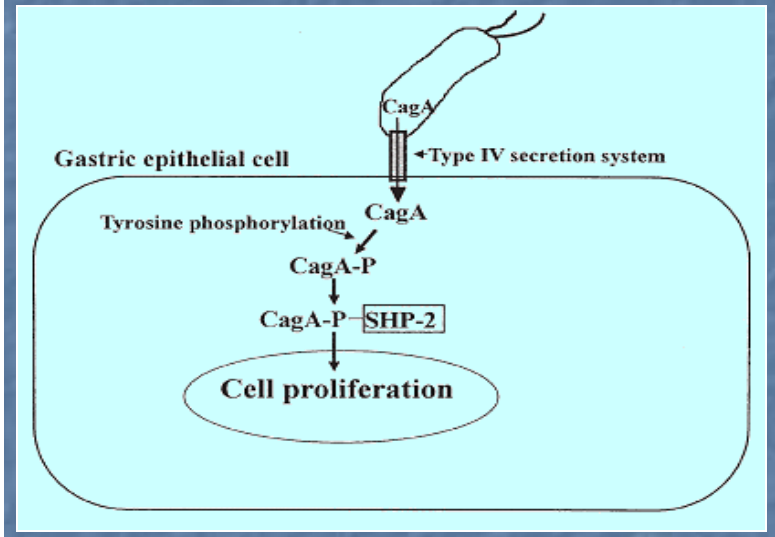
[1]Department of Preventive Medicine, Seoul National University College of Medicine, 28 Yongon-dong Chongno-gu, Seoul, 110-799, Korea; [2]Center for Health Services Research, Vanderbilt University Medical Center, Nashville, TN, USA; [3]Department of Preventive Medicine, Konkuk University College of Medicine, 322 Danwol-dong, Chungju-si, Chungcheongbuk-do 380-701, Korea; [4]Research Institute for National Cancer Control and Evaluation, National Cancer Center, 809 Madu1-dong, Ilsandong-gu, Goyang-si, Gyeonggi-do 410-769, Korea; [5]National Cancer Center, 809 Madu1-dong, Ilsandong-gu, Goyang-si, Gyeonggi-do 410-769, Korea

In a nested-case control study of 100 cases of gastric cancer and 400 matched controls in relation to virulence factors of *Helicobacter pylori* in a Korean cohort, CagA seropositivity was significantly associated with a higher risk of gastric cancer among *H. pylori*-infected subjects (OR = 3.57, 95% CI 1.05–12.14).

British Journal of Cancer (2006) **95,** 639–641. doi:10.1038/sj.bjc.6603309 www.bjcancer.com
Published online 8 August 2006

Keywords: gastric cancer; *Helicobacter pylori*; CagA; Cohort study; Korea

Gastric cancer is the first major incident cancer with an age-standardized incidence rate of 69.6 in males and 26.8 in females per 100 000 in Korea, the highest in the world (Ferlay *et al*, 2004; *et al*, 2002). Participants over age 30 years were recruited from 1993 through 2004. A detailed standardized questionnaire on general lifestyle, physical activity, dietary habit, reproductive



Gwack et al. Brit J Cancer 2006

Helicobacter Pylori Ab positivity

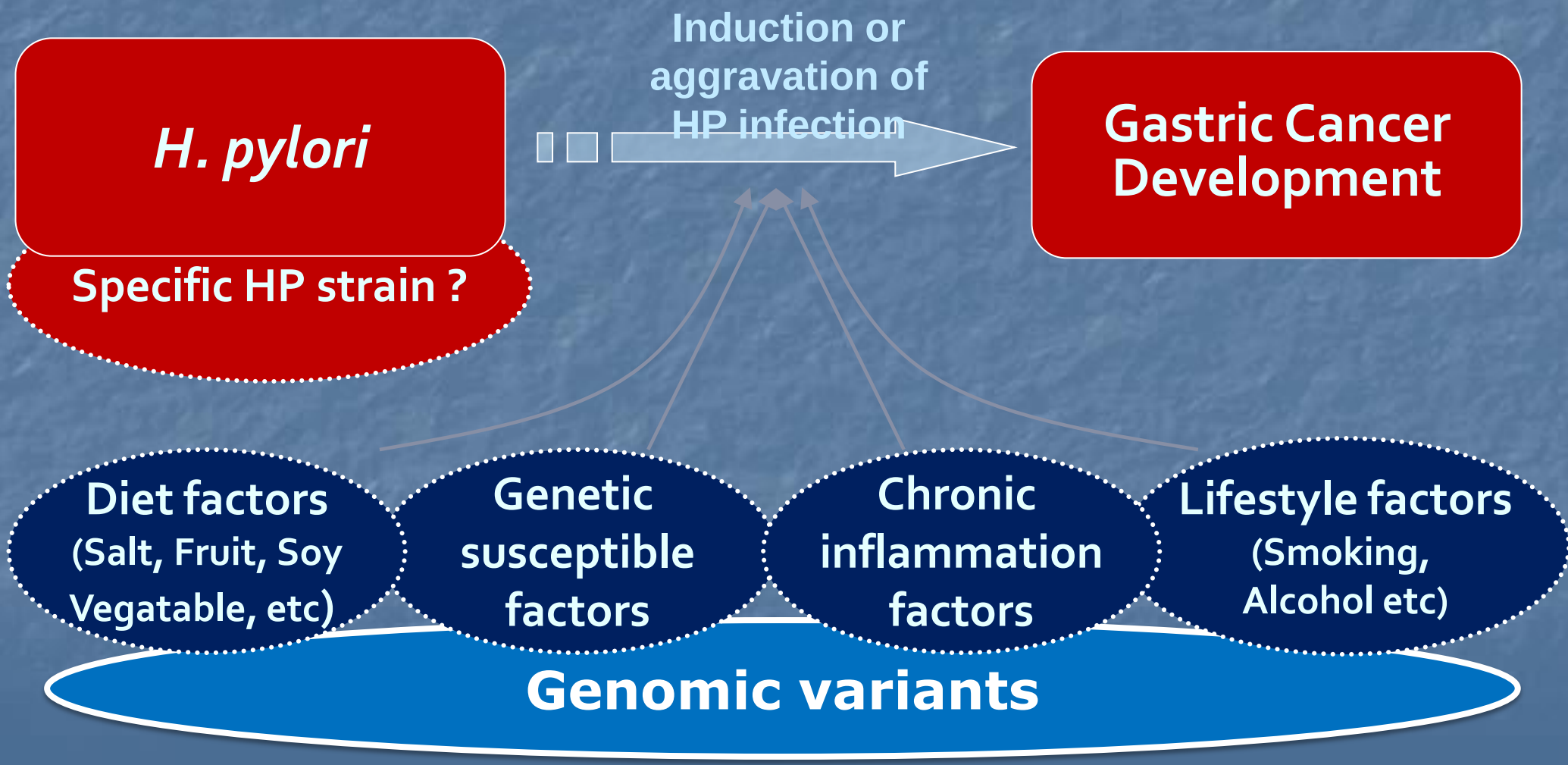
Association of *H. pylori* and Gastric Cancer

	Cases	Controls	OR (95% CI)
Blaser et al., 1995 (Japanese-American)	109	109	5.4 (2.1 - 13.7)
Limburg et al., 2001 (Chinese)	181	192	1.6 (1.03 - 2.4)
Shin et al., 2005 (Korean)	86	344	1.1 (0.8 - 1.4)

