한국지질동맥경화학회, 부산 BEXCO, 2010년 4월16일

Dietary intake of folate, vitamin B2, vitamin B6, vitamin B12, genetic polymorphism of related enzymes, and risk of breast cancer: a case-control study in Korea

KIM Mi Kyung

Cancer Epidemiology Division,

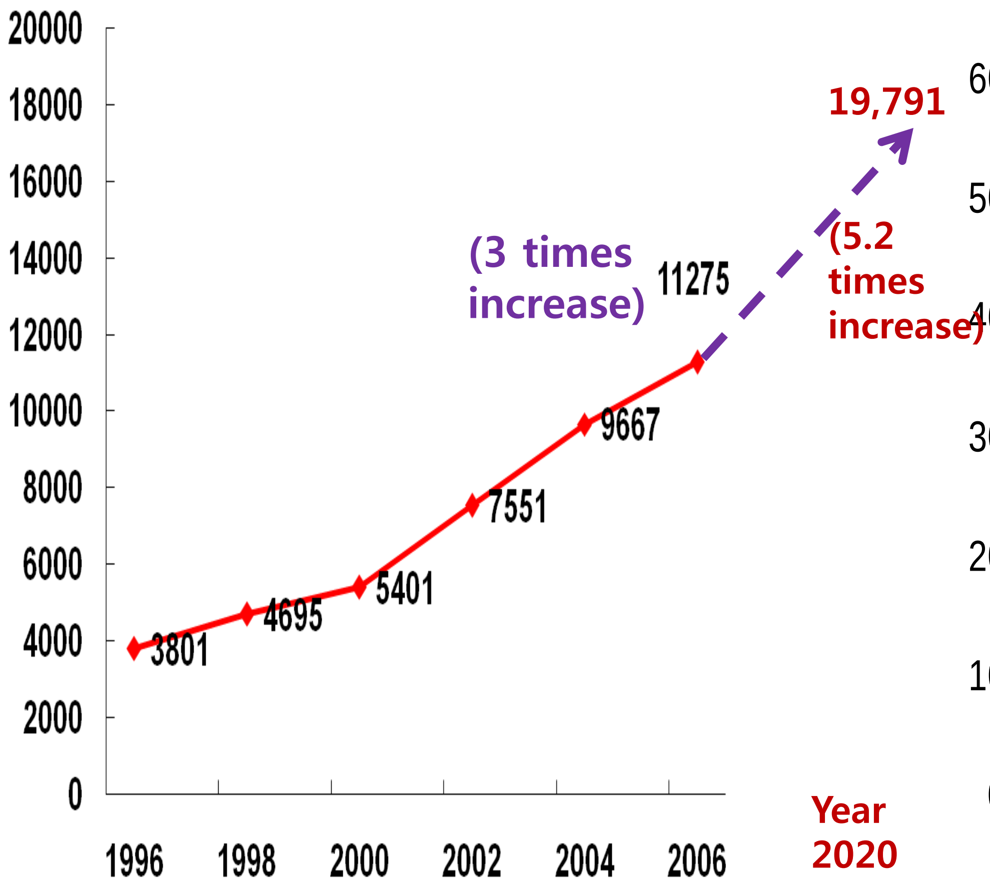
National Cancer Center

Outline of the talk

1. Breast cancer in Korea
2. Diet as a cause of breast cancer
3. Folate and breast cancer
4. Common variation of folate-metabolizing gene in breast carcinogenesis
5. Interaction of folate and folate-metabolizing gene in breast carcinogenesis
6. Is folate good for everyone?

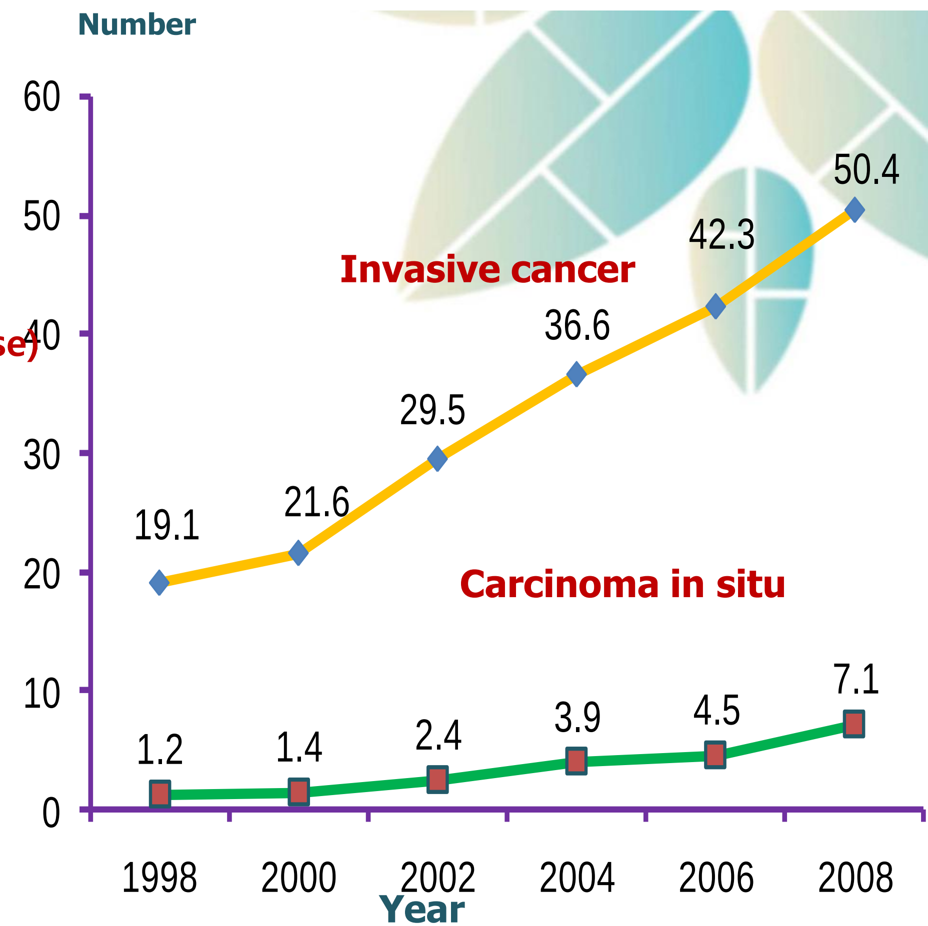
Epidemiology of Breast Cancer in Korea

Number of new breast cancer patients



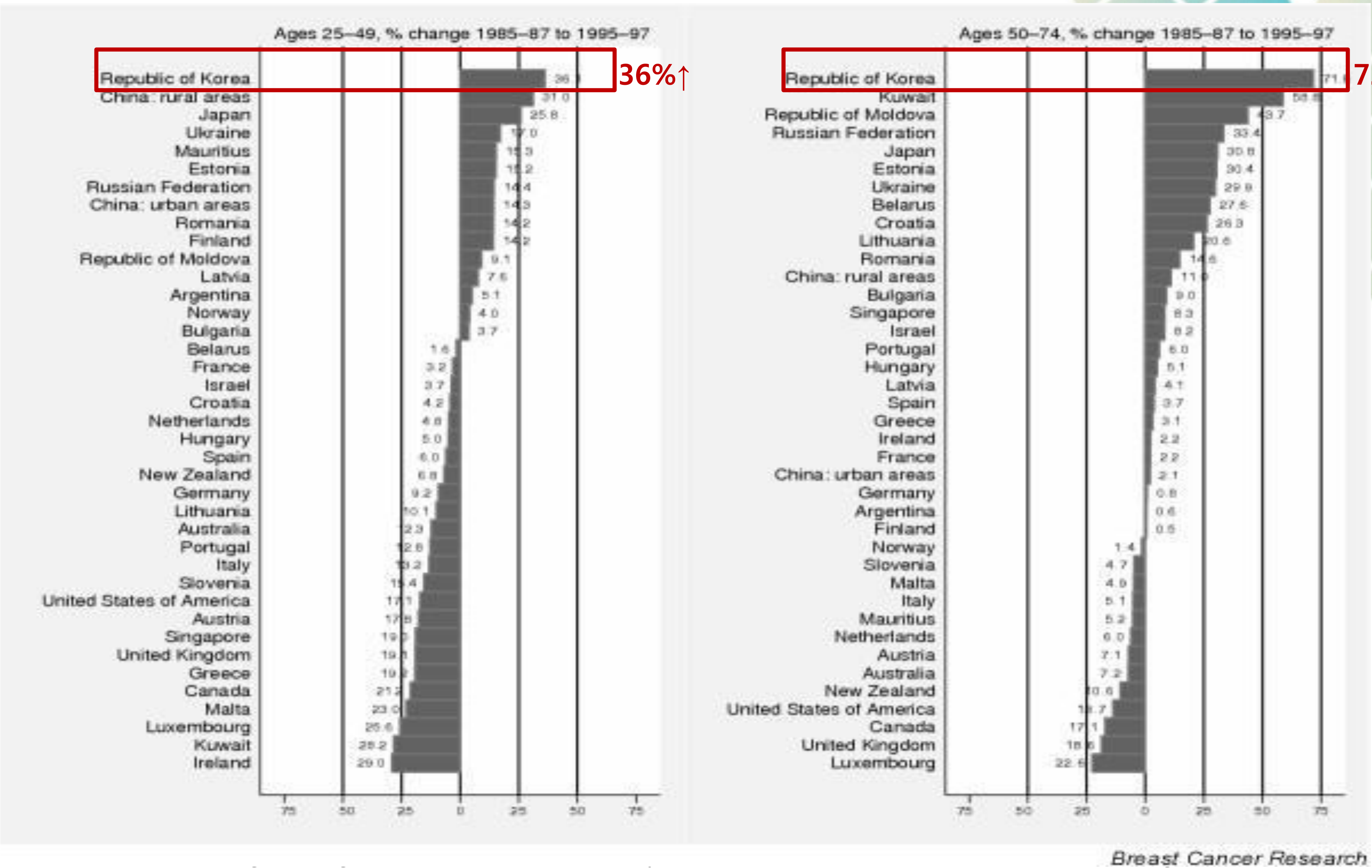
Korean Breast Cancer Society:Choi YH, JBC, 2005

Crude Incidence of Breast Cancer



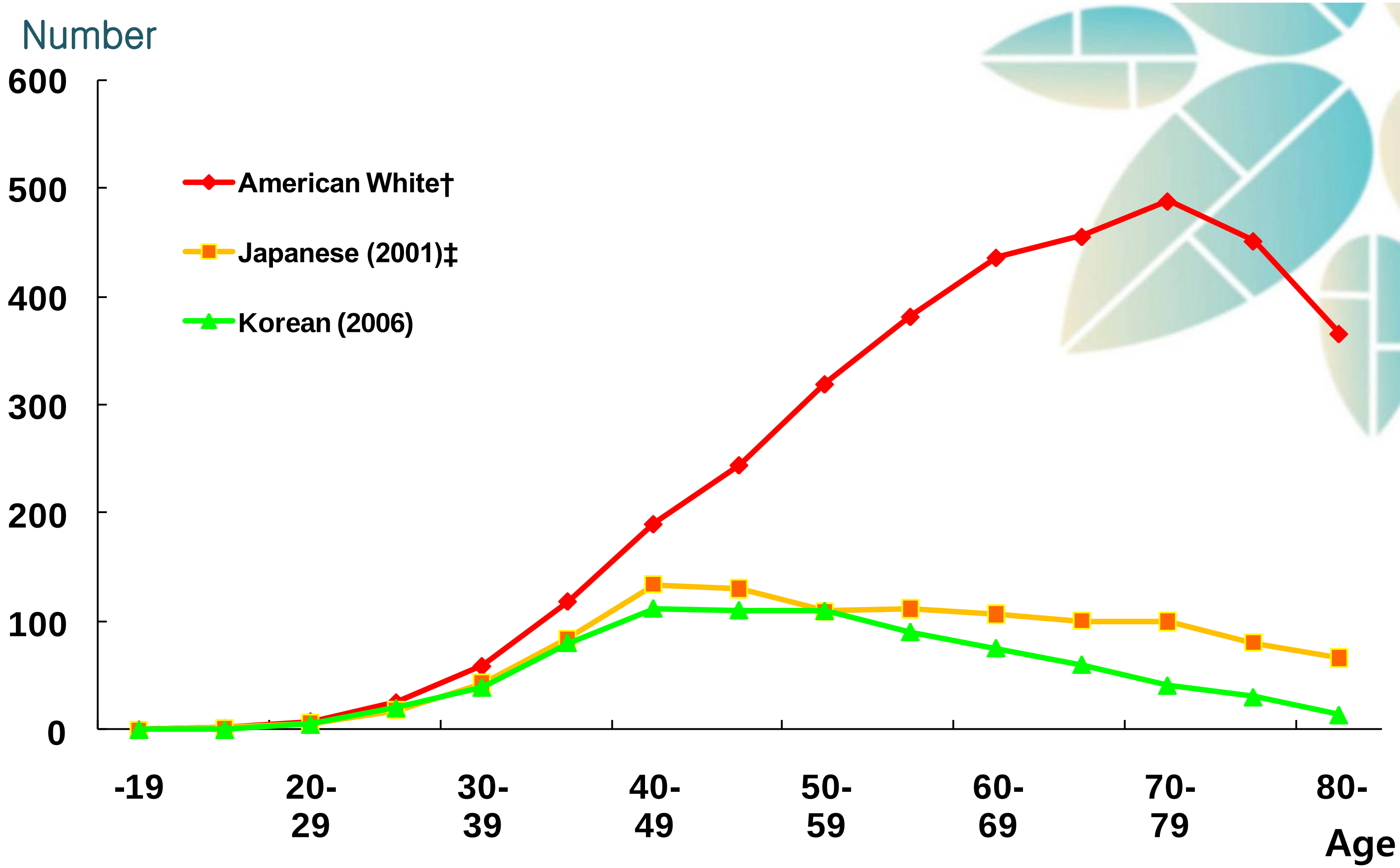
patients number per 100,000 women

% of change in breast cancer mortality between1985~87 and 1995~97



25–49 years in selected countries worldwide, sorted by descending order of magnitude of the change (earlier period is 1988–90 for China, later period is 1994–96 for Argentina). Source: http://www-depdb.iarc.fr/who/menu.htm.

Age-specific Crude Incidence* of USA, Japan and Korea

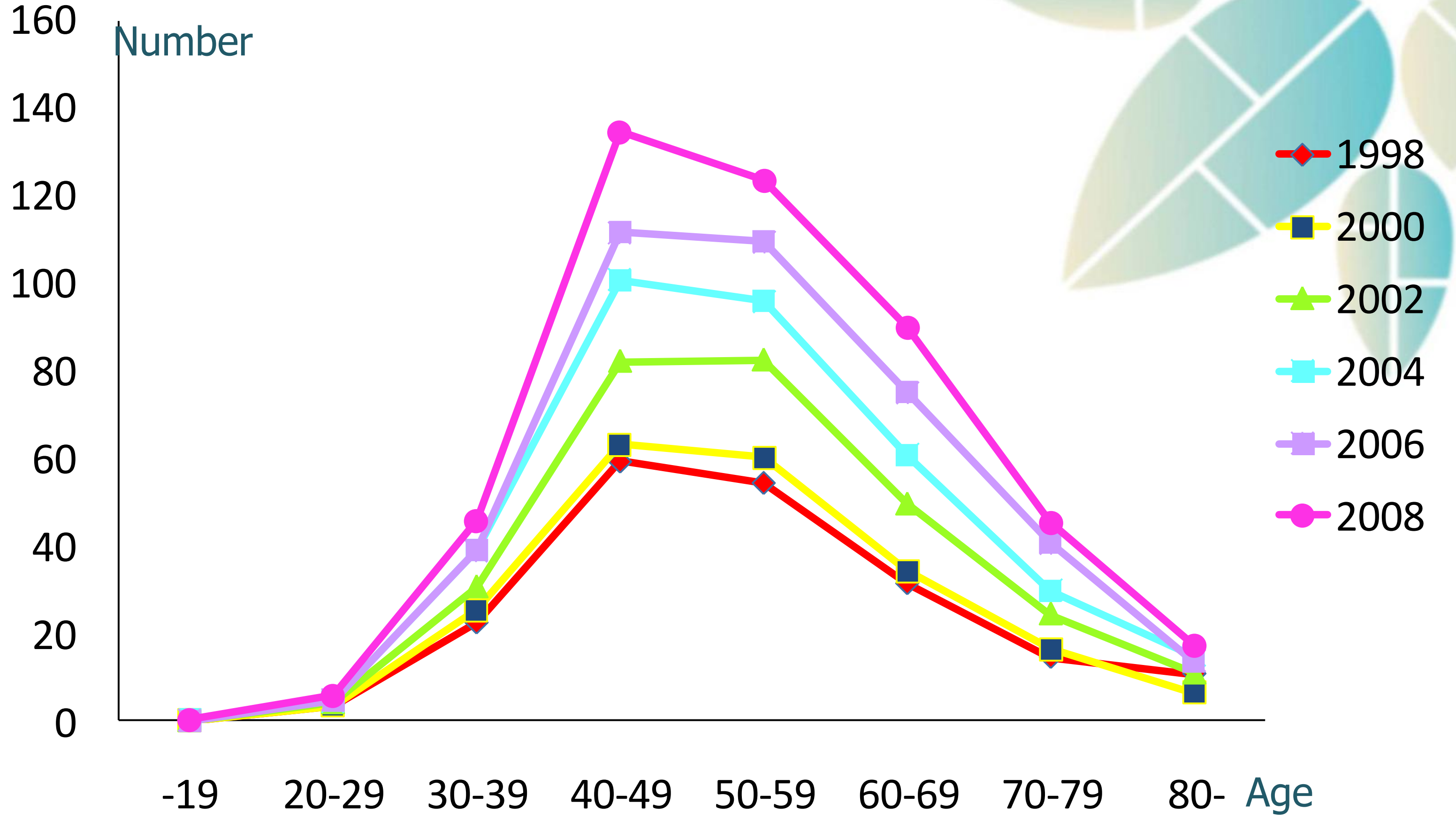


* patients number per 100,000 women

† SEER 17 data (2001-2004)

‡ Cancer statistics in Japan (2007)

Age-specific Crude Incidence* of Korean Female Breast Cancer



* Patients with Invasive ductal carcinoma and Ductal carcinoma in-situ patients number per 100,000 women

Food, Nutrition and the Prevention of Cancer: a Global Perspective, World Cancer Research Fund, American Institute for Cancer Research, **2007**

Risk and protective environmental factors of breast cancer

Evidence level	Reproductive /hormonal	Lifestyles	Others
Established	Early menarche Late menopause Nulliparity Later first fullterm pregnancy	Obesity **Alcohol consumption**	Family history of breast cancer
Probable	Breast feeding Number of fullterm pregnancy Hormonal replacement therapy Recent oral contraceptive use	Physical activity **Fruit and vegetable consumption** Smoking NSAID use **High saturated fat and well-done meat intake**	Ionizing radiation

J Kor Med Assoc 2009; 52(10): 937-945

Causes of cancer (IARC)

Causes	% of all cancers
Tobacco	15-30%
Chronic infections	10-25%
Nutrition	30%
Occupational factors	< 5%, each
Genetic factors	
Reproductive factors	
Alcohol drinking	
Environmental pollution	3%, each
Solar & ionizing radiations	

Cancer Deaths Avoidable by Dietary Change

Type of cancer	Deaths%[a]	Percent avoidable	
		Doll-Peto, 1981	Willett, 1994
Lung	28	20	20 (10-30)
Colon/rectum	11	90	70 (50-80)
Breast	8	50	50 (20-80)
Prostate	7	(with other)	75 (20-80)
Pancreas	5	50	50 (10-50)
Stomach	5	35	35 (30-70)
Endometrium	1	50	50 (50-80)
Gallbladder	1	50	50 (50-80)
Larynx, cervix, mouth, esophagus	6	20	20 (10-30)
Other types	28	10	10
Overall estimate		35	32 (20-42)

[a] Percent estimated deaths, 1993.

Doll & Peto, JNCI, 1981; Willett W, Environ Health Perspect 103:165-70, 1995

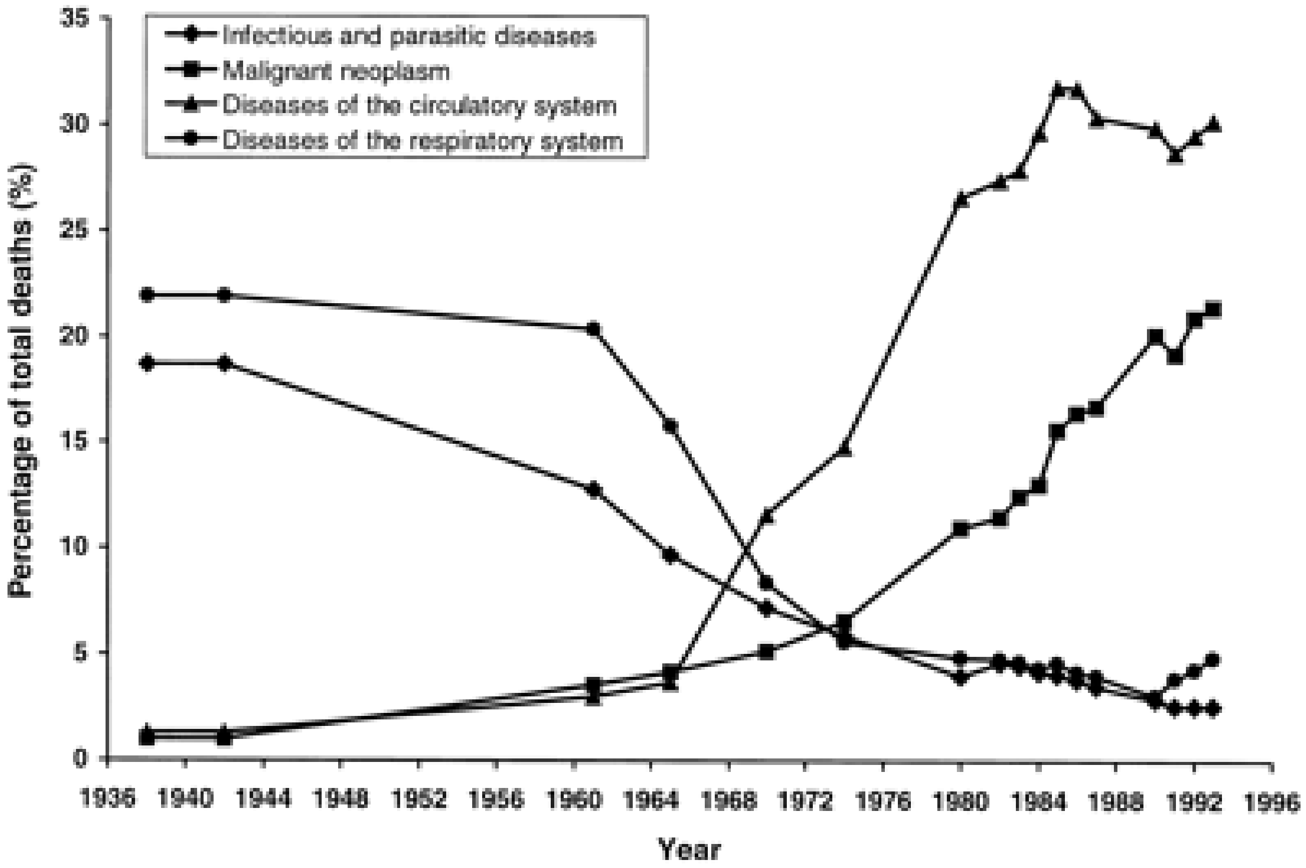
한국인 유방암의 원인(위험요인)은?

Risk and protective environmental factors for breast cancers in Korea

Risk and preventable factors for breast cancer	Minimum to maximum relative risk
Established factors, reported in Korea	
Reproductive/hormonal	
Late menarche	0.2~0.8
Later menopause	1.4~6.3
Nulliparous women	1.3~2.0
Later age of the first full-term pregnancy	1.2~4.1
Lifestyles	
Obesity among postmenopausal women	1.1~2.0
Alcohol consumption	1.2~2.3
Family history of breast cancer	
- the first relatives	7.9
- first and second degree	1.5~2.3
Probable factors in Korea	
Breast feeding	0.2~0.8
Exercise	0.3~1.0
Cigarette smoking	1.3~3.2
Fruit and vegetable consumption	0.6 (graph, tomato, soybean)
Probable factors in Western population but not significant in Korea	
Hormonal replacement therapy in postmenopausal women	1.0
Paternal age	1.0~1.6
Not reported factors in Korea	
High saturated fat and well-done meat intake	not reported in Korea
Birth weight	1.0~1.5
Ionizing radiation	0.7~1.1
Aspirin	0.8~1.1

J Kor Med Assoc 2009; 52(10): 937-945

Health & Nutrition Transition in Korea



Source: Kim S, AJCN, 2000

Changes of dietary life in KOREA

The story is not over…..

