General Risk Factors and Gene-Environmental Interaction for Breast Cancer in Korea

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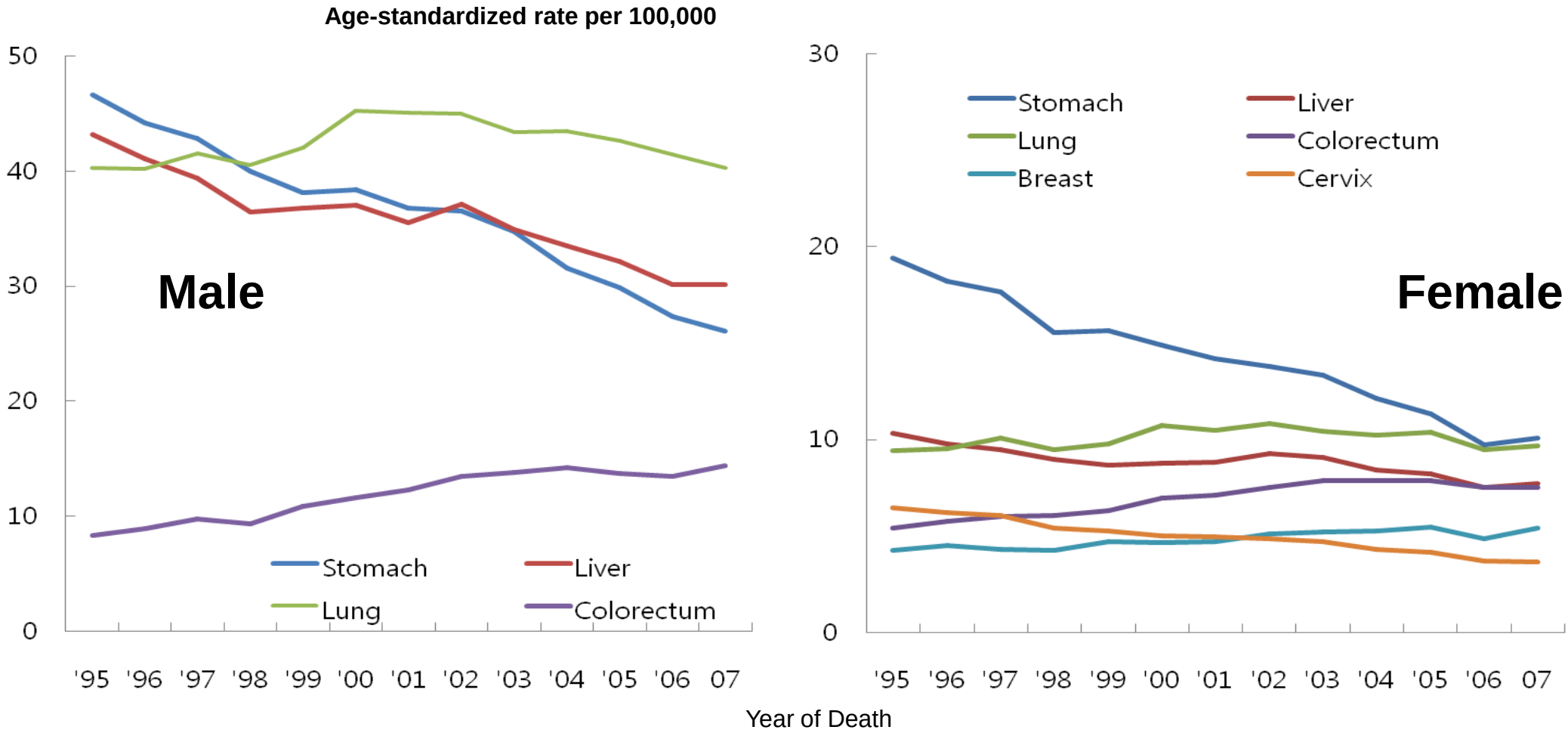
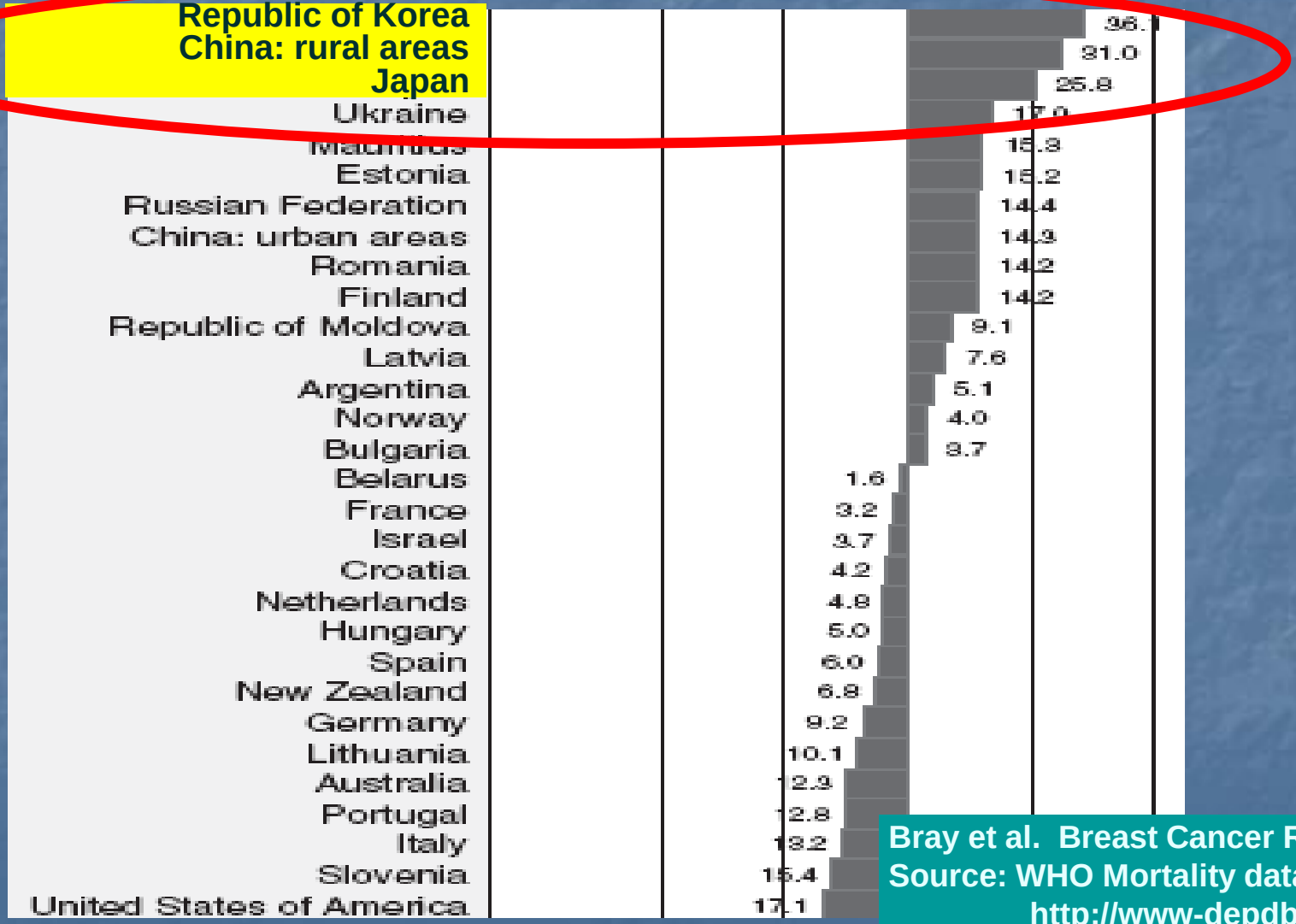
Trend in Major Cancer Mortality Rates



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

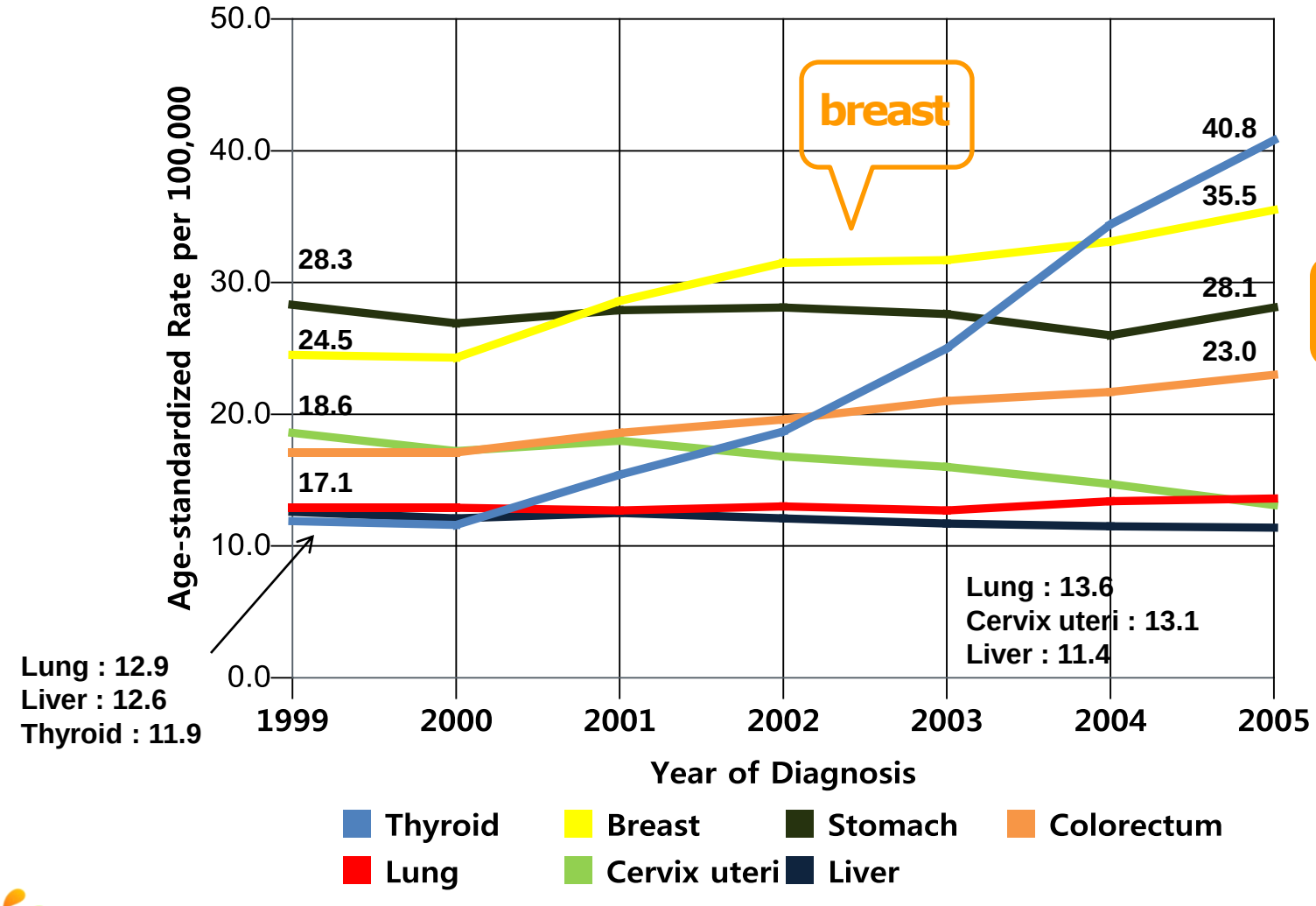
Change in Breast Cancer Mortality

Ages 25-49, % Change during 1985-87 to 1995-97



Bray et al. Breast Cancer Res 2004
Source: WHO Mortality database
http://www-depdb.iarc.fr/

Trend of Age-standardized Incidence Rate by Site
Female, 1999-2005, Korea



Site	Annual Percent Change (%)
Thyroid	25.5
Breast	6.8
Stomach	-0.4
Colorectum	5.5
Lung	0.8
Cervix uteri	-5.2
Liver	-1.7

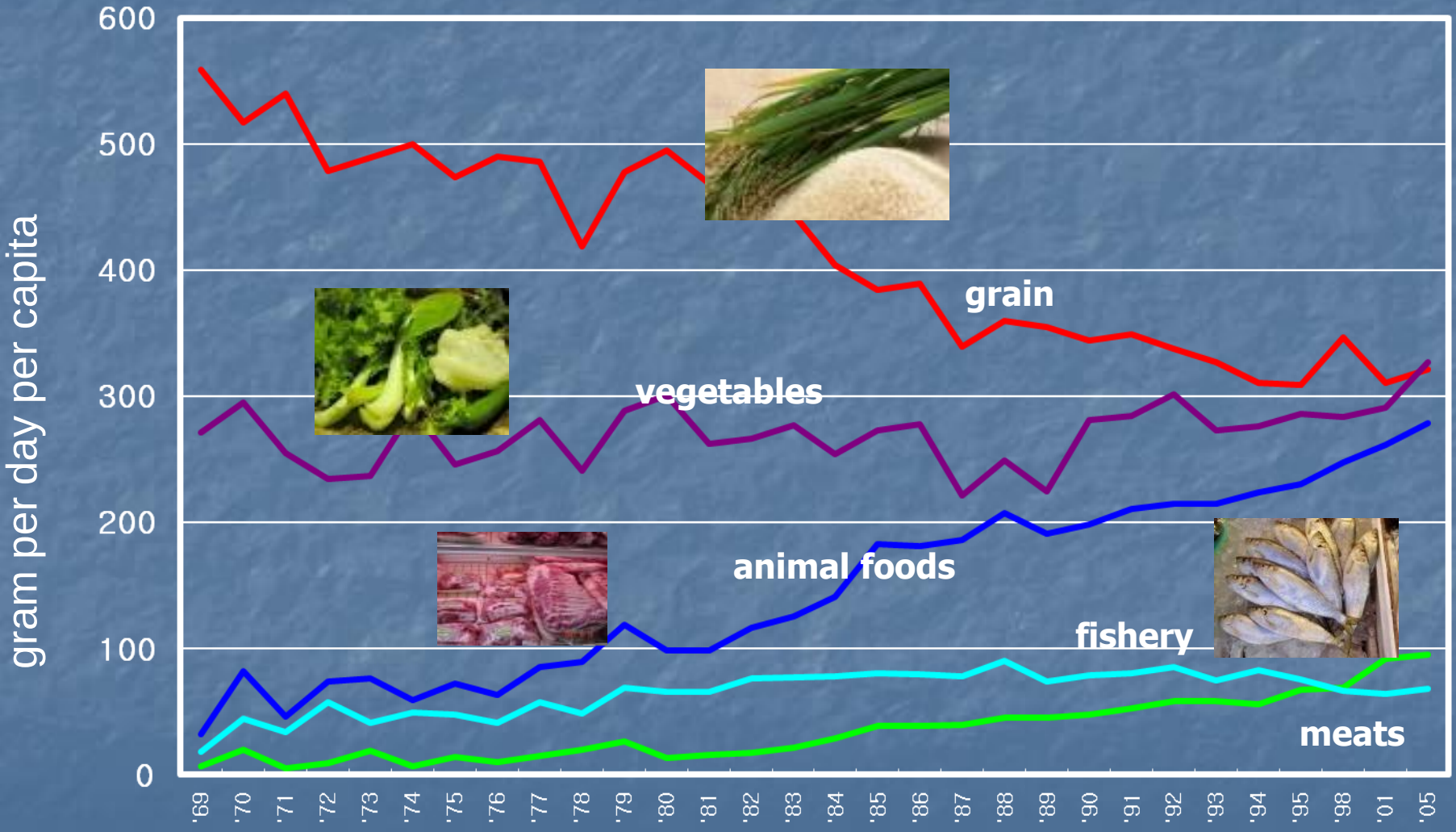
보건복지가족부
MINISTRY FOR HEALTH, WELFARE AND FAMILY AFFAIRS