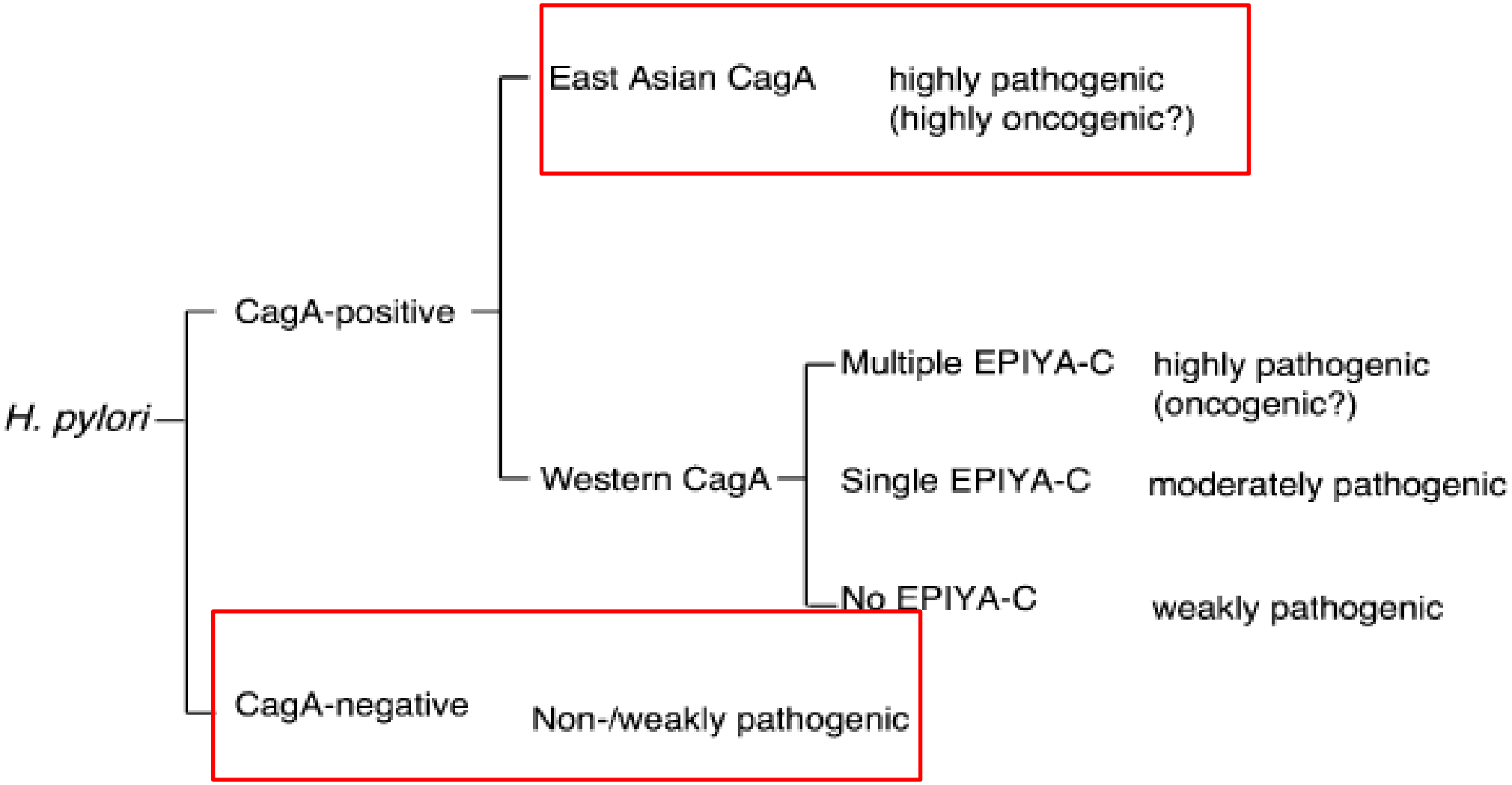
*Western Blot

Br J Cancer 2005

Our Hypothesis for Gastric Cancer development



CagA in Asians
(Hatakeyama, Cancer Sci 2005)



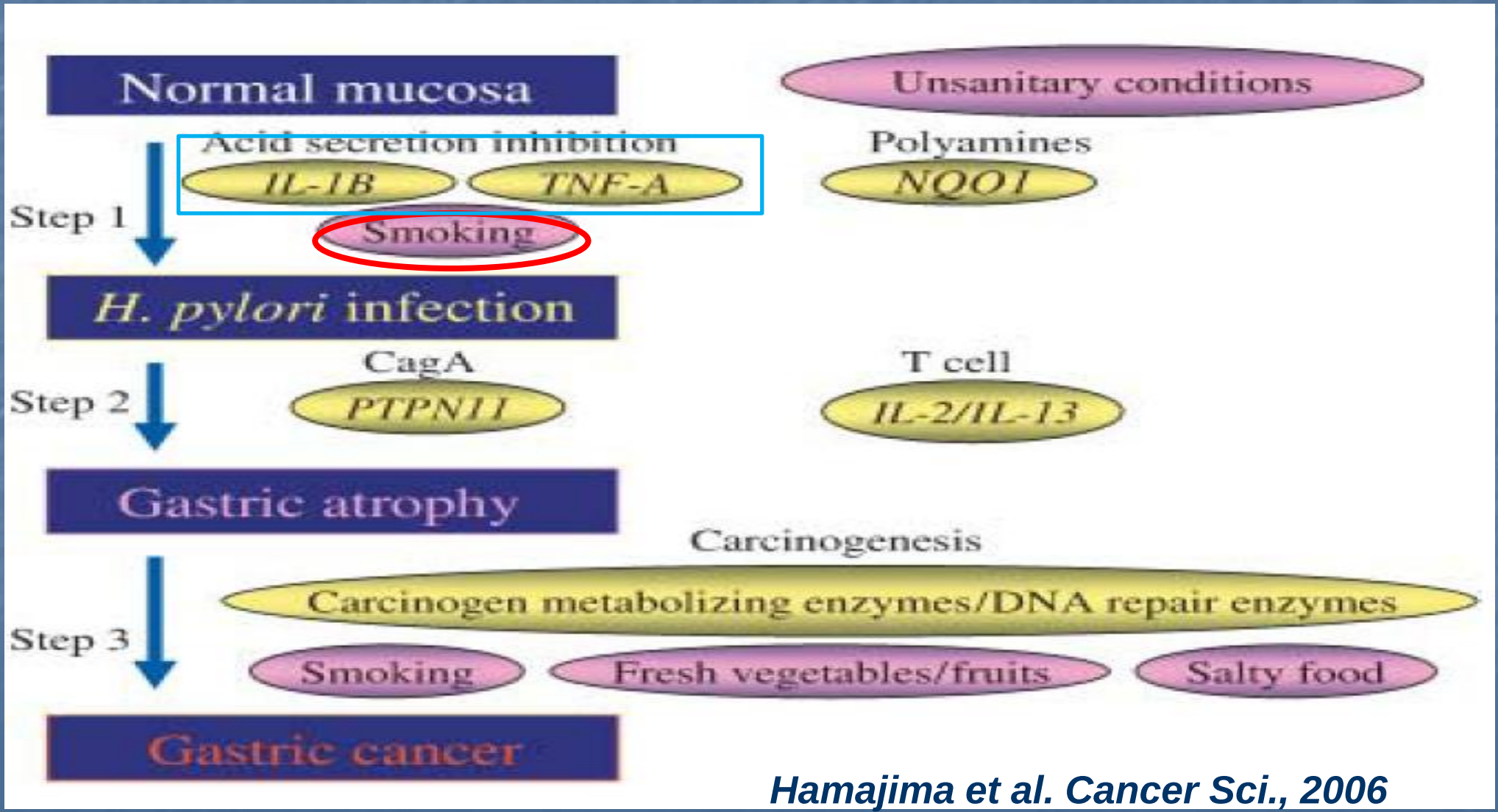
CagA & VagA specific HP infection and GC risk

Subgroups	Cases No. (%)	Controls No. (%)	OR* (95% CI†)
H. pylori positive			
CagA			
Negative	3 (3)	35 (10)	1.0
Positive	86 (97)	325 (90)	**3.7 (1.1-12.7)**
VacA			
Negative	25 (28)	118 (33)	1.0
Positive	64 (72)	242 (68)	**1.4 (0.8-2.4)**
H. Pylori negative			
CagA			
Negative	7 (64)	28 (70)	1.0
Positive	4 (36)	12 (30)	1.0 (0.1-11.7)
VacA			
Negative	11 (100)	40 (100)	
Positive	0 (0)	0 (0)	- -

HelicoBlot 2.1™ (MP Diagnostics, Singapore)

(BCR 2007)