Dietary agents with anti-cancer properties


Artichoke (Silymarin)


Oleander (Oleanderin)


Tomato (Lycopene)


Garlic (Diallyl sulfide, ajoene, S-allyl cysteine, allicin)


Carrots (β-carotenes)


Tea (Catechins)


Red grapes (Resveratrol)


Red chilli (Capsaicin)


Turmeric (Curcumin)


Cloves (Eugenol & isoeugenol)


Honey-bee propolis (Caffeic acid, CAPE)


Cruciferous vegetables (Sulforaphane)


Pomegranate (Ellagic acid)


Ginger (6-Gingerol)


Basil (Ursolic acid)


Fennel, (Anethol)


Soybean (Genistein)

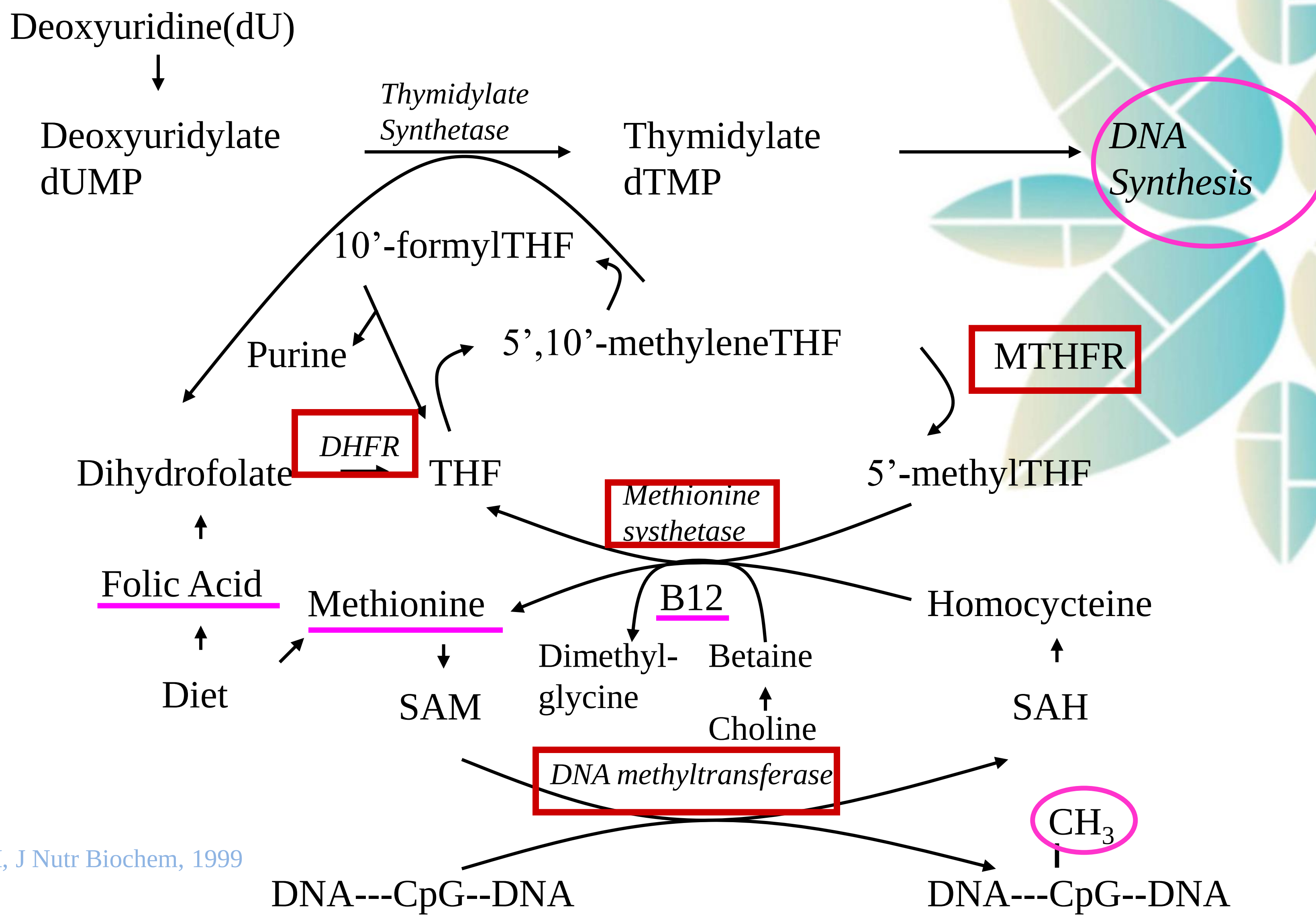

Aloe (Emodin)

Folate reduce breast cancer risk?



Folate

- Water-soluble B vitamin, one-carbon transfer
- Macrocytic anemia, neural tube defects, cardiovascular diseases, and many cancers
- Major functions of folate
  - nucleic acid synthesis
  - plays an important part in DNA metabolism
    → DNA methylation & DNA synthesis



Kim YI, J Nutr Biochem, 1999

FIGURE 1 Simplified scheme of folate involving DNA synthesis and methylation.
B12, vitamin B-12; DHFR, dihydrofolate reductase; CH_3, methyl group;
CpG, cytosine-guanine dinucleotide sequence; MTHFR, methylenetetrahydrofolate reductase;
SAH, *S*-adenosylhomocysteine; SAM, *S*-adenosylmethionine; THF, tetrahydrofolate.

Epidemiologic evidences on folate and breast cancer risk

- More than 25 epidemiologic studies suggest that diminished folate status leads to an increased risk of cancer and supplementation of folate may have a protective effect against development of cancer.

  (*JNCI 1996,2000; IJC 1999; CR2001;CCC 2003; CEBP2006*).

- Epidemiologic evidence available thus far has not been consistent, nor has it provided unequivocal support for the purported inverse relationship between folate status and breast cancer risk

Possible reasons for these discrepancies

- *Folate-Gene interactions in Breast Cancer Risk Modifications:*

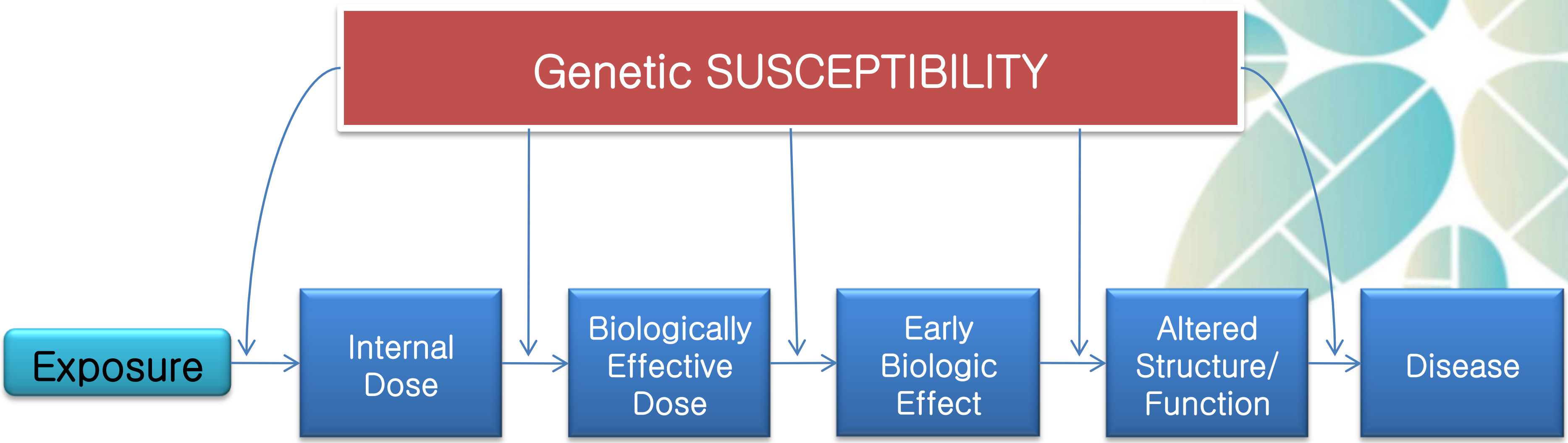
  - by polymorphisms of critical genes.

  - MTHFR, MTR, MTRR, TS etc.

- *Folate-Alcohol (or other environmental factors) interactions in Breast Cancer Risk Modifications :*

  - *alcohol: folate antagonist*

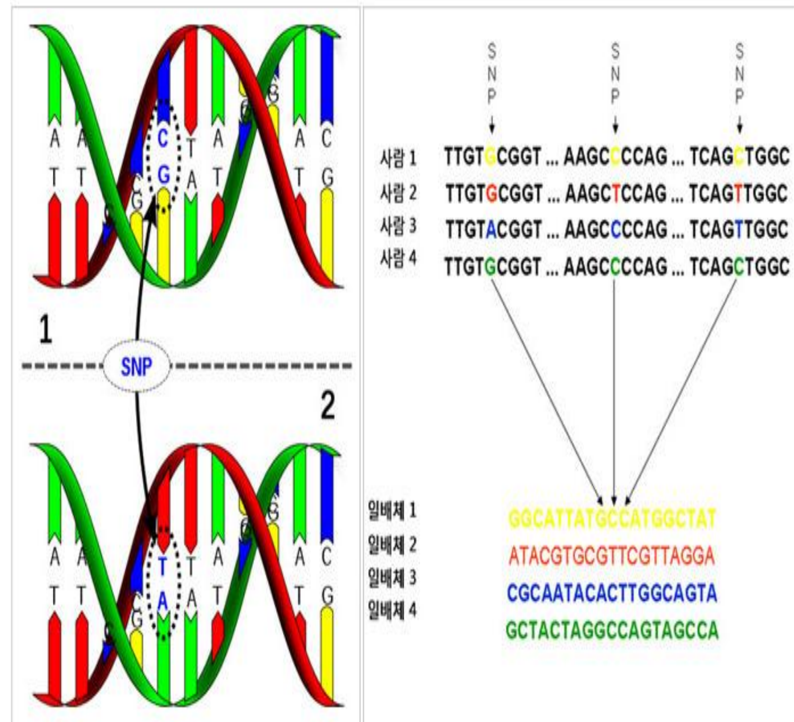
Limited Evidence in Asian countries !!



A continuum of biomarker categories reflecting the carcinogenic process resulting from xenobiotic exposures

Single Nucleotide Polymorphism (SNP)

- A tiny change in the gene sequence
  : only a single nucleotide change
- Allele frequency: 1/1000 to 1/2
  in populations
- Functional consequences:
  - alteration in protein function, thus metabolic pathway
  - alteration in promotor activity, thus metabolic pathway
  - no known alteration but association with parameter level



Vol 447 | 28 June 2007 | doi:10.1038/nature05887

Genome-wide association study identifies novel breast cancer susceptibility loci

SNPs in five novel independent loci exhibited strong and consistent evidence of association with breast cancer (P,1027). Four of these contain plausible causative genes (FGFR2, TNRC9, MAP3K1 and LSP1).

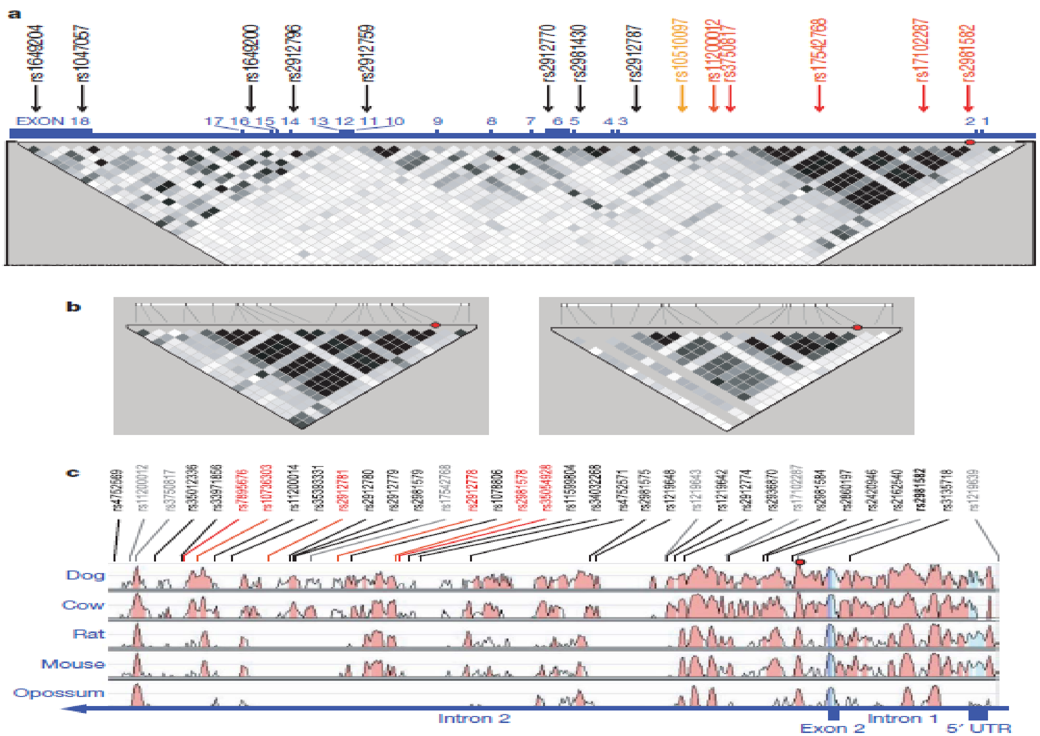


Figure 3 | The *FGFR2* locus. a, Map of the whole *FGFR2* gene, viewed relative to common SNPs on HapMap. The gene is 126 kb long and in reverse 3′–5′ orientation on chromosome 10. Exon positions are illustrated with respect to the 67 SNPs with m.a.f. > 5% in HapMap CEU (therefore the map is not to physical scale). Numbered SNPs are those tested in the genome-wide study. SNPs in black were not significant in stage 1. Those in red were significant at $P < 0.0001$ after stage 2. rs10510097 (orange) was significant in stage 1, but failed quality control in stage 2 owing to deviation from Hardy–Weinberg equilibrium. Squares indicate pairwise r^2 on a greyscale (black = 1, white = 0). Red circle indicates rs2981582. **b,** Resequenced 32 kb region, shown relative to SNPs in CEU with m.a.f. > 5%, showing pairwise LD for SNPs in HapMap CEU (left panel) and JPT/CHB (right panel). Red circle indicates rs2981582, shown in bold black. **c,** Sequence conservation of 32 kb region in five species, relative to human sequence (http://pipeline.lbl.gov/methods.shtml)[35]. Red circle indicates rs2981582. SNPs in grey are those used in the initial tagging of known common HapMap SNPs within the block. SNPs in black are correlated with rs2981582 with $r^2 > 0.6$ in European samples. Six SNPs in red were those consistent with being the causative variant on the basis of the genetic data (not excluded at odds of 100:1 relative to the SNP with the strongest association, rs7895676).

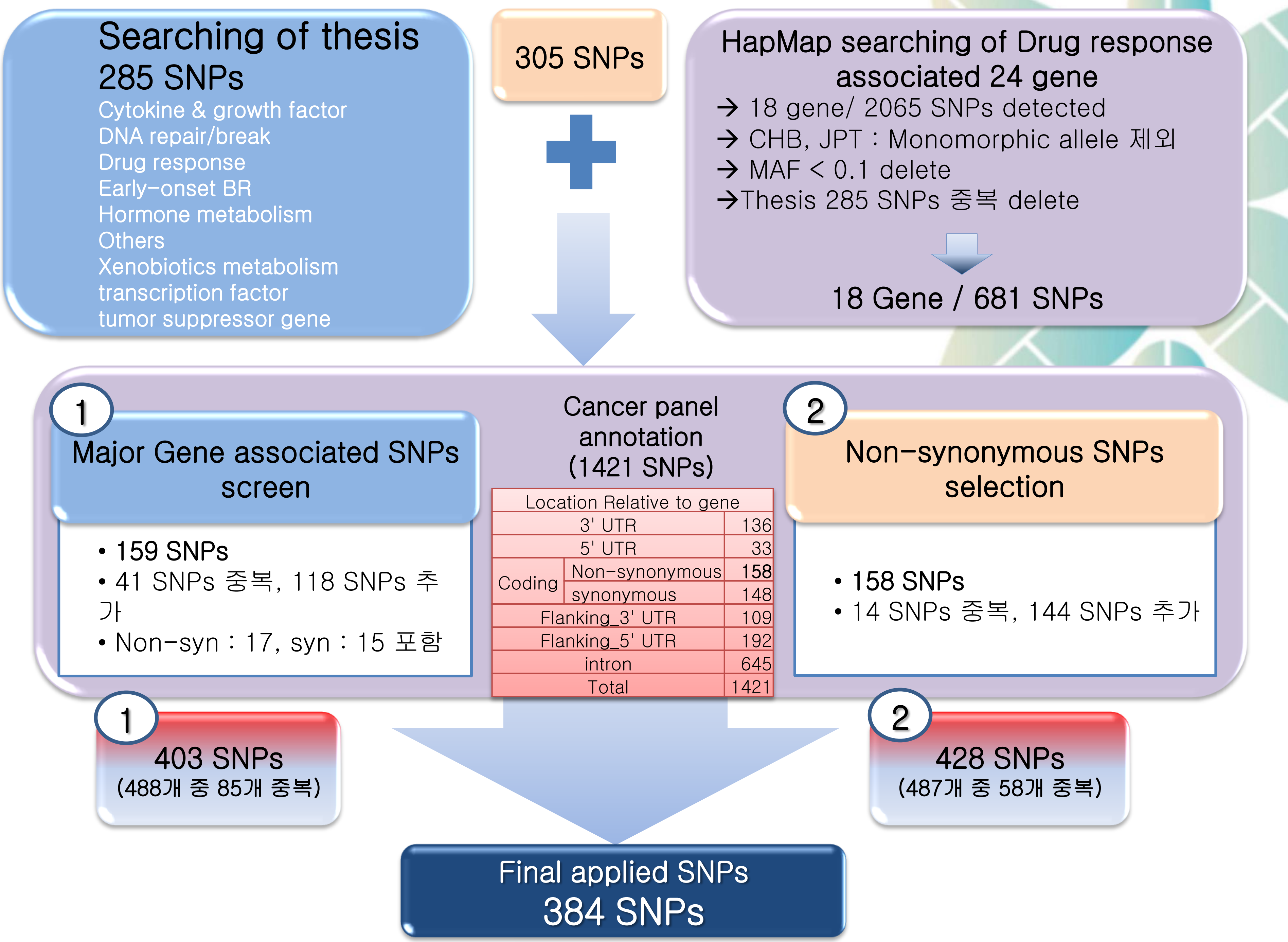
nature genetics

Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2

Table 1 Estimated odds ratios and tests of association for rs4973768 and rs6504950

Marker (chromosome, position)	Alleles[a]	Stage (cases/controls)	MAF[b]	Per-allele OR (95% CI)[c]	Heterozygote OR (95% CI)[d]	Homozygote OR (95% CI)[e]	*P* trend
rs4973768 (3p24, 27391017)	C/T	Stage 1 (388/355)	0.46	1.33 (1.07–1.64)	1.45 (1.01–2.07)	1.76 (1.15–2.68)	0.0087
		Stage 2 (3,951/3,870)	0.47	1.06 (0.99–1.03)	0.99 (0.89–1.10)	1.13 (0.99–1.28)	0.081
		Stage 3 (3,872/3,925)	0.48	1.13 (1.06–1.20)	1.03 (0.93–1.15)	1.27 (1.12–1.44)	0.00025
		Stage 4 (30,256/34,063)	0.46 (0.21)	1.11 (1.08–1.13)	1.12 (1.08–1.17)	1.23 (1.17–1.29)	1.4×10^{-18}
		Combined					4.1×10^{-23}
rs6504950 (17q23, 50411470)	G/A	Stage 1 (390/357)	0.31	0.76 (0.61–0.96)	0.83 (0.61–1.13)	0.52 (0.31–0.89)	0.018
		Stage 2 (3,976/3,894)	0.29	0.90 (0.84–0.96)	0.86 (0.78–0.94)	0.86 (0.73–1.02)	0.0020
		Stage 3 (3,870/3,923)	0.28	0.91 (0.85–0.98)	0.89 (0.81–0.97)	0.88 (0.73–1.04)	0.012
		Stage 4 (30,470/33,302)	0.27 (0.08)	0.95 (0.92–0.97)	0.96 (0.92–0.99)	0.89 (0.83–0.95)	0.00010
		Combined					1.4×10^{-8}

[a]Major/minor allele (+ strand), based on the allele frequency in Europeans. [b]Minor allele frequency in Europeans (minor allele frequency in Southeast Asians in stage 4 shown in brackets). [c]Odds ratios (OR) per copy of the minor allele. [d]OR for heterozygotes relative to homozygotes for the common allele. [e]OR for homozygotes for the rare allele, relative to homozygotes for the common allele.



Location Relative to gene		
3' UTR		136
5' UTR		33
Coding	Non-synonymous	158
	synonymous	148
Flanking_3' UTR		109
Flanking_5' UTR		192
intron		645
Total		1421

<Searching of thesis>

Group	No. of Gene	No. of SNPs
Cytokine & growth factor	10	94
DNA repair/break	9	23
Drug response	5	17
Early-onset BR	5	39
Hormone metabolism	4	36
Others	46	112
Xenobiotics metabolism	21	50
transcription factor	4	6
tumor suppressor gene	3	14
Total	**107 Gene / 384 SNPs**	

<Distribution of Gene/SNPs from thesis>

Cytokine & growth factor	FGFR2	6	Hormone metabolism	AR	6	Others	ATK1	5	Others	RELN	1
	IGF1	23		ERBB2	13		ECHDC1	2		RHOA	1
	IGF1R	55		PGR	15		H19	1		RUNDC3B	1
	IGFBP3	2		SULT1E1	2		MMP8	1		TLR6	1
	ITGA3	1	Transcription factor	A2BP1	1		MRPS30	2		TNP1	1
	ITGA6	1		EHMT1	1		RB1	1		TOP2A	1
	ITGB3	1		FLJ45983	1		RNF146	2		PON1	2
	MAP3K1	1		GATA3	3		BUB3	1		POU5F1P1	1
	LOC643714	1	Tumor suppressor	APC	11		C17orf37	1		RELN	1
	TOX3	3		LSP1	2		C6orf163	1		RHOA	1
DNA repair / break	ATM	3		PRDM2	1		C6orf97	2		RUNDC3B	1
	ATP1B2	1	Xenobiotics Metabolism	ADH1B	1		CYP19A1	3		TLR6	1
	BARD1	7		ADH1C	1		EGFR	11		TNP1	1
	BRCA2	2		AURKA	7		EHMT2	1		TOP2A	1
	CHEK2	1		AXIN2	5		FGFR1	8			
	LIG4	1		CASP8	1		FLJ41481	1			
	TP53	3		CCND1	4		G0S2	1			
	WDR79	4		CCND3	1		HCN1	3			
	XRCC1	1		CCNE1	1		HDAC8	1			
Drug response	XRCC2	1		CDK6	1		KDR	8			
	XRCC3	3		CDKN1A	2		KIAA1239	1			
	ABCB1	11		CDKN1B	1		KIT	11			
	DHFR	1		CDKN2A	1		LOC64371	1			
	MTHFR	1		DNMT3A	1		MAP2K1	4			
Early-onset BR	COMT	1		DNMT3B	1		MAP2K2	5			
	CYP1A1	1		GPX4	1		MET	11			
	CYP1B1	2		HSD11B1	4		MOCS2	1			
	ESR1	27		ICAM5	1		MYC	1			
	ESR2	8		IRS2	11		NBN	2			
				NUMA1	1		P2RY5	1			
				PTGIS	3		PON1	2			
				TBXAS1	1		POU5F1P1	1			