국립암센터

Health and Welfare Statistics
Republic of Korea

population:	49 M (south)
(18th rank in the world)	23 M (north) as of 2007
life expectancy:	75.7 yrs (M)
	82.4 yrs (F)
aging (65+):	7.2% (2000)
	14.4% (2019)
	20.0% (2026)
health insurance:	universal coverage
per capita GNI:	USD 20,000 (2007)

Selected Food Intake in Korea
(1969-2005)



Source: National Health and Nutrition Survey Report, 2007

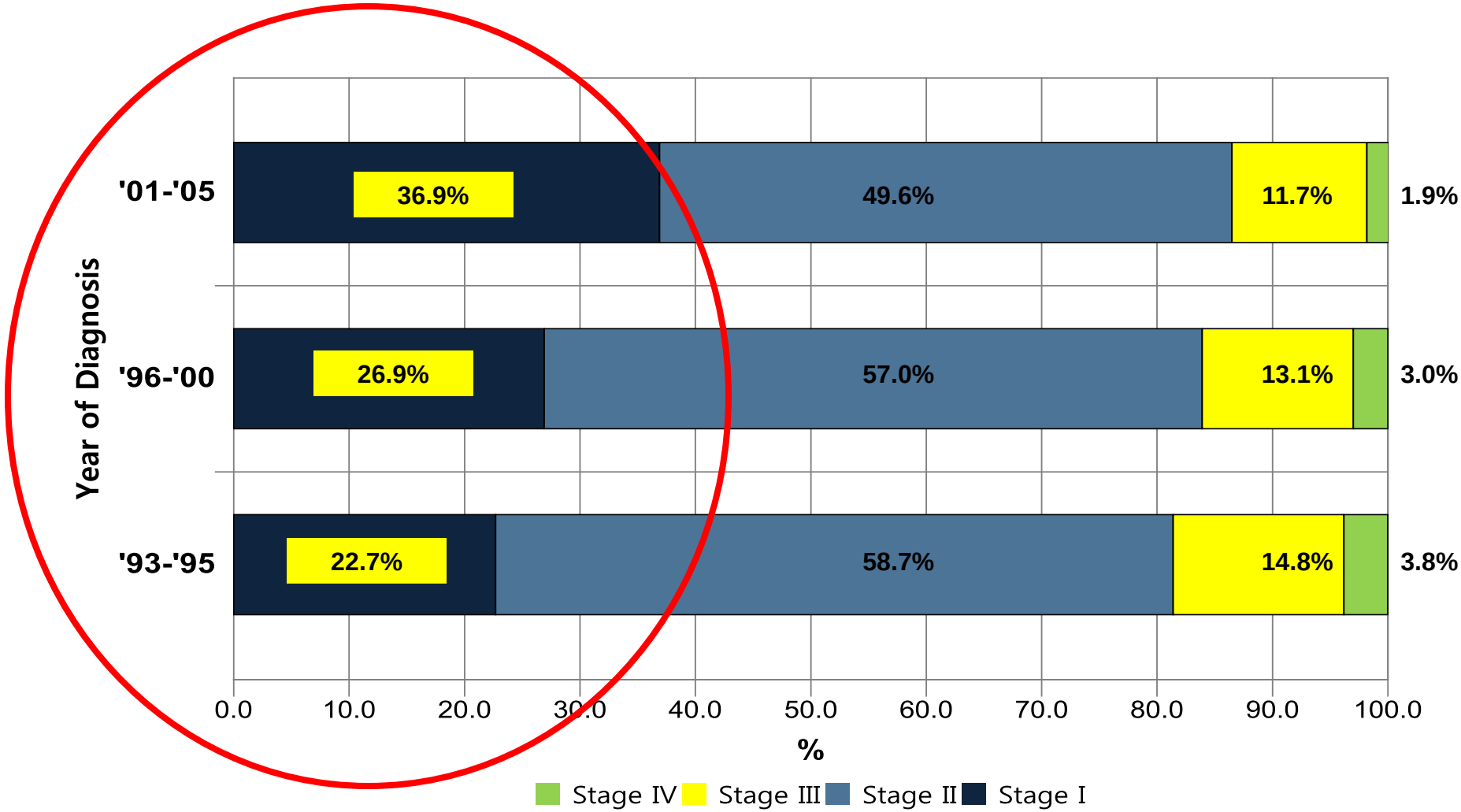
Lifestyle Changes in Korea

- mean age at first marriage
  - 24.9 (1990) ➔ 27.3 (2003) ➔ 28.1 (2007)
- total fertility rate
  - 2.0 (1980) ➔ 1.19 (2003) ➔ 1.26 (2007)
- age at menarche*
  - 13.5 (1988) ➔ 12.7 (1998)
- total calorie supply (per capita per day)
  - 2,622 (1983) ➔ 2,927 Kcal (2006)

Source: ***National Statistical Office. 2007***

*** Cho et al. 1999**

Stage Frequency of Breast Cancer



Source: Korea Central Cancer Registry,
Korean Breast Cancer Society

Screening rates, All Combined, Korea

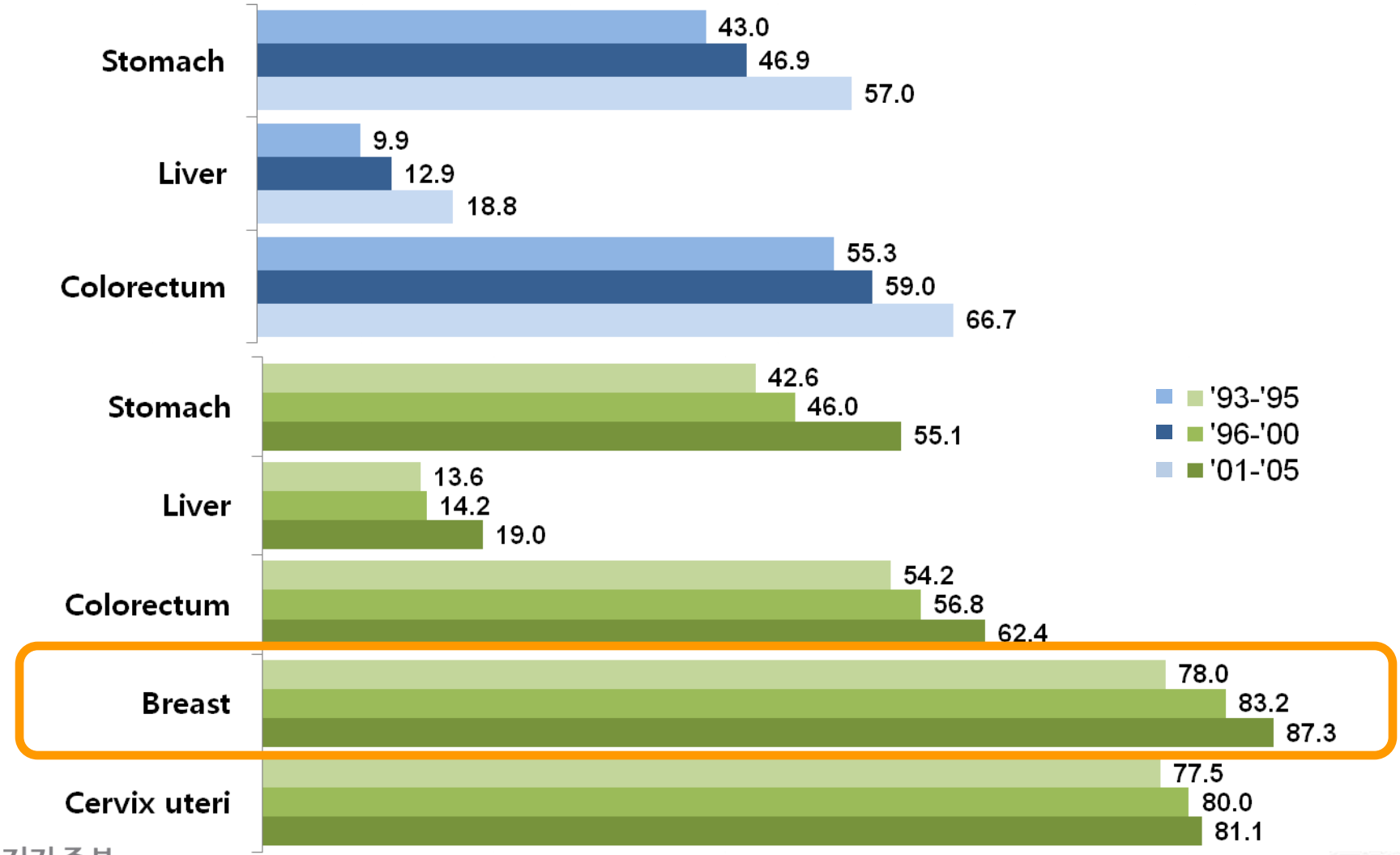
unit: %

Cancers	2004	2005	2006	2007
Stomach	39.2	39.4	43.3	45.6
Liver	20.0	16.3	16.5	22.7
Colon	19.9	25.4	29.4	34.1
Breast	**33.2**	**38.4**	**40.6**	**45.8**
U. cervix	58.3	38.4	54.9	57.0

Source: National Cancer Center. Nationwide Survey for Health Screening Performance Rate, 2004~2007

Note: Cancer screening performance rate by any programs in a given year under the screening guideline recommended by the National Cancer Center and the Ministry of Health & Welfare

Five Year Survival of Cancer Sites of National Screening Program



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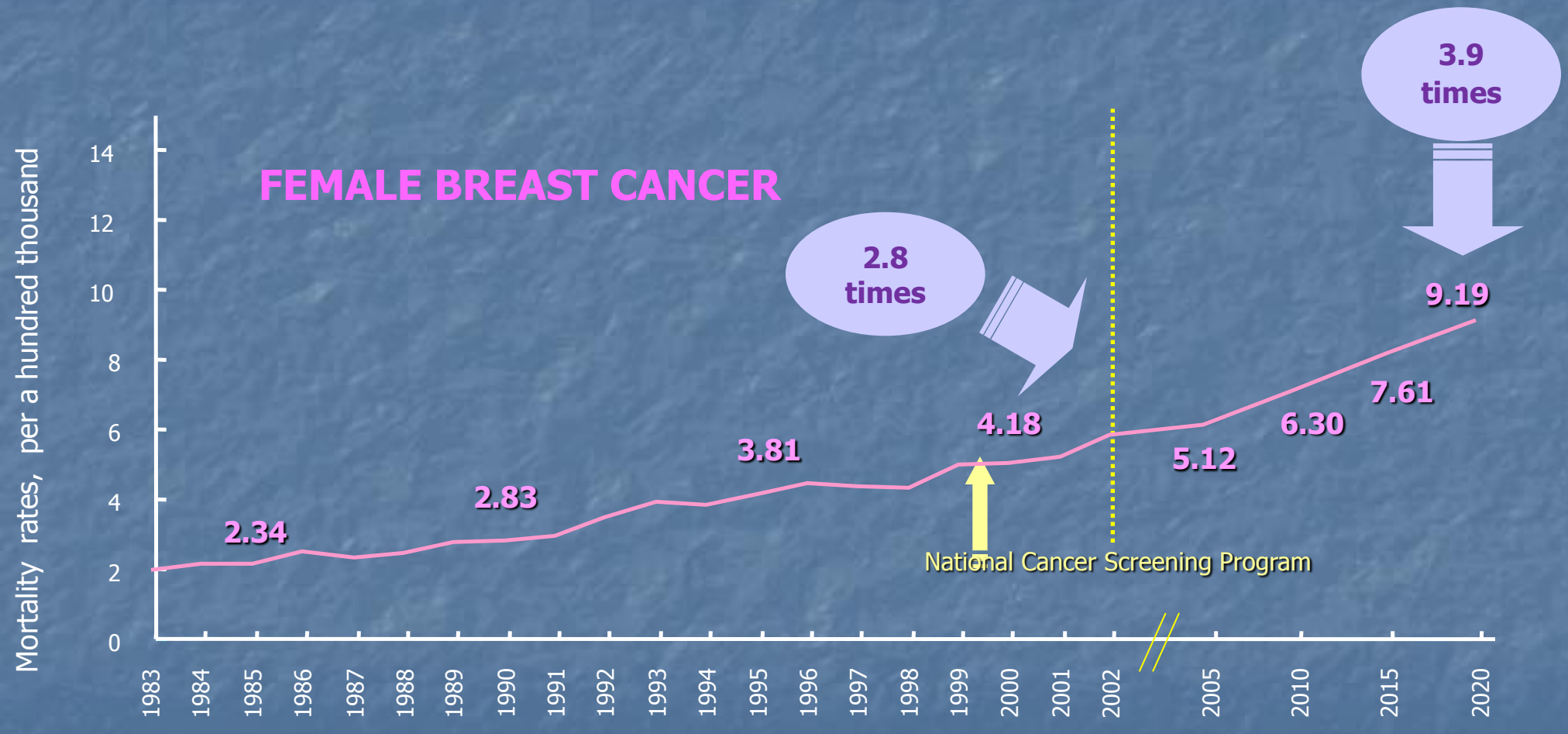
Projection of Breast Cancer Mortality
Korea, all ages, 2005-2020