Multi-factorial etiology in Gastric carcinogenesis



Hamajima et al. Cancer Sci., 2006

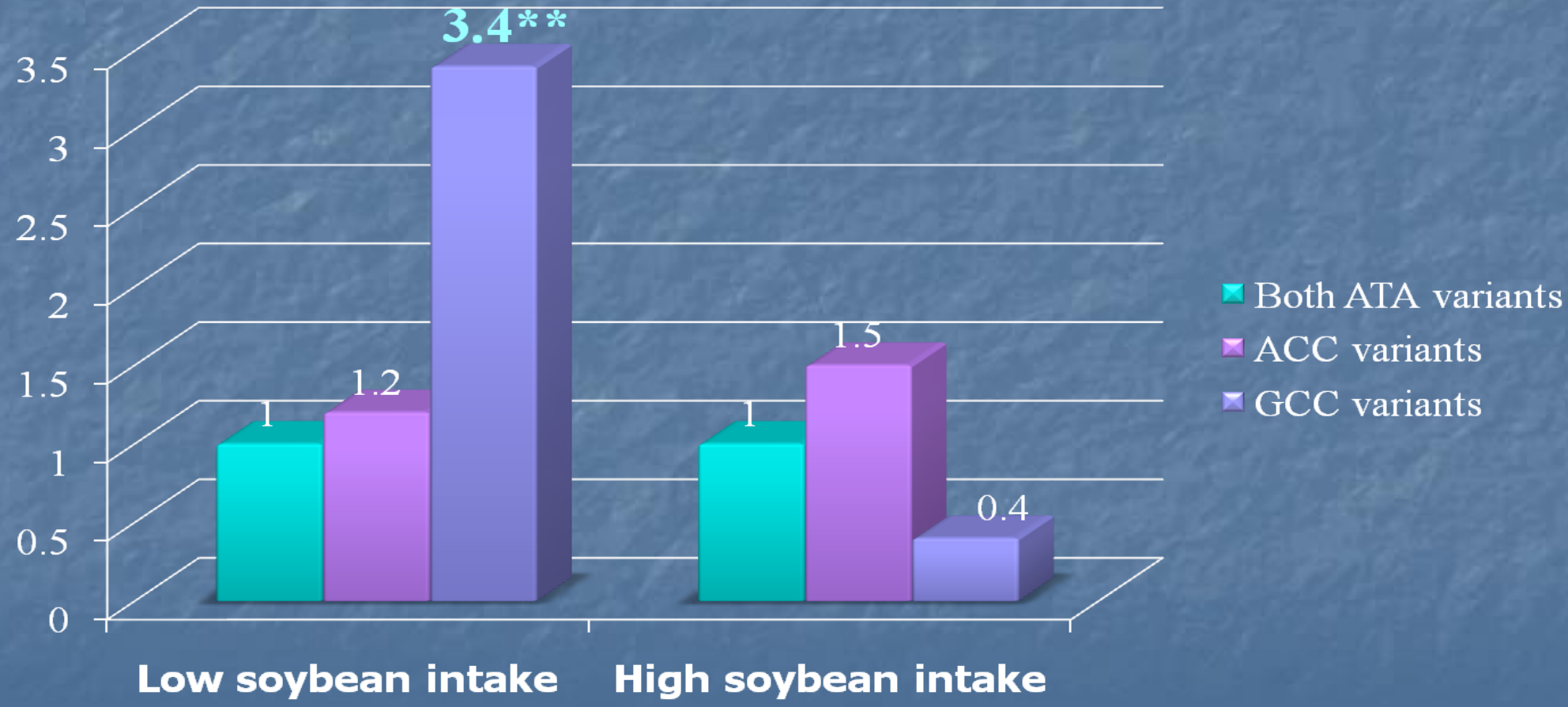
Cigarette Smoking & Gastric Cancer Risk

- **Cigarette Smoking**

	Cases (n=84) No. (%)	Controls (n=336) No. (%)	OR*(95% CI)
Smoking			
Never	26 (31)	141 (42)	1.0
Ever	58 (69)	193 (58)	2.7 (1.2-6.1)

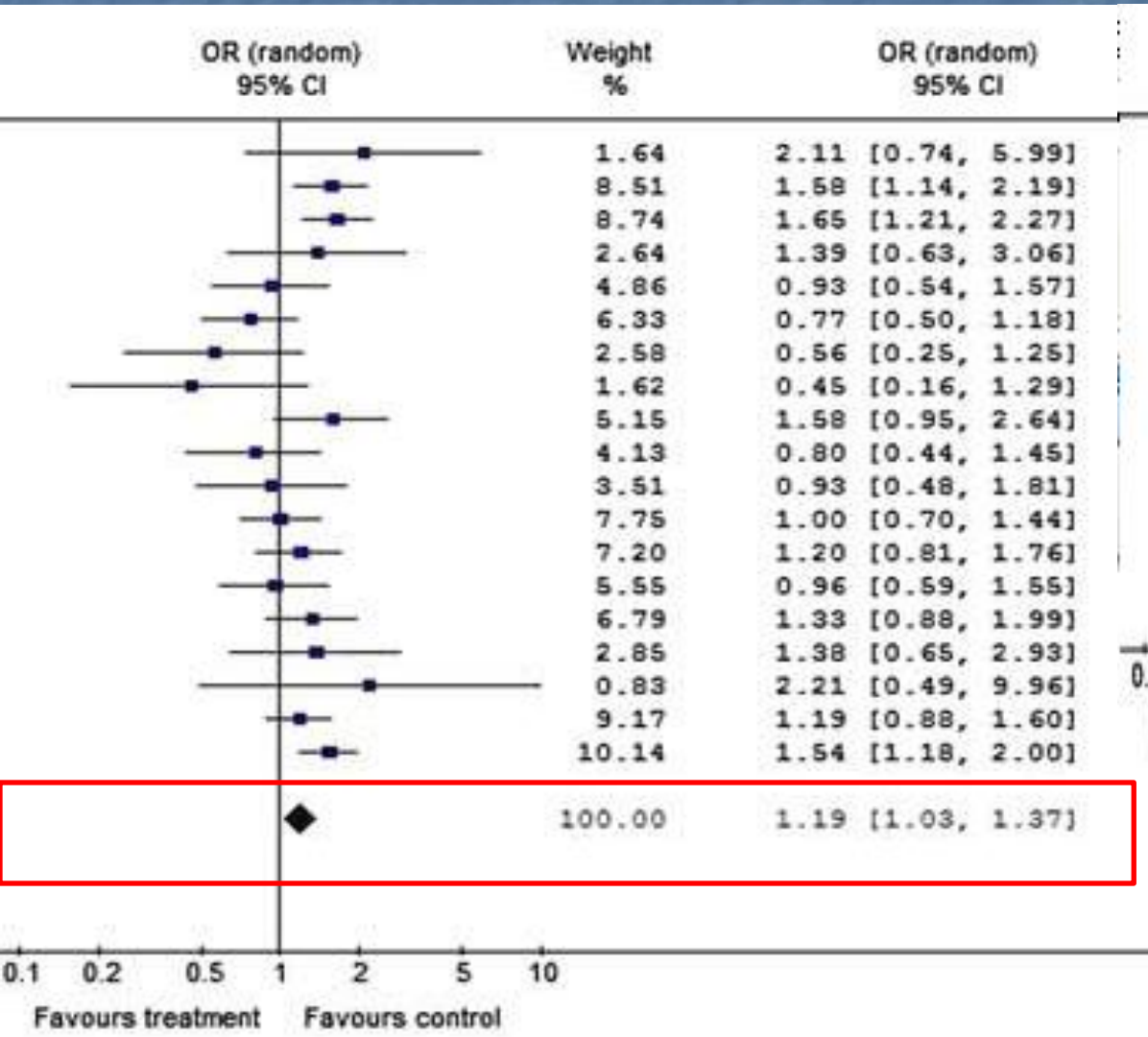
(Kim, J Prev Med Pub Health, 2007)

Interaction between IL-10 and soy intake modify gastric cancer risk

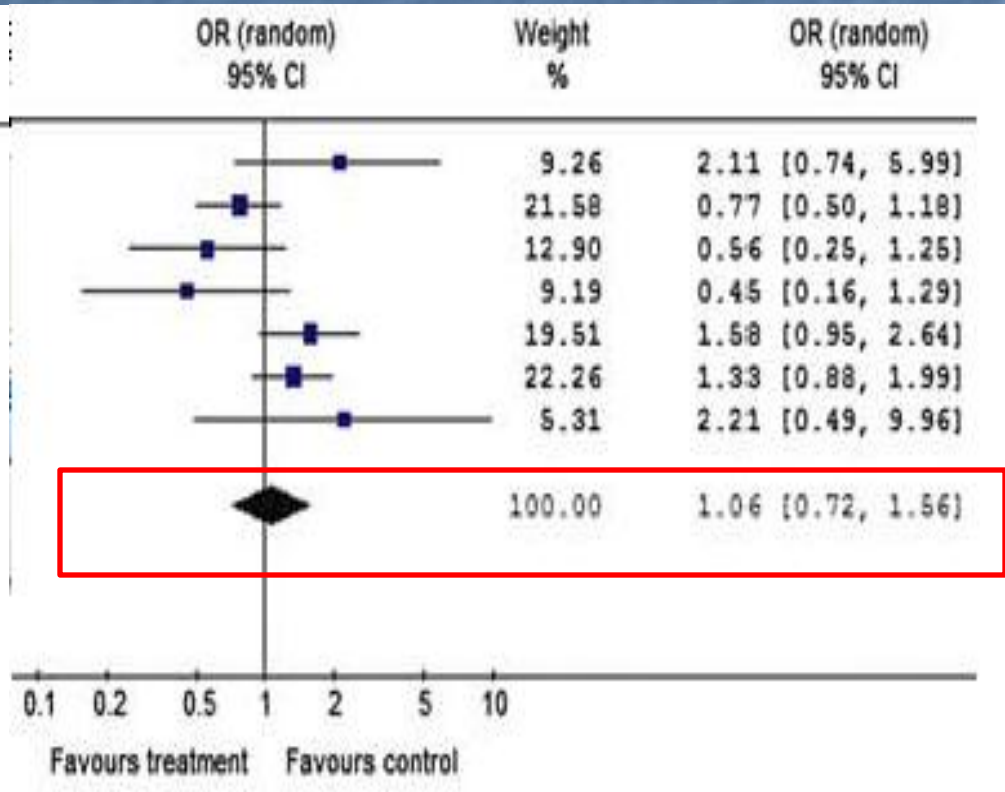


Ko et al. J Nutrition., 2009

TNFA-308 and gastric cancer risk : meta-analysis (J Hum Genet 2008 Mar (EPBU))