		ERPR				HER2				TN			
		Hetero	Minor	Hetero	Minor	Hetero	Minor	Hetero	Minor	Hetero	Minor	Hetero	Minor
Gene	rs #	OR (CI 95%)[1]		OR (CI 95%)[2]		OR (CI 95%)[1]		OR (CI 95%)[2]		OR (CI 95%)[1]		OR (CI 95%)[2]	
HSD11B1	rs2235543	0.96(0.70-1.32)	0.82(0.53-1.28)	0.64(0.38-1.07)	0.65(0.32-1.36)	0.81(0.59-1.10)	0.73(0.47-1.13)	0.51(0.31-0.85)	0.65(0.32-1.34)	1.00(0.72-1.38)	0.84(0.54-1.33)	0.59(0.35-1.01)	0.75(0.35-1.60)
2p(19150424)	rs4666451	0.43(0.20-0.90)		0.45(0.16-1.23)		1.14(0.65-1.98)		1.14(0.48-2.75)		1.08(0.61-1.94)		1.05(0.41-2.71)	
CYP1B1	rs1056836	1.00(0.69-1.45)	3.50(0.70-17.50)	0.77(0.44-1.33)	1.63(0.18-14.42)	1.18(0.83-1.68)	1.68(0.28-10.14)	0.88(0.52-1.51)	0.83(0.08-8.32)	1.46(1.03-2.08)	3.34(0.64-17.38)	1.12(0.64-1.95)	1.63(0.18-14.86)
BARD1	rs2229571	1.47(1.08-2.00)	0.85(0.52-1.39)	1.72(1.04-2.84)	0.94(0.46-1.93)	1.15(0.84-1.56)	0.87(0.55-1.39)	1.28(0.78-2.10)	0.79(0.39-1.60)	1.07(0.78-1.46)	0.69(0.42-1.14)	1.20(0.72-2.02)	0.68(0.32-1.46)
FGFR2	rs12505080	1.28(0.91-1.79)	1.05(0.69-1.61)	1.05(0.62-1.79)	0.93(0.48-1.80)	1.08(0.78-1.50)	1.06(0.70-1.59)	1.00(0.59-1.70)	1.05(0.55-2.01)	1.62(1.14-2.30)	1.19(0.77-1.85)	1.38(0.79-2.41)	1.21(0.61-2.41)
KIT	rs2237038	0.69(0.50-0.95)	0.74(0.48-1.15)	0.64(0.38-1.07)	0.79(0.40-1.58)	1.01(0.74-1.40)	0.75(0.48-1.18)	0.94(0.56-1.56)	0.66(0.33-1.34)	1.05(0.75-1.46)	1.01(0.65-1.58)	1.00(0.58-1.70)	0.83(0.40-1.73)
KIT	rs981959	0.69(0.50-0.95)	0.72(0.46-1.11)	0.63(0.38-1.06)	0.75(0.37-1.50)	1.00(0.73-1.39)	0.71(0.45-1.11)	0.91(0.55-1.52)	0.60(0.29-1.23)	1.08(0.77-1.51)	1.03(0.65-1.62)	0.97(0.57-1.67)	0.81(0.39-1.69)
KIT	rs2237023	0.86(0.63-1.17)	1.02(0.63-1.65)	0.94(0.58-1.53)	0.94(0.45-1.96)	1.22(0.89-1.66)	1.19(0.73-1.93)	1.47(0.90-2.39)	0.97(0.46-2.04)	1.04(0.75-1.44)	1.73(1.09-2.74)	1.13(0.68-1.88)	1.17(0.55-2.49)
KIT	rs6810872	0.84(0.61-1.14)	1.00(0.62-1.62)	0.92(0.57-1.50)	0.91(0.43-1.90)	1.20(0.88-1.63)	1.15(0.71-1.87)	1.46(0.89-2.37)	0.93(0.44-1.97)	1.03(0.75-1.43)	1.70(1.07-2.70)	1.14(0.68-1.89)	1.14(0.54-2.42)
KDR	rs17709898	1.47(1.08-1.99)	1.14(0.62-2.11)	1.49(0.92-2.41)	0.78(0.33-1.84)	1.20(0.89-1.62)	1.07(0.59-1.95)	1.18(0.73-1.92)	0.75(0.32-1.76)	1.16(0.85-1.58)	1.20(0.66-2.18)	1.02(0.61-1.69)	0.72(0.30-1.75)
KDR	rs1870377	1.39(1.00-1.93)	1.22(0.80-1.87)	1.29(0.77-2.14)	1.10(0.56-2.16)	1.33(0.96-1.84)	1.30(0.86-1.97)	1.31(0.79-2.18)	1.35(0.70-2.60)	1.05(0.76-1.45)	0.97(0.63-1.49)	0.95(0.56-1.61)	0.91(0.46-1.81)
KDR	rs7673274	1.02(0.75-1.39)	0.62(0.32-1.20)	0.96(0.59-1.57)	0.51(0.21-1.22)	0.84(0.61-1.14)	0.51(0.26-1.00)	0.69(0.42-1.13)	0.37(0.15-0.89)	1.18(0.86-1.61)	0.95(0.52-1.75)	1.05(0.63-1.74)	0.59(0.25-1.42)
STE or SULT1E1	rs1881668	1.27(0.92-1.74)	1.50(0.96-2.33)	0.96(0.58-1.59)	1.08(0.54-2.14)	1.26(0.92-1.71)	1.46(0.94-2.26)	0.89(0.55-1.47)	1.05(0.54-2.07)	1.52(1.10-2.09)	1.22(0.76-1.96)	1.14(0.68-1.91)	0.89(0.43-1.85)
ADH1B	rs1042026	0.95(0.69-1.29)	1.25(0.54-2.88)	0.95(0.59-1.55)	1.22(0.32-4.58)	0.99(0.73-1.35)	0.98(0.41-2.35)	0.99(0.61-1.59)	0.90(0.23-3.48)	0.65(0.47-0.90)	0.98(0.41-2.34)	0.69(0.41-1.15)	0.79(0.19-3.28)
5p12	rs4415084	0.91(0.65-1.27)	0.66(0.44-1.00)	0.95(0.57-1.59)	1.03(0.53-2.01)	0.95(0.69-1.32)	0.60(0.40-0.91)	1.16(0.70-1.93)	0.94(0.48-1.83)	1.01(0.72-1.42)	0.88(0.58-1.33)	1.17(0.69-1.99)	1.32(0.66-2.62)
5q(52454339bp)	rs30099	0.95(0.69-1.32)	1.23(0.79-1.92)	1.66(1.01-2.73)	1.50(0.77-2.95)	0.75(0.55-1.02)	0.83(0.53-1.29)	1.28(0.79-2.09)	0.99(0.50-1.94)	0.87(0.62-1.21)	1.34(0.86-2.08)	1.41(0.83-2.38)	1.73(0.87-3.44)
CDKN1A	rs3176336	1.36(1.00-1.84)	0.74(0.40-1.34)	1.03(0.64-1.65)	0.66(0.27-1.59)	1.16(0.85-1.57)	1.04(0.61-1.78)	1.00(0.62-1.61)	1.12(0.49-2.57)	1.28(0.94-1.74)	0.88(0.50-1.57)	1.04(0.63-1.72)	0.83(0.34-2.04)
ESR1	rs851984	1.17(0.82-1.67)	0.12(0.02-0.92)	0.95(0.55-1.63)	0.06(0.01-0.53)	0.92(0.64-1.33)	0.85(0.33-2.18)	0.78(0.45-1.35)	0.42(0.13-1.40)	1.13(0.79-1.63)	0.49(0.15-1.59)	0.89(0.51-1.58)	0.23(0.06-0.92)
ESR1	rs851982	1.13(0.79-1.61)	0.12(0.02-0.91)	0.94(0.55-1.63)	0.06(0.01-0.53)	0.88(0.61-1.27)	0.95(0.38-2.36)	0.77(0.45-1.33)	0.47(0.15-1.51)	1.12(0.78-1.60)	0.49(0.15-1.58)	0.90(0.51-1.59)	0.23(0.06-0.92)
ESR1	rs2881766	1.37(0.99-1.91)	1.53(1.00-2.33)	1.31(0.79-2.16)	1.76(0.86-3.61)	1.22(0.88-1.67)	1.07(0.70-1.65)	1.12(0.68-1.83)	1.37(0.67-2.77)	1.41(1.01-1.95)	0.93(0.59-1.48)	1.38(0.82-2.33)	1.11(0.51-2.38)
ESR1	rs926778	1.73(1.24-2.41)	1.68(1.09-2.57)	2.55(1.54-4.24)	2.66(1.33-5.31)	1.34(0.98-1.84)	0.89(0.57-1.39)	1.87(1.15-3.04)	1.43(0.71-2.86)	1.37(0.99-1.89)	0.90(0.57-1.42)	2.07(1.24-3.48)	1.66(0.80-3.45)
ESR1	rs3020366	1.00(0.73-1.39)	0.56(0.36-0.87)	1.04(0.62-1.75)	0.50(0.26-0.96)	1.40(1.01-1.94)	0.83(0.54-1.27)	1.41(0.84-2.37)	0.67(0.35-1.27)	1.28(0.91-1.80)	1.05(0.68-1.60)	1.21(0.70-2.08)	0.78(0.40-1.51)
ESR1	rs2273206	1.62(1.18-2.22)	1.60(1.00-2.56)	2.44(1.48-4.03)	2.06(0.98-4.36)	1.22(0.90-1.65)	0.83(0.50-1.36)	1.72(1.06-2.80)	1.02(0.47-2.21)	1.38(1.01-1.88)	0.93(0.56-1.55)	2.31(1.38-3.87)	1.39(0.62-3.11)
ESR1	rs750686	0.91(0.65-1.26)	0.57(0.37-0.88)	0.73(0.43-1.25)	0.41(0.21-0.80)	1.15(0.82-1.60)	0.82(0.54-1.25)	0.89(0.52-1.54)	0.59(0.31-1.14)	1.21(0.85-1.71)	1.08(0.71-1.64)	0.91(0.52-1.62)	0.68(0.35-1.34)
ESR1	rs3798577	0.80(0.58-1.11)	1.13(0.73-1.74)	0.87(0.53-1.45)	0.99(0.51-1.92)	0.69(0.51-0.94)	0.68(0.43-1.07)	0.69(0.42-1.14)	0.51(0.26-1.02)	0.57(0.42-0.79)	0.60(0.38-0.96)	0.57(0.34-0.96)	0.50(0.24-1.03)
ESR1	rs910416	1.05(0.76-1.44)	1.01(0.65-1.58)	1.13(0.69-1.86)	1.17(0.59-2.32)	0.84(0.62-1.14)	0.54(0.34-0.88)	0.89(0.55-1.45)	0.49(0.24-1.01)	0.77(0.56-1.06)	0.60(0.37-0.96)	0.88(0.53-1.47)	0.87(0.42-1.80)
IGFBP3	rs2854744	1.59(1.16-2.17)	0.39(0.19-0.82)	1.44(0.88-2.36)	0.38(0.14-1.00)	1.02(0.74-1.40)	0.58(0.32-1.05)	0.86(0.52-1.41)	0.52(0.22-1.23)	1.34(0.97-1.85)	0.80(0.44-1.43)	1.20(0.72-2.01)	0.50(0.20-1.29)
EGFR	rs6593207	1.37(1.01-1.86)	1.19(0.71-2.00)	1.24(0.77-2.01)	1.06(0.48-2.37)	1.47(1.09-1.98)	1.03(0.61-1.75)	1.31(0.81-2.11)	0.84(0.37-1.89)	1.22(0.90-1.66)	0.45(0.23-0.88)	1.21(0.73-1.99)	0.44(0.17-1.16)
EGFR	rs11977388	1.25(0.92-1.70)	0.90(0.54-1.48)	1.13(0.69-1.83)	0.75(0.36-1.58)	1.44(1.06-1.94)	0.87(0.52-1.43)	1.26(0.78-2.04)	0.67(0.31-1.41)	1.19(0.88-1.63)	0.65(0.37-1.12)	1.18(0.71-1.96)	0.59(0.26-1.34)
EGFR	rs10228436	1.14(0.83-1.57)	1.05(0.68-1.61)	0.99(0.60-1.63)	0.92(0.47-1.78)	1.48(1.08-2.03)	1.06(0.69-1.64)	1.27(0.77-2.10)	0.80(0.41-1.58)	1.33(0.97-1.84)	0.77(0.48-1.23)	1.27(0.75-2.14)	0.80(0.39-1.66)
ABCB1	rs1045642	1.41(1.03-1.93)	1.18(0.74-1.90)	0.98(0.60-1.61)	0.92(0.43-1.97)	1.01(0.75-1.37)	0.81(0.51-1.31)	0.71(0.44-1.16)	0.71(0.33-1.52)	0.97(0.70-1.33)	1.22(0.77-1.92)	0.63(0.37-1.05)	1.03(0.48-2.22)
ABCB1	rs2091766	0.87(0.64-1.19)	0.58(0.36-0.93)	1.11(0.68-1.82)	0.79(0.39-1.60)	0.88(0.64-1.19)	0.68(0.43-1.06)	1.08(0.67-1.76)	0.87(0.44-1.76)	0.89(0.64-1.22)	0.89(0.57-1.38)	1.11(0.67-1.85)	1.02(0.50-2.10)
ABCB1	rs868755	1.12(0.81-1.53)	1.17(0.73-1.87)	0.85(0.52-1.41)	1.05(0.48-2.31)	0.87(0.64-1.18)	1.06(0.67-1.66)	0.72(0.44-1.18)	1.13(0.52-2.42)	0.79(0.57-1.09)	1.18(0.75-1.85)	0.58(0.35-0.98)	1.30(0.60-2.84)
ABCB1	rs2520464	0.97(0.71-1.34)	0.65(0.42-1.02)	1.26(0.76-2.09)	0.76(0.40-1.47)	0.85(0.62-1.16)	0.65(0.42-0.99)	1.00(0.60-1.64)	0.69(0.36-1.32)	0.99(0.71-1.37)	0.85(0.55-1.31)	1.18(0.70-2.00)	0.83(0.42-1.64)
ABCB1	rs1978095	1.09(0.80-1.48)	1.01(0.50-2.01)	1.20(0.74-1.95)	1.00(0.37-2.73)	1.38(1.02-1.86)	1.68(0.90-3.14)	1.52(0.94-2.47)	1.58(0.61-4.13)	1.34(0.99-1.83)	1.71(0.90-3.24)	1.35(0.82-2.23)	1.59(0.59-4.26)
CDK6	rs3757823	0.88(0.61-1.25)	0.52(0.34-0.79)	0.75(0.42-1.34)	0.54(0.28-1.04)	0.86(0.60-1.23)	0.62(0.41-0.93)	0.69(0.39-1.23)	0.61(0.32-1.16)	1.02(0.70-1.48)	0.72(0.47-1.09)	0.94(0.51-1.74)	0.79(0.40-1.56)
Q129R	rs662	0.80(0.59-1.09)	0.73(0.45-1.17)	0.66(0.40-1.07)	0.66(0.31-1.40)	1.13(0.83-1.53)	0.67(0.41-1.11)	0.90(0.55-1.47)	0.66(0.31-1.42)	0.70(0.51-0.95)	0.53(0.32-0.88)	0.52(0.31-0.87)	0.47(0.21-1.04)
MET	rs41736	1.44(1.01-2.05)	0.90(0.60-1.36)	1.32(0.76-2.29)	0.95(0.50-1.82)	1.21(0.86-1.71)	0.84(0.57-1.26)	0.98(0.57-1.68)	0.89(0.47-1.68)	1.37(0.95-1.96)	1.01(0.67-1.53)	1.11(0.63-1.95)	0.98(0.50-1.92)
MET	rs41739	1.46(1.02-2.08)	0.91(0.60-1.38)	1.36(0.78-2.37)	0.95(0.50-1.83)	1.24(0.88-1.74)	0.84(0.57-1.25)	1.02(0.59-1.75)	0.88(0.47-1.66)	1.40(0.98-2.01)	1.01(0.67-1.53)	1.15(0.65-2.04)	0.99(0.51-1.94)
TBXAS1	rs6971207	1.19(0.87-1.63)	1.60(1.00-2.55)	1.63(1.01-2.65)	2.22(0.97-5.10)	1.03(0.76-1.39)	0.63(0.37-1.09)	1.28(0.79-2.06)	0.99(0.42-2.37)	1.35(0.98-1.85)	1.52(0.93-2.46)	1.84(1.11-3.06)	2.56(1.09-5.98)
FGFR1	rs6983315	0.73(0.53-0.99)	0.93(0.59-1.48)	0.54(0.32-0.89)	0.63(0.31-1.25)	0.89(0.65-1.20)	0.93(0.58-1.48)	0.71(0.43-1.16)	0.64(0.32-1.29)	0.93(0.67-1.27)	1.29(0.82-2.04)	0.75(0.44-1.26)	0.76(0.37-1.55)
CDKN2A	rs3731239	0.71(0.50-1.01)	0.61(0.24-1.58)	0.58(0.34-0.99)	0.37(0.11-1.23)	0.85(0.61-1.19)	0.25(0.07-0.91)	0.73(0.43-1.21)	0.15(0.03-0.65)	0.94(0.67-1.32)	0.79(0.32-1.96)	0.80(0.47-1.37)	0.31(0.08-1.14)
[illegible]	[illegible]	0.71(0.52-0.97)	0.67(0.42-1.07)	0.81(0.50-1.32)	0.98(0.45-2.12)	0.70(0.52-0.96)	0.66(0.41-1.04)	0.84(0.52-1.36)	1.06(0.49-2.27)	0.53(0.39-0.73)	0.64(0.40-1.02)	0.69(0.42-1.15)	1.00(0.45-2.20)
[illegible]	[illegible]	1.22(0.90-1.66)	1.41(0.83-2.39)	2.30(1.37-3.87)	1.00(0.48-2.11)	1.26(0.94-1.71)	1.04(0.60-1.81)	2.48(1.48-4.15)	0.86(0.40-1.85)	0.94(0.69-1.29)	0.71(0.39-1.30)	1.61(0.94-2.75)	0.65(0.29-1.46)
[illegible]	[illegible]	1.17(0.84-1.64)	1.52(1.00-2.31)	1.88(1.12-3.15)	1.76(0.93-3.32)	1.05(0.76-1.46)	1.36(0.90-2.06)	1.67(1.00-2.78)	1.61(0.86-3.00)	1.11(0.80-1.55)	1.06(0.68-1.65)	1.44(0.85-2.44)	1.15(0.59-2.23)
[illegible]	[illegible]	1.25(0.92-1.69)	1.33(0.78-2.27)	2.24(1.33-3.76)	0.95(0.45-2.01)	1.25(0.92-1.68)	1.04(0.60-1.80)	2.37(1.42-3.98)	0.84(0.39-1.82)	0.96(0.71-1.31)	0.64(0.34-1.20)	1.63(0.95-2.78)	0.58(0.26-1.34)
[illegible]	[illegible]	1.29(0.93-1.78)	1.58(1.02-2.45)	2.05(1.24-3.40)	1.60(0.83-3.07)	1.17(0.85-1.59)	1.27(0.82-1.96)	1.92(1.17-3.16)	1.40(0.73-2.69)	1.05(0.77-1.44)	0.94(0.59-1.49)	1.54(0.92-2.58)	1.06(0.53-2.11)
[illegible]	[illegible]	1.41(1.03-1.95)	1.56(1.01-2.40)	2.10(1.26-3.49)	1.45(0.76-2.76)	1.28(0.93-1.74)	1.28(0.83-1.97)	1.97(1.20-3.26)	1.33(0.70-2.52)	1.11(0.81-1.53)	1.01(0.64-1.58)	1.54(0.91-2.59)	1.07(0.54-2.09)
FGFR2	rs2981582	1.54(1.13-2.10)	1.09(0.66-1.81)	1.79(1.09-2.92)	0.98(0.46-2.07)	1.30(0.96-1.76)	1.19(0.74-1.93)	1.64(1.01-2.68)	1.21(0.58-2.52)	1.23(0.90-1.68)	0.82(0.48-1.41)	1.36(0.82-2.26)	0.83(0.38-1.82)
LSP1	rs661348	1.08(0.78-1.49)	1.16(0.75-1.77)	1.47(0.89-2.42)	1.05(0.56-1.99)	1.40(1.02-1.93)	1.33(0.87-2.04)	1.88(1.14-3.11)	1.19(0.63-2.27)	1.13(0.82-1.56)	0.83(0.52-1.32)	1.53(0.91-2.57)	0.70(0.35-1.41)
H19	rs2107425	1.11(0.78-1.58)	0.94(0.61-1.44)	1.07(0.62-1.85)	0.95(0.48-1.86)	0.68(0.49-0.94)	0.58(0.38-0.87)	0.61(0.36-1.03)	0.60(0.31-1.15)	0.80(0.57-1.13)	0.76(0.50-1.17)	0.75(0.42-1.31)	0.79(0.39-1.58)
NUMA1	rs3750913	0.57(0.34-0.95)	1.09(0.15-7.80)	0.86(0.38-1.96)	0.30(0.04-2.25)	0.86(0.55-1.34)		1.56(0.71-3.39)		1.16(0.75-1.79)	0.62(0.06-6.84)	1.36(0.62-3.01)	0.20(0.02-2.23)
PGR	rs1042839	9.40(1.17-75.52)		1.02(0.99-1.05)	2.86(0.35-23.32)	1.08(0.07-17.29)		0.28(0.02-4.49)					
PGR	rs1042838	9.48(1.18-76.18)		2.87(0.35-23.46)		2.17(0.20-23.99)		0.50(0.04-5.73)					
PGR	rs566351	1.15(0.83-1.58)	0.66(0.22-2.00)	1.79(1.04-3.10)	0.65(0.15-2.80)	1.17(0.85-1.60)	1.14(0.44-2.91)	1.77(1.03-3.04)	0.94(0.24-3.77)	1.04(0.75-1.44)	1.09(0.42-2.88)	1.48(0.84-2.62)	1.41(0.35-5.69)
IGF-1	rs6214	0.98(0.69-1.39)	0.87(0.58-1.31)	0.78(0.43-1.40)	0.70(0.37-1.34)	0.77(0.54-1.08)	0.80(0.54-1.18)	0.59(0.33-1.05)	0.52(0.28-0.98)	0.91(0.64-1.31)	0.88(0.59-1.32)	0.70(0.38-1.29)	0.58(0.30-1.14)
IGF1	rs2373721	1.14(0.83-1.58)	1.30(0.60-2.83)	0.84(0.51-1.38)	3.93(0.50-31.14)	0.71(0.51-0.99)	1.31(0.63-2.76)	0.60(0.37-0.99)	4.18(0.54-32.43)	1.06(0.77-1.48)	0.95(0.41-2.21)	0.86(0.52-1.43)	3.23(0.39-26.62)
IGF-1	rs7136446	1.18(0.86-1.63)	1.43(0.67-3.07)	0.85(0.52-1.39)	3.98(0.50-31.50)	0.71(0.51-0.99)	1.31(0.63-2.76)	0.60(0.37-0.99)	4.18(0.54-32.43)	1.05(0.76-1.46)	1.04(0.46-2.38)	0.85(0.51-1.42)	3.45(0.42-28.19)
IGF-1	rs9989002	0.95(0.68-1.32)	1.26(0.53-3.02)	0.69(0.42-1.15)	2.65(0.33-21.45)	0.60(0.42-0.85)	1.67(0.75-3.71)	0.59(0.35-0.98)	3.89(0.50-30.33)	1.00(0.71-1.39)	1.09(0.44-2.74)	0.84(0.50-1.41)	2.85(0.34-23.92)
IGF-1	rs7956547	0.97(0.70-1.36)	1.03(0.41-2.58)	0.66(0.40-1.10)	2.02(0.24-16.87)	0.68(0.48-0.96)	1.20(0.51-2.81)	0.60(0.36-1.00)	2.79(0.35-22.08)	1.05(0.75-1.48)	0.86(0.32-2.29)	0.84(0.50-1.41)	1.89(0.21-16.80)
IGF1	rs10778176	1.15(0.83-1.59)	0.70(0.45-1.07)	0.89(0.53-1.51)	0.53(0.28-1.02)	1.00(0.73-1.38)	0.70(0.47-1.06)	0.79(0.47-1.33)	0.52(0.28-0.99)	1.08(0.78-1.51)	0.71(0.46-1.09)	0.91(0.52-1.58)	0.51(0.26-1.01)
IGF-1	rs35765	1.92(1.17-3.17)	0.41(0.04-3.95)	1.52(0.72-3.18)	0.46(0.03-7.59)	1.34(0.79-2.25)		0.91(0.43-1.97)		1.18(0.68-2.04)		0.69(0.30-1.57)	
BRCA2	rs144848	0.97(0.72-1.32)	1.35(0.70-2.62)	0.93(0.58-1.49)	1.15(0.41-3.27)	0.73(0.54-0.98)	1.77(0.96-3.25)	0.70(0.44-1.12)	1.78(0.65-4.85)	1.06(0.78-1.43)	1.19(0.59-2.37)	0.88(0.54-1.44)	1.25(0.42-3.72)
IRS2	rs9515118	1.18(0.87-1.60)	0.50(0.26-0.96)	1.55(0.95-2.51)	0.75(0.27-2.11)	1.05(0.77-1.43)	1.07(0.64-1.81)	1.31(0.80-2.13)	1.85(0.73-4.68)	1.26(0.93-1.72)	0.92(0.52-1.63)	1.51(0.91-2.53)	1.96(0.72-5.35)
IRS2	rs754204	0.99(0.73-1.34)	1.29(0.75-2.23)	0.79(0.49-1.27)	1.08(0.46-2.57)	0.94(0.70-1.27)	1.26(0.73-2.15)	0.79(0.49-1.26)	1.12(0.48-2.63)	0.70(0.52-0.96)	0.89(0.50-1.58)	0.60(0.37-0.99)	0.64(0.25-1.61)
IRS2	rs9559648	1.13(0.83-1.53)	0.95(0.42-2.14)	0.86(0.54-1.39)	0.58(0.19-1.83)	0.92(0.68-1.25)	1.21(0.58-2.53)	0.69(0.43-1.11)	0.75(0.26-2.18)	0.66(0.48-0.92)	1.15(0.54-2.45)	0.51(0.30-0.84)	0.67(0.22-2.09)
IRS2	rs9559654	1.26(0.92-1.71)	1.26(0.53-2.95)	0.90(0.55-1.45)	0.86(0.26-2.87)	1.00(0.73-1.36)	1.49(0.67-3.31)	0.70(0.43-1.14)	0.93(0.29-2.97)	0.79(0.57-1.10)	1.14(0.48-2.68)	0.58(0.35-0.96)	0.85(0.25-2.93)
CYP20	rs4646	1.00(0.74-1.36)	1.00(0.60-1.67)	1.56(0.94-2.58)	1.17(0.55-2.50)	1.01(0.75-1.38)	0.86(0.51-1.45)	1.62(0.99-2.67)	0.81(0.37-1.78)	0.92(0.67-1.25)	0.76(0.44-1.30)	1.74(1.03-2.94)	0.96(0.43-2.17)
CYP1A1	rs1048943	1.19(0.87-1.63)	1.73(0.89-3.39)	1.33(0.81-2.18)	1.63(0.53-5.06)	1.10(0.81-1.49)	1.05(0.51-2.17)	1.16(0.71-1.90)	1.12(0.35-3.58)	1.48(1.09-2.03)	2.10(1.08-4.10)	1.48(0.89-2.45)	1.62(0.50-5.23)
IGF1R	rs4966007	1.15(0.83-1.60)	1.58(1.04-2.41)	1.28(0.78-2.10)	2.30(1.12-4.70)	1.05(0.77-1.43)	0.93(0.60-1.44)	1.23(0.76-1.99)	1.39(0.67-2.90)	1.15(0.83-1.59)	1.12(0.72-1.75)	1.28(0.77-2.14)	1.58(0.74-3.37)
IGF1R	rs4966009	1.12(0.81-1.55)	1.53(1.00-2.34)	1.27(0.77-2.08)	2.10(1.02-4.31)	1.05(0.77-1.44)	0.96(0.61-1.49)	1.26(0.77-2.04)	1.35(0.65-2.80)	1.14(0.83-1.58)	1.19(0.76-1.85)	1.27(0.76-2.13)	1.59(0.75-3.38)
IGF1R	rs1574213	0.99(0.73-1.35)	1.16(0.49-2.72)	0.94(0.58-1.51)		0.96(0.71-1.30)	1.78(0.82-3.85)	0.99(0.61-1.59)		0.89(0.65-1.22)	2.19(1.03-4.69)	0.91(0.55-1.50)	
IGF1R	rs8032477	0.83(0.59-1.16)	0.62(0.41-0.94)	1.17(0.69-1.97)	0.73(0.39-1.38)	1.05(0.74-1.47)	0.74(0.49-1.12)	1.41(0.83-2.38)	0.85(0.45-1.59)	1.13(0.79-1.61)	0.91(0.59-1.39)	1.70(0.97-2.98)	1.15(0.59-2.22)
IGF1R	rs2670501	0.90(0.65-1.24)	0.89(0.57-1.38)	0.90(0.55-1.47)	1.10(0.53-2.29)	0.81(0.59-1.11)	0.92(0.60-1.40)	0.74(0.45-1.20)	1.09(0.53-2.24)	0.72(0.52-0.99)	0.74(0.48-1.16)	0.77(0.46-1.28)	1.04(0.49-2.24)
IGF1R	rs1521481	1.11(0.82-1.51)	0.92(0.51-1.69)	0.80(0.50-1.28)	0.92(0.34-2.45)	1.17(0.86-1.58)	0.49(0.24-0.99)	0.80(0.50-1.28)	0.54(0.19-1.54)	1.02(0.75-1.40)	0.99(0.55-1.80)	0.86(0.53-1.41)	1.11(0.40-3.10)
IGF1R	rs4966035	0.85(0.61-1.20)	0.97(0.64-1.47)	0.61(0.35-1.04)	1.14(0.55-2.35)	0.76(0.54-1.06)	0.90(0.60-1.35)	0.51(0.30-0.87)	1.09(0.53-2.23)	0.68(0.48-0.96)	0.99(0.66-1.48)	0.51(0.29-0.89)	1.44(0.69-3.03)
IGF1R	rs7165875	0.87(0.62-1.23)	1.04(0.69-1.57)	0.59(0.34-1.02)	1.06(0.52-2.15)	0.78(0.56-1.09)	0.91(0.61-1.35)	0.50(0.29-0.87)	0.96(0.48-1.93)	0.74(0.52-1.05)	1.06(0.71-1.58)	0.50(0.28-0.89)	1.36(0.66-2.80)
IGF1R	rs3743259	0.84(0.59-1.19)	1.12(0.75-1.69)	0.56(0.32-0.98)	1.06(0.52-2.17)	0.72(0.52-1.01)	0.91(0.61-1.37)	0.46(0.26-0.80)	0.90(0.44-1.83)	0.68(0.48-0.96)	1.04(0.69-1.57)	0.45(0.25-0.80)	1.24(0.60-2.58)
IGF1R	rs2684803	1.58(1.16-2.17)	1.30(0.81-2.08)	1.59(0.98-2.59)	1.42(0.68-2.98)	1.06(0.78-1.43)	1.07(0.68-1.69)	1.08(0.67-1.75)	1.15(0.55-2.41)	1.29(0.95-1.77)	0.99(0.61-1.62)	1.37(0.83-2.27)	1.32(0.61-2.84)
IGF1R	rs1546713	1.58(1.16-2.17)	1.26(0.78-2.03)	1.62(0.99-2.63)	1.43(0.68-2.99)	1.06(0.78-1.43)	1.07(0.68-1.69)	1.10(0.68-1.77)	1.16(0.56-2.43)	1.28(0.94-1.75)	0.99(0.61-1.61)	1.37(0.83-2.28)	1.31(0.61-2.81)
IGF1R	rs7166558	1.63(1.19-2.23)	1.35(0.84-2.17)	1.69(1.04-2.75)	1.51(0.72-3.17)	1.07(0.79-1.45)	1.07(0.68-1.70)	1.13(0.70-1.83)	1.17(0.56-2.45)	1.28(0.93-1.75)	1.02(0.63-1.66)	1.42(0.86-2.36)	1.40(0.65-3.00)
IGF1R	rs2229765	1.62(1.18-2.22)	1.37(0.86-2.20)	1.66(1.01-2.71)	1.47(0.70-3.08)	1.04(0.76-1.41)	1.09(0.69-1.72)	1.09(0.67-1.76)	1.13(0.54-2.36)	1.27(0.93-1.74)	1.00(0.61-1.64)	1.35(0.81-2.25)	1.28(0.60-2.76)
IGF1R	rs11635251	0.92(0.68-1.25)	0.41(0.23-0.74)	0.77(0.47-1.24)	0.24(0.10-0.56)	1.01(0.75-1.37)	0.85(0.52-1.39)	0.78(0.48-1.27)	0.63(0.31-1.31)	1.08(0.80-1.48)	0.73(0.43-1.24)	0.93(0.56-1.53)	0.53(0.24-1.16)
IGF1R	rs8038056	1.18(0.87-1.61)	0.81(0.49-1.34)	1.70(1.04-2.79)	1.03(0.46-2.30)	1.09(0.81-1.48)	0.81(0.50-1.32)	1.45(0.89-2.37)	1.18(0.54-2.60)	1.42(1.04-1.93)	0.40(0.21-0.76)	1.81(1.08-3.01)	0.43(0.16-1.12)
IGF1R	rs12916884	0.95(0.70-1.29)	0.35(0.20-0.62)	0.68(0.42-1.10)	0.28(0.12-0.63)	1.11(0.82-1.50)	0.69(0.43-1.10)	0.80(0.49-1.29)	0.64(0.31-1.32)	1.16(0.85-1.58)	0.60(0.36-1.00)	0.87(0.53-1.45)	0.59(0.27-1.28)
IGF1R	rs7166565	1.30(0.95-1.77)	1.01(0.63-1.61)	1.59(0.98-2.59)	1.39(0.63-3.05)	1.15(0.85-1.57)	1.04(0.66-1.64)	1.26(0.78-2.04)	1.57(0.73-3.38)	1.39(1.02-1.91)	0.86(0.52-1.42)	1.49(0.91-2.47)	0.90(0.39-2.10)
IGF1R	rs939626	0.97(0.71-1.32)	0.64(0.35-1.15)	1.51(0.91-2.53)	0.60(0.25-1.47)	1.07(0.79-1.45)	0.62(0.34-1.12)	1.66(1.00-2.75)	0.64(0.26-1.55)	1.08(0.79-1.47)	0.51(0.26-0.98)	1.34(0.78-2.30)	0.48(0.18-1.24)
IGF1R	rs12437963	1.35(0.98-1.86)	1.37(0.88-2.15)	1.05(0.64-1.71)	2.44(1.06-5.65)	1.04(0.76-1.42)	1.14(0.74-1.77)	0.85(0.52-1.36)	1.89(0.82-4.40)	1.01(0.73-1.39)	1.10(0.70-1.73)	0.75(0.45-1.24)	1.90(0.80-4.49)
TNRC9/LOC643714	rs8051542	1.28(0.94-1.73)	1.09(0.49-2.40)	1.49(0.91-2.43)	1.70(0.35-8.22)	1.37(1.02-1.86)	1.68(0.82-3.44)	1.78(1.09-2.90)	3.35(0.75-15.00)	0.98(0.71-1.34)	1.58(0.77-3.26)	1.29(0.77-2.16)	2.97(0.65-13.69)
TNRC9 or TOX3	rs3803662	0.68(0.49-0.93)	0.68(0.43-1.06)	0.76(0.46-1.25)	0.66(0.34-1.31)	0.64(0.47-0.87)	0.58(0.37-0.90)	0.66(0.40-1.07)	0.42(0.21-0.85)	0.93(0.68-1.29)	0.80(0.51-1.27)	1.01(0.60-1.70)	0.92(0.45-1.89)
ATP1B2	rs1641512	1.02(0.75-1.40)	0.62(0.39-0.99)	1.28(0.79-2.08)	0.95(0.46-1.99)	1.09(0.79-1.49)	1.13(0.74-1.71)	1.45(0.89-2.36)	1.89(0.93-3.82)	0.93(0.67-1.27)	0.74(0.47-1.16)	1.15(0.69-1.90)	1.06(0.50-2.24)
AXIN2	rs4791171	1.02(0.75-1.40)	0.97(0.61-1.53)	1.08(0.66-1.76)	1.04(0.51-2.12)	0.73(0.54-0.99)	0.48(0.29-0.79)	0.79(0.49-1.28)	0.51(0.24-1.07)	0.87(0.63-1.19)	0.82(0.52-1.31)	1.03(0.62-1.71)	0.87(0.41-1.85)
AXIN2	rs11079571	1.05(0.77-1.43)	0.98(0.56-1.72)	1.18(0.72-1.91)	1.08(0.45-2.58)	1.43(1.06-1.94)	1.56(0.92-2.64)	1.63(1.00-2.64)	1.68(0.72-3.91)	1.13(0.82-1.54)	1.39(0.82-2.39)	1.11(0.66-1.85)	1.28(0.53-3.07)
AXIN2	rs3923087	1.09(0.79-1.48)	1.14(0.71-1.83)	1.17(0.72-1.91)	1.32(0.63-2.75)	0.71(0.53-0.96)	0.56(0.34-0.93)	0.78(0.49-1.27)	0.61(0.28-1.32)	0.84(0.61-1.15)	1.01(0.63-1.61)	0.97(0.59-1.60)	1.09(0.50-2.37)
AXIN2	rs3923086	0.96(0.70-1.33)	0.80(0.30-2.13)	0.67(0.42-1.08)		0.62(0.44-0.86)	0.47(0.16-1.39)	0.44(0.27-0.72)		0.97(0.70-1.35)	0.96(0.37-2.47)	0.70(0.43-1.15)	
MAP2K2	rs350916	1.02(0.75-1.39)	0.56(0.33-0.96)	1.00(0.62-1.62)	0.64(0.30-1.40)	1.26(0.93-1.71)	1.09(0.69-1.74)	1.26(0.78-2.05)	1.27(0.61-2.66)	1.29(0.94-1.78)	1.30(0.82-2.08)	1.30(0.79-2.16)	1.39(0.65-3.00)
MAP2K2	rs350913	1.12(0.83-1.53)	0.55(0.33-0.92)	1.13(0.70-1.83)	0.60(0.28-1.26)	1.36(1.00-1.85)	1.02(0.65-1.61)	1.40(0.86-2.27)	1.12(0.55-2.26)	1.41(1.02-1.94)	1.25(0.79-1.98)	1.49(0.89-2.48)	1.36(0.65-2.83)
MAP2K2	rs7258366	1.38(1.02-1.87)	0.82(0.47-1.43)	1.22(0.76-1.96)	1.09(0.46-2.62)	1.40(1.03-1.88)	1.02(0.61-1.71)	1.20(0.75-1.92)	1.27(0.54-3.02)	1.60(1.17-2.18)	1.51(0.91-2.50)	1.37(0.84-2.24)	1.53(0.63-3.71)
MAP2K2	rs12459484	1.39(1.02-1.91)	1.04(0.66-1.64)	1.24(0.77-2.01)	1.66(0.73-3.76)	1.43(1.05-1.95)	1.04(0.66-1.62)	1.17(0.73-1.89)	1.83(0.81-4.10)	1.76(1.27-2.45)	1.87(1.21-2.91)	1.56(0.94-2.60)	2.89(1.26-6.65)
PTGIS	rs6095541	0.86(0.57-1.30)	4.55(0.51-40.97)	1.95(0.87-4.37)		0.98(0.66-1.45)	3.24(0.34-31.27)	2.30(1.05-5.05)		0.82(0.54-1.25)	1.18(0.07-18.94)	1.14(0.48-2.68)	
AURKA	rs8173	0.96(0.70-1.31)	1.64(1.01-2.66)	0.94(0.58-1.53)	1.24(0.60-2.59)	0.99(0.73-1.34)	1.60(0.99-2.59)	1.10(0.68-1.79)	1.31(0.63-2.71)	1.11(0.82-1.52)	1.39(0.83-2.31)	0.99(0.60-1.64)	0.84(0.38-1.83)
COMT	rs4680	0.83(0.61-1.12)	0.93(0.51-1.72)	0.93(0.58-1.49)	0.87(0.33-2.25)	0.72(0.53-0.97)	1.14(0.64-2.01)	0.76(0.47-1.21)	1.13(0.45-2.84)	0.68(0.50-0.93)	1.17(0.65-2.08)	0.73(0.44-1.19)	1.29(0.49-3.35)