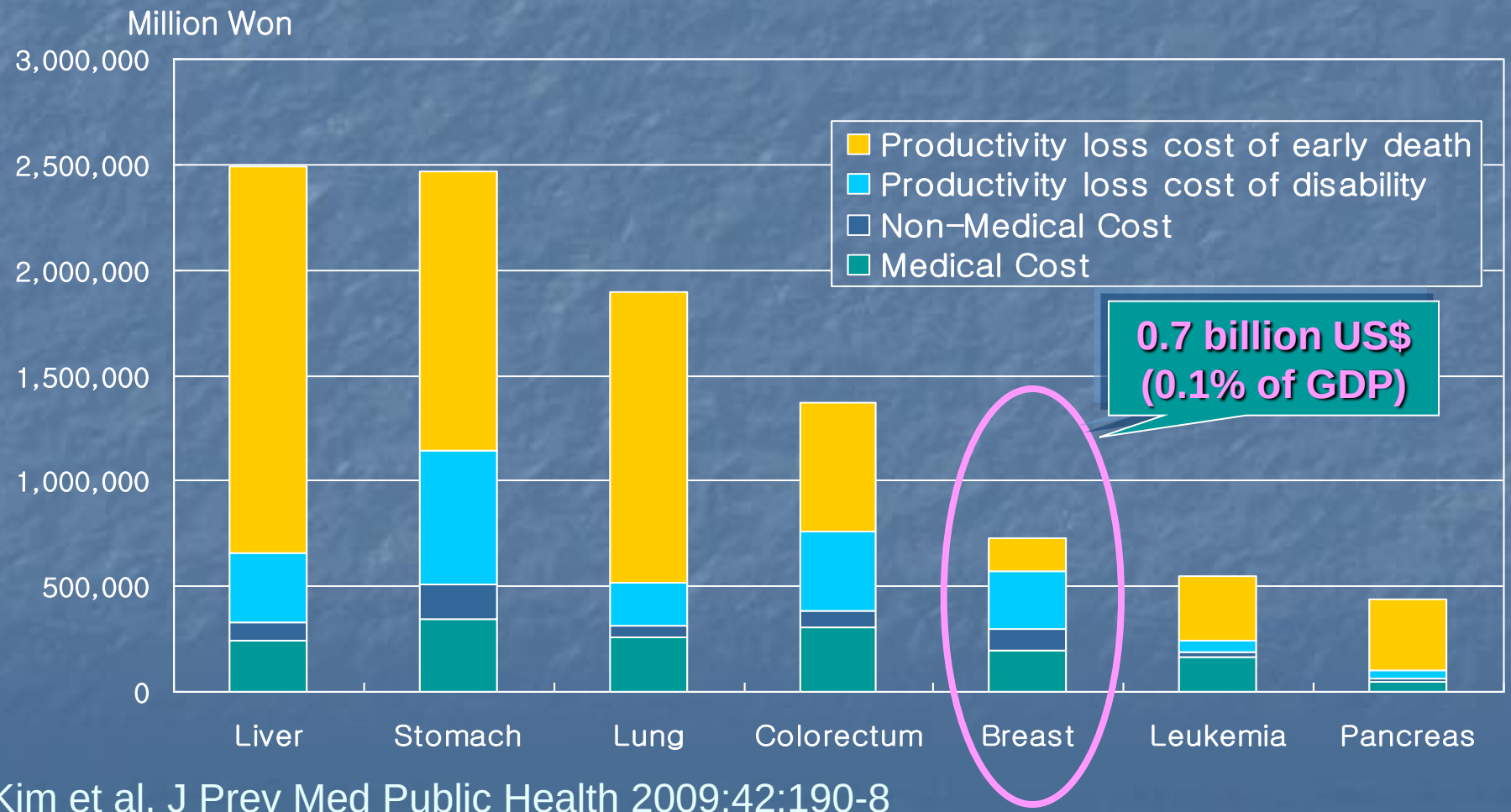


Source : *National Statistical Office* 2002
Choi et al. Asian Pacific J Cancer Prev 2005

based on Poisson regression model

Economic Burden of Cancer Korea, 2005

Total : 14 billion US$ (1.7% of GDP)



Kim et al. J Prev Med Public Health 2009;42:190-8

Are There Any Differences in

Breast Cancer Risk Factors

of Korean Women?

Large-scale, Multi-center
Hospital Based Case-Control Study in Korea

- Cases : Histologically confirmed incident cases
- Controls : No cancer nor systemic diseases

- Direct interview with questionnaire
- Blood samples

- 29% of total breast cancer patients of Korea

<Seoul National University Hospital>

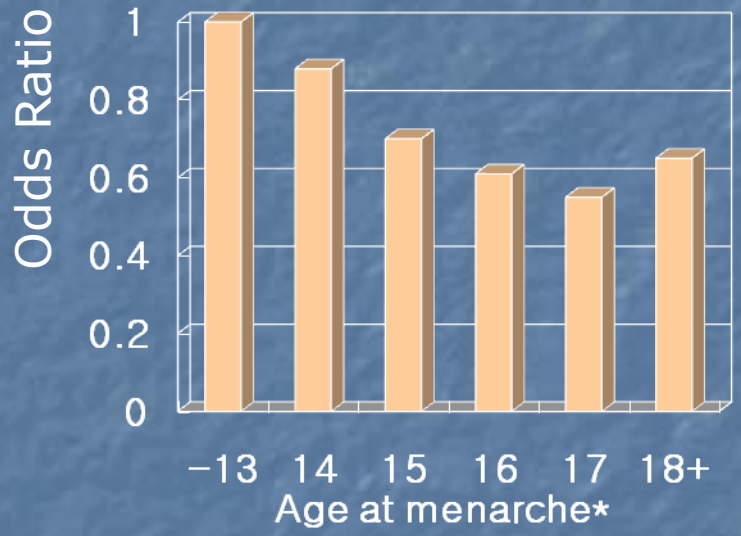
<Asan Medical Center>

Number of breast cancer cases and controls, 1993-2006

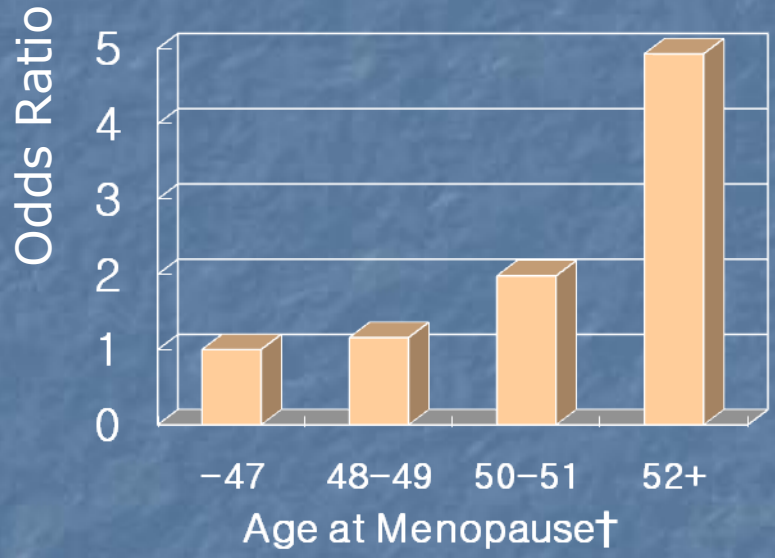
Year	Cases	Controls
1995-2003	2,076	726
2004-2006	1,728	665
Total	3,804	1,391

Age at Menarche and Menopause
Case-control study, Korea, 1997-2003

***p* trend 0.02**



***p* trend <0.001**



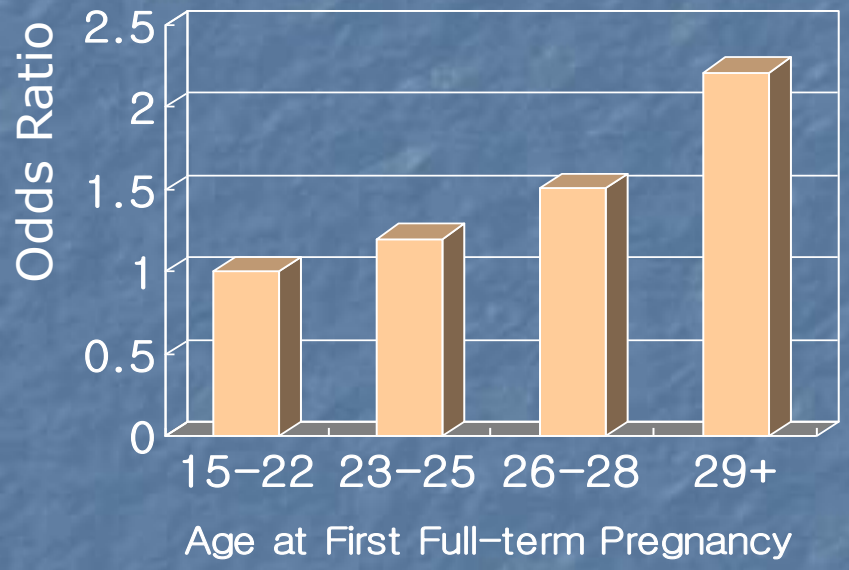
* Adjusted for age, hospital, family history of breast cancer, BMI

† Adjusted for age, hospital, family history of breast cancer, BMI, age at menarche

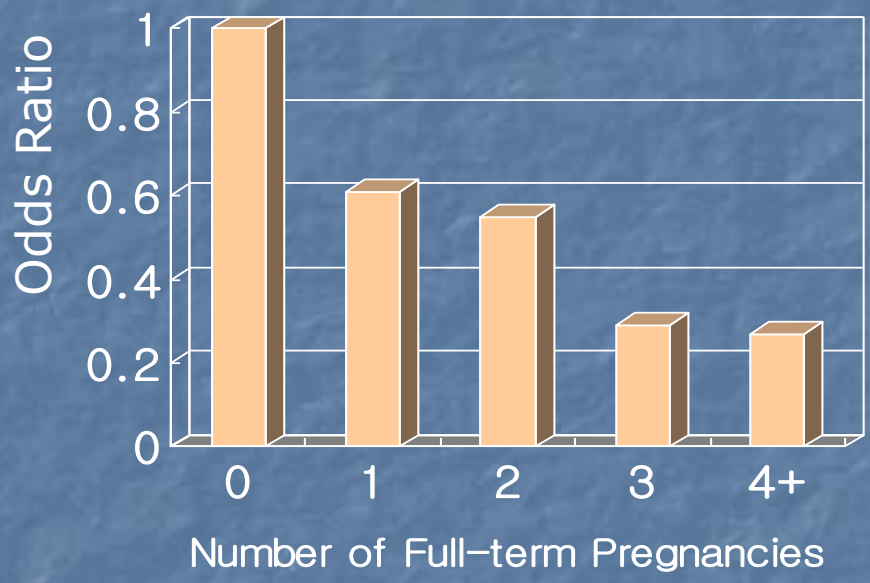
Source: Kim et al. *Eur J Cancer Prev* 2007

Reproductive Factors
Case-control study, Korea, 1997-2003

***p* trend <0.001**



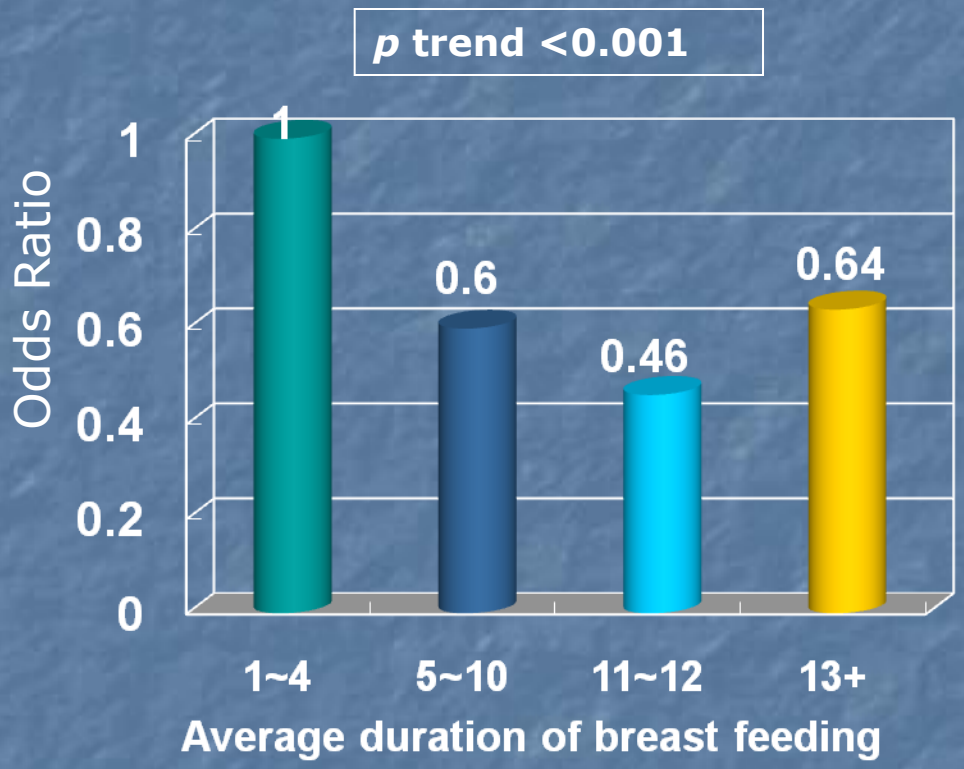
***p* trend <0.001**

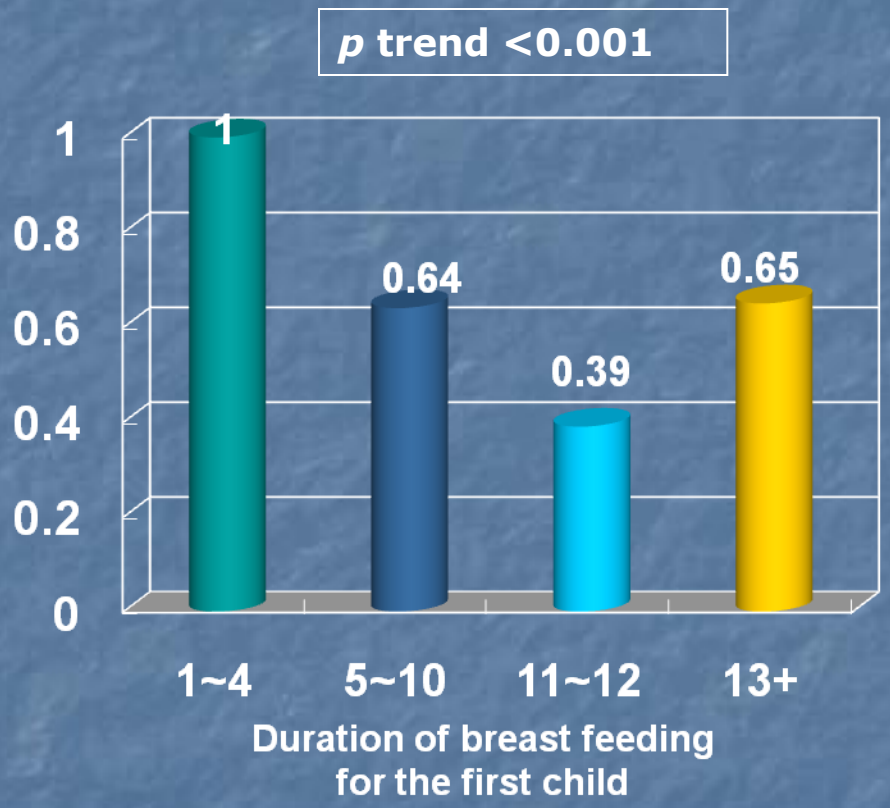


Adjusted for age, hospital, family history of breast cancer, BMI, menopausal status, age at menarche