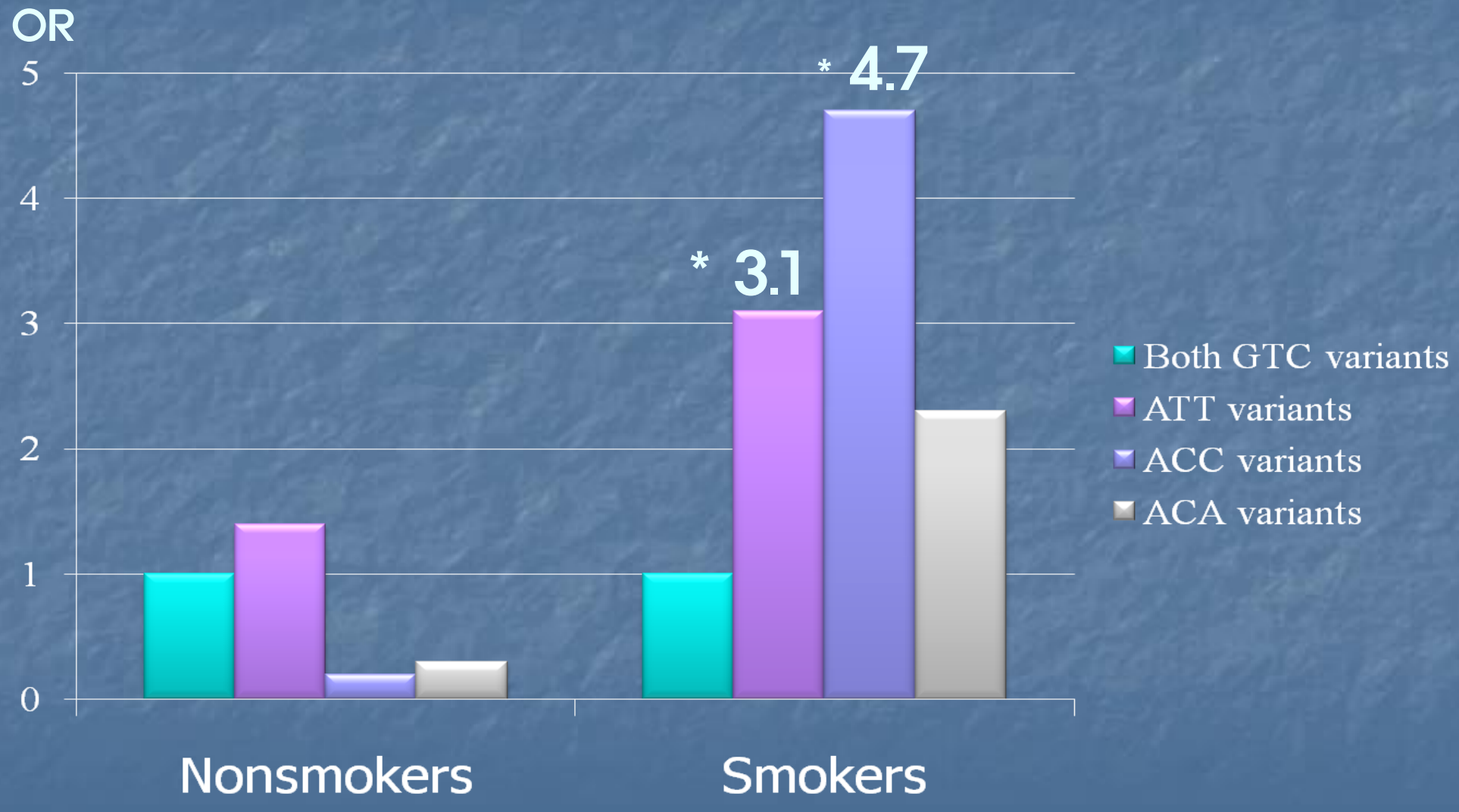


Caucasians



Asians

TNFA gene variants including -308 (Block1 including 6 SNPs)



Yang et al. BMC cancer, 2009

Diet factors

Food items	Cases	Person-year		aRR*	(95% CI)
Green-vegetable					
≤ 1-4times /week	18	7,689		1.00	
≥ 1 time/day	54	30,172		0.73	(0.42-1.26)
Fruits					
≤ 1-4times /month	23	14,409		1.00	
≥ 1-4times /week	49	24,342		1.52	(0.91-2.51)
Soybean/Tofu					
≤ 1-4times /month	56	23,333		1.00	
≥ 1-4times /week	17	15,336		0.54	(0.31-0.93)

Ko et al., Public Health Nutrition, in submission

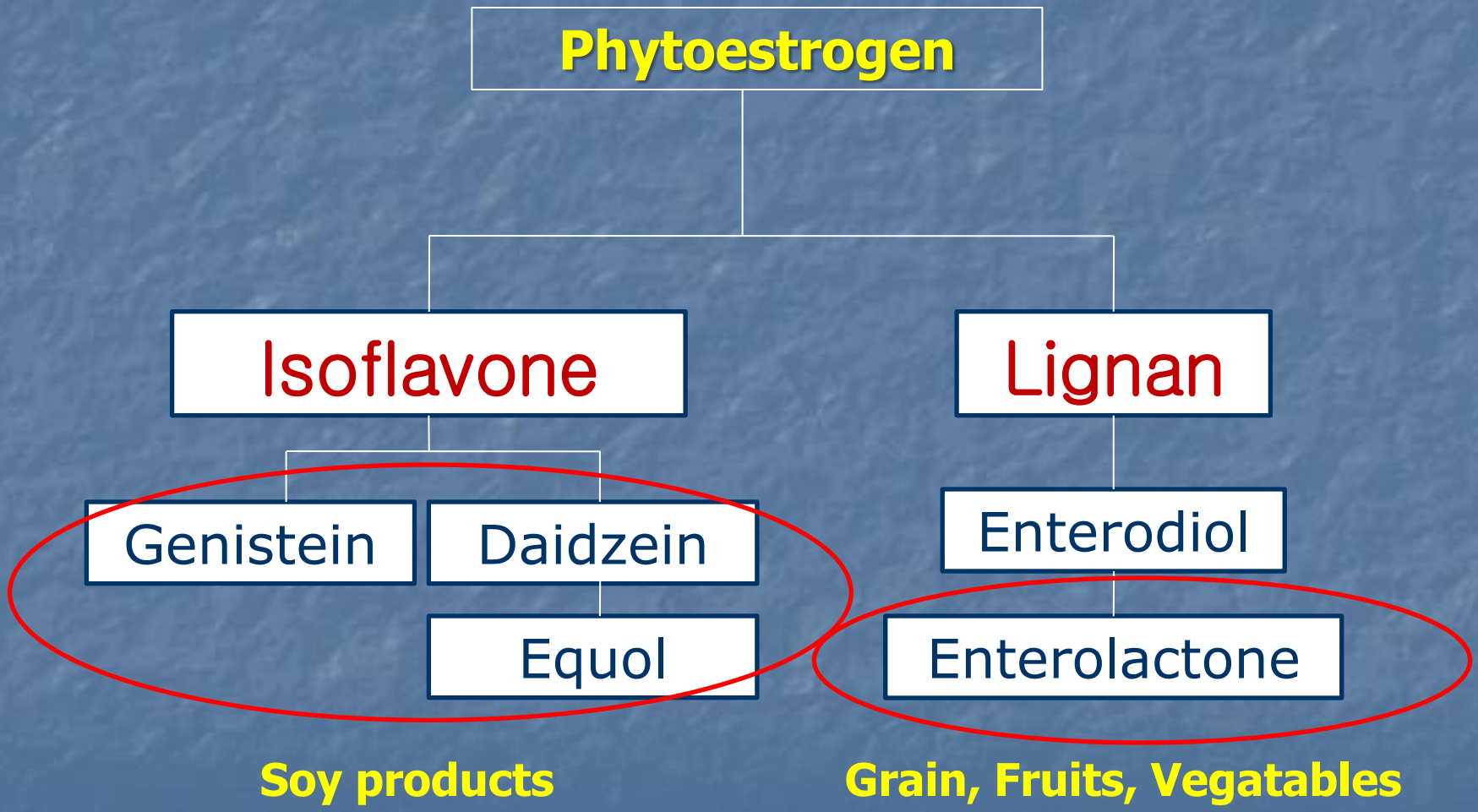
Inconsistency in previous epidemiological studies
for association between soy products for gastric cancer risk

- A few epidemiological studies
- mostly case-control design
  - Questionnaire-based diet information
    : **information bias** (recall bias, memory decay, etc)
- Measurement error
- Different cut-off value