102 SNPs

Adjusted odds ratios of selected SNPs for breast cancer risk

	ERPR		HER2		TN	
	Hetero	Minor	Hetero	Minor	Hetero	Minor
Gene	OR (CI 95%)[2]		OR (CI 95%)[2]		OR (CI 95%)[2]	
ESR1	0.87(0.53-1.45)	0.99(0.51-1.92)	0.69(0.42-1.14)	0.51(0.26-1.02)	0.57(0.34-0.96)	0.50(0.24-1.03)
ABCB1	0.85(0.52-1.41)	1.05(0.48-2.31)	0.72(0.44-1.18)	1.13(0.52-2.42)	0.58(0.35-0.98)	1.30(0.60-2.84)
Q129R	0.66(0.40-1.07)	0.66(0.31-1.40)	0.90(0.55-1.47)	0.66(0.31-1.42)	0.52(0.31-0.87)	0.47(0.21-1.04)
TBXAS1	1.63(1.01-2.65)	2.22(0.97-5.10)	1.28(0.79-2.06)	0.99(0.42-2.37)	1.84(1.11-3.06)	2.56(1.09-5.98)
IRS2	0.86(0.54-1.39)	0.58(0.19-1.83)	0.69(0.43-1.11)	0.75(0.26-2.18)	0.51(0.30-0.84)	0.67(0.22-2.09)
IRS2	0.90(0.55-1.45)	0.86(0.26-2.87)	0.70(0.43-1.14)	0.93(0.29-2.97)	0.58(0.35-0.96)	0.85(0.25-2.93)
CYP20	1.56(0.94-2.58)	1.17(0.55-2.50)	1.62(0.99-2.67)	0.81(0.37-1.78)	1.74(1.03-2.94)	0.96(0.43-2.17)
IGF1R	1.70(1.04-2.79)	1.03(0.46-2.30)	1.45(0.89-2.37)	1.18(0.54-2.60)	1.81(1.08-3.01)	0.43(0.16-1.12)
MAP2K2	1.24(0.77-2.01)	1.66(0.73-3.76)	1.17(0.73-1.89)	1.83(0.81-4.10)	1.56(0.94-2.60)	2.89(1.26-6.65)

IGF1, IRS2, IGF1R

	ERPR				HER2				TN			
	Hetero	Minor	Hetero	Minor	Hetero	Minor	Hetero	Minor	Hetero	Minor	Hetero	Minor
Gene	OR (CI 95%)[1]		OR (CI 95%)[2]		OR (CI 95%)[1]		OR (CI 95%)[2]		OR (CI 95%)[1]		OR (CI 95%)[2]	
IGF-1	0.98(0.69-1.39)	0.87(0.58-1.31)	0.78(0.43-1.40)	0.70(0.37-1.34)	0.77(0.54-1.08)	0.80(0.54-1.18)	0.59(0.33-1.05)	0.52(0.28-0.98)	0.91(0.64-1.31)	0.88(0.59-1.32)	0.70(0.38-1.29)	0.58(0.30-1.14)
IGF1	1.14(0.83-1.58)	1.30(0.60-2.83)	0.84(0.51-1.38)	3.93(0.50-31.14)	0.71(0.51-0.99)	1.31(0.63-2.76)	0.60(0.37-0.99)	4.18(0.54-32.43)	1.06(0.77-1.48)	0.95(0.41-2.21)	0.86(0.52-1.43)	3.23(0.39-26.62)
IGF-1	1.18(0.86-1.63)	1.43(0.67-3.07)	0.85(0.52-1.39)	3.98(0.50-31.50)	0.71(0.51-0.99)	1.31(0.63-2.76)	0.60(0.37-0.99)	4.18(0.54-32.43)	1.05(0.76-1.46)	1.04(0.46-2.38)	0.85(0.51-1.42)	3.45(0.42-28.19)
IGF-1	0.95(0.68-1.32)	1.26(0.53-3.02)	0.69(0.42-1.15)	2.65(0.33-21.45)	0.60(0.42-0.85)	1.67(0.75-3.71)	0.59(0.35-0.98)	3.89(0.50-30.33)	1.00(0.71-1.39)	1.09(0.44-2.74)	0.84(0.50-1.41)	2.85(0.34-23.92)
IGF-1	0.97(0.70-1.36)	1.03(0.41-2.58)	0.66(0.40-1.10)	2.02(0.24-16.87)	0.68(0.48-0.96)	1.20(0.51-2.81)	0.60(0.36-1.00)	2.79(0.35-22.08)	1.05(0.75-1.48)	0.86(0.32-2.29)	0.84(0.50-1.41)	1.89(0.21-16.80)
IGF1	1.15(0.83-1.59)	0.70(0.45-1.07)	0.89(0.53-1.51)	0.53(0.28-1.02)	1.00(0.73-1.38)	0.70(0.47-1.06)	0.79(0.47-1.33)	0.52(0.28-0.99)	1.08(0.78-1.51)	0.71(0.46-1.09)	0.91(0.52-1.58)	0.51(0.26-1.01)
IGF-1	1.92(1.17-3.17)	0.41(0.04-3.95)	1.52(0.72-3.18)	0.46(0.03-7.59)	1.34(0.79-2.25)		0.91(0.43-1.97)		1.18(0.68-2.04)		0.69(0.30-1.57)	
BRCA2	0.97(0.72-1.32)	1.35(0.70-2.62)	0.93(0.58-1.49)	1.15(0.41-3.27)	0.73(0.54-0.98)	1.77(0.96-3.25)	0.70(0.44-1.12)	1.78(0.65-4.85)	1.06(0.78-1.43)	1.19(0.59-2.37)	0.88(0.54-1.44)	1.25(0.42-3.72)
IRS2	1.18(0.87-1.60)	0.50(0.26-0.96)	1.55(0.95-2.51)	0.75(0.27-2.11)	1.05(0.77-1.43)	1.07(0.64-1.81)	1.31(0.80-2.13)	1.85(0.73-4.68)	1.26(0.93-1.72)	0.92(0.52-1.63)	1.51(0.91-2.53)	1.96(0.72-5.35)
IRS2	0.99(0.73-1.34)	1.29(0.75-2.23)	0.79(0.49-1.27)	1.08(0.46-2.57)	0.94(0.70-1.27)	1.26(0.73-2.15)	0.79(0.49-1.26)	1.12(0.48-2.63)	0.70(0.52-0.96)	0.89(0.50-1.58)	0.60(0.37-0.99)	0.64(0.25-1.61)
IRS2	1.13(0.83-1.53)	0.95(0.42-2.14)	0.86(0.54-1.39)	0.58(0.19-1.83)	0.92(0.68-1.25)	1.21(0.58-2.53)	0.69(0.43-1.11)	0.75(0.26-2.18)	0.66(0.48-0.92)	1.15(0.54-2.45)	0.51(0.30-0.84)	0.67(0.22-2.09)
IRS2	1.26(0.92-1.71)	1.26(0.53-2.95)	0.90(0.55-1.45)	0.86(0.26-2.87)	1.00(0.73-1.36)	1.49(0.67-3.31)	0.70(0.43-1.14)	0.93(0.29-2.97)	0.79(0.57-1.10)	1.14(0.48-2.68)	0.58(0.35-0.96)	0.85(0.25-2.93)
CYP1A1	1.19(0.87-1.63)	1.73(0.89-3.39)	1.33(0.81-2.18)	1.63(0.53-5.06)	1.10(0.81-1.49)	1.05(0.51-2.17)	1.16(0.71-1.90)	1.12(0.35-3.58)	1.48(1.09-2.03)	2.10(1.08-4.10)	1.48(0.89-2.45)	1.62(0.50-5.23)
IGF1R	1.15(0.83-1.60)	1.58(1.04-2.41)	1.28(0.78-2.10)	2.30(1.12-4.70)	1.05(0.77-1.43)	0.93(0.60-1.44)	1.23(0.76-1.99)	1.39(0.67-2.90)	1.15(0.83-1.59)	1.12(0.72-1.75)	1.28(0.77-2.14)	1.58(0.74-3.37)
IGF1R	1.12(0.81-1.55)	1.53(1.00-2.34)	1.27(0.77-2.08)	2.10(1.02-4.31)	1.05(0.77-1.44)	0.96(0.61-1.49)	1.26(0.77-2.04)	1.35(0.65-2.80)	1.14(0.83-1.58)	1.19(0.76-1.85)	1.27(0.76-2.13)	1.59(0.75-3.38)
IGF1R	0.99(0.73-1.35)	1.16(0.49-2.72)	0.94(0.58-1.51)		0.96(0.71-1.30)	1.78(0.82-3.85)	0.99(0.61-1.59)		0.89(0.65-1.22)	2.19(1.03-4.69)	0.91(0.55-1.50)	
IGF1R	0.83(0.59-1.16)	0.62(0.41-0.94)	1.17(0.69-1.97)	0.73(0.39-1.38)	1.05(0.74-1.47)	0.74(0.49-1.12)	1.41(0.83-2.38)	0.85(0.45-1.59)	1.13(0.79-1.61)	0.91(0.59-1.39)	1.70(0.97-2.98)	1.15(0.59-2.22)
IGF1R	0.90(0.65-1.24)	0.89(0.57-1.38)	0.90(0.55-1.47)	1.10(0.53-2.29)	0.81(0.59-1.11)	0.92(0.60-1.40)	0.74(0.45-1.20)	1.09(0.53-2.24)	0.72(0.52-0.99)	0.74(0.48-1.16)	0.77(0.46-1.28)	1.04(0.49-2.24)
IGF1R	1.11(0.82-1.51)	0.92(0.51-1.69)	0.80(0.50-1.28)	0.92(0.34-2.45)	1.17(0.86-1.58)	0.49(0.24-0.99)	0.80(0.50-1.28)	0.54(0.19-1.54)	1.02(0.75-1.40)	0.99(0.55-1.80)	0.86(0.53-1.41)	1.11(0.40-3.10)
IGF1R	0.85(0.61-1.20)	0.97(0.64-1.47)	0.61(0.35-1.04)	1.14(0.55-2.35)	0.76(0.54-1.06)	0.90(0.60-1.35)	0.51(0.30-0.87)	1.09(0.53-2.23)	0.68(0.48-0.96)	0.99(0.66-1.48)	0.51(0.29-0.89)	1.44(0.69-3.03)
IGF1R	0.87(0.62-1.23)	1.04(0.69-1.57)	0.59(0.34-1.02)	1.06(0.52-2.15)	0.78(0.56-1.09)	0.91(0.61-1.35)	0.50(0.29-0.87)	0.96(0.48-1.93)	0.74(0.52-1.05)	1.06(0.71-1.58)	0.50(0.28-0.89)	1.36(0.66-2.80)
IGF1R	0.84(0.59-1.19)	1.12(0.75-1.69)	0.56(0.32-0.98)	1.06(0.52-2.17)	0.72(0.52-1.01)	0.91(0.61-1.37)	0.46(0.26-0.80)	0.90(0.44-1.83)	0.68(0.48-0.96)	1.04(0.69-1.57)	0.45(0.25-0.80)	1.24(0.60-2.58)
IGF1R	1.58(1.16-2.17)	1.30(0.81-2.08)	1.59(0.98-2.59)	1.42(0.68-2.98)	1.06(0.78-1.43)	1.07(0.68-1.69)	1.08(0.67-1.75)	1.15(0.55-2.41)	1.29(0.95-1.77)	0.99(0.61-1.62)	1.37(0.83-2.27)	1.32(0.61-2.84)
IGF1R	1.58(1.16-2.17)	1.26(0.78-2.03)	1.62(0.99-2.63)	1.43(0.68-2.99)	1.06(0.78-1.43)	1.07(0.68-1.69)	1.10(0.68-1.77)	1.16(0.56-2.43)	1.28(0.94-1.75)	0.99(0.61-1.61)	1.37(0.83-2.28)	1.31(0.61-2.81)
IGF1R	1.63(1.19-2.23)	1.35(0.84-2.17)	1.69(1.04-2.75)	1.51(0.72-3.17)	1.07(0.79-1.45)	1.07(0.68-1.70)	1.13(0.70-1.83)	1.17(0.56-2.45)	1.28(0.93-1.75)	1.02(0.63-1.66)	1.42(0.86-2.36)	1.40(0.65-3.00)
IGF1R	1.62(1.18-2.22)	1.37(0.86-2.20)	1.66(1.01-2.71)	1.47(0.70-3.08)	1.04(0.76-1.41)	1.09(0.69-1.72)	1.09(0.67-1.76)	1.13(0.54-2.36)	1.27(0.93-1.74)	1.00(0.61-1.64)	1.35(0.81-2.25)	1.28(0.60-2.76)
IGF1R	0.92(0.68-1.25)	0.41(0.23-0.74)	0.77(0.47-1.24)	0.24(0.10-0.56)	1.01(0.75-1.37)	0.85(0.52-1.39)	0.78(0.48-1.27)	0.63(0.31-1.31)	1.08(0.80-1.48)	0.73(0.43-1.24)	0.93(0.56-1.53)	0.53(0.24-1.16)
IGF1R	1.18(0.87-1.61)	0.81(0.49-1.34)	1.70(1.04-2.79)	1.03(0.46-2.30)	1.09(0.81-1.48)	0.81(0.50-1.32)	1.45(0.89-2.37)	1.18(0.54-2.60)	1.42(1.04-1.93)	0.40(0.21-0.76)	1.81(1.08-3.01)	0.43(0.16-1.12)
IGF1R	0.95(0.70-1.29)	0.35(0.20-0.62)	0.68(0.42-1.10)	0.28(0.12-0.63)	1.11(0.82-1.50)	0.69(0.43-1.10)	0.80(0.49-1.29)	0.64(0.31-1.32)	1.16(0.85-1.58)	0.60(0.36-1.00)	0.87(0.53-1.45)	0.59(0.27-1.28)
IGF1R	1.30(0.95-1.77)	1.01(0.63-1.61)	1.59(0.98-2.59)	1.39(0.63-3.05)	1.15(0.85-1.57)	1.04(0.66-1.64)	1.26(0.78-2.04)	1.57(0.73-3.38)	1.39(1.02-1.91)	0.86(0.52-1.42)	1.49(0.91-2.47)	0.90(0.39-2.10)
IGF1R	0.97(0.71-1.32)	0.64(0.35-1.15)	1.51(0.91-2.53)	0.60(0.25-1.47)	1.07(0.79-1.45)	0.62(0.34-1.12)	1.66(1.00-2.75)	0.64(0.26-1.55)	1.08(0.79-1.47)	0.51(0.26-0.98)	1.34(0.78-2.30)	0.48(0.18-1.24)
IGF1R	1.35(0.98-1.86)	1.37(0.88-2.15)	1.05(0.64-1.71)	2.44(1.06-5.65)	1.04(0.76-1.42)	1.14(0.74-1.77)	0.85(0.52-1.36)	1.89(0.82-4.40)	1.01(0.73-1.39)	1.10(0.70-1.73)	0.75(0.45-1.24)	1.90(0.80-4.49)