Source: Kim et al. *Eur J Cancer Prev* 2007

Breast Feeding
Case-control study, Korea, 1997-2003



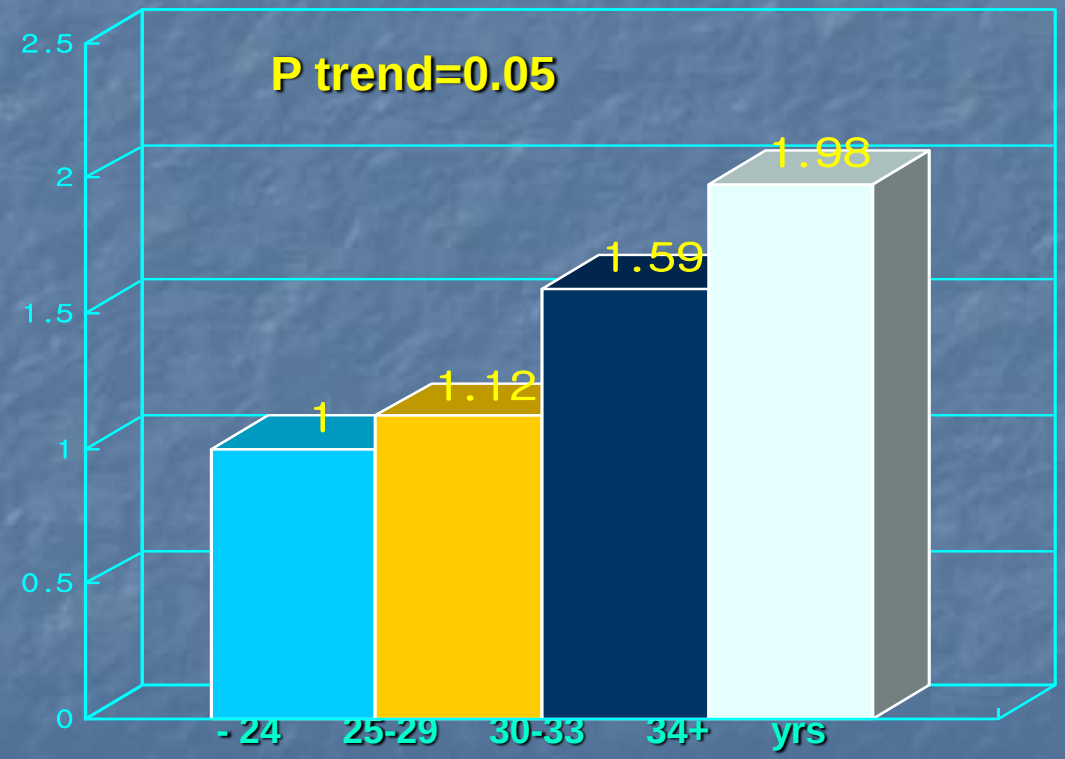


Adjusted for age, hospital, family history of breast cancer, BMI, menopausal status, age at menarche, number of live-birth, age at full-term pregnancy

Source: Kim et al. *Eur J Cancer Prev* 2007

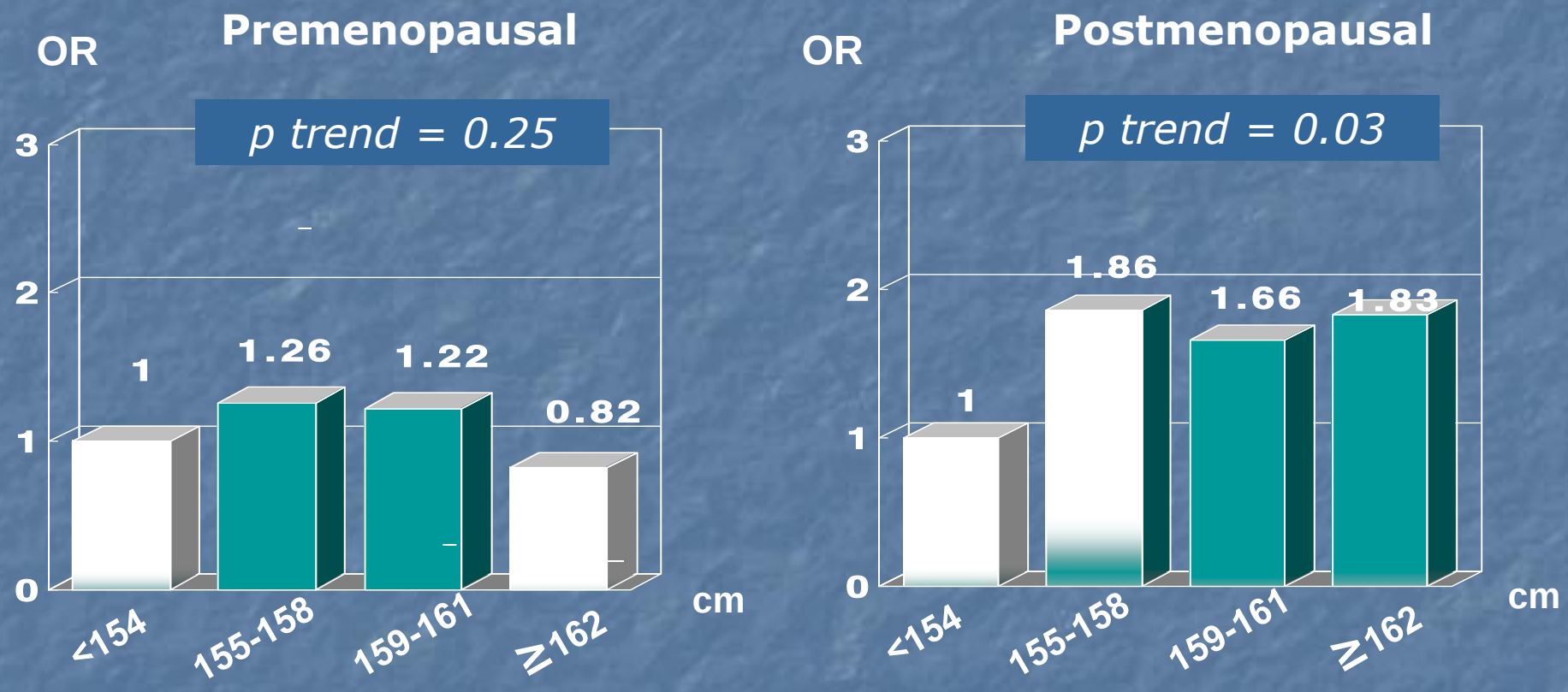
Lifetime Exposure to Estrogen

Korean
(Kim et al. 2004)



Height and Breast Cancer

Korea, 1997-2003

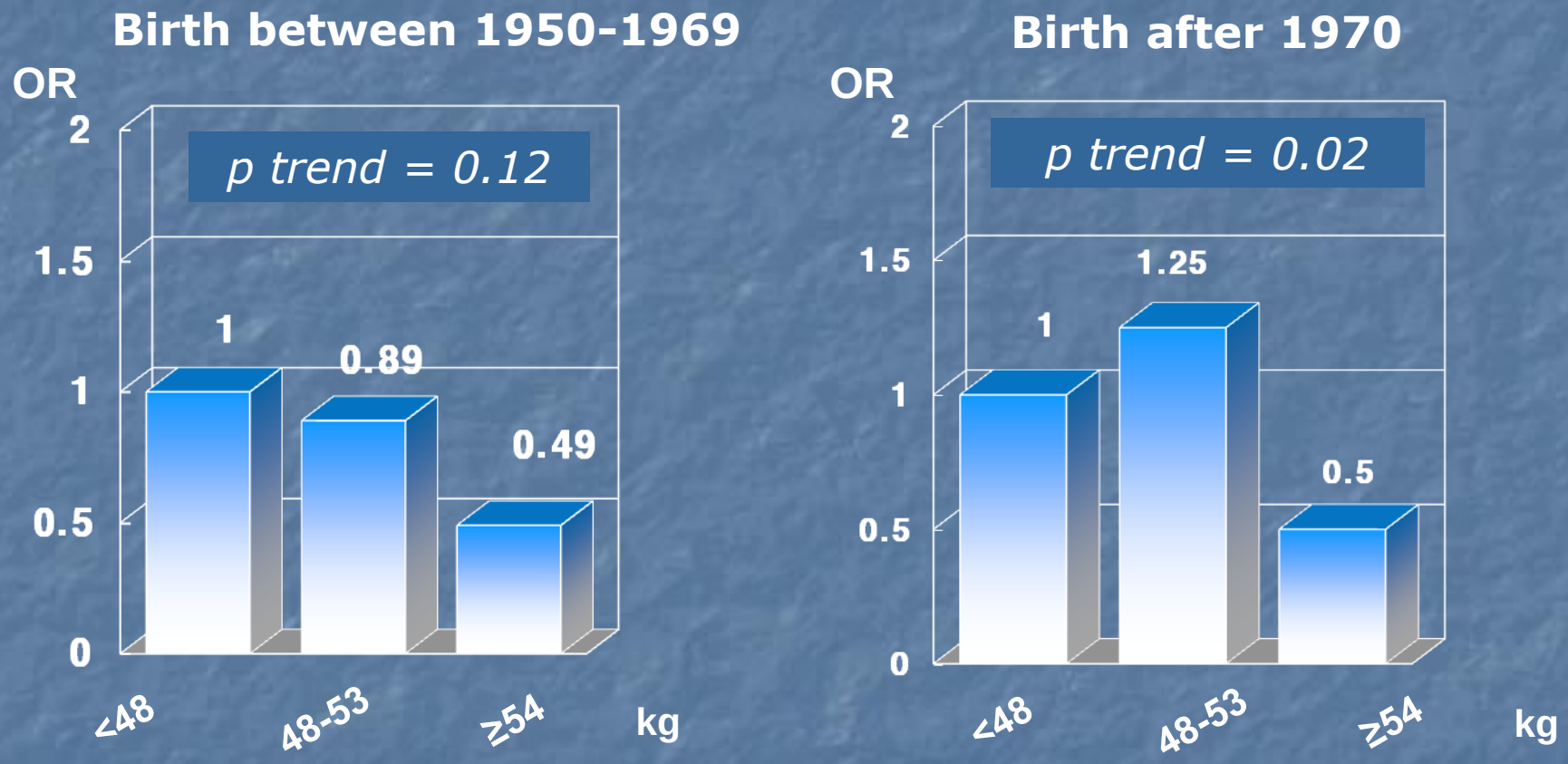


P for interaction between pre- and postmenopausal women = 0.02

adjusted for age, hospital, family history of breast cancer, age at menarche, age at first full-term pregnancy, number of full-term pregnancy, history of hormone replacement therapy

Kim et al. presented in Asian Pacific Cancer Conference. Sep 2005

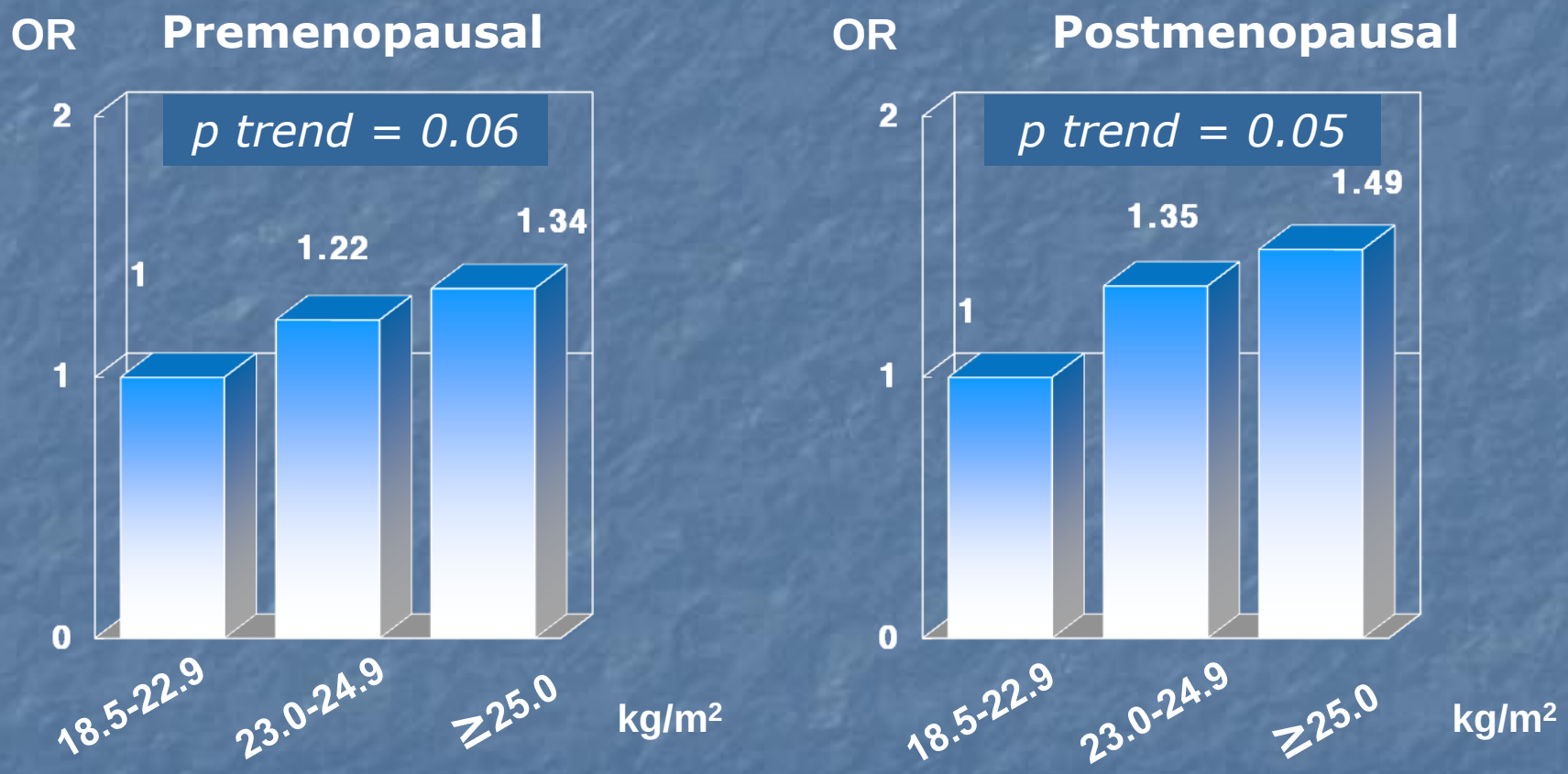
Mean Weight at Late Teens and Breast Cancer
Korea, 1997-2003



adjusted for age, hospital, family history of breast cancer, age at menarche, age at first full-term pregnancy, number of full-term pregnancy, history of hormone replacement therapy