→ Biomarkers for soy products

Phytoestrogen biomarkers

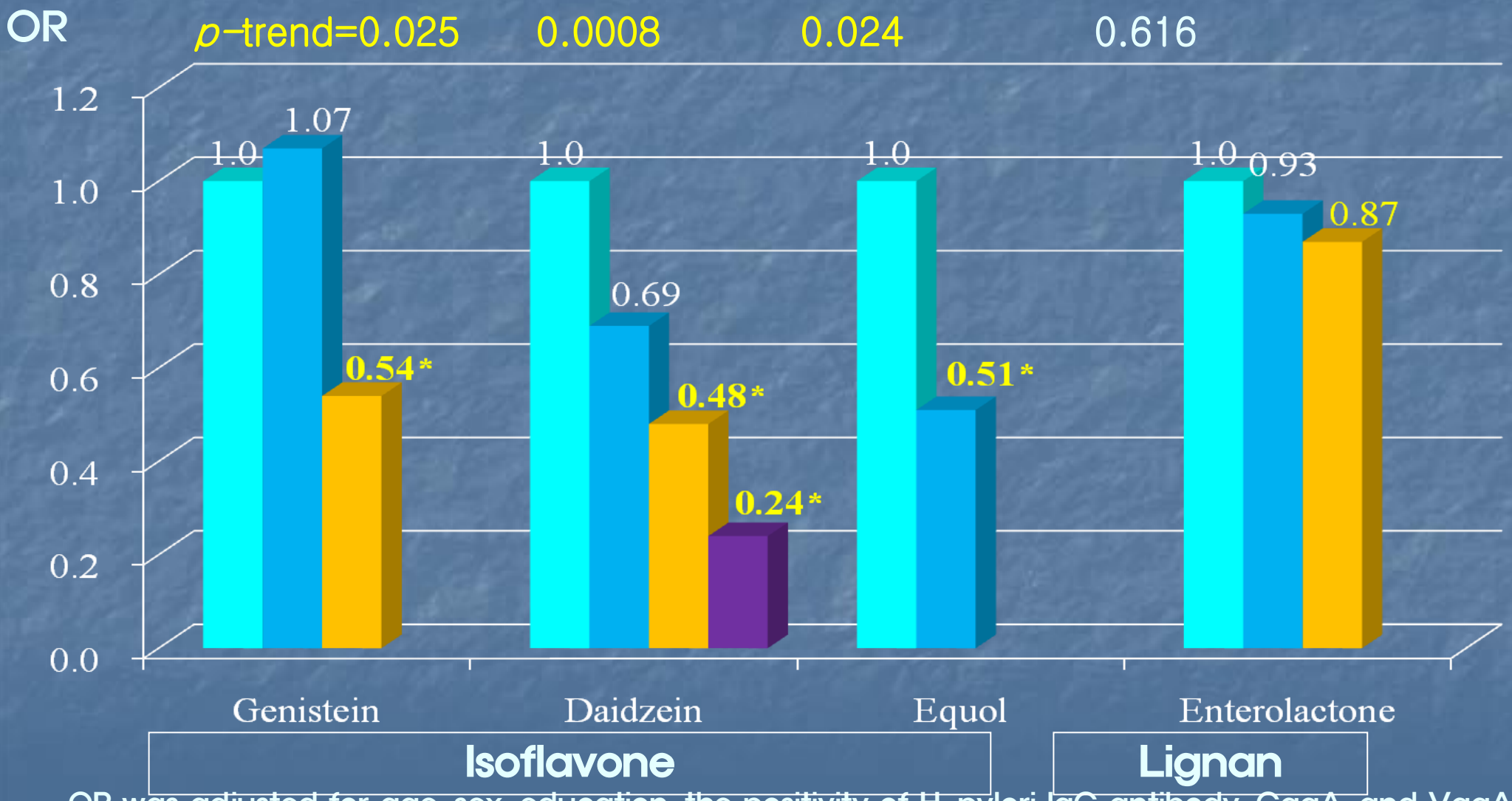
Time resolved fluoroimmunoassay (TR-FIA) kits (Labmaster™, Finland)



Rice. Endocr Relat Cancer. *2006*

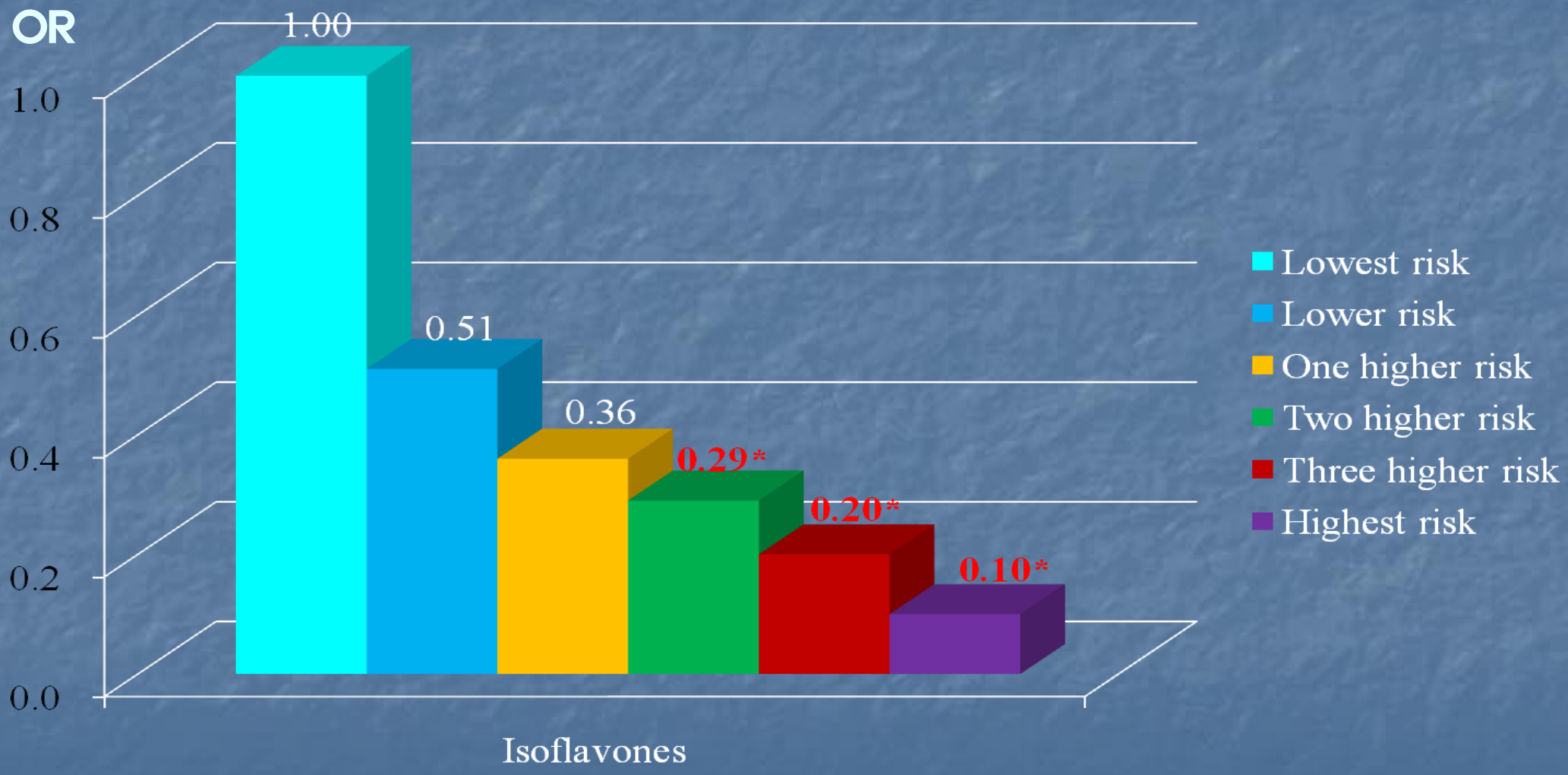
Higher concentration of phytoestrogen biomarker