Common Genetic Variations in *MTHFR, MTR, DHFR* and *MTRR* gene

Gene(s)	SNP rs	SNP position	Distance from previous SNP	Alleles	Function	Amino acid change	Amino acid position	Validated	Min frequency	Max frequency
MTHFR	rs12404124	chr1:11808135	18	G/T	Promoter	–	–	Y	0.458333	0.483333
MTHFR	rs13306554	chr1:11790703	59	C/T	Coding exon	P/P	202	N	–	–
MTHFR	rs13306555	chr1:11789546	39	C/T	Coding exon	A/A	302	N	–	–
MTHFR	rs1476413	chr1:11786566	190	A/G	Intron (boundary)	–	–	Y	0.108333	0.341667
MTHFR	rs1801131	chr1:11788742	19	A/C	Coding exon	E/A	429	Y		
MTHFR	rs1801133	chr1:11790644	511	C/T	Coding exon	A/V	222	Y	0.108333	0.488889
MTHFR	rs1931226	chr1:11798240	70	G/T	Intron	–	–	Y	0	0.0583333
MTHFR	rs2066461	chr1:11795614	72	A/C	Coding exon	T/T	115	Y	–	–
MTHFR	rs2066462	chr1:11789162	141	C/T	Coding exon	S/S	352	Y	–	–
MTHFR	rs2066466	chr1:11795542	433	A/G	Coding exon	T/T	139	Y	–	–
MTHFR	rs2066470	chr1:11797323	86	C/T	Coding exon	P/P	39	Y	–	–
MTHFR	rs2066472	chr1:11797237	36	A/G	Coding exon	R/Q	68	Y	–	–
MTHFR	rs2077360	chr1:11783145	740	A/G	Exon	–	–	Y	0	0.42
MTHFR	rs2184226	chr1:11781702	694	A/G	Exon	–	–	Y	0.01	0.12
MTHFR	rs2274974	chr1:11785585	102	A/G	Coding exon	G/E	566	N	–	–
MTHFR	rs2274976	chr1:11785193	562	A/G	Coding exon	R/Q	594	Y	–	–
MTHFR	rs3737964	chr1:11801310	593	A/G	Promoter	–	–	Y	0.0795455	0.308333
MTHFR	rs3927589	chr1:11788759	17	G/T	Coding exon	E/D	423	N	–	–
DHFR	rs4846042	chr1:11771565	248	A/C	3' UTR	–	–	Y	0	0.2
DHFR	rs4846048	chr1:11780518	54	A/G	3' UTR	–	–	Y	0.0930233	0.4
DHFR	rs4846051	chr1:11788723	858	A/G	Coding exon	F/F	435	Y	–	–
DHFR	rs6664734	chr1:11789507	169	C/T	Coding exon	V/V	315	N	–	–
DHFR	rs7525338	chr1:11796598	1	C/T	Intron	–	–	Y	0	0.1
DHFR	rs7533315	chr1:11794949	212	C/T	Intron	–	–	Y	0.266667	0.308333
MTR	rs12749581	chr1:233292889	1032	A/G	Coding exon	R/Q	52	N	–	–
MTR	rs1805087	chr1:233374541	370	A/G	Coding exon	D/G	919	Y	0.166667	0.169643
MTR	rs11799647	chr1:233386962	71	A/G	Coding exon	I/V	1259	N	–	–
MTRR	rs1801394	chr5:7923973	12	A/G	Coding exon	I/M	22	Y	–	–
MTRR	rs1532268	chr5:7931179	348	A/G	Coding exon	S/L	175	Y	–	–
MTRR	rs2303080	chr5:7931424	232	A/T	Coding exon	S/T	257	Y	0	0.170455
MTRR	rs10064631	chr5:7938907	381	C/G	Coding exon	L/V	333	Y	–	–
MTRR	rs162036	chr5:7938959	52	A/G	Coding exon	K/R	350	Y	–	–
MTRR	rs2287780	chr5:7942304	88	C/T	Coding exon	R/C	415	Y	–	–
MTRR	rs16879334	chr5:7944506	405	C/G	Coding exon	P/R	450	Y	–	–
MTRR	rs16879355	chr5:7946013	297	C/T	Coding exon	A/V	515	Y	–	–
MTRR	rs10380	chr5:7950191	55	C/T	Coding exon	H/Y	595	Y	–	–

Background

- We have previously found that vegetable intake was associated with an reduced risk of breast cancer.

- Especially **green yellow vegetable**, not white vegetable was strongly associated with breast cancer risk

  - aOR*=0.32 (95% CI 0.24-0.42) for green vegetable
  - aOR*=1.06 (95% CI 0.81-1.38) for white vegetable

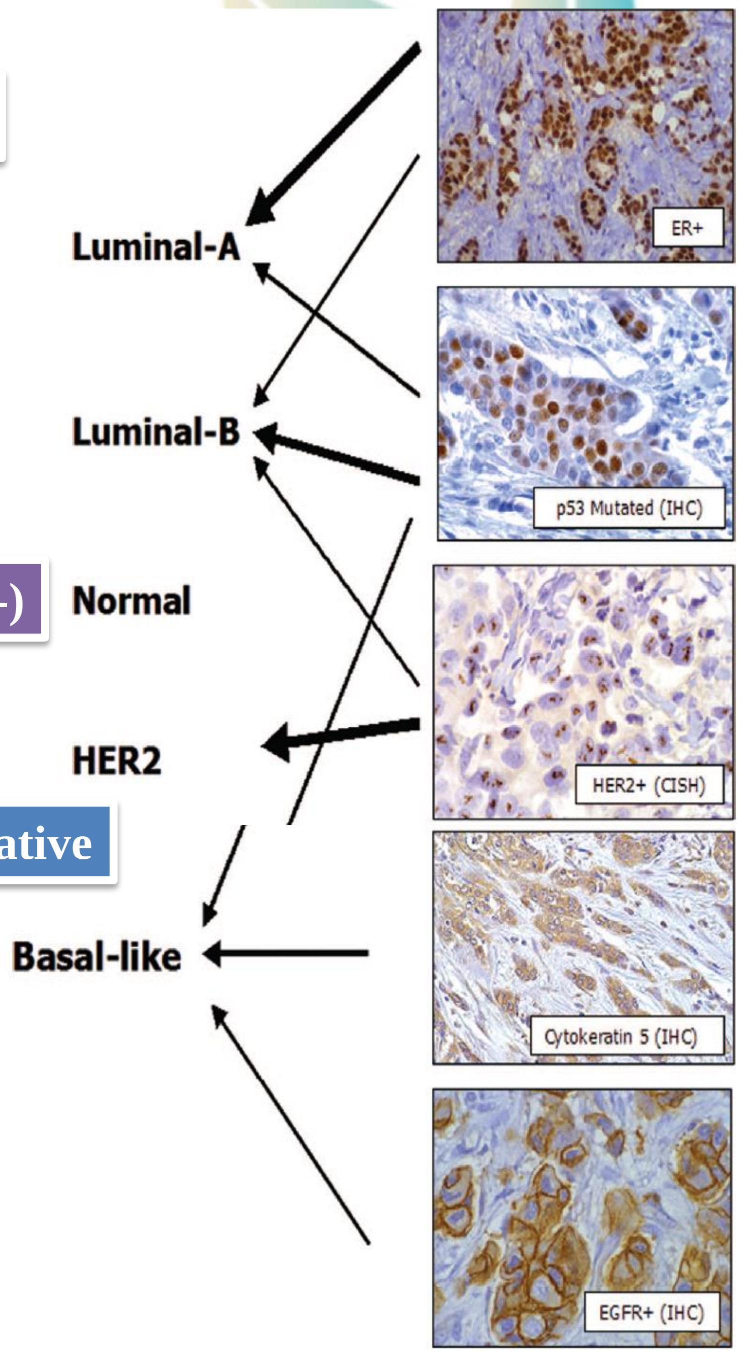
* for top vs. bottom tertiles

Study Aim

To examine the association between folate, vitamin B2, B6, B12 and the risk of breast cancer, as well as the potential modifying effect by two common polymorphisms of the MTHFR, MTR, MTRR & DHFR gene on folate and vitamin B status-associated risk in a multicenter hospital-based case-control study

Molecular Classification of Breast Cancer

- ER(+) or PR(+)
  - HER2 (+) → Luminal A
  - HER2 (-) → Luminal B
- ER(-) and PR(-)
  - HER2 (+) → HER2(+)
  - HER2 (-) → Triple Negative



IHC and FISH test and pathologic exam

Study Population

- Exclude participants with implausible total energy intake or incomplete diet data
- Exclude participants with history of cancer

Breast cancer cases	**1021**
Luminal A	345
Luminal B	227
HER2	124
Triple Negative	325
Controls	**390**

Dietary Ass

Used dish-based semiq
frequency questionn
95 food items

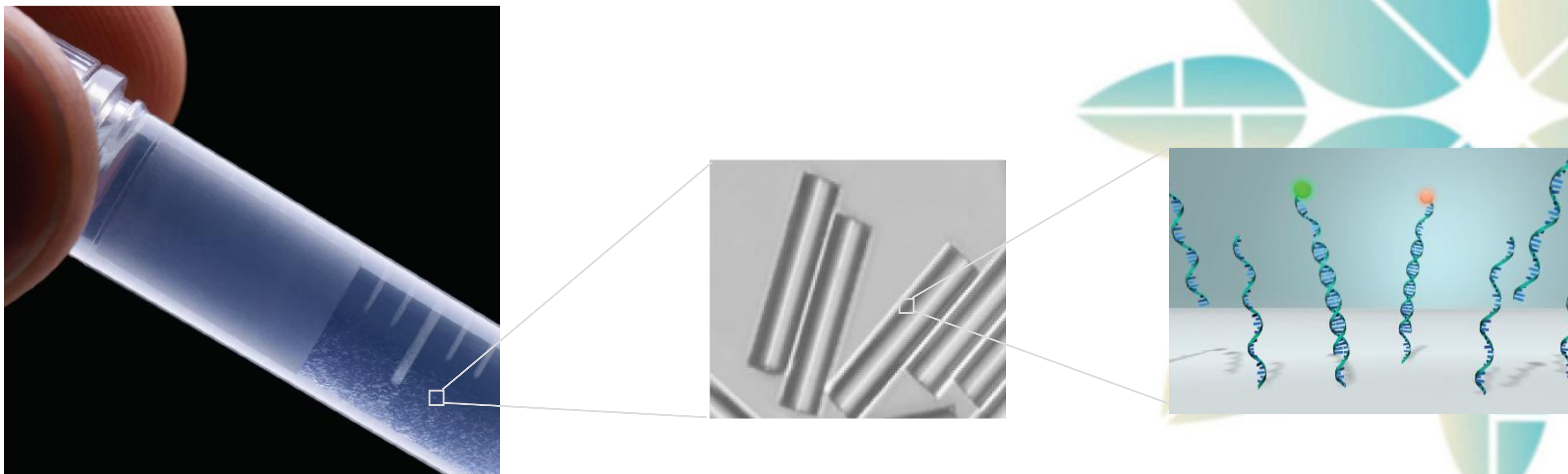
32. 다음부터 제시되는 음식에 대하여 귀하가 드시는 평균 횟수와 양을 기입하여 주십시오.
(양을 기입하실 때 상단 사진에 제시된 음식의 크기와 양을 참고하여 답해 주십시오)

32-1. 주식류

< 사진1. 잡곡밥 >	< 사진2. 비빔밥 >	< 사진3. 칼국수 >	< 사진4. 만두국 >	< 사진5. 샌드위치 >

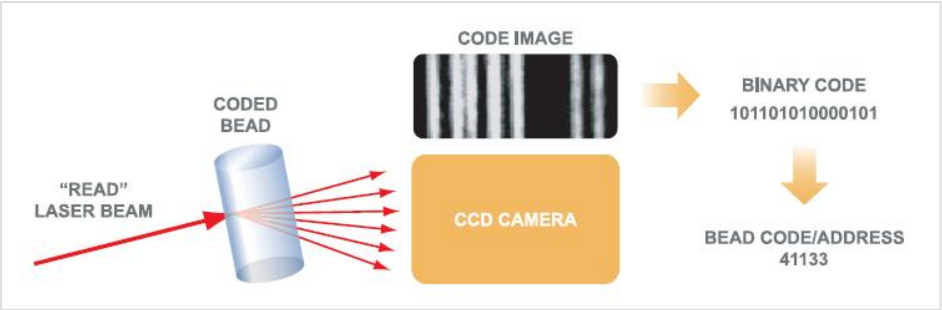
음식명	섭취 빈도수 하루 3회	하루 2회	하루 1회	1주 5-6회	1주 3-4회	1주 1-2회	한 달 2-3회	한 달 1회	안 먹음 0회	한 번의 섭취량
쌀밥, 찰밥, 누룽지	□	□	□	□	□	□	□	□	□	□ ½공기 이하 □ 1공기 (사진1) □ 1.5공기 이상
잡곡밥, 보리밥, 콩밥, 팥밥 등	□	□	□	□	□	□	□	□	□	□ ½공기 이하 □ 1공기 (사진1) □ 1.5공기 이상
죽류	□	□	□	□	□	□	□	□	□	□ ½공기 이하 □ 1공기 □ 1.5공기 이상
비빔밥, 볶음밥, 덮밥, 카레라이스 등	□	□	□	□	□	□	□	□	□	□ ½인분 이하 □ 1인분 (사진2) □ 1.5인분 이상
김밥, 야채김밥, 참치김밥, 회초밥, 유부초밥	□	□	□	□	□	□	□	□	□	□ ½인분 이하 □ 1인분 (김밥1줄, 회초밥4개, 유부초밥3개) □ 1.5인 이상
국수, 수제비, 냉면, 쫄면, 칼국수(해물)	□	□	□	□	□	□	□	□	□	□ ½인분 이하 □ 1인분 (사진3) □ 1.5인분 이상
우동, 스파게티, 자장면, 짬뽕	□	□	□	□	□	□	□	□	□	□ ½인분 이하 □ 1인분 □ 1.5인분 이상
라면, 컵라면	□	□	□	□	□	□	□	□	□	□ ½개 이하 □ 1개 □ 1.5개 이상
떡국, 떡만두국, 만두국	□	□	□	□	□	□	□	□	□	□ ½인분 이하 □ 1인분 (사진4, 만두 8개) □ 1.5인분 이상
식빵, 토스트 (잼/버터), 샌드위치	□	□	□	□	□	□	□	□	□	□ 1장 이하 □ 2장 (사진5) □ 3장 이상
미숫가루, 시리얼	□	□	□	□	□	□	□	□	□	□ ½컵 이하 □ 한 컵 □ 1.5컵 이상

Veracode Technology



Veracode (coded bead)

- Assay type: Golden Gate Assay (allele specific extension)
- Marker density: 96 – 384 SNPs
- Marker type: Custom SNPs
- Sample per exp.: 16 or 96
- Average call rate : > 99%
- Reproducibility: > 99.9%

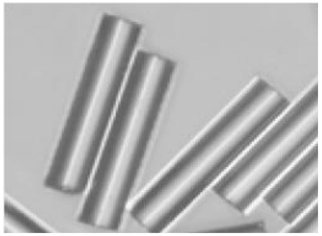


Veracode – code detection technology

Research Process by Using Veracode Technology

OPA (Oligo Pool All)

Golden-Gate Assay

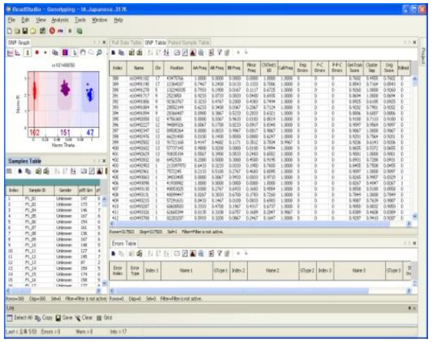


Veracode

Scanning

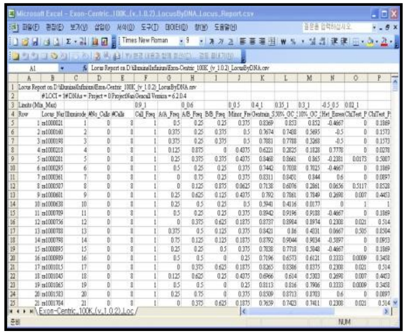
BeadXpress scanner

Intensity data analysis



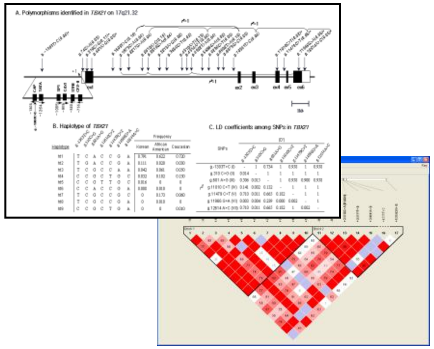
Beadstudio 3.0

Genotype exporting



Genotype data

Statistical analysis



Final data reporting

Results

Folate, Vit B2, B6, B12,and the risk of breast cancer

		Overall	Luminal A	Luminal B	HER2	Triple Negati
Nutrient	Tertile	OR (95% CI)[1]	OR (95% CI)[1]	OR (95% CI)[1]	OR (95% CI)[1]	OR (95% CI)[1]
Folate	<291	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	291-434	0.85(0.67-1.09)	0.90(0.67-1.20)	0.82(0.59-1.16)	0.83(0.55-1.23)	0.81(0.55-1.20)
	434≤	**0.65(0.51-0.84)**	**0.73(0.54-0.98)**	**0.48(0.33-0.70)**	**0.60(0.39-0.93)**	0.75(0.51-1.12)
Vitamin B2	<1.0	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1.0-1.4	0.98(0.76-1.26)	0.99(0.74-1.33)	0.93(0.66-1.33)	0.91(0.61-1.37)	1.08(0.74-1.59)
	1.4≤	0.88(0.68-1.14)	0.98(0.72-1.32)	0.80(0.56-1.16)	0.79(0.51-1.21)	0.85(0.57-1.27)
Vitamin B6	<1.5	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1.5-2.1	0.99(0.77-1.26)	1.06(0.80-1.41)	0.79(0.56-1.11)	0.97(0.65-1.43)	1.12(0.77-1.61)
	2.1≤	**0.55(0.42-0.71)**	**0.57(0.42-0.78)**	**0.52(0.36-0.76)**	**0.52(0.33-0.82)**	**0.55(0.36-0.85)**
Vitamin B12	<3.2	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	3.2-5.1	0.79(0.62-1.02)	0.85(0.63-1.13)	0.71(0.50-1.01)	0.79(0.53-1.18)	0.77(0.52-1.15)
	5.1≤	**0.69(0.53-0.88)**	**0.69(0.51-0.94)**	**0.57(0.40-0.83)**	**0.65(0.43-1.00)**	0.87(0.59-1.28)

OR (95% CI)[1] : adjusted age, BMI, smoking status, alcohol consumption.

MTHFR, DHFR, and the risk of breast cancer

		Overall	Luminal A	Luminal B	HER2	Triple Nega
Gene	rs#	OR (95% CI)[2]	OR (95% CI)[2]	OR (95% CI)[2]	OR (95% CI)[2]	OR (95% CI)[2]
MTHFR	rs1801131					
	AA	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	AC/CC	0.90(0.67-1.19)	0.84(0.59-1.20)	0.86(0.57-1.29)	1.14(0.70-1.85)	0.91(0.56-1.48)
DHFR	rs1677666					
	CC	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	CG	1.29(0.68-2.46)	1.29(0.60-2.79)	1.86(0.84-4.13)	1.44(0.50-4.12)	0.25(0.03-1.89)

OR (95% CI)[2] : Multinomial logistic regression model adjusted age, BMI, smoking status, alcohol consumptio n, age at menarche, age at first parturition.