Kim et al. presented in AACR 2006

Body Mass Index and Breast Cancer
Korea, 2004-2005



adjusted for age, hospital, family history of breast cancer, age at menarche, age at first full-term pregnancy, number of full-term pregnancy, history of hormone replacement therapy

Kim et al. Cancer Epidemiol Biomarkers Prev 2009

Risk and Protective Factors of
Breast Cancer in Korean Women

- established
  - early menarche
  - late menopause
  - nulli-parity
  - later FFTP
  - family history
  - obesity (postmenopausal)
  - alcohol drinking
  - breast feeding
  - HRT
- probable
  - smoking
  - physical activity
  - NSAID use
  - oral contraceptives
  - ionizing radiation

Yoo et al. Am J Epidemiol 1992
Yoo et al. CCC 1993
Suh et al. J Korean Med Sci 1996
Yoo et al. Am J Epidemiol 1997
Yoo et al. J Korean Med Sci 2002
Choi et al. BMC Cancer 2005
Kim et al. Eu J Cancer Prev 2007

Life-time Risk of Breast Cancer

Over-nutrition in childhood

Genetic susceptibility

Early menarche
Late menopause

Estrogen-augmented-by-Progesterone

Physical exercise
Postmenopausal obesity

Nulli-parity
Late marriage
Late FTP
No lactation
HRT

Comparison of Established Risk Factors
of Breast Cancer to western women

- Western women
  - early menarche
  - late menopause
  - nulli-parity
  - later FFTP
  - family history
  - obesity (postmenopausal)
  - alcohol drinking
  - breast feeding
  - HRT

- Korean women
  - early menarche (weak)
  - postmenopausal obesity (moderate)
  - breast feeding (strong)
  - HRT (weak)

Dietary Factors May Prevent Breast Cancer

How

Strong

Is

The

Evidence?

Dietary Factors May Cause Breast Cancer

Ecologic Correlation Study between Nutrients Intake and Breast Cancer Mortality in Korea

Nutrients/capita/day	lag (yrs)	r	lag (yrs)	r	lag (yrs)	r
Protein,animal source (%)	12	0.83	11	0.74	10	0.77
Total lipid (g)	12	0.58	11	0.63	10	0.64
Total carbohydrate (g)	12	-0.70	11	-0.63	10	-0.37
Energy from cereal (%)	12	-0.77	11	-0.53	10	-0.74

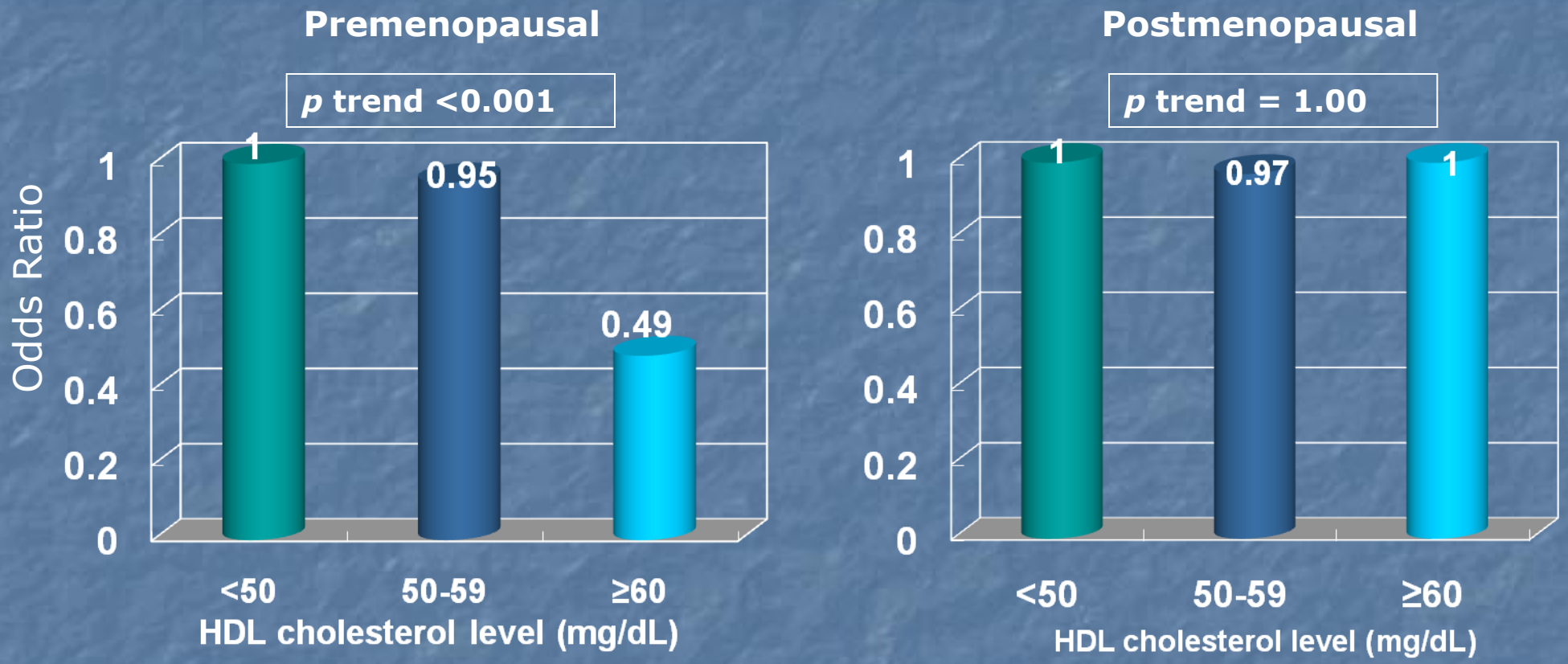
Yoo et al. Seoul J Med 1993

Average Intake of Nutrients

Nutrients	Breast Cancer	Control	P Value
Energy (kcal)	2266±553.5	2119±581.5	<0.001
Protein (g)	100±32.5	93±32.4	0.002
Fat (g)	66±27.3	60±25.9	0.001
Carbohydrate (g)	316±62.4	300±74.3	0.001
Ca (mg)	713±227.4	744±303.1	0.093
P (mg)	1504±424.6	1427±464.2	0.010
Fe (mg)	16±4.6	16±5.8	0.198
Na (mg)	9864±3213	9107±3752	0.001
K (mg)	4061±1085	3788±1322	0.001
Vitamin A (RE)	1096±442.9	955±483.3	<0.001
Vitamin B1(mg)	1.76±0.54	1.50±0.58	<0.001
Vitamin B2(mg)	1.74±0.55	1.65±0.58	0.038
Vitamin B6(mg)	1.26±0.46	1.14±0.49	<0.001
Niacin(mg)	22±7.2	20±6.95	<0.001
Vitamin C(mg)	201±72.6	168±105.2	<0.001
Vitamin E(TE)	11.9±5.3	9.9±5.6	<0.001
Folate(ug)	108±38.9	111±62.0	0.430
Zn(mg)	6.59±1.23	6.08±1.38	<0.001

HDL cholesterol and breast cancer

Case-control study, Korea, 2004-2005

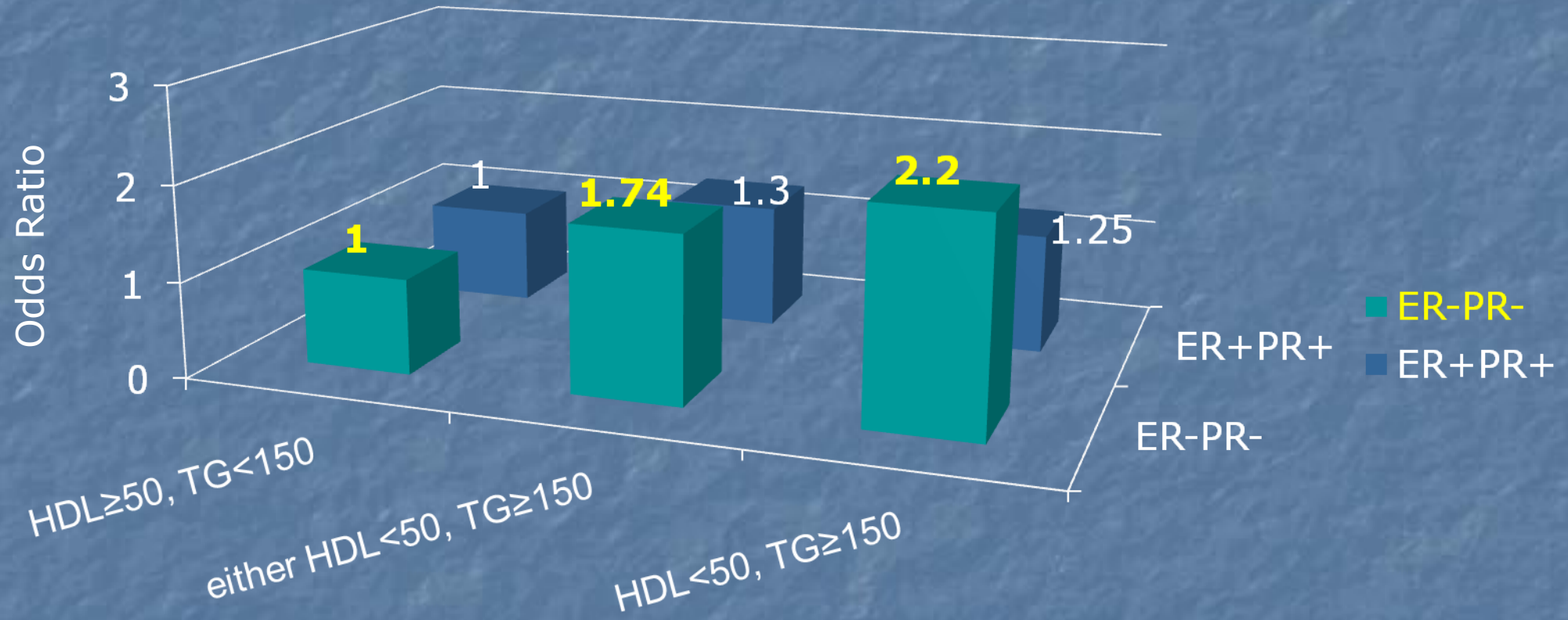


Adjusted for age, family history of breast cancer, BMI, age at menarche, age at full-term pregnancy, and total cholesterol

Kim et al. Cancer Epidemiol Biomarkers Prev 2009

HDL, TG and breast cancer by ERPR

Case-control study, Korea, 2004-2005

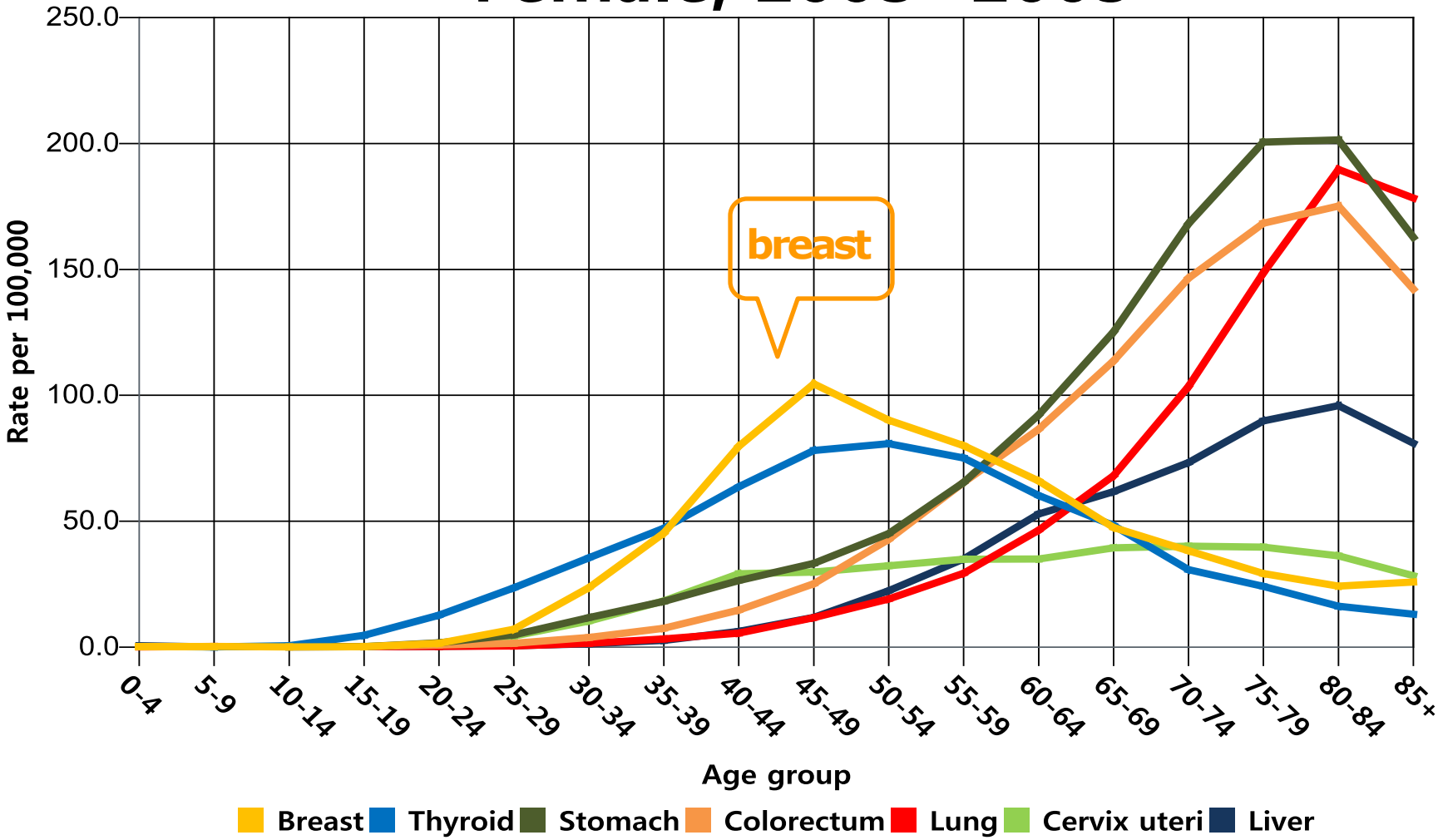


Adjusted for age, family history of breast cancer, menopausal status, BMI, age at menarche, age at full-term pregnancy and total cholesterol