Ko et al., CEBP. In submission



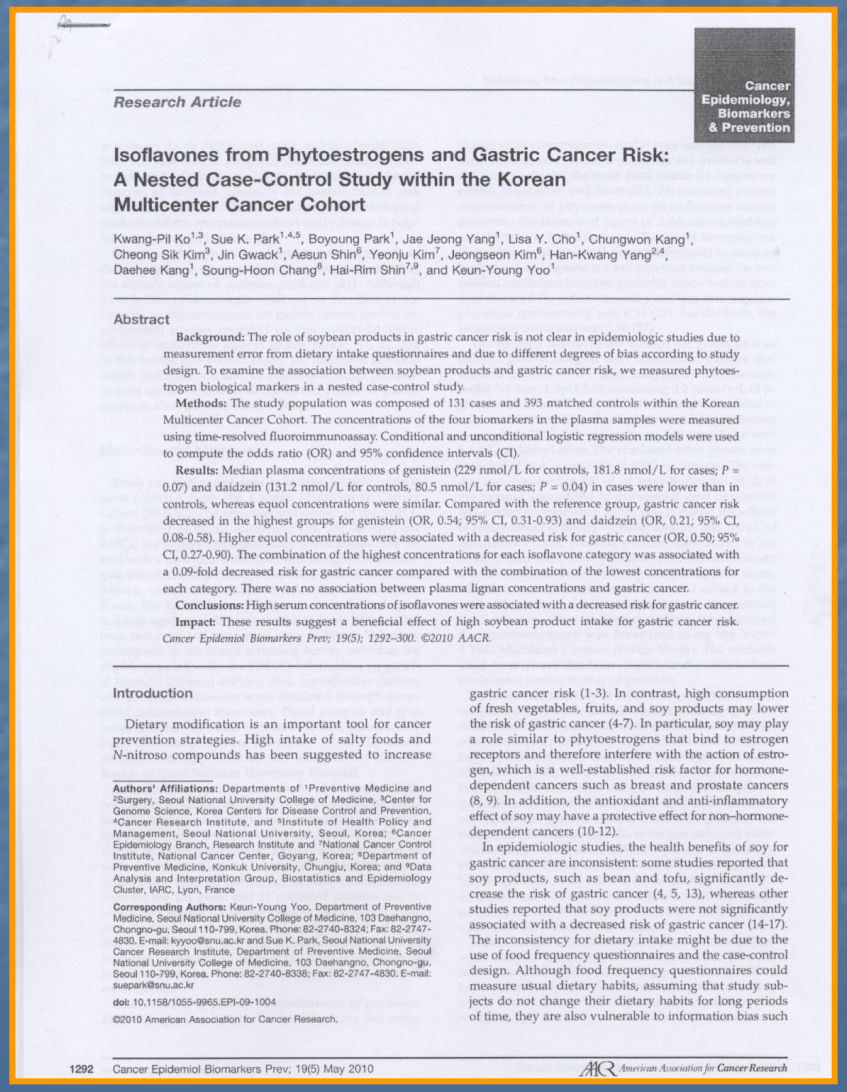
OR was adjusted for age, sex, education, the positivity of H. pylori IgG antibody, CagA, and VagA, cigarette smoking, gastritis history, and alcohol consumption

Three isoflavone combination for gastric cancer risk



OR was adjusted for age, sex, education, the positivity of H. pylori IgG antibody, CagA, and VagA, cigarette smoking, gastritis history, and alcohol consumption

Publications, KMCC Studies



Research Article

Cancer Epidemiology, Biomarkers & Prevention

Isoflavones from Phytoestrogens and Gastric Cancer Risk: A Nested Case-Control Study within the Korean Multicenter Cancer Cohort

Kwang-Pil Ko[1,3], Sue K. Park[1,4,5], Boyoung Park[1], Jae Jeong Yang[1], Lisa Y. Cho[1], Chungwon Kang[1], Cheong Sik Kim[3], Jin Gwack[1], Aesun Shin[6], Yeonju Kim[7], Jeongseon Kim[6], Han-Kwang Yang[2,4], Daehee Kang[1], Soung-Hoon Chang[8], Hai-Rim Shin[7,9], and Keun-Young Yoo[1]

Abstract

Background: The role of soybean products in gastric cancer risk is not clear in epidemiologic studies due to measurement error from dietary intake questionnaires and due to different degrees of bias according to study design. To examine the association between soybean products and gastric cancer risk, we measured phytoestrogen biological markers in a nested case-control study.

Methods: The study population was composed of 131 cases and 393 matched controls within the Korean Multicenter Cancer Cohort. The concentrations of the four biomarkers in the plasma samples were measured using time-resolved fluoroimmunoassay. Conditional and unconditional logistic regression models were used to compute the odds ratio (OR) and 95% confidence intervals (CI).

Results: Median plasma concentrations of genistein (229 nmol/L for controls, 181.8 nmol/L for cases; P = 0.07) and daidzein (131.2 nmol/L for controls, 80.5 nmol/L for cases; P = 0.04) in cases were lower than in controls, whereas equol concentrations were similar. Compared with the reference group, gastric cancer risk decreased in the highest groups for genistein (OR, 0.54; 95% CI, 0.31-0.93) and daidzein (OR, 0.21; 95% CI, 0.08-0.58). Higher equol concentrations were associated with a decreased risk for gastric cancer (OR, 0.50; 95% CI, 0.27-0.90). The combination of the highest concentrations for each isoflavone category was associated with a 0.09-fold decreased risk for gastric cancer compared with the combination of the lowest concentrations for each category. There was no association between plasma lignan concentrations and gastric cancer.

Conclusions: High serum concentrations of isoflavones were associated with a decreased risk for gastric cancer.

Impact: These results suggest a beneficial effect of high soybean product intake for gastric cancer risk.

Cancer Epidemiol Biomarkers Prev; 19(5); 1292–300. ©2010 AACR.

Introduction

Dietary modification is an important tool for cancer prevention strategies. High intake of salty foods and *N*-nitroso compounds has been suggested to increase gastric cancer risk (1-3). In contrast, high consumption of fresh vegetables, fruits, and soy products may lower the risk of gastric cancer (4-7). In particular, soy may play a role similar to phytoestrogens that bind to estrogen receptors and therefore interfere with the action of estrogen, which is a well-established risk factor for hormone-dependent cancers such as breast and prostate cancers (8, 9). In addition, the antioxidant and anti-inflammatory effect of soy may have a protective effect for non–hormone-dependent cancers (10-12).

In epidemiologic studies, the health benefits of soy for gastric cancer are inconsistent: some studies reported that soy products, such as bean and tofu, significantly decrease the risk of gastric cancer (4, 5, 13), whereas other studies reported that soy products were not significantly associated with a decreased risk of gastric cancer (14-17). The inconsistency for dietary intake might be due to the use of food frequency questionnaires and the case-control design. Although food frequency questionnaires could measure usual dietary habits, assuming that study subjects do not change their dietary habits for long periods of time, they are also vulnerable to information bias such

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doi: 10.1158/1055-9965.EPI-09-1004

Ko et al. Isoflavones of phytoestrogens and gastric cancer risk: a nested case-control study within the Korean Multi-Center Cancer Cohort. Cancer Epidemiol Biomarkers Prev 2009;19(5):1292-300

Publications, KMCC Studies

Supplemental Material can be found at: http://jn.nutrition.org/cgi/content/full/jn.108.101865/DC1

The Journal of Nutrition
Nutritional Epidemiology

Soybean Product Intake Modifies the Association between Interleukin-10 Genetic Polymorphisms and Gastric Cancer Risk[1–3]

Kwang-Pil Ko,[4] Sue K. Park,[4,5] Lisa Y. Cho,[4] Jin Gwack,[4] Jae Jeong Yang,[4] Aesun Shin,[6] Cheong Sik Kim,[7] Yeonju Kim,[8] Daehee Kang,[4,5] Soung-Hoon Chang,[8] Hai-Rim Shin,[6] and Keun-Young Yoo[4]*

[4]Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea; [5]Seoul National University Cancer Research Institute, Seoul, Korea; [6]National Cancer Control Research Institute, National Cancer Center, Goyang, Korea; [7]Center for Genome Science, Korea Center for Disease Control and Prevention, Seoul, Korea; and [8]Department of Preventive Medicine, Konkuk University College of Medicine, Chungju, Korea

Abstract

In this study, our aim was to investigate the association of inflammation-related genetic polymorphisms and gastric cancer risk and to examine whether the combined effect of soybean product intake modified cancer risk. Eighty-four incident gastric cancer cases and 336 matched controls were selected from the Korean Multi-Center Cancer Cohort. We selected 14 single nucleotide polymorphisms (SNP) from 5 genes (*interleukin (IL)-1β, IL-2, IL-4, IL-8,* and *IL-10*) and used unconditional logistic regression model to calculate the odds ratios (OR) and 95% CI adjusting for *H. pylori* seropositivity, smoking, age, sex, enrollment year, and residential area. The risk for gastric cancer in relation to genetic polymorphisms and haplotypes were assessed according to soybean product intake levels. Although no single SNP effect was found, the combined effect between *IL-10* gene variants of *−592 GG/GA, −819 TC/CC,* or *−1082 AG/GG* and low intake of soybean products had an increased risk for gastric cancer compared with the group with no risk gene variants and a high intake of soybean products (OR [95% CI] = 2.82 [1.04–7.62], 2.75 [1.02–7.44], and 4.34 [1.51–12.5], respectively). Among the low-soybean product intake group, *IL-10 CCG* haplotype had an increased risk of gastric cancer (OR = 3.38 [1.40–8.13]) relative to the *ATA* haplotype. Our results suggest that the association between IL-10 genetic polymorphisms and gastric cancer risk was modified by soybean product intake. J. Nutr. 139: 1008–1012, 2009.