MTHFR: Methylenetetrahydrofolate reductase
DHFR: Dihydrofolate reductase

Gene-gene interaction with breast cancer risk

MTHFR	DHFR	Overall	Luminal A	Luminal B	HER2	TN
rs1801131	rs1677666	OR (95% CI)[2]	OR (95% CI)[2]	OR (95% CI)[2]	OR (95% CI)[2]	OR (95% CI)[2]
AC/AA	CC	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
AC/AA	CG	0.93(0.31-2.78)	0.83(0.20-3.48)	0.89(0.17-4.65)	2.27(0.52-9.90)	-
AA	CC	1.09(0.81-1.46)	1.16(0.80-1.67)	1.09(0.72-1.66)	0.93(0.56-1.53)	1.08(0.66-1.75)
AA	CG	1.66(0.73-3.77)	1.82(0.70-4.76)	**2.64(1.00-7.01)**	0.88(0.18-4.33)	0.42(0.05-3.46)

OR (95% CI)[2] : Multinomial logistic regression model adjusted age, BMI, smoking status, alcohol consumption, age at menarche, age at first parturition.

MTHFR & folate with the risk of breast cancer

MTHFR	Folate T1	Folate T2	Folate T3	interaction *p*	*p* trend
Overall					
AA	1 (ref)	0.81(0.54-1.21)	**0.48(0.31-0.72)**		
AC/CC	0.78(0.49-1.25)	0.78(0.48-1.26)	**0.47(0.28-0.79)**	0.159	**0.014**
Luminal A					
AA	1 (ref)	0.81(0.49-1.34)	**0.56(0.34-0.94)**		
AC/CC	0.82(0.46-1.46)	0.71(0.39-1.30)	**0.45(0.23-0.87)**	0.114	**0.032**
Luminal B					
AA	1 (ref)	0.76(0.44-1.31)	**0.34(0.18-0.64)**		
AC/CC	0.57(0.29-1.12)	0.79(0.42-1.50)	**0.42(0.20-0.89)**	0.356	**0.032**
HER2					
AA	1 (ref)	0.90(0.46-1.77)	**0.31(0.13-0.73)**		
AC/CC	1.05(0.50-2.22)	1.12(0.53-2.39)	**0.30(0.10-0.92)**	0.656	0.265
Triple Negative					
AA	1 (ref)	0.81(0.41-1.60)	0.69(0.35-1.38)		
AC/CC	0.83(0.38-1.82)	0.64(0.27-1.50)	0.82(0.36-1.85)	0.718	0.446

MTHFR & vitamin B2 with the risk of breast

MTHFR	Vitamin B2			interaction *p*	*p* trend
	T1	T2	T3		
Overall					
AA	1 (ref)	1.01(0.67-1.52)	0.68(0.44-1.03)		
AC/CC	1.04(0.64-1.68)	0.87(0.54-1.41)	**0.52(0.31-0.88)**	0.093	**0.049**
Luminal A					
AA	1 (ref)	1.05(0.64-1.72)	0.64(0.37-1.08)		
AC/CC	0.98(0.54-1.78)	0.85(0.48-1.53)	**0.43(0.21-0.86)**	0.074	**0.040**
Luminal B					
AA	1 (ref)	0.93(0.53-1.64)	0.77(0.43-1.37)		
AC/CC	0.89(0.44-1.78)	0.84(0.43-1.65)	0.60(0.29-1.24)	0.285	0.213
HER2					
AA	1 (ref)	0.76(0.37-1.53)	0.51(0.24-1.10)		
AC/CC	0.98(0.44-2.17)	1.07(0.50-2.26)	0.54(0.21-1.38)	0.998	0.609
Triple Negative					
AA	1 (ref)	1.39(0.71-2.74)	0.80(0.39-1.68)		
AC/CC	1.57(0.73-3.37)	0.75(0.31-1.81)	0.64(0.25-1.65)	0.234	0.289

MTHFR & Vitamin B6 with the risk of breast

MTHFR	VitaminB6			interaction *p*	*p* trend
	T1	T2	T3		
Overall					
AA	1 (ref)	0.88(0.59-1.32)	**0.44(0.28-0.68)**		
AC/CC	1.03(0.64-1.67)	0.90(0.56-1.44)	**0.27(0.15-0.47)**	**0.012**	**0.002**
Luminal A					
AA	1 (ref)	0.85(0.53-1.38)	**0.42(0.24-0.73)**		
AC/CC	0.97(0.54-1.75)	0.87(0.49-1.55)	**0.18(0.08-0.41)**	**0.013**	**0.003**
Luminal B					
AA	1 (ref)	0.77(0.44-1.33)	**0.53(0.29-0.97)**		
AC/CC	0.95(0.49-1.84)	0.69(0.35-1.36)	**0.42(0.20-0.89)**	0.124	**0.047**
HER2					
AA	1 (ref)	0.84(0.43-1.66)	**0.38(0.17-0.89)**		
AC/CC	1.16(0.53-2.50)	1.43(0.69-2.95)	**0.07(0.01-0.55)**	0.409	0.241
Triple Negative					
AA	1 (ref)	1.25(0.66-2.36)	**0.35(0.15-0.85)**		
AC/CC	1.25(0.58-2.68)	0.82(0.36-1.87)	**0.43(0.16-1.14)**	0.195	0.087

MTHFR & Vitamin B12 with the risk of breast

MTHFR	VitaminB12			interaction *p*	*p* trend
	T1	T2	T3		
Overall					
AA	1 (ref)	0.80(0.52-1.22)	**0.57(0.38-0.86)**		
AC/CC	0.91(0.57-1.46)	0.76(0.47-1.23)	**0.39(0.23-0.68)**	0.063	**0.013**
Luminal A					
AA	1 (ref)	0.84(0.50-1.39)	**0.48(0.28-0.80)**		
AC/CC	0.78(0.43-1.40)	0.79(0.44-1.41)	**0.29(0.14-0.62)**	0.067	**0.009**
Luminal B					
AA	1 (ref)	0.70(0.39-1.25)	0.58(0.33-1.02)		
AC/CC	0.92(0.49-1.76)	0.69(0.35-1.35)	**0.30(0.13-0.71)**	0.089	**0.038**
HER2					
AA	1 (ref)	0.73(0.35-1.52)	0.60(0.29-1.24)		
AC/CC	1.20(0.56-2.55)	0.89(0.39-1.99)	0.49(0.18-1.32)	0.741	0.538
Triple Negative					
AA	1 (ref)	0.95(0.47-1.92)	0.82(0.41-1.65)		
AC/CC	1.01(0.45-2.23)	0.67(0.28-1.62)	0.82(0.34-1.97)	0.584	0.490

DHFR & Folate with the risk of breast

DHFR	Folate			interaction *p*	*p* trend
	T1	T2	T3		
Overall					
CC	1 (ref)	0.87(0.63-1.22)	**0.51(0.36-0.72)**		
CG	1.22(0.45-3.29)	0.85(0.30-2.41)	0.93(0.21-4.01)	0.574	0.014
Luminal A					
CC	1 (ref)	0.88(0.58-1.33)	**0.55(0.36-0.86)**		
CG	1.66(0.55-5.01)	0.35(0.07-1.82)	1.36(0.26-7.08)	0.745	0.083
Luminal B					
CC	1 (ref)	0.87(0.55-1.38)	**0.42(0.25-0.71)**		
CG	1.15(0.31-4.33)	1.72(0.51-5.72)	1.22(0.20-7.57)	0.137	0.155
HER2					
CC	1 (ref)	0.93(0.54-1.60)	**0.30(0.15-0.62)**		
CG	0.97(0.18-5.09)	1.60(0.37-6.90)	-	0.639	**0.033**
Triple Negative					
CC	1 (ref)	0.81(0.46-1.43)	0.78(0.44-1.36)		
CG	0.48(0.06-4.23)	-	-	0.165	0.142

DHFR & VitaminB2 with the risk of breast

DHFR	VitaminB2			interaction *p*	*p* trend
	T1	T2	T3		
Overall					
CC	1 (ref)	0.92(0.66-1.29)	**0.62(0.43-0.88)**		
CG	1.11(0.40-3.12)	1.64(0.51-5.26)	0.62(0.18-2.09)	0.629	0.105
Luminal A					
CC	1 (ref)	0.94(0.62-1.42)	0.55(0.35-0.86)		
CG	0.95(0.26-3.55)	1.66(0.45-6.18)	0.67(0.15-2.94)	0.624	0.119
Luminal B					
CC	1 (ref)	0.90(0.56-1.45)	0.73(0.44-1.20)		
CG	1.44(0.38-5.48)	2.36(0.59-9.44)	1.23(0.28-5.44)	0.170	0.970
HER2					
CC	1 (ref)	0.94(0.53-1.66)	0.58(0.31-1.11)		
CG	2.31(0.60-8.95)	0.93(0.10-8.82)	-	0.852	0.255
Triple Negative					
CC	1 (ref)	0.91(0.53-1.58)	0.62(0.34-1.13)		
CG	-	0.85(0.09-8.05)	-	0.205	**0.049**

DHFR & VitaminB6 with the risk of breast

DHFR	VitaminB6			interaction *p*	*p* trend
	T1	T2	T3		
Overall					
CC	1 (ref)	0.89(0.64-1.24)	**0.35(0.24-0.51)**		
CG	1.16(0.43-3.18)	0.77(0.25-2.38)	0.85(0.24-3.02)	0.582	**0.0005**
Luminal A					
CC	1 (ref)	0.88(0.59-1.32)	**0.31(0.19-0.51)**		
CG	1.26(0.39-4.11)	0.66(0.17-2.58)	0.83(0.18-3.90)	0.697	**0.002**
Luminal B					
CC	1 (ref)	0.75(0.47-1.19)	**0.46(0.27-0.77)**		
CG	1.23(0.33-4.61)	1.17(0.29-4.69)	1.68(0.40-7.12)	0.121	0.254
HER2					
CC	1 (ref)	1.08(0.63-1.86)	**0.28(0.13-0.59)**		
CG	2.18(0.57-8.39)	0.62(0.07-5.64)	-	0.904	**0.028**
Triple Negative					
CC	1 (ref)	0.98(0.58-1.66)	**0.34(0.17-0.67)**		
CG	-	0.52(0.06-4.77)	-	0.214	**0.002**

DHFR & VitaminB12 with the risk of breast

DHFR	VitaminB12			interaction *p*	*p* trend
	T1	T2	T3		
Overall					
CC	1 (ref)	0.80(0.57-1.13)	**0.53(0.37-0.75)**		
CG	1.13(0.41-3.12)	1.23(0.31-4.87)	0.72(0.25-2.08)	0.629	**0.022**
Luminal A					
CC	1 (ref)	0.87(0.58-1.31)	**0.44(0.28-0.70)**		
CG	1.04(0.31-3.57)	1.55(0.33-7.38)	0.63(0.17-2.37)	0.697	**0.024**
Luminal B					
CC	1 (ref)	0.72(0.45-1.15)	**0.50(0.30-0.82)**		
CG	1.59(0.45-5.54)	1.59(0.30-8.35)	0.99(0.26-3.74)	0.238	0.247
HER2					
CC	1 (ref)	0.75(0.42-1.34)	**0.54(0.29-1.00)**		
CG	1.70(0.39-7.31)	0.98(0.10-10.08)	0.54(0.06-4.77)	0.839	0.220
Triple Negative					
CC	1 (ref)	0.82(0.47-1.45)	0.79(0.45-1.41)		
CG	-	-	0.52(0.06-4.62)	0.276	0.204

Conclusions of this study

- Folate, and one carbon metabolizing nutrients were inversely associated with breast cancer risk

- MTHFR and DHFR genetic polymorphisms may modify susceptibility to breast cancer.

MTHFR polymorphisms, dietary folate intake and breast cancer risk in Chinese women

- a case-control study
- with 669 cases and 682 population-based controls
- in the Jiangsu Province of China
- 83-item food frequency questionnaire

Dietary folate
aOR = 0.70 (0.53~0.92) for top vs. bottom tertiles

J Hum Genet. 2009 Jul;54(7):414-8

MTHFR genotypes and folate intake with breast cancer risk: Shanghai Breast Cancer Cohort Study

genotype	Dietary folate intake				*p* for interaction
	Q4	Q3	Q2	Q1	
C677T					
CC	1.00	1.76	1.75	1.94 (1.15-3.26)	
CT	1.16	1.50	1.73	2.17 (1.34-3.51)	0.048
TT	0.70	1.66	2.17	2.51 (1.37-4.60)	
A1298C					
AA	1.00	1.59	1.94	2.18 (1.46-3.25)	0.71
AC/CC	1.05	1.80	1.59	1.94 (1.23-3.05)	

CEBP, 2004

Dietary intake of folate, vit B2, vit B6, vit B12, genetic polymorphism of related enzymes, and risk of breast cancer: A case-control study in Japan

Ma E, Iwasaki M, Tsugane S et al. National Cancer Center, Tokyo, Japan.

Nutr Cancer. 2009;61(4):447-56.

A hospital based, case-control study in Nagano Prefecture, Japan
388 pairs of patients with histologically confirmed invasive breast cancer and age- and area-matched controls selected from medical checkup examinees.

Dietary intake of folate and related B vitamins and genotypes of MTHFR or MTR have no overall association with breast cancer risk in Japanese women

BMC Cancer

BioMed Central

2009 Open Access

Research article

Dietary intake of folate, vitamin B_6, and vitamin B_{12}, genetic polymorphism of related enzymes, and risk of breast cancer: a case-control study in Brazilian women

Enbo Ma[1], Motoki Iwasaki*[1], Ishihara Junko[1,2], Gerson Shigeaki Hamada[3], Ines Nobuko Nishimoto[4], Solange Maria Torchia Carvalho[5], Juvenal Motola Jr[6], Fábio Martins Laginha[6] and Shoichiro Tsugane[1]

Nutrient intake	Premenopausal		Postmenopausal	
	aOR*(95% CI)	P trend	aOR*(95% CI)	P trend
Folate (ug/d)	**2.17(1.23~3.83)**	**0.01**	0.91(0.59~1.41)	0.68
Vitamin B6 (mg/d)	0.81(0.48~1.37)	0.41	**1.54(1.01~2.35)**	**0.04**

* for top vs. bottom tertiles

Is folic acid good for everyone?

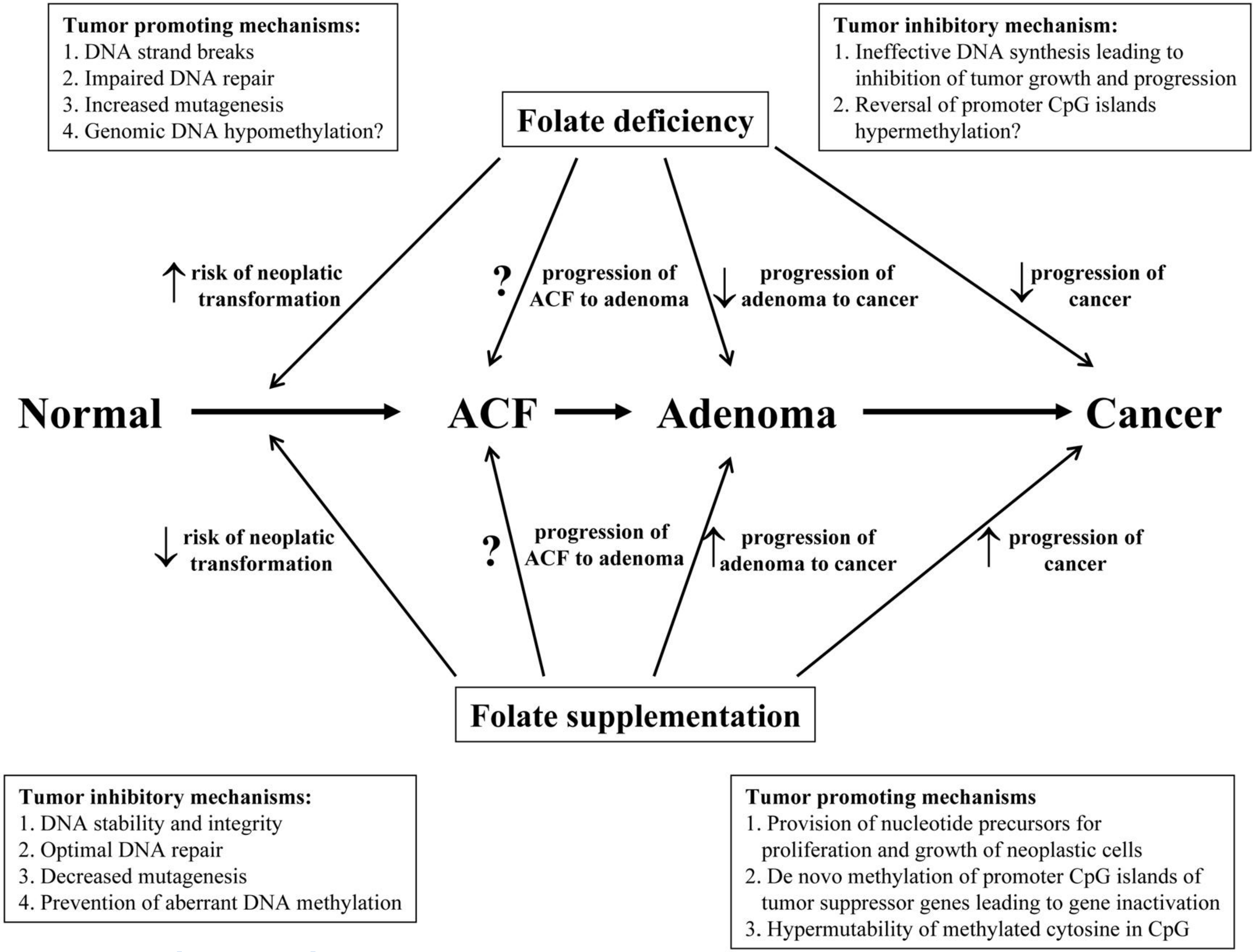
Fortification of food with folic acid to reduce the number of neural tube defects was introduced 10 y ago in North America.

High blood concentrations of folic acid may be related to decreased natural killer cell cytotoxicity, and high folate status may reduce the response to antifolate drugs used against malaria, rheumatoid arthritis, psoriasis, and cancer.

Folate has a dual effect on cancer, protecting against cancer initiation but facilitating progression and growth of preneoplastic cells and subclinical cancers, which are common in the population. Thus, a high folic acid intake may be harmful for some people.

Kim YI, AJCN 2008

Dual modulatory role of folate in carcinogenesis



Kim YI, Mol Nutr Food Res, 2007

Folate:
a magic bullet or a double edged sword for cancer prevention ?

Colorectal cancer

Folate: a magic bullet or a double edged sword for colorectal cancer prevention?

Y-I Kim

Low folate status might inhibit colorectal carcinogenesis and high folate status may promote colorectal carcinogenesis, contradicting findings from epidemiological studies showing an inverse relationship between folate status and risk of colorectal cancer

Gut 2006

Cancer Incidence and Mortality After Treatment With Folic Acid and Vitamin B_{12}

Marta Ebbing, MD
Kaare Harald Bønaa, MD, PhD
Ottar Nygård, MD, PhD
Egil Arnesen, MD
Per Magne Ueland, MD, PhD
Jan Erik Nordrehaug, MD, PhD
Knut Rasmussen, MD, PhD
Inger Njølstad, MD, PhD
Helga Refsum, MD, PhD
Dennis W. Nilsen, MD, PhD

Context Recently, concern has been raised about the safety of folic acid, particularly in relation to cancer risk.

Objective To evaluate effects of treatment with B vitamins on cancer outcomes and all-cause mortality in 2 randomized controlled trials.

Design, Setting, and Participants Combined analysis and extended follow-up of participants from 2 randomized, double-blind, placebo-controlled clinical trials (Norwegian Vitamin Trial and Western Norway B Vitamin Intervention Trial). A total of 6837 patients with ischemic heart disease were treated with B vitamins or placebo between 1998 and 2005, and were followed up through December 31, 2007.

Interventions Oral treatment with folic acid (0.8 mg/d) plus vitamin B_{12} (0.4 mg/d) and vitamin B_6 (40 mg/d) (n=1708); folic acid (0.8 mg/d) plus vitamin B_{12} (0.4 mg/d) (n=1703); vitamin B_6 alone (40 mg/d) (n=1705); or placebo (n=1721).

Treatment with folic acid plus vitamin B12 was associated with increased cancer Outcomes and all-cause mortality in patients with ischemic heart disease in Norway, where there is no folic acid fortification of foods.

... did not receive such treatment were diagnosed with cancer (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.03-1.41; *P*=.02). A total of 136 (4.0%) who received folic acid plus vitamin B_{12} vs 100 (2.9%) who did not receive such treatment died from cancer (HR, 1.38; 95% CI, 1.07-1.79; *P*=.01). A total of 548 patients (16.1%) who received folic acid plus vitamin B_{12} vs 473 (13.8%) who did not receive such treatment died from any cause (HR, 1.18; 95% CI, 1.04-1.33; *P*=.01). Results were mainly driven by increased lung cancer incidence in participants who received folic acid plus vitamin B_{12}. Vitamin B_6 treatment was not associated with any significant effects.

Conclusion Treatment with folic acid plus vitamin B_{12} was associated with increased cancer outcomes and all-cause mortality in patients with ischemic heart disease in Norway, where there is no folic acid fortification of foods.

Trial Registration clinicaltrials.gov Identifier: NCT00671346

JAMA. 2009;302(19):2119-2126 www.jama.com

F ... for nucleotide biosynthesis, DNA replication, and methyl group supply, and thus for cell growth and repair.[1] Folic acid is the synthetic form of folate used in vitamin supplements and in fortified foods. Most epidemiological studies have found inverse associations between folate intake and risk of colorectal cancer,[2] although such associations have been inconsistent or absent for other cancers.[3-8] Experimental evidence suggests that folate deficiency may pro-

No relation of folate supplementation with cancer risk

A randomized trial on folic acid supplementation and risk of recurrent colorectal adenoma[1–3]

Kana Wu, Elizabeth A Platz, Walter C Willett, Charles S Fuchs, Jacob Selhub, Bernard A Rosner, David J Hunter, and Edward Giovannucci

ABSTRACT

Background: Evidence from observational studies suggests that inadequate folate status enhances colorectal carcinogenesis, but results from some randomized trials do not support this hypothesis.

Objective: To assess the effect of folic acid supplementation on recurrent colorectal adenoma, we conducted a cost-efficient, double-blind, randomized trial among participants of 2 large prospective cohorts, the Health Professionals Follow-Up Study and the Nurses' Health Study.

Design: Participants were randomly assigned to receive folic acid (1 mg/d) (n = 338) or placebo (n = 334) for 3–6.5 y. The primary endpoint was any new diagnosis of adenoma during the study period (May 1996–March 2004). Secondary outcomes were adenoma by site and stage and number of recurrent adenomas. Associations were also examined by plasma folate concentrations at baseline.

Results: Incidence of at least one recurrent adenoma was not significantly associated with folic acid supplementation [relative risk (RR): 0.82; 95% CI: 0.59,1.13; $P = 0.22$]. Among participants with low plasma folate concentrations at baseline ($\leq$7.5 ng/mL), those randomly assigned to receive folic acid experienced a significant decrease in adenoma recurrence (RR: 0.61; 95% CI: 0.42, 0.90; $P = 0.01$), whereas for subjects with high folate concentrations at baseline (>7.5 ng/mL), supplemental folic acid had no significant effect (RR: 1.28; 95% CI: 0.82, 1.99; $P = 0.27$, $P_{interaction} = 0.01$). Contrary to findings from another clinical trial, there was no evidence for an increased risk of advanced or multiple adenomas.

Conclusions: Our results do not support an overall protective effect of folic acid supplementation on adenoma recurrence. Folic acid supplementation may be beneficial among those with lower folate concentrations at baseline. This trial was registered at clinical trials.gov as NCT00512850. *Am J Clin Nutr* 2009;90:1623–31.

supplemented group were found to have recurrent adenomas after 24 mo compared with 28% in the placebo group; however, differences were not statistically significant.

On the contrary, 2 recent large clinical trials, the Aspirin/Folate Polyp Prevention Study (AFPPS) (5) and the United Kingdom Colorectal Adenoma Prevention (ukCAP) trial (6) showed little evidence for a protective effect of FA supplementation on recurrent adenomas, and in 1 of these 2 trials, FA supplementation was associated with higher risk of advanced and multiple adenomas (5). This article reports on another randomized trial of FA supplementation (1 mg/d) and recurrent adenoma among participants of 2 large prospective cohorts, the Health Professionals Follow-Up Study (HPFS) and the Nurses' Health Study (NHS). In both cohorts, previous analyses had suggested that higher folate consumption was associated with a lower risk of colorectal adenoma (7).