Kim et al. Cancer Epidemiol Biomarkers Prev 2009

Age-specific Incidence Rates of Major Sites

Female, 2003~2005



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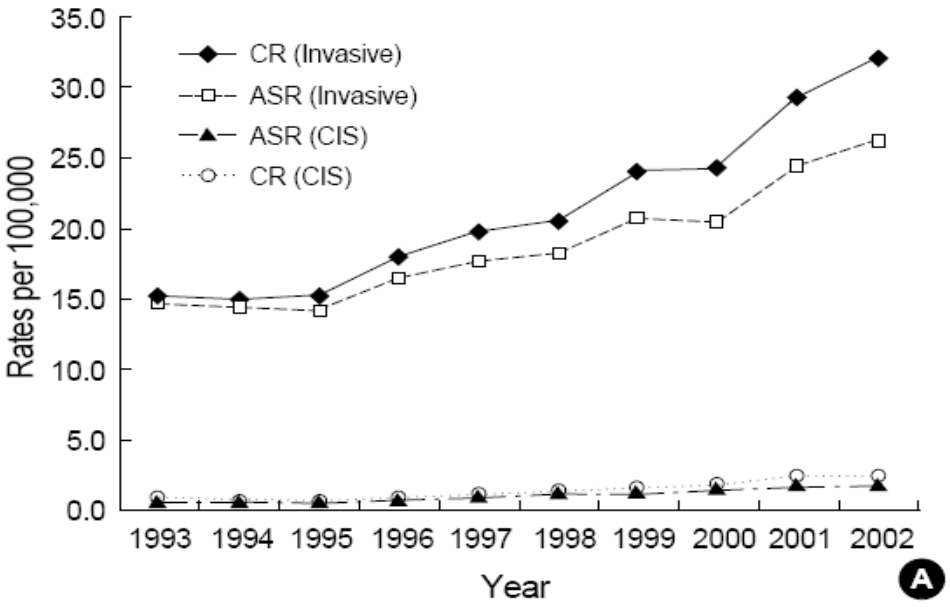
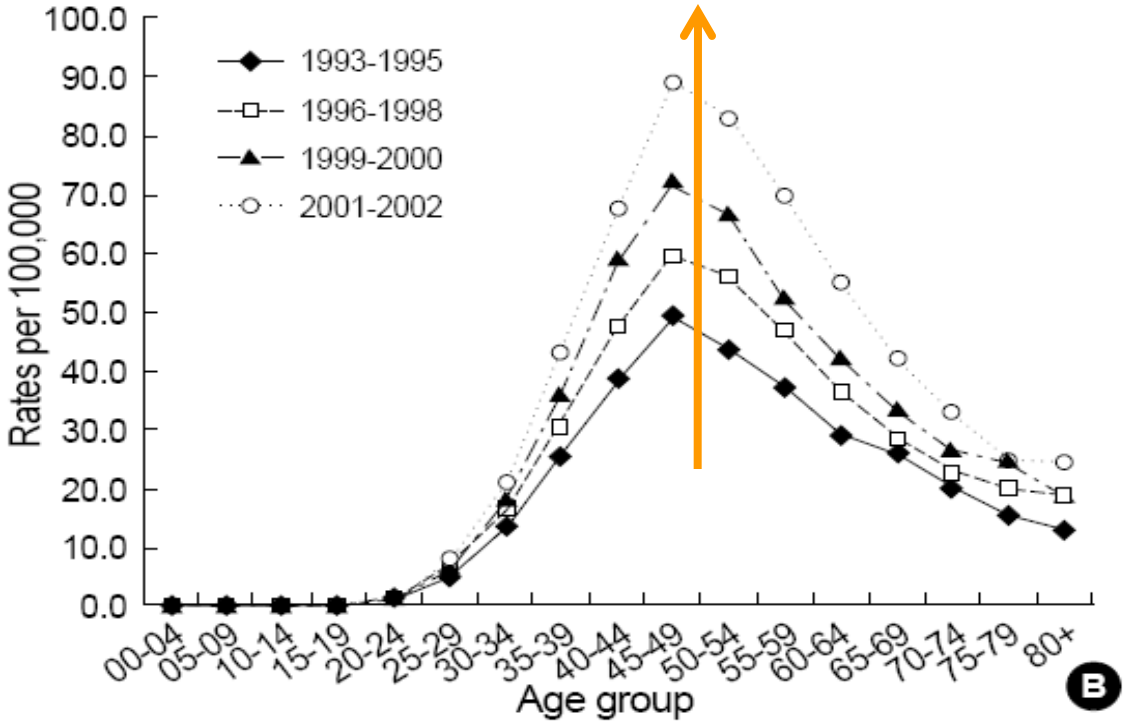
Incidence trends of female breast cancer in 1993-2002, Korea



(A)Incidence trends of female invasive breast cancer and CIS by year of diagnosis



(B) Age-specific incidence rates of female invasive breast cancer by time period of diagnosis

J Korean Med Sci 2007; 22 (Suppl): S11-6

ER/PR Status in US by ethnic group

Unit: %

Ethnic Groups	ER+PR+	ER+PR-	ER-PR+	ER-PR-
White	63.9	12.8	3.6	19.8
Blacks	48.3	11.8	5.1	34.8
Hispanic	56.7	12.0	4.6	26.7
Japanese	65.6	12.5	4.8	17.1
Chinese	60.6	11.7	5.1	22.6
Korean*	46.5	12.8	4.7	36.1
Filipino	60.2	11.6	4.9	23.3

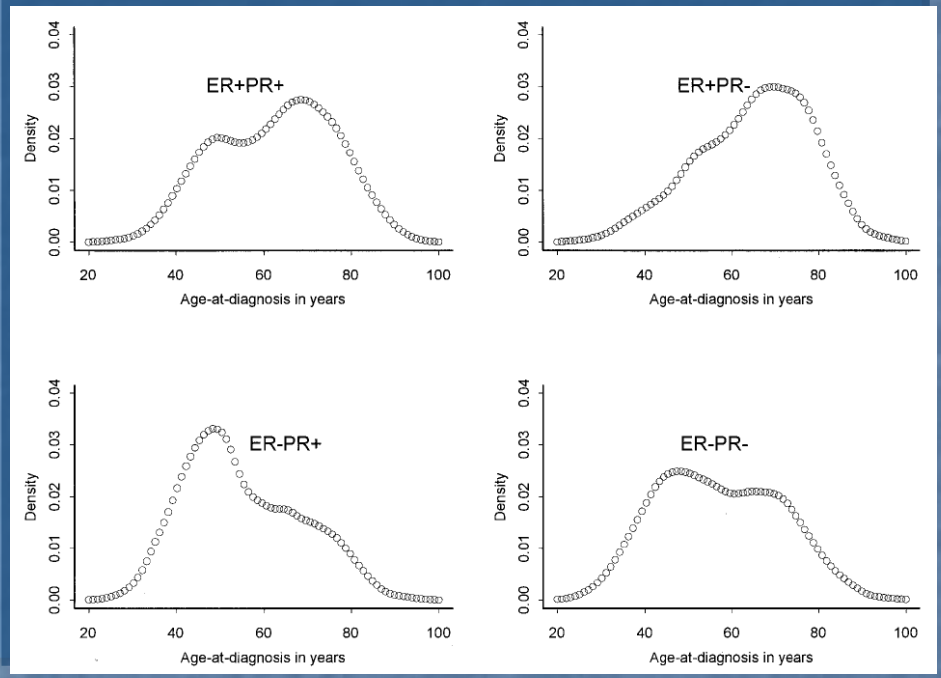


Fig. Age frequency density plot

Chu et al. Cancer 2001;92:37-45

*Li et al. Cancer Epidemiol Biomarkers Prev 2002;11:601-7

Figure from Anderson et al. JCO 2001;19:18-27

ER/PR Status

28,210 Korea Breast Cancer Society, 1992-2006

ER/PR	ER+	ER-	Total
PR+	46.2%	7.3%	53.5%
PR-	12.5%	34.0%	46.5%
Total	58.7%	41.3%	100%

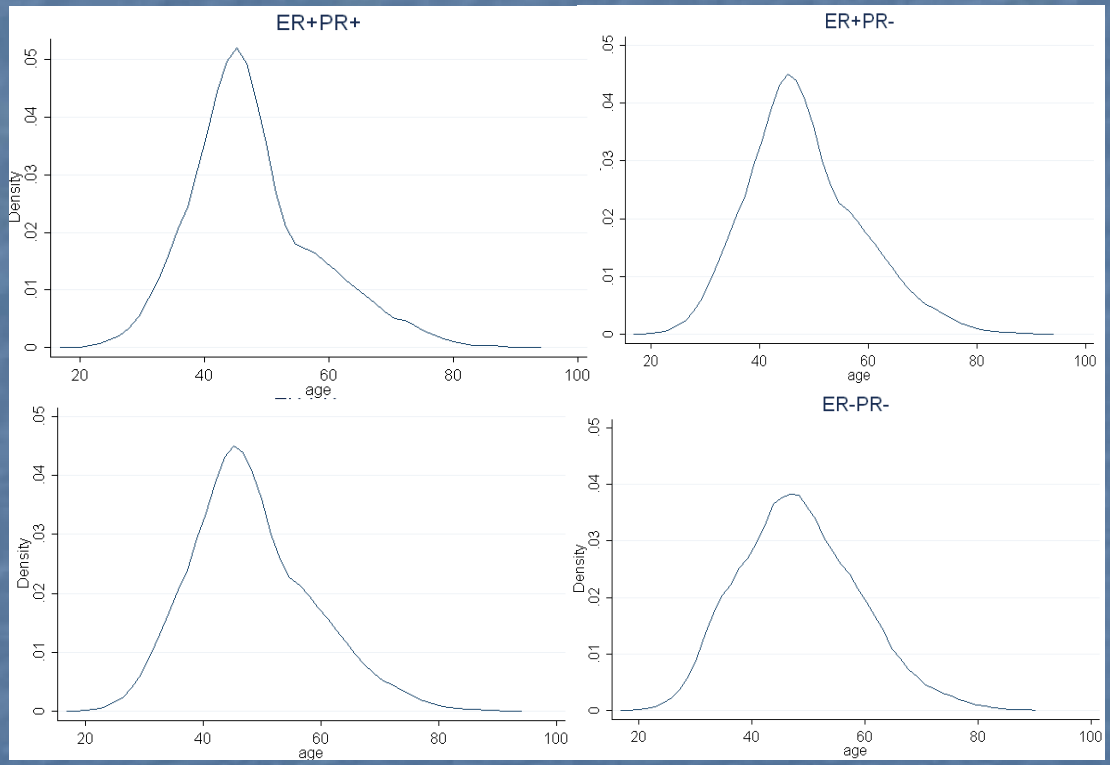
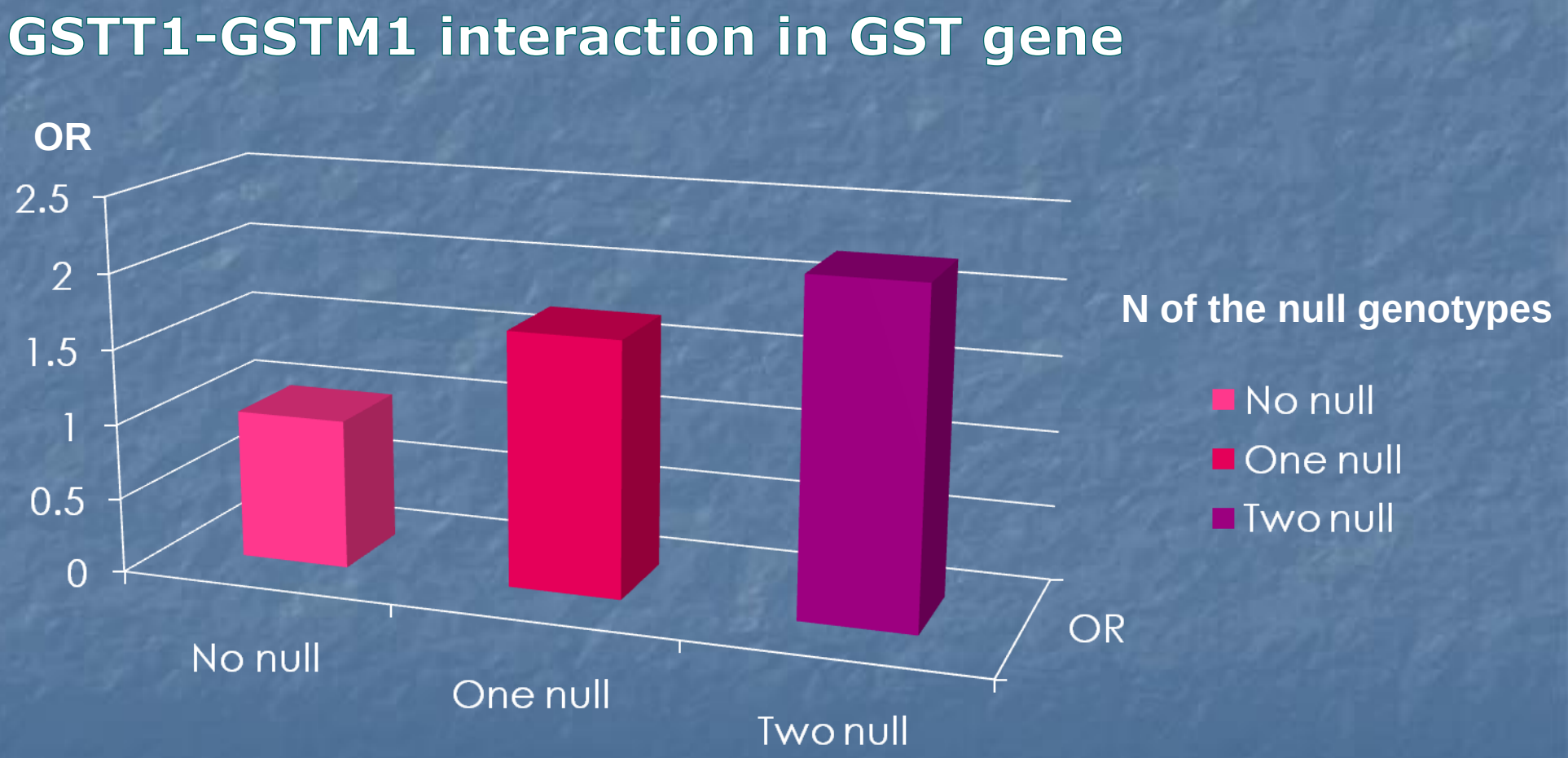


Fig. Age frequency density plot

Kim et al. presented in AACR 2009

Are There Any Differences in Genetic Polymorphisms of Breast Cancer in Korea?