Introduction

Gastric cancer is the fourth most common cancer and second leading cause of cancer deaths in the world (1). Numerous epidemiologic studies that evaluated gastric cancer risk factors have reported *Helicobacter pylori* infection as a significant risk factor (2–4) and the International Agency for Research on Cancer classified *H. pylori* as a gastric carcinogen (5).

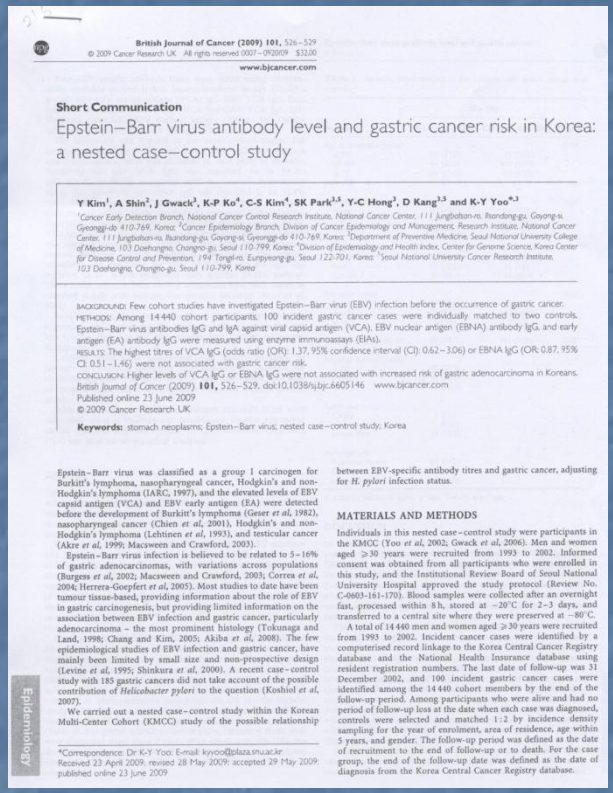
Although *H. pylori* infection is a known risk factor of gastric cancer, <3% of *H. pylori* carriers develop gastric cancer (6). Thus, *H. pylori* virulence factors (7,8) and environmental factors such as smoking (9), dietary factors, and several biological markers, including plasma glucose concentration (10), have been proposed in the etiology of gastric carcinogenesis (11,12). Genetic susceptibility may also underlie the association of gastric cancer risk (13).

Chronic *H. pylori* infection of the gastric epithelium can induce chronic inflammation, which is a critical step in gastric carcinogenesis (14). In chronic gastric inflammation, activated neutrophils and mononuclear cells produce different types of cytokines that are proinflammatory cytokines, including interleukin (IL)[9]-*1β*, IL-6, IL-8, and antiinflammatory cytokines, including IL-10 (15,16). Although many studies have assessed the association between genetic polymorphisms of inflammation-related cytokine and gastric cancer, the results have been inconsistent. Also in terms of environmental factors, previous epidemiologic studies indicated that high consumption of soy food may lower the risk of gastric cancer (17,18).

In this study, we investigated the association between inflammation-related genetic polymorphisms of the IL genes -1β, -2, -4, -8, and -10 and gastric cancer risk. Additionally, we examined whether the combined effect of intake of soybean product that is abundant in the Korean diet and IL genetic polymorphisms modify the risk of gastric cancer.

[1] Supported by a grant of the National R&D Program for Cancer Control, Ministry of Health and Welfare, Republic of Korea (0620140).
[2] Author disclosures: K. P. Ko, S. K. Park, L. Y. Cho, J. Gwack, J. J. Yang, A. Shin, C. S. Kim, Y. Kim, D. Kang, S. H. Chang, H. R. Shin, and K. Y. Yoo, no conflicts of interest.
[3] Supplemental Table 1 is available with the online posting of this paper at jn.nutrition.org.
* To whom correspondence should be addressed. E-mail: kyyoo@snu.ac.kr.
[9] Abbreviations used: IL, interleukin; OR, odds ratio; SNP, single nucleotide polymorphism.

Ko et al. Association between interleukin-10 genetic polymorphisms and gastric cancer risk. J Nutr 2009;139:1008-12



British Journal of Cancer (2009) 101, 526–529

www.bjcancer.com

Short Communication

Epstein–Barr virus antibody level and gastric cancer risk in Korea: a nested case–control study

Y Kim[1], A Shin[2], J Gwack[3], K-P Ko[4], C-S Kim[4], SK Park[3,5], Y-C Hong[3], D Kang[3,5] and K-Y Yoo[*,3]

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BACKGROUND: Few cohort studies have investigated Epstein–Barr virus (EBV) infection before the occurrence of gastric cancer.
METHODS: Among 14 440 cohort participants, 100 incident gastric cancer cases were individually matched to two controls. Epstein–Barr virus antibodies IgG and IgA against viral capsid antigen (VCA), EBV nuclear antigen (EBNA) antibody IgG, and early antigen (EA) antibody IgG were measured using enzyme immunoassays (EIAs).
RESULTS: The highest titres of VCA IgG (odds ratio (OR): 1.37, 95% confidence interval (CI): 0.62–3.06) or EBNA IgG (OR: 0.87, 95% CI: 0.51–1.46) were not associated with gastric cancer risk.
CONCLUSION: Higher levels of VCA IgG or EBNA IgG were not associated with increased risk of gastric adenocarcinoma in Koreans.
British Journal of Cancer (2009) **101,** 526–529. doi:10.1038/sj.bjc.6605146 www.bjcancer.com
Published online 23 June 2009

Keywords: stomach neoplasms; Epstein–Barr virus; nested case–control study; Korea

Epstein–Barr virus was classified as a group 1 carcinogen for Burkitt's lymphoma, nasopharyngeal cancer, Hodgkin's and non-Hodgkin's lymphoma (IARC, 1997), and the elevated levels of EBV capsid antigen (VCA) and EBV early antigen (EA) were detected before the development of Burkitt's lymphoma (Geser *et al*, 1982), nasopharyngeal cancer (Chien *et al*, 2001), Hodgkin's and non-Hodgkin's lymphoma (Lehtinen *et al*, 1993), and testicular cancer (Akre *et al*, 1999; Macsween and Crawford, 2003).

Epstein–Barr virus infection is believed to be related to 5–16% of gastric adenocarcinomas, with variations across populations (Burgess *et al*, 2002; Macsween and Crawford, 2003; Correa *et al*, 2004; Herrera-Goepfert *et al*, 2005). Most studies to date have been tumour tissue-based, providing information about the role of EBV in gastric carcinogenesis, but providing limited information on the association between EBV infection and gastric cancer, particularly adenocarcinoma – the most prominent histology (Tokunaga and Land, 1998; Chang and Kim, 2005; Akiba *et al*, 2008). The few epidemiological studies of EBV infection and gastric cancer, have mainly been limited by small size and non-prospective design (Levine *et al*, 1995; Shinkura *et al*, 2000). A recent case–control study with 185 gastric cancers did not take account of the possible contribution of *Helicobacter pylori* to the question (Koshiol *et al*, 2007).

We carried out a nested case–control study within the Korean Multi-Center Cohort (KMCC) study of the possible relationship between EBV-specific antibody titres and gastric cancer, adjusting for *H. pylori* infection status.

MATERIALS AND METHODS

Individuals in this nested case–control study were participants in the KMCC (Yoo *et al*, 2002; Gwack *et al*, 2006). Men and women aged ⩾30 years were recruited from 1993 to 2002. Informed consent was obtained from all participants who were enrolled in this study, and the Institutional Review Board of Seoul National University Hospital approved the study protocol (Review No. C-0603-161-170). Blood samples were collected after an overnight fast, processed within 8 h, stored at −20°C for 2–3 days, and transferred to a central site where they were preserved at −80°C.

A total of 14 440 men and women aged ⩾30 years were recruited from 1993 to 2002. Incident cancer cases were identified by a computerised record linkage to the Korea Central Cancer Registry database and the National Health Insurance database using resident registration numbers. The last date of follow-up was 31 December 2002, and 100 incident gastric cancer cases were identified among the 14 440 cohort members by the end of the follow-up period. Among participants who were alive and had no period of follow-up loss at the date when each case was diagnosed, controls were selected and matched 1 : 2 by incidence density sampling for the year of enrolment, area of residence, age within 5 years, and gender. The follow-up period was defined as the date of recruitment to the end of follow-up or to death. For the case group, the end of the follow-up date was defined as the date of diagnosis from the Korea Central Cancer Registry database.