SUBJECTS AND METHODS

Study cohort

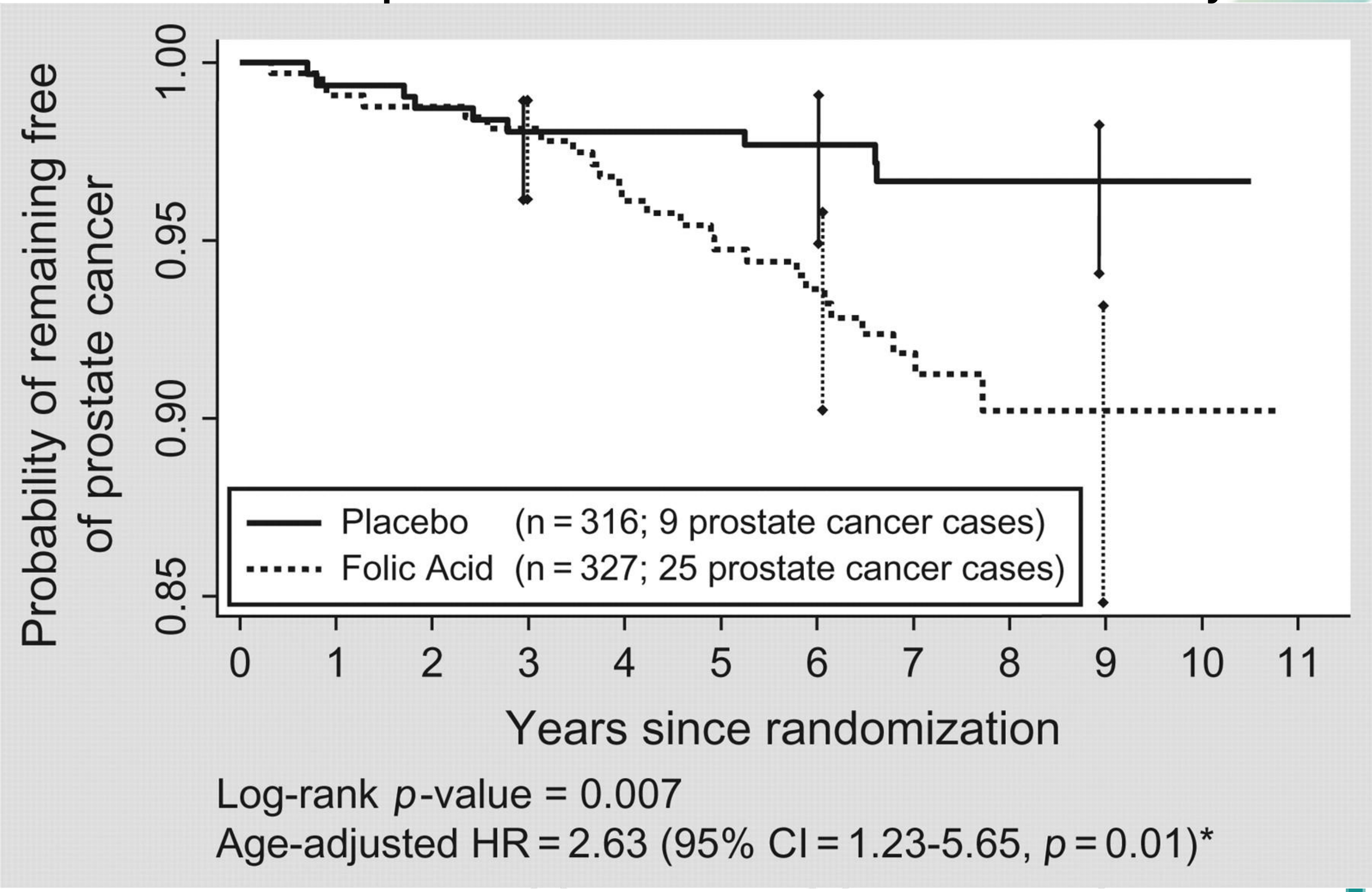
The CONSORT (Consolidated Standards of Reporting Trials) flowchart (8) for the NHS/HPFS Folic Acid Prevention Trial is shown in **Figure 1**. Because adenoma recurrence trials are typically expensive to conduct, we designed a double-blind randomized intervention trial that could be conducted efficiently and at low cost. We used the resources of 2 large US cohorts, the HPFS and the NHS, and were able to absorb much of the costly

[1] From the Departments of Nutrition (KW, WCW, DJH, and EG), Epidemiology (WCW, DJH, and EG), and Biostatistics (BR), Harvard School of

Folic Acid and Risk of Prostate Cancer: Results From a Randomized Clinical Trial

Jane C. Figueiredo, Maria V. Grau, Robert W. Haile, Robert S. Sandler, Robert W. Summers, Robert S. Bresalier, Carol A. Burke, Gail E. McKeown-Eyssen, John A. Baron

Kaplan-Meier plot of the prostate cancer-free status over time among the 643 men randomized to placebo and folic acid treatment in this study



Figueiredo, J. C. et al. J. Natl. Cancer Inst. 2009 101:432-435; doi:10.1093/jnci/djp019

JNCI

Folic Acid and Risk of Prostate Cancer: Results From a Randomized Clinical Trial

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Table 1. Association of folic acid treatment, baseline dietary intake, and circulating levels of folate with risk of subsequent prostate cancer*

	Adjusted for age		Adjusted for multiple factors	
Risk factor	**HR (95% CI)†**	***P* value†**	**HR (95% CI)**	***P* value**
Folic acid supplementation	2.63 (1.23 to 5.65)	.01	2.58 (1.14 to 5.86)‡	.02
Dietary folate§	0.70 (0.48 to 1.04)	.08	0.65 (0.35 to 1.20)‖	.17
Nonmultivitamin users	0.77 (0.50 to 1.19)	.24	0.70 (0.37 to 1.33)‖	.28
Multivitamin users	0.53 (0.21 to 1.32)	.17	0.49 (0.18 to 1.36)‖	.17
Plasma folate¶	0.56 (0.32 to 0.98)	.04	0.68 (0.35 to 1.30)#	.25
Nonmultivitamin users	0.41 (0.18 to 0.96)	.04	0.42 (0.17 to 1.04)#	.06
Multivitamin users	1.01 (0.55 to 1.86)	.97	1.11 (0.58 to 2.15)#	.75
Red blood cell folate**	0.82 (0.57 to 1.17)	.27	1.19 (0.77 to 1.83)#	.43
Nonmultivitamin users	0.73 (0.46 to 1.16)	.18	0.91 (0.54 to 1.53)#	.64
Multivitamin users	1.81 (0.95 to 3.45)	.07	2.04 (1.08 to 3.87)#	.03

J Natl Cancer Inst 2009;101:432–435

Public health implications of nutrient (folate)-gene interactions for cancer prevention/treatment

- Gene-environment interaction study have provided so far important insight into whether a nutrient is causally associated with cancer risk

- If nutrient-gene interaction is established, should individuals be genotyped and their diets targeted based on the results?

Still unanswered !

Summary of talk

- Folate may affect cancer risk through one-carbon metabolism.
- Interactions of folate with MTHFR genotypes also may modify cancer risks.
- Limited evidence of epidemiologic study in Asian countries
- Well-designed prospective studies and randomized controlled trials in Asia are needed;

1) to find the optimal timing, doses, and forms that maximize efficacy and minimize adverse effects
2) to identify subjects who will get benefit from interventions with folate
3) to assess the role of folate in the primary prevention of cancer and also in treatment of cancer patients.

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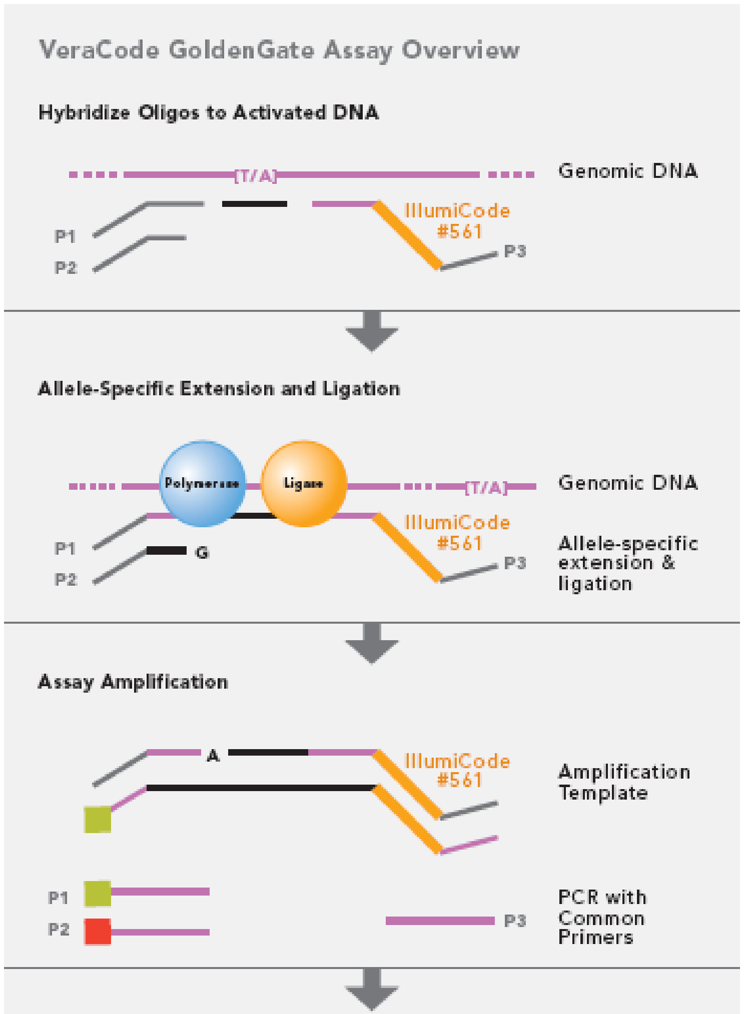
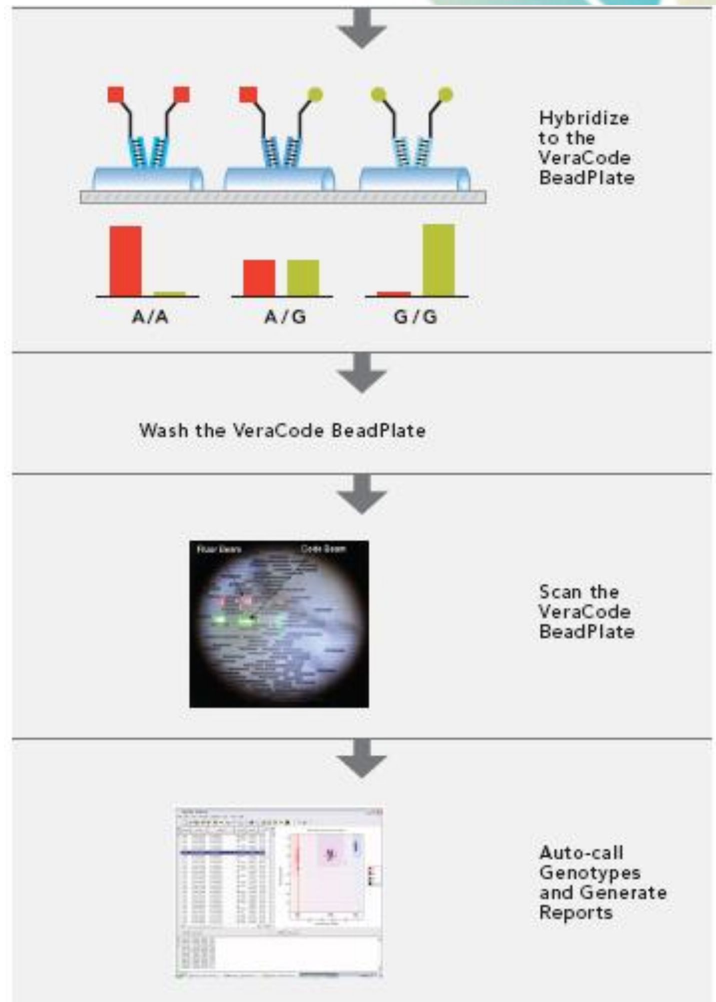
NCC Intramural Research Fund

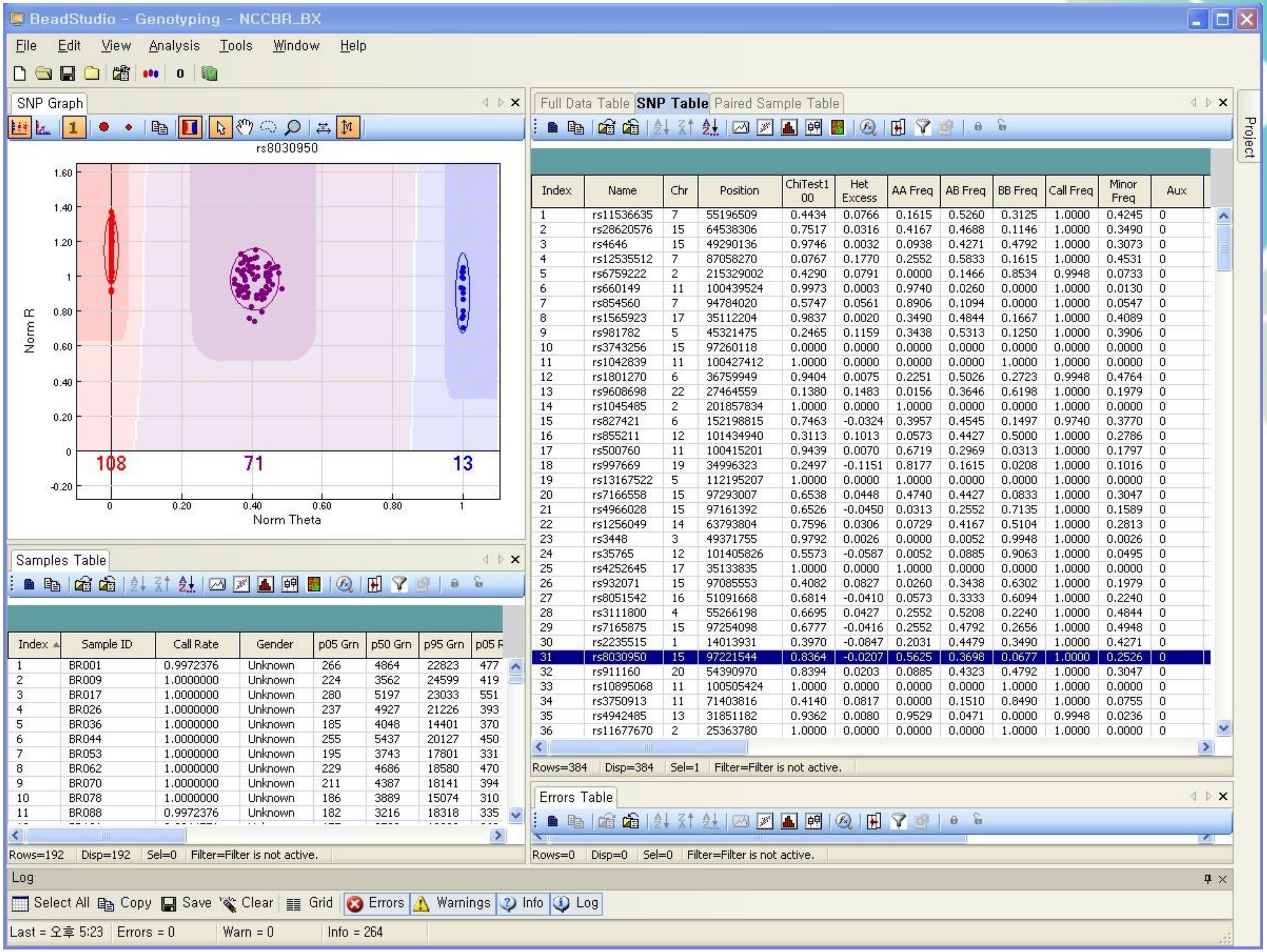
Thanks for your attention !

Veracode Overview (Golden-Gate Assay)





NCCBR – BeadStudio: Genotype calling



Index	Sample ID	Call Rate	Gender	p05 Grn	p50 Grn	p95 Grn	p05 R
1	BR001	0.9972376	Unknown	266	4864	22823	477
2	BR009	1.0000000	Unknown	224	3562	24599	419
3	BR017	1.0000000	Unknown	280	5197	23033	551
4	BR026	1.0000000	Unknown	237	4927	21226	393
5	BR036	1.0000000	Unknown	185	4048	14401	370
6	BR044	1.0000000	Unknown	255	5437	20127	450
7	BR053	1.0000000	Unknown	195	3743	17801	331
8	BR062	1.0000000	Unknown	229	4686	18580	470
9	BR070	1.0000000	Unknown	211	4387	18141	394
10	BR078	1.0000000	Unknown	186	3889	15074	310
11	BR088	0.9972376	Unknown	182	3216	18318	335

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1	rs11536635	7	55196509	0.4434	0.0766	0.1615	0.5260	0.3125	1.0000	0.4245	0
2	rs28620576	15	64538306	0.7517	0.0316	0.4167	0.4688	0.1146	1.0000	0.3490	0
3	rs4646	15	49290136	0.9746	0.0032	0.0938	0.4271	0.4792	1.0000	0.3073	0
4	rs12535512	7	87058270	0.0767	0.1770	0.2552	0.5833	0.1615	1.0000	0.4531	0
5	rs6759222	2	215329002	0.4290	0.0791	0.0000	0.1466	0.8534	0.9948	0.0733	0
6	rs660149	11	100439524	0.9973	0.0003	0.9740	0.0260	0.0000	1.0000	0.0130	0
7	rs854560	7	94784020	0.5747	0.0561	0.8906	0.1094	0.0000	1.0000	0.0547	0
8	rs1565923	17	35112204	0.9837	0.0020	0.3490	0.4844	0.1667	1.0000	0.4089	0
9	rs981782	5	45321475	0.2465	0.1159	0.3438	0.5313	0.1250	1.0000	0.3906	0
10	rs3743256	15	97260118	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0
11	rs1042839	11	100427412	1.0000	0.0000	0.0000	0.0000	1.0000	1.0000	0.0000	0
12	rs1801270	6	36759949	0.9404	0.0075	0.2251	0.5026	0.2723	0.9948	0.4764	0
13	rs9608698	22	27464559	0.1380	0.1483	0.0156	0.3646	0.6198	1.0000	0.1979	0
14	rs1045485	2	201857834	1.0000	0.0000	1.0000	0.0000	0.0000	1.0000	0.0000	0
15	rs827421	6	152198815	0.7463	-0.0324	0.3957	0.4545	0.1497	0.9740	0.3770	0
16	rs855211	12	101434940	0.3113	0.1013	0.0573	0.4427	0.5000	1.0000	0.2786	0
17	rs500760	11	100415201	0.9439	0.0070	0.6719	0.2969	0.0313	1.0000	0.1797	0
18	rs997669	19	34996323	0.2497	-0.1151	0.8177	0.1615	0.0208	1.0000	0.1016	0
19	rs13167522	5	112195207	1.0000	0.0000	1.0000	0.0000	0.0000	1.0000	0.0000	0
20	rs7166558	15	97293007	0.6538	0.0448	0.4740	0.4427	0.0833	1.0000	0.3047	0
21	rs4966028	15	97161392	0.6526	-0.0450	0.0313	0.2552	0.7135	1.0000	0.1589	0
22	rs1256049	14	63793804	0.7596	0.0306	0.0729	0.4167	0.5104	1.0000	0.2813	0
23	rs3448	3	49371755	0.9792	0.0026	0.0000	0.0052	0.9948	1.0000	0.0026	0
24	rs35765	12	101405826	0.5573	-0.0587	0.0052	0.0885	0.9063	1.0000	0.0495	0
25	rs4252645	17	35133835	1.0000	0.0000	1.0000	0.0000	0.0000	1.0000	0.0000	0
26	rs932071	15	97085553	0.4082	0.0827	0.0260	0.3438	0.6302	1.0000	0.1979	0
27	rs8051542	16	51091668	0.6814	-0.0410	0.0573	0.3333	0.6094	1.0000	0.2240	0
28	rs3111800	4	55266198	0.6695	0.0427	0.2552	0.5208	0.2240	1.0000	0.4844	0
29	rs7165875	15	97254098	0.6777	-0.0416	0.2552	0.4792	0.2656	1.0000	0.4948	0
30	rs2235515	1	14013931	0.3970	-0.0847	0.2031	0.4479	0.3490	1.0000	0.4271	0
31	rs8030950	15	97221544	0.8364	-0.0207	0.5625	0.3698	0.0677	1.0000	0.2526	0
32	rs911160	20	54390970	0.8394	0.0203	0.0885	0.4323	0.4792	1.0000	0.3047	0
33	rs10895068	11	100505424	1.0000	0.0000	0.0000	0.0000	1.0000	1.0000	0.0000	0
34	rs3750913	11	71403816	0.4140	0.0817	0.0000	0.1510	0.8490	1.0000	0.0755	0
35	rs4942485	13	31851182	0.9362	0.0080	0.9529	0.0471	0.0000	0.9948	0.0236	0
36	rs11677670	2	25363780	1.0000	0.0000	0.0000	0.0000	1.0000	1.0000	0.0000	0

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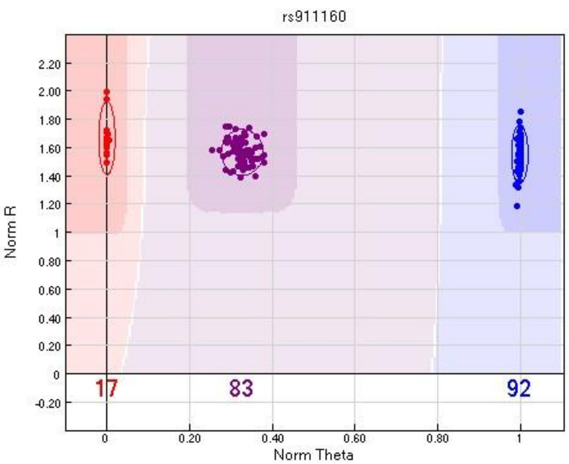
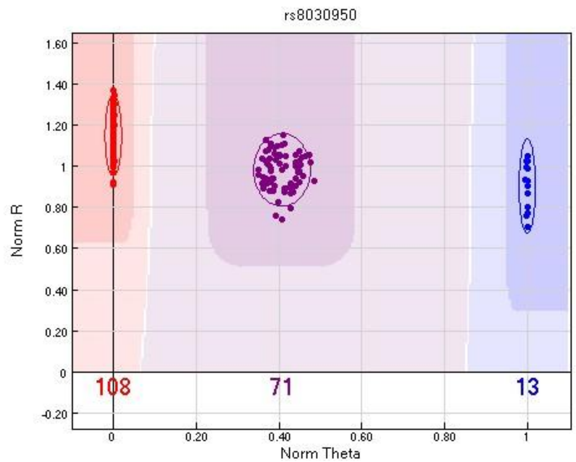
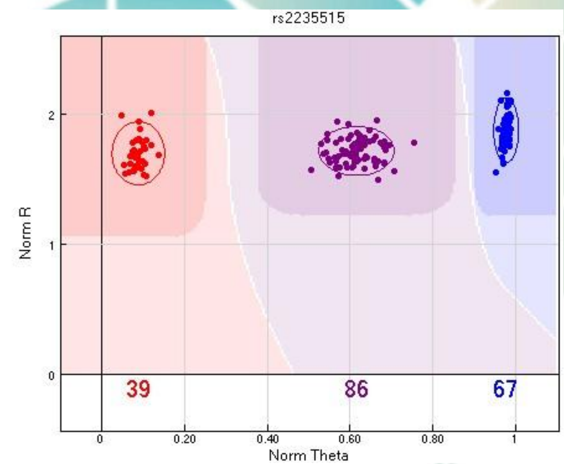
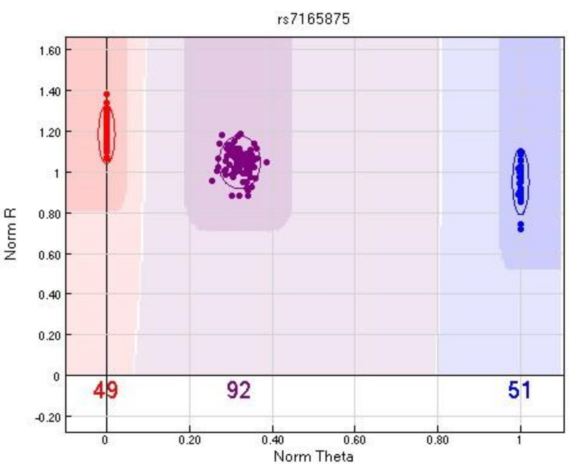
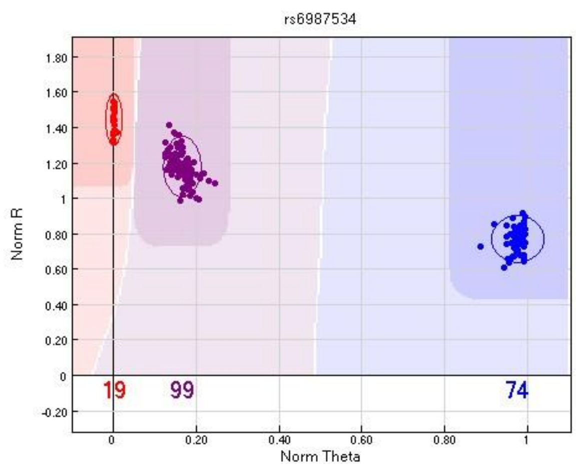
NCCBR – Genotype Cluster Image