SNP-SNP interaction in a gene

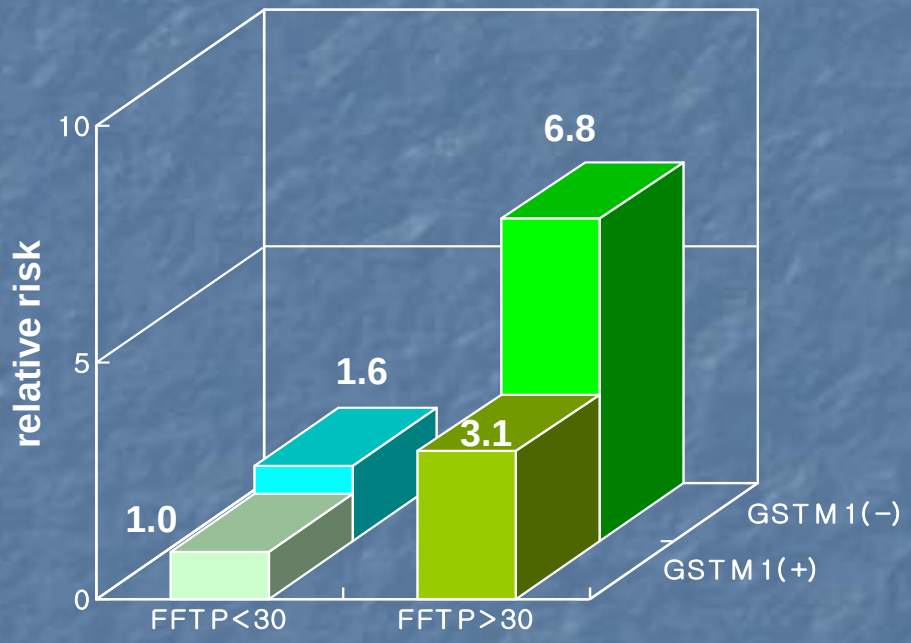


Park et al. *Pharmacogenetics* 2001

Interaction of Parity and GSTM1/T1

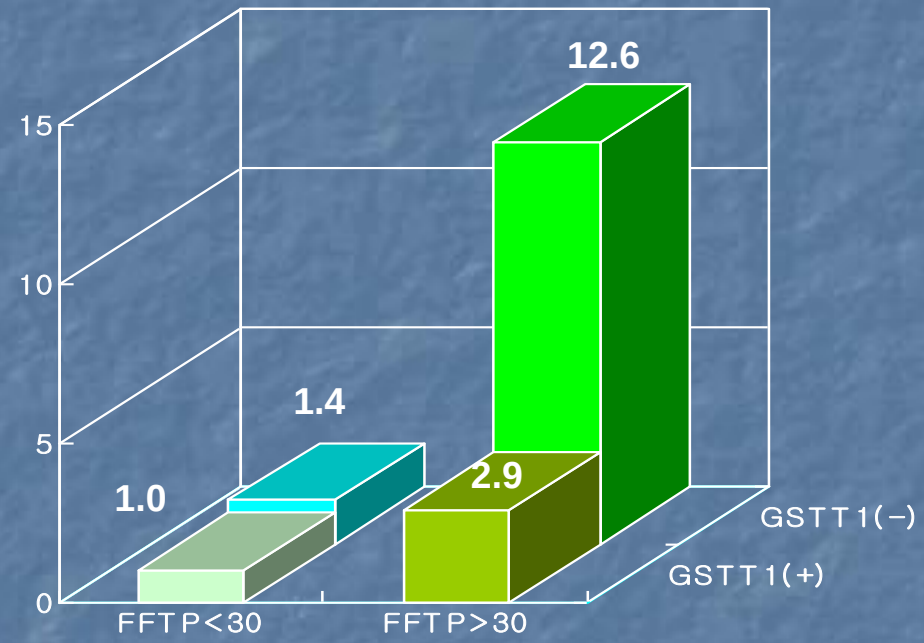
Case-control Study, Premenopausal

GSTM1



$P_{interaction}<0.01$

GSTT1

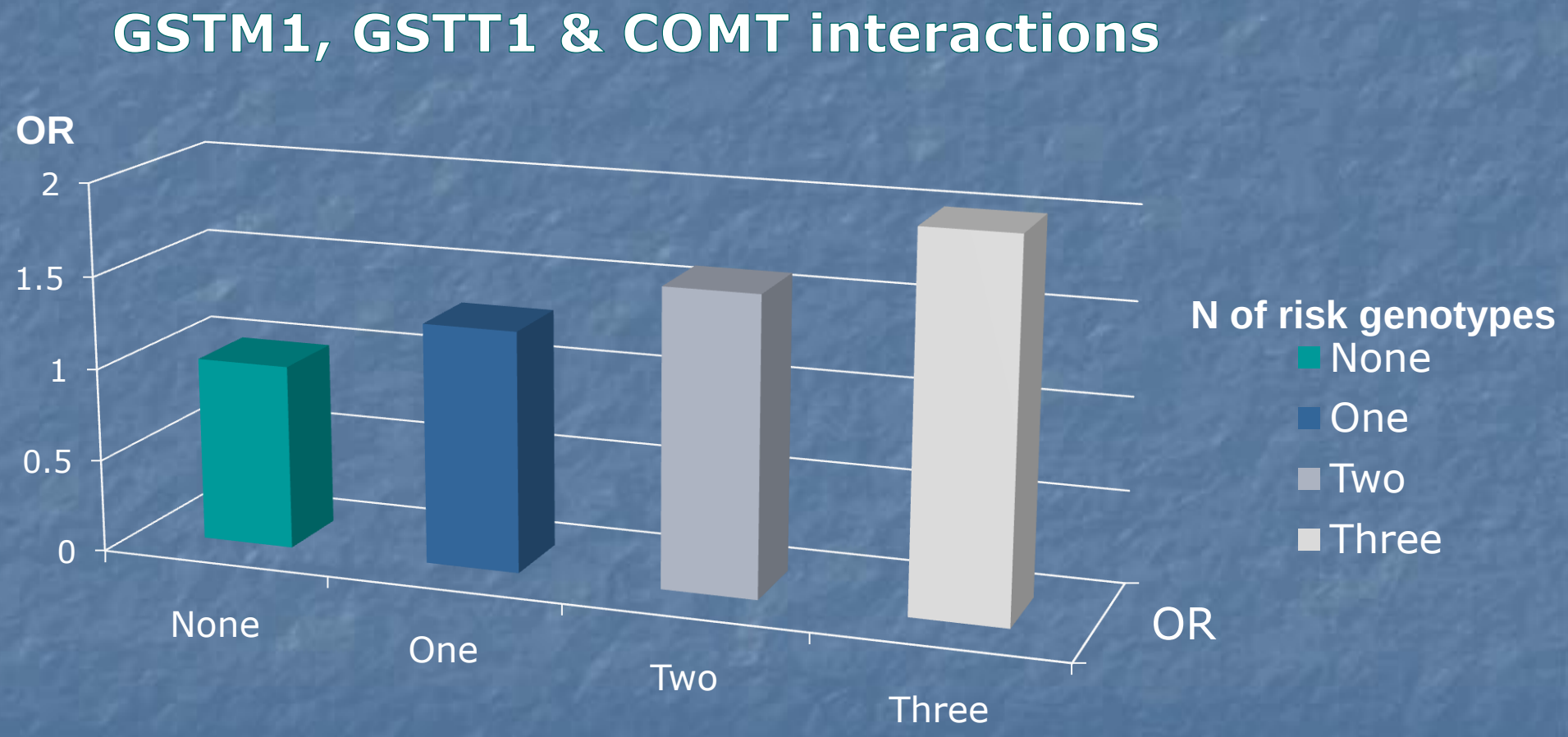


$P_{interaction}<0.01$

*FFTP : age at first full-term pregnancy

Park et al. Breast Cancer Res Tr 2003

Gene-Gene interaction



Park et al. *Breast Cancer Res Tr* 2004

Interaction between CYP2E1 Genotypes and Alcohol Consumption for Breast Cancer

Alcohol consumption	*CYP2E1*	
	c1/c1	c1/c2 or c2/c2
< 1/month	1.0	0.7 (0.48-1.09)
≥ 1/month	1.1 (0.70-1.80)	1.9† (0.99-3.83)

†p for interaction=0.043

Choi et al. Pharmacogenetics, 2003

Interaction between CYP19 Genotypes and Alcohol Consumption for Breast Cancer

Alcohol consumption	*CYP19*	
	Arg/Arg [No. cases/controls]	Arg/Cys or Cys/Cys [No. cases/controls]
< 1/month	1.0 (reference)[a] [111/134]	1.2 (0.8-1.9) [97/95]
³ 1/month	1.1 (0.7-1.9) [39/42]	3.3 (1.7-6.5)[b] [41/17]

[a]Odds ratios were adjusted for age, education, body-mass index, family history of breast cancer, age at first full-term pregnancy, and duration of breast feeding:
[b]*P* for interaction=0.044.

Lee et al. Brit J Cancer 2003

DNA Repair Genes

category	genes
direct repair	*AGT (MGMT)*
BER (base excision repair)	*XRCC1, hOGG1, LIG4, APE, TDG, UDG*
NER (nucleotide excision repair)	*ERCC2/4, ERCC1, ERCC5, XPC*
DSBR (double-strand break repair)	*XRCC3, ATM, XRCC2, XRCC4, XRCC6, LIG4, RAD51/52*
mismatch repair	*hPMS1/2, hMLH1, hMSH2/3, hMSH6*

Interaction between *ATM* Diplotype and Folate Intake in Breast Cancer Risk

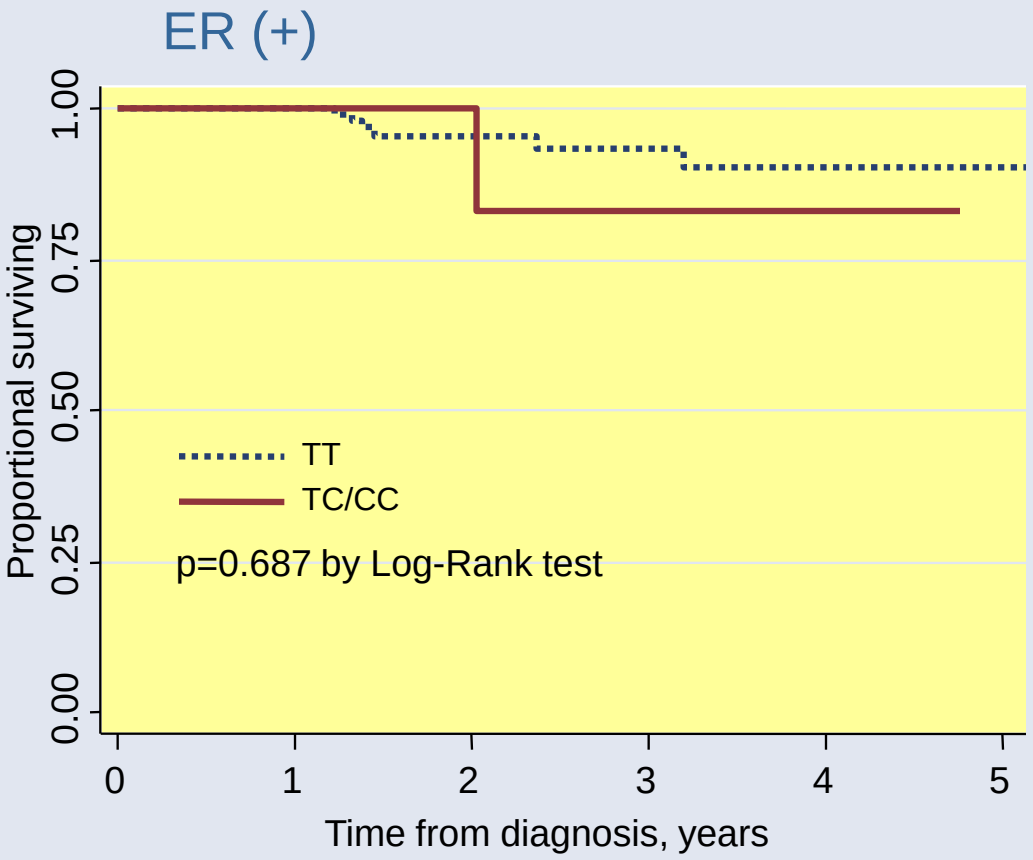
	ATM diplotype [a,b]	
Folate intake	**[ATTGT:ATTGT]**	**[ATTGT:others] & [others:others]**
≥111 µg/day	**1.0 (ref.)**	**1.1 (0.6-2.0)**
<111 µg/day	**0.8 (0.3-1.9)**	**1.9 (1.0-3.7)**

[a]Composed of five polymorphic sites: -5144A>T, IVS21+1049T>C, IVS3355T>C, IVS34+60G>A, and 3393T>G

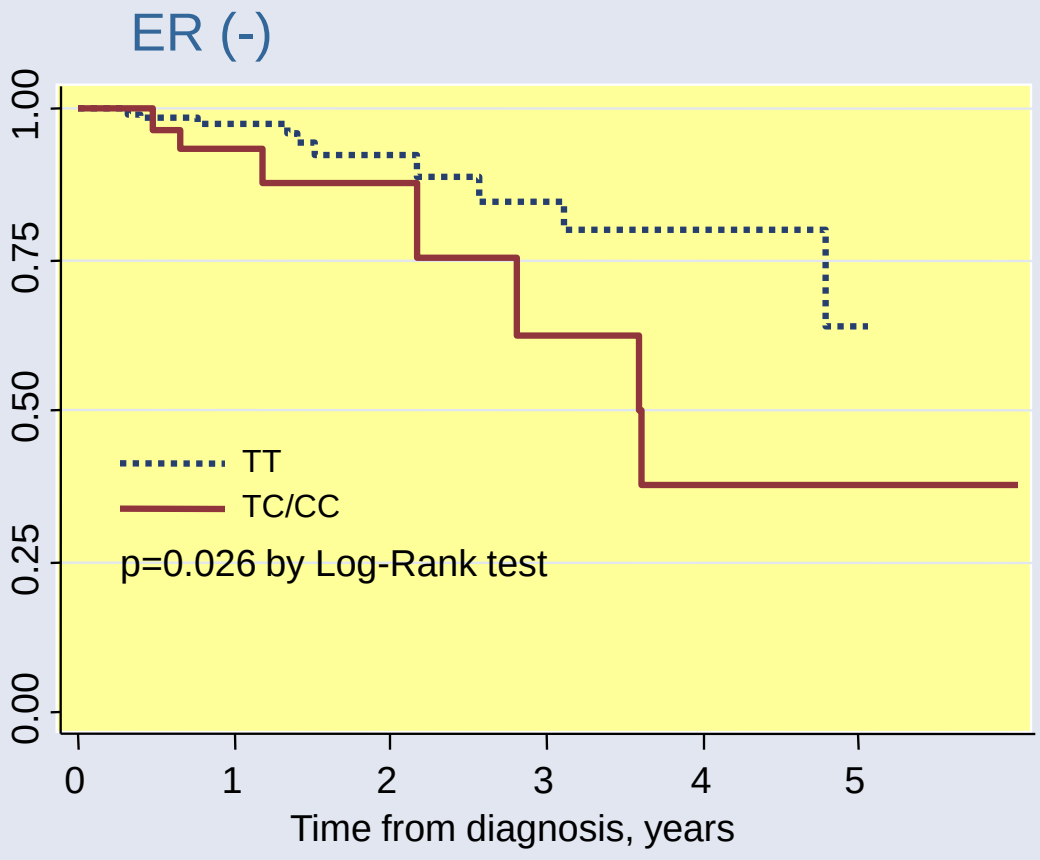
[b]Odds ratios adjusted for age, education, body-mass index, family history of breast cancer, age at first full-term pregnancy, and duration of breast feeding