*Correspondence: Dr K-Y Yoo; E-mail: kyyoo@plaza.snu.ac.kr
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Kim et al. Epstein-Barr virus antibody level and gastric adenocarcinoma risk in Korea: A nested case-control study. Brit J Cancer 2009;101:526-9

Cohort Studies Using KMCC Under Review or in Press

Association between smoking and gastric cancer risk in a community-based cohort study in Korea

Epstein-Barr virus infection and gastric cancer in Korea: a nested case-control study

Fasting serum glucose level and gastric cancer risk in a nested case-control study

Factors of metabolic syndrome and risk of cancer: The Korean Multi-center Cancer Cohort (KMCC) and the Incheon Health Examinees Cohort (IHEC)

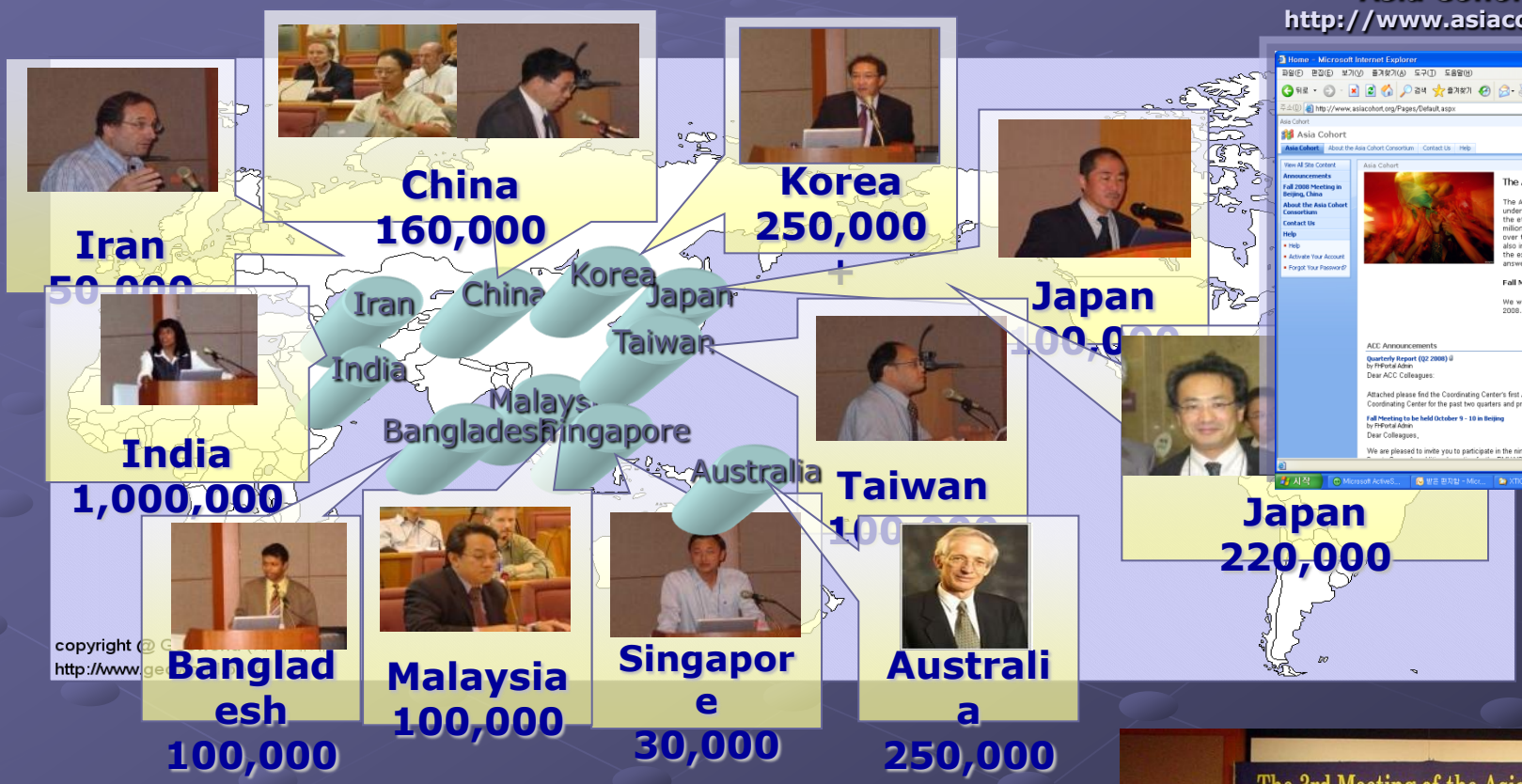
Cigarette smoking, alcohol drinking, tuberculosis and risk of lung cancer: The Korean Multi-center Cancer Cohort Study

Serum glucose level and subsequent liver cancer risk in a Korean prospective cohort (KMCC)

Future studies

- Studying in genes and proteins
  on carcinogenesis pathways of gastric cancer and other cancers

Asia Cohort Consortium



Asia Cohort Consortium Portal
http://www.asiacohort.org/Pages/Default.aspx

- Executive Committee
- Steering Committee
- Working Groups (9)
- Coordinating Center at FHCRC

NEW
Korean Genome Epidemiologic Study: KoGES
Korean CDC

Began in Nov. 2004 (~2010)

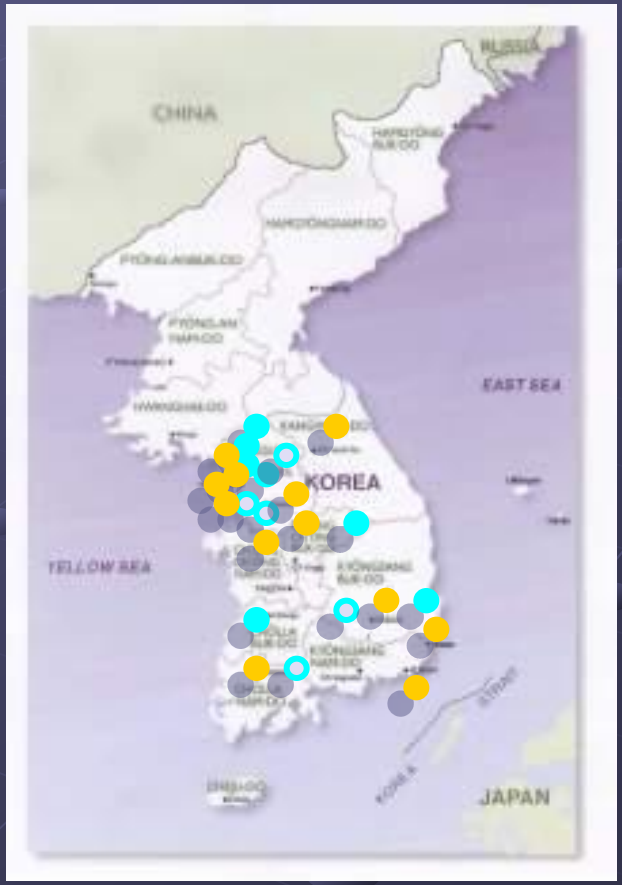
90,000 from community-based model
160,000 from institution-based model
(250,000 Health Examinee)

- 12 geographic sites for model I
- 12 medical institutions for model II

→ 130,000 persons enrolled (as of Dec. 2007)

- interviewer-administered questionnaire
- bio-repository: central / backup
- repeated measurements every 2 or 5 years

- Asia Cohort Consortium (ACC) protocol



Source : Yoo et al. 2005

National Cancer Center – Korea

Korean NCC Cohort

Cancer Screenee Cohort

National Center for Cancer Prevention and Early Detection

questionnaire

blood / urine

tumor bank

30,000 men & women (~2007)

target: 100,000 (5,000/yr)

Health Promotion Fund

Ministry of Health & Welfare

Health Promotion Act (1995)

major source : tobacco sales tax
(KT&G: Korea Tobacco & Ginseng Co.)
Korea Tomorrow & Global

15 cents / 1.5 ~ 2.0 dollars / pack (~ 2004)
35 cents / 1.9 ~ 2.5 dollars / pack (2005.1.1)

Health Promotion Fund: 1.9 billion USD (2008)

- infrastructure for health promotion
- social indirect investments for health
- genome cohort : 10 million USD (2006)

保健福祉部
健康增進基金

NATIONAL CANCER CENTER

International Collaboration

Letter of Intent btw NCI-USA / NCC-Korea (July 10, 2006)

Future Collaboration

Breast Cancer Association Consortium

The Breast Cancer Association Consortium. Commonly studied single-nucleotide polymorphisms and breast cancer: Results from the Breast Cancer Association Consortium. J Natl Cancer Inst 2006;98(19):1382-96

Cox et al. A common coding variant in *CASP8* is associated with breast cancer risk. Nature Genet 2007;39(5):352-8

Easton et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007 ;447(7148):1087-93

Gaudet et al. Five polymorphisms and breast cancer risk: Results from the Breast Cancer Association Consortium. Cancer Epidemiol Biomarkers Prev 2009;18:1610-6

KMCC / KoGES / K-NCC Cohort

- rapid changes in disease patterns, incl. cancer
- wide range of exposure variables / genetic heterogeneity
- direct interview questionnaire with FFQ
- limited information on pesticide usage
- bio-repository for blood and urine / DBMS / informed consent
- completeness of F-up / repeated measurements
- Asian collaboration on epidemiological studies incl. g-e interaction