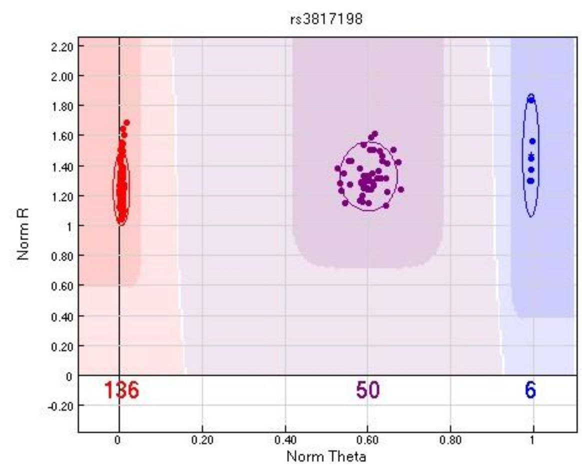












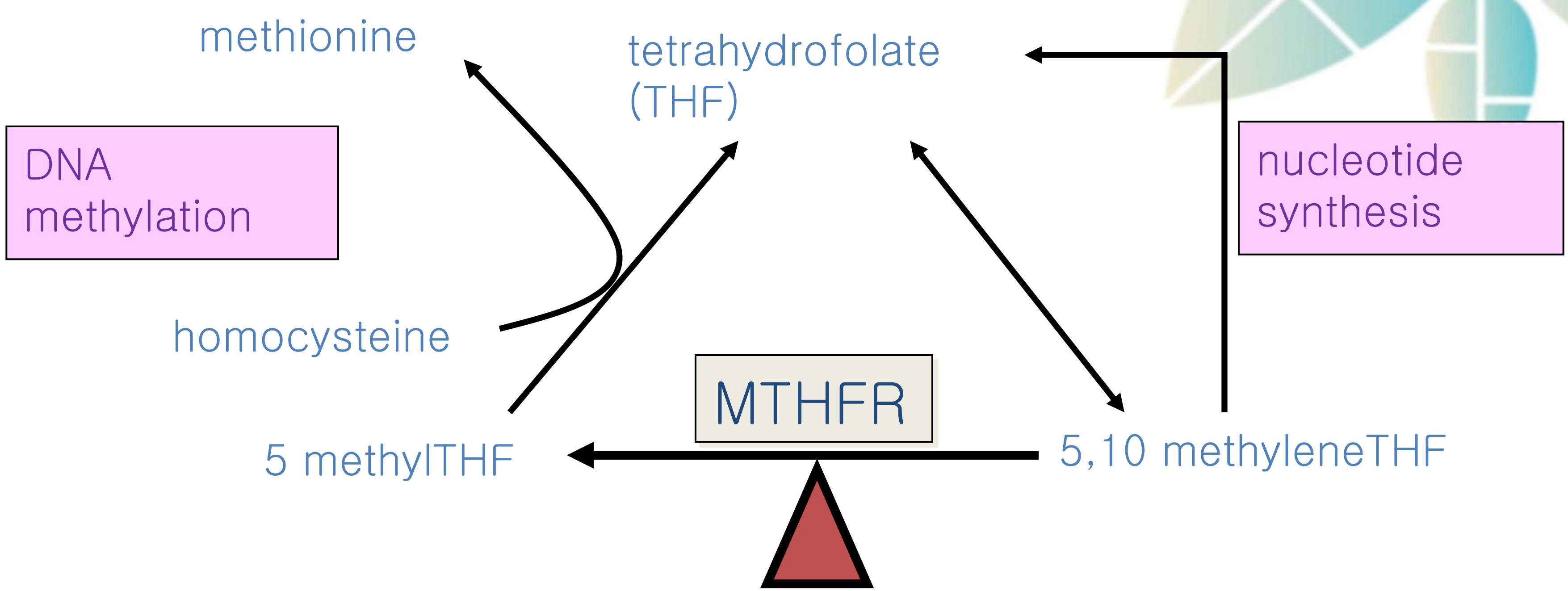
Single Nucleotide Polymorphism (SNP)

- A tiny change in the gene sequence
  : only a single nucleotide change

- Allele frequency: 1/1000 to 1/2 in populations

- Functional consequences:
  - alteration in protein function, thus metabolic pathway
  - alteration in promotor activity, thus metabolic pathway
  - no known alteration but association with parameter leve

Methylenetetrahydrofolate reductase (MTHFR)



Methylenetetrahydrofolate reductase (MTHFR)

- MTHFR: 5,10-methyl THF → 5-methyl THF

- A common polymorphism (*677C→T*) in the *MTHFR* gene causes heat sensitivity (thermolabile variant) and reduced enzymatic activity *in vivo and in vitro.*

- C677T
  - cytosine to thymidine conversion at 677
  - alanine → valine
  - enzyme activity: CC(100%), CT(65%), TT(30%)
  - frequency of TT: 10-15%

- A1298C
  - adenine to cytosine conversion at 1298
  - glutamate → alanine

Pill or Food?

- A population study demonstrated that the risk of lung cancer is inversely associated with dietary folate but not with intake of fortified folate, supplemented folate, or total folate intake.
  (Shen, CEBP 2003;12:980)

- The supplementation with folate in a single synthetic chemical form, folic acid, might not be as effective as high folate diets, which contain more physiologic forms of folate and other nutrients needed for folate metabolism.

Can we prevent cancer with B-vitamins?

- It sounds like a simple question.
- In fact, finding the answer is a complex puzzle worthy of Sherlock Holmes.

"Someone has been nibbling at our research again"

Public Health Implications of Nutrient-Gene Interactions for Cancer Prevention

- ❑ Gene-environment interaction study have provided so far important insight into whether a nutrient is causally associated with cancer risk

- ❑ If nutrient-gene interaction is established, should individuals be genotyped and their diets targeted based on the results?

- ❑more carefully designed studies and scientific evidences are needed

Still unanswered !

1. SNP/Sample success rate

	Design	Success	Success rate
# of SNPs	384	354	92.2%
# of Samples	1,440	1,418	98.5%

2. Genotype call rate

# of expected genotypes 354x1418=501,972
# of observed genotypes: 501,055
Call rate: 501,055/501,972=99.8%

3. Minor allele frequency

MAF	# of SNPs	%
Monomorphic	25	7.1%
≤0.1	45	12.7%
≤0.2	42	11.9%
≤0.3	66	18.6%
≤0.4	103	29.1%
≤0.5	73	20.6%
Total	354	100%

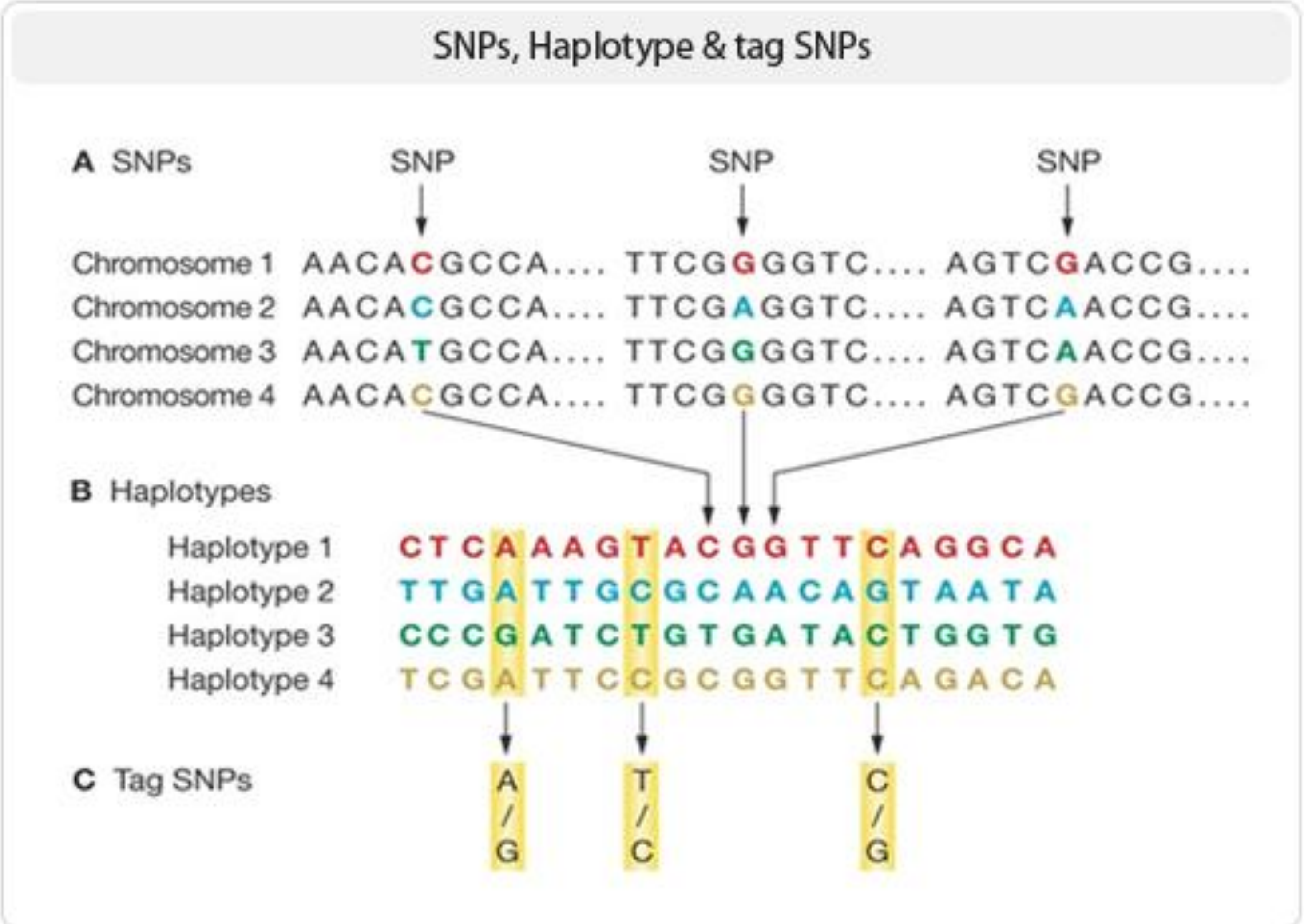
Breast	1021
Luminal A	345
Luminal B	227
HER2	124
TN	325
Control	390

Association of 384 SNPs with the risk of breast cancer

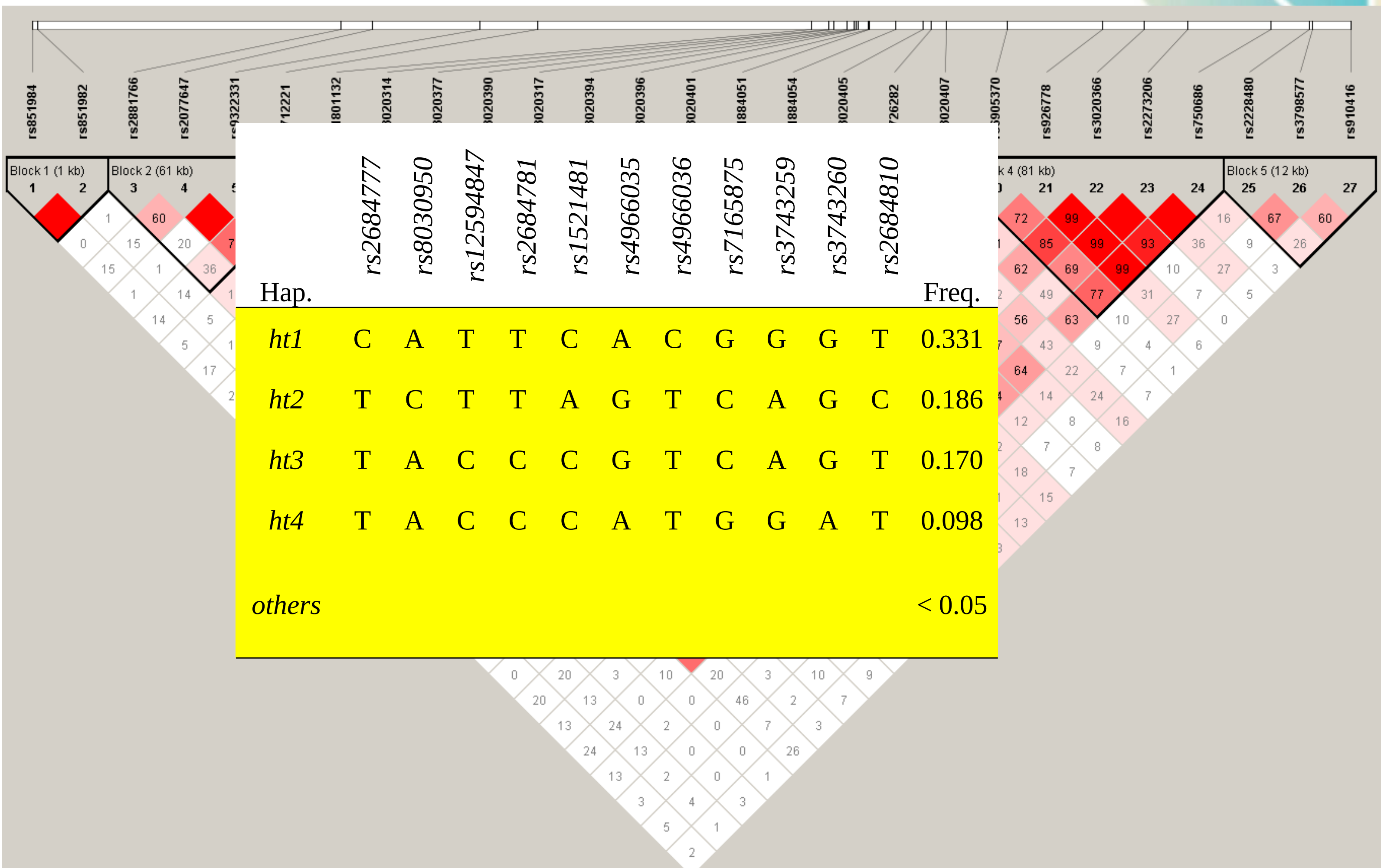
Case-control study

Breast	1021
Luminal A	345
Luminal B	227
HER2	124
TN	325
Control	390

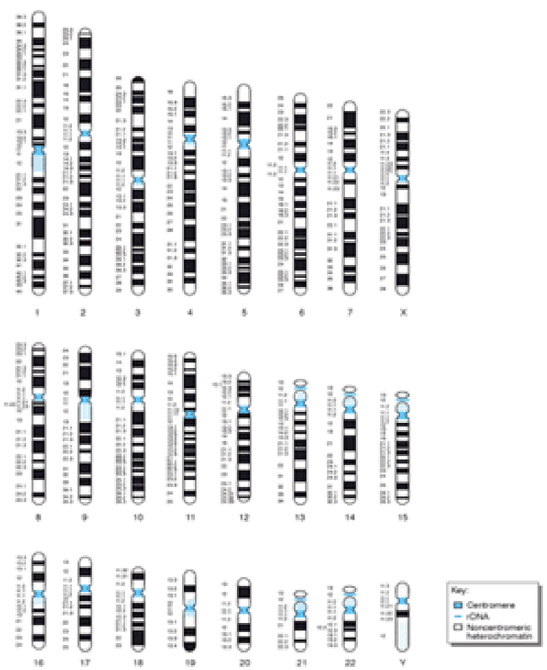
htSNP (haplotype tagging SNP)



IRS2



Hap.	rs2684777	rs8030950	rs12594847	rs2684781	rs1521481	rs4966035	rs4966036	rs7165875	rs3743259	rs3743260	rs2684810	Freq.
ht1	C	A	T	T	C	A	C	G	G	G	T	0.331
ht2	T	C	T	T	A	G	T	C	A	G	C	0.186
ht3	T	A	C	C	C	G	T	C	A	G	T	0.170
ht4	T	A	C	C	C	A	T	G	G	A	T	0.098
others												< 0.05



Total genomic size = 3,079 Mb
Total number of genes = 32,884 genes

Homo sapiens Build 36.3 (2008.06)

chr #	Size (Mb)	Genes #
1	247	3186
2	243	2093
3	200	1638
4	191	1300
5	181	1448
6	171	1843
7	159	
8	146	
9	140	
10	135	
11	134	
12	132	
13	114	
14	106	
15	100	
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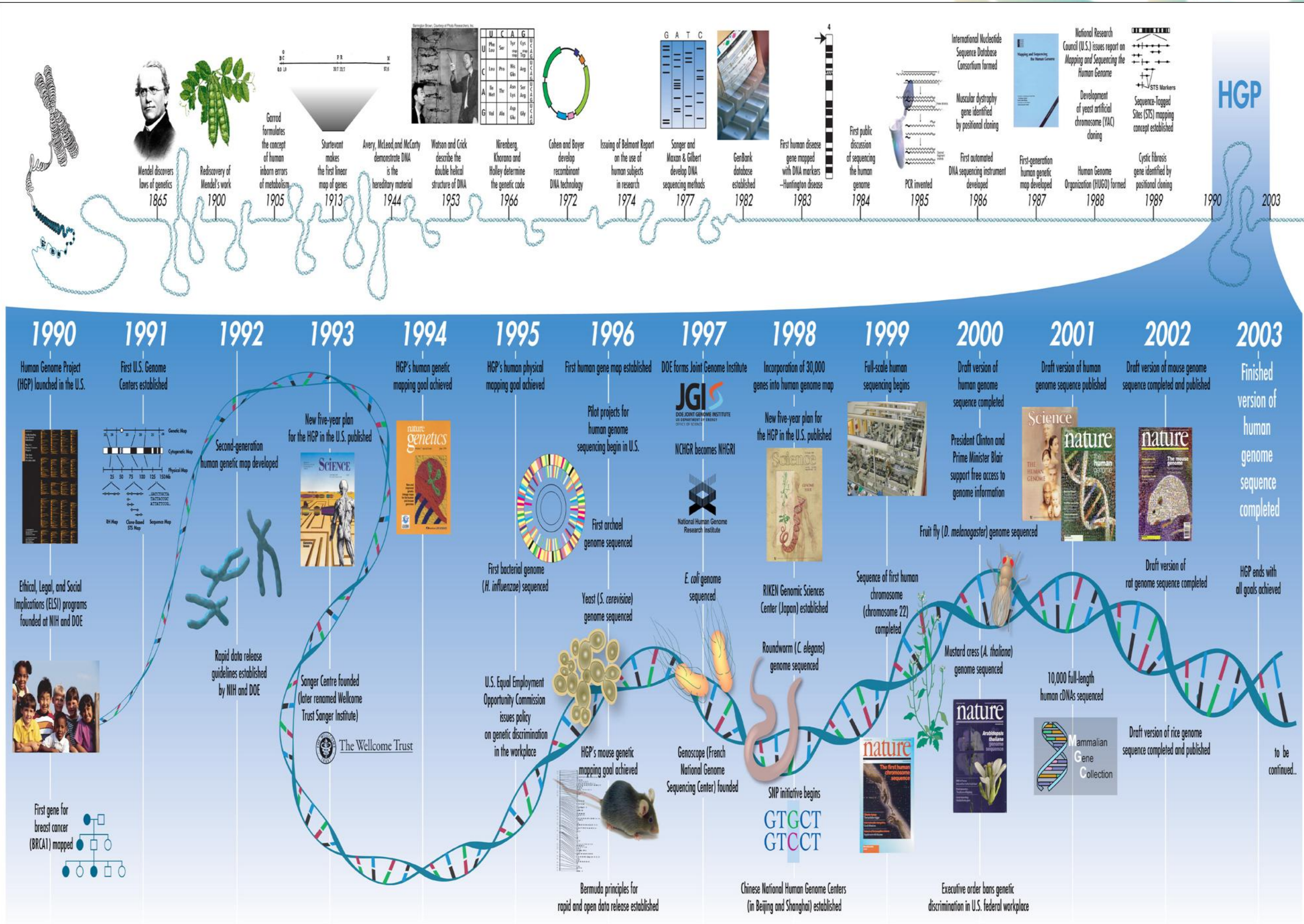
17	79	
18	76	
19	64	
20	62	
21	47	
22	50	
X	155	
Y	58	



Mendel discovers laws of genetics
1865
Rediscovery of Mendel's work
1900
Garrod formulates the concept of human inborn errors of metabolism
1905
Sturtevant makes the first linear map of genes
1913
Avery, McLeod, and McCarty demonstrate DNA is the hereditary material
1944
Watson and Crick describe the double helical structure of DNA
1953
Nirenberg, Khorana and Holley determine the genetic code
1966
Cohen and Boyer develop recombinant DNA technology
1972
Issuing of Belmont Report on the use of human subjects in research
1974
G A T C
Sanger and Maxam & Gilbert develop DNA sequencing methods
1977
GenBank database established
1982
First human disease gene mapped with DNA markers –Huntington disease
1983
First public discussion of sequencing the human genome
1984
PCR invented
1985
International Nucleotide Sequence Database Consortium formed
Muscular dystrophy gene identified by positional cloning
First automated DNA sequencing instrument developed
1986
First-generation human genetic map developed
1987
National Research Council (U.S.) issues report on Mapping and Sequencing the Human Genome
Development of yeast artificial chromosome (YAC) cloning
Human Genome Organization (HUGO) formed
1988
STS Markers
Sequence-Tagged Sites (STS) mapping concept established
Cystic fibrosis gene identified by positional cloning
1989
HGP
1990
2003
1990
Human Genome Project (HGP) launched in the U.S.
Ethical, Legal, and Social Implications (ELSI) programs founded at NIH and DOE
First gene for breast cancer (BRCA1) mapped
1991
First U.S. Genome Centers established
Genetic Map
Cytogenetic Map
Physical Map
RH Map
Clone-Based STS Map
Sequence Map
1992
Second-generation human genetic map developed
Rapid data release guidelines established by NIH and DOE
1993
New five-year plan for the HGP in the U.S. published
Science
Sanger Centre founded (later renamed Wellcome Trust Sanger Institute)
The Wellcome Trust
1994
HGP's human genetic mapping goal achieved
nature genetics
1995
HGP's human physical mapping goal achieved
First bacterial genome (H. influenzae) sequenced
U.S. Equal Employment Opportunity Commission issues policy on genetic discrimination in the workplace
1996
First human gene map established
Pilot projects for human genome sequencing begin in U.S.
First archael genome sequenced
Yeast (S. cerevisiae) genome sequenced
HGP's mouse genetic mapping goal achieved
Bermuda principles for rapid and open data release established
1997
DOE forms Joint Genome Institute
JGI
DOE JOINT GENOME INSTITUTE
US DEPARTMENT OF ENERGY
NCHGR becomes NHGRI
National Human Genome Research Institute
E. coli genome sequenced
Genoscope (French National Genome Sequencing Center) founded
1998
Incorporation of 30,000 genes into human genome map
New five-year plan for the HGP in the U.S. published
Science
RIKEN Genomic Sciences Center (Japan) established
Roundworm (C. elegans) genome sequenced
SNP initiative begins
GTGCT
GTCCT
Chinese National Human Genome Centers (in Beijing and Shanghai) established
1999
Full-scale human sequencing begins
Sequence of first human chromosome (chromosome 22) completed
nature
The first human chromosome sequence
2000
Draft version of human genome sequence completed
President Clinton and Prime Minister Blair support free access to genome information
Fruit fly (D. melanogaster) genome sequenced
Mustard cress (A. thaliana) genome sequenced
nature
Arabidopsis thaliana genome sequence
Executive order bans genetic discrimination in U.S. federal workplace
2001
Draft version of human genome sequence published
Science
THE HUMAN GENOME
nature
the human genome
10,000 full-length human cDNAs sequenced
Mammalian Gene Collection
2002
Draft version of mouse genome sequence completed and published
nature
the mouse genome
Draft version of rat genome sequence completed
Draft version of rice genome sequence completed and published
2003
Finished version of human genome sequence completed
HGP ends with all goals achieved
to be continued..