Lee et al. Cancer Epidemiol Biomarkers Prev 2005

Disease Free Survival of Breast Cancer
by SULT1E1 genotypes IVS4-1653 T>C



TC/CC vs. TT, HR=1.8 (95% CI=0.21-15.69)



TC/CC vs. TT, HR=3.3 (95% CI=1.21-9.07)

Choi et al. Cancer Epidemiol Biomarkers Prev 2005

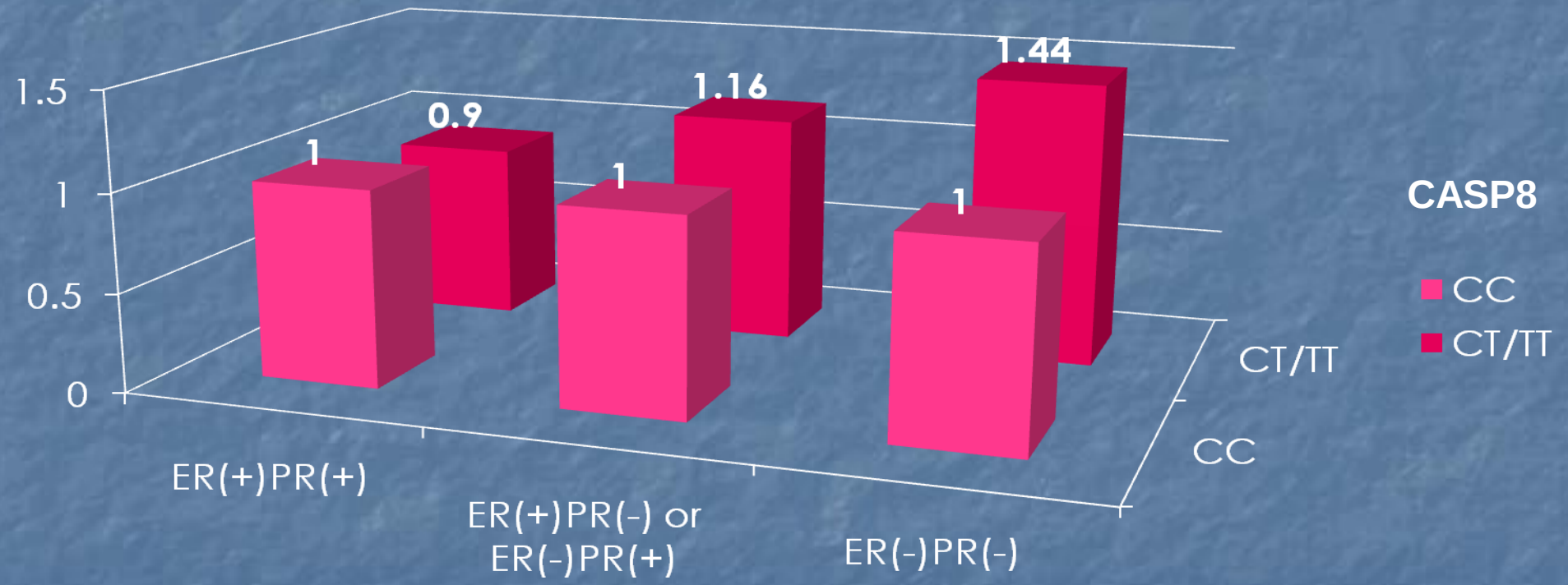
CASP8 polymorphisms, estrogen and progesterone receptor status, and breast cancer risk

- Study size
  - Enrolled from 2001-2005
  - 1,599 cases and 1,536 controls
- Role of CASP8
  - Location (band 2q33-34) has been known to be involved in tumorigenesis with loss of heterogeneity (LOH) in a number of human cancers
- Results
  - 5'-UTR T allele and breast cancer risk was prominent in ER(+) and PR(+) pre-menopausal women, whereas the association was found prominent in ER(−) or PR(−) cases among post-menopausal women.

Han et al. Breast Cancer Res Treat 2008;110:387-93

[Gene-Pathological marker] interaction

[CASP8 - estrogen and progesterone receptor] for breast cancer risk



Han et al. Breast Cancer Res Treat 2008;110:387-93

Genome Epidemiologic Studies on Breast Cancer at Seoul National University (since 2000)

GST M1/T1 & alcohol	Pharmacogenetics (2000)
COMT	Pharmacogenetics (2001)
XRCC1/3	Pharmacogenetics (2002), Breast Cancer Res Tr (2007)
GST & reproductive Factors	Breast Cancer Res Tr (2002)
CYP2E1/ALDH2	Pharmacogenetics (2003)
hOGG1	Breast Cancer Res Tr (2003)
Cytochrome P450-19/1B1/1Aa	Br J Cancer (2003), Exp Mol Med (2006)
ER-alpha	Breast Cancer Res Tr (2003)
TGF-β1 & TNF-β	Breast Cancer Res Tr (2005)
ATM	CEBP (2005)
SULT1A1 & SULT1E1	CEBP (2005)
ERCC2 / ERCC4	Exp Mol Med (2005)
IL-1β & IL-1RN	Breast Cancer Res Tr (2006)
eNOS, hormone receptor	Breast Cancer Res Tr (2006)
HIF 1-A	Clinica Chimica Acta (2008)
DNA repair genes	Asian Pacific J Cancer Prev (2008)
Innate immunity genes	Carcinogenesis (2009)
common SNiPs	J Natl Cancer Inst (2006)
CASP8	Nature Genetics (2007)
Genome-wide Association	Nature (2007)
XRCC3 Thr241Met	Breast Cancer Res Tr (2007)
Five SNiPs	CEBP (2008)

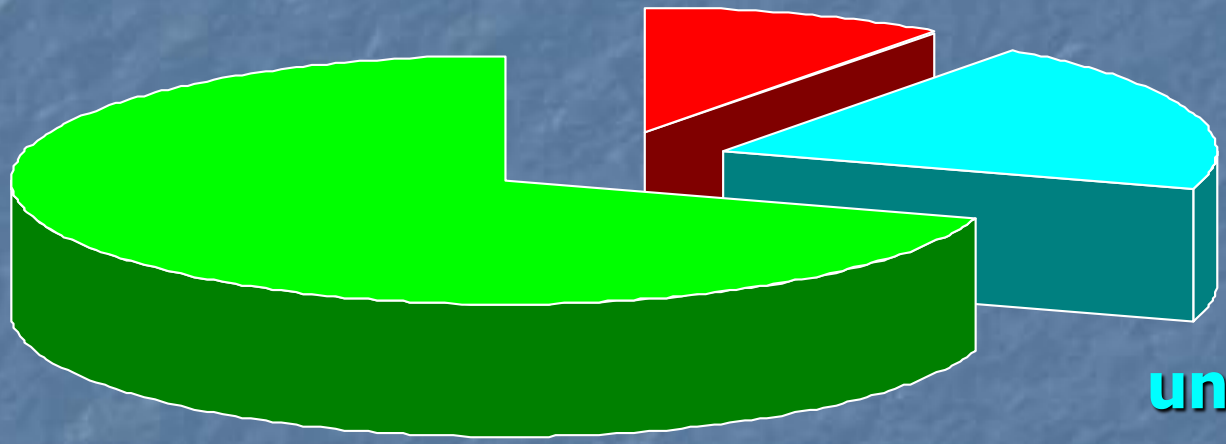
Breast Cancer Association Consortium

How much is explained about breast cancer?

inherited 5~10%(?)

environmental

45-50%



unknown

KOJACH: KOrea / JApan / CHina

Workshop of KOJACH-I, II Cooperative Studies on Cancer

Risk and Protective Factors for Breast and Colorectal Cancer

Beijing Guangxi Hotel,
Beijing, China
October 10th, 2008

Supported by
Grant-in-Aid for Scientific Research on Special Priority Area, MEXT, Japan, 2000-2009

General information of KOJACH-I, II cooperative studies

Chairperson: Yoon-OK Ahn (Korea)

Progress report of KOJACH Study — K Tajima

KOJACH-I Study

Chairperson: K-Y Yoo (Korea), C-M Gao (China)

Risk factors for colorectal cancer in Japan — T Kawase & K Matsuo
Risk factors for colorectal cancer in Korea — D-H Kim & Y-O Ahn
Risk factors for colorectal cancer in Chongqing — Z-Y Zhou & J Cao

KOJACH-II Study

Chairperson: H Tanaka (Japan), J Cao (China)

Risk factors for breast cancer in Japan — K Matsuo & H Tanaka
Risk factors for breast cancer in Korea — S-K Park, Y-J Kim & K-Y Yoo
Risk factors for breast & colorectal cancer in Nanjing — J-H Ding & C-M Gao

Business Meeting — Chairperson: K Tajima (Japan)

Achievement in Breast Cancer Research SNUMC Group, 2006-2009

[Breast Cancer Statistics]

Ahn et al. Chronological changes of clinical characteristics in 31,115 new breast cancer patients among Koreans during 1996-2004. Breast Cancer Res Tr 2006;99:209-14 【IF=4.671】

Lee et al. Population-based breast cancer statistics in Korea during 1993-2002. Incidence, mortality, and survival. J Korean Med Sci 2007;22(suppl):S11-6 【IF=0.725】

Yi et al. Evaluation of the satisfaction and usefulness of a web-based educational program for breast cancer patients. The Open Medical Informatics Journal 2008;2:129-137 【IF=】

Achievement in Breast Cancer Research SNUMC Group, 2006-2009

[Sero-Epidemiological C-C Study]

Kim et al. Dose-dependant protective effect of lactation against breast cancer in ever-lactated women in Korea. Dose-dependent protective effect of breast-feeding against breast cancer among ever-lactated women in Korea. Eu J Cancer Prev 2007;16(2):124-9 【IF=1.993】

Kim et al. Serum high-density lipoprotein cholesterol and breast cancer risk by menopausal status, body mass index and hormonal receptor in Korea. Cancer Epidemiol Biomarkers Prev 2009;18(2):508-15 【IF=4.642】

Kim et al. Dietary factors and breast cancer in Korea: ecological study. Breast J 2010 (accepted) 【IF=1.739】

Park et al. Intrauterine environments and breast cancer risk: Meta-analysis and systematic review. Breast Cancer Res 2008 Jan 21;10(1):R8【IF=4.157】

Yang et al. Effects of bisphenol A on breast cancer and its risk factors. Arch Toxicol 2009;(doi: 10.1007/s00204-008-0364-0)【IF=1.756】

Achievement in Breast Cancer Research
SNUMC Group, 2006-2009

[Molecular Epidemiology]

Lee et al. Genetic polymorphisms of interleukin-1 beta (IL-1B) and IL-1 receptor antagonist (IL-1RN) and breast cancer risk in Korean women. Breast Cancer Res Tr 2006;96(2):197-202【IF=4.671】

Kim et al. Genetic polymorphisms of Ataxia Telangiectasia Mutated affect lung cancer risk. Human Molecular Genetics 2006;15(7):1181-6【IF=8.099】

Choi et al. Genetic polymorphisms of eNOS, hormone receptor status, and survival of breast cancer. Breast Cancer Res Tr 2006;100:213-8【IF=4.671】

Shin et al. Cytochrome P450 1A1(CYP1A1) polymorphisms and breast cancer risk in Korean women Exp Mol Med 2007;39(3):361-6【IF=2.296】

Lee et al. Genetic polymorphism of XRCC3 Thr^{241}Met and breast cancer risk: case-control study in Korean women and meta-analysis of 12 studies. Breast Cancer Res Treat 2007;103(1):71-6【IF=4.671】

Lee et al. Genetic polymorphisms of NOS3 are associated with the risk of invasive breast cancer with lymph node involvement. Breast Cancer Res Tr 2007;106:433-8【IF=4.671】

Han et al. *CASP8* polymorphisms, estrogen and progesterone receptor status and breast cancer risk. Breast Cancer Res Tr 2008;110(2):387-93【IF=4.671】

Lee et al. Candidate gene approach evaluates association between innate immunity genes and breast cancer risk in Korean women. Carcinogenesis 2009; 10.1093/carcin/bgp084【IF=5.406】

Achievement in Breast Cancer Research SNUMC Group, 2006-2009

[Breast Cancer Association Consortium (BCAC)]

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 【IF=15.271】

Cox et al. A common coding variant in *CASP8* is associated with breast cancer risk. Nature Genet 2007;39(5):352-8 【IF=24.176】

Easton et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007 ;447(7148):1087-93 【IF=26.681】

Gaudet et al. Five polymorphisms and breast cancer risk: Results from the Breast Cancer Association Consortium. Cancer Epidemiol Biomarkers Prev 2009; (accepted) 【IF=4.642】

Ahmed et al. Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2. Nature Genet 2009; (published online XX XX 2009; doi:10.1038/ngXXXX) 【IF=25.556】

Udler et al. FGFR2 variants and breast cancer risk: fine-scale mapping using African American studies and analysis of chromatin conformation. Hum Mol Genet 2009 (accepted) 【IF=7.806】

Milne et al. Risk of estrogen receptor positive and negative breast cancer and SNP rs13387042 on 2q35. J Natl Cancer Inst 2009; (accepted 13/05/2009). 【IF=15.271】

Collaborative Research Works on Breast Cancer Epidemiology since 1991

- Descriptive epidemiologic studies [0 / 10]
- Risk factor analysis of breast cancer [3 / 14]
- Risk factors of BC according to ER and PR status [3 / 6]
- Molecular genetic study on breast cancer [3 / 41]
- Differences in risk factors of colon cancer by subsite [1 / 2]
- Cancer control strategy and cancer prevention [2 / 9]

[collaborative / total published]

The breast that has never lactated is more liable to become cancerous (JE Lane-Claypon, 1926).

1911

2009


感謝합니다!
Thank You for Your Attention!