

Genetic polymorphisms in the population and cancer risk

Kari Hemminki

German Cancer Research Center, Heidelberg

Family Medicine, Karolinska Institute, Huddinge



American Journal of --- EPIDEMIOLOGY

Volume 161

Number 9

May 1, 2005

Copyright © 2005 by The Johns Hopkins

Bloomberg School of Public Health

Sponsored by the Society for Epidemiologic Research

Published by Oxford University Press

SPECIAL ARTICLE

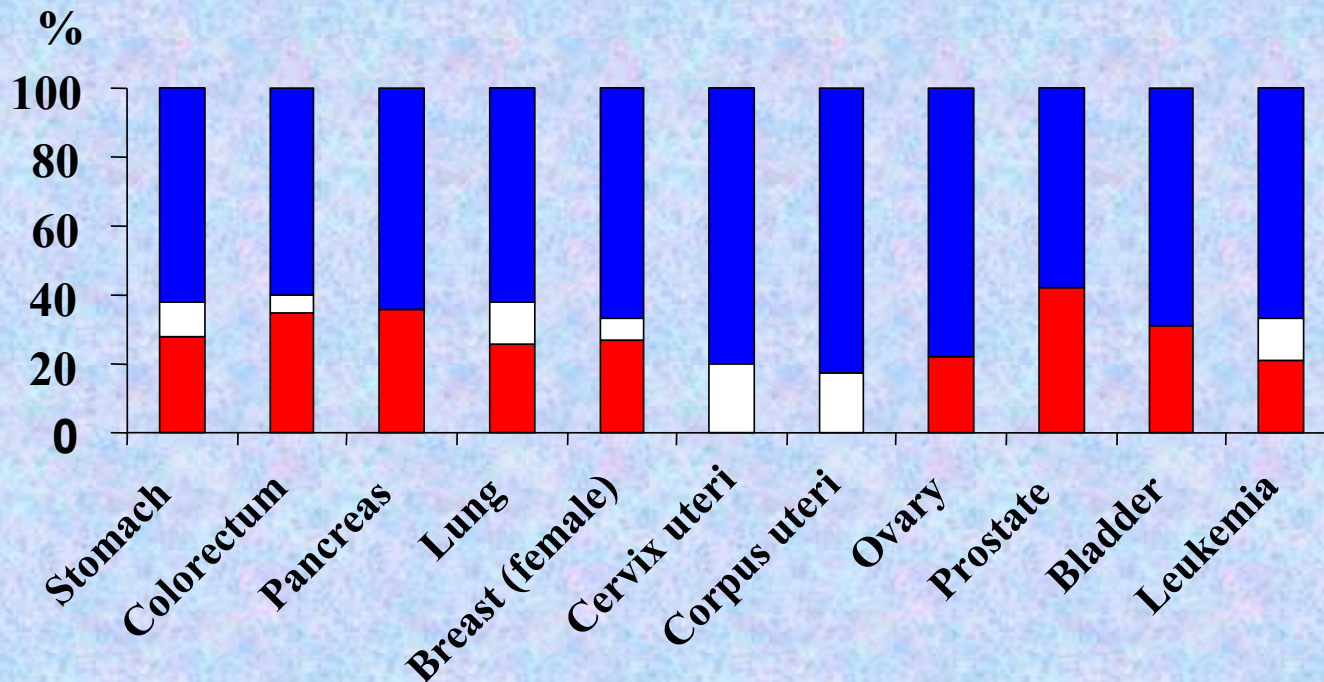
Do We Need Genomic Research for the Prevention of Common Diseases with Environmental Causes?

Muin J. Khoury, Robert Davis, Marta Gwinn, Mary Lou Lindegren, and Paula Yoon

„Given that gene-environment interactions underlie almost all human diseases.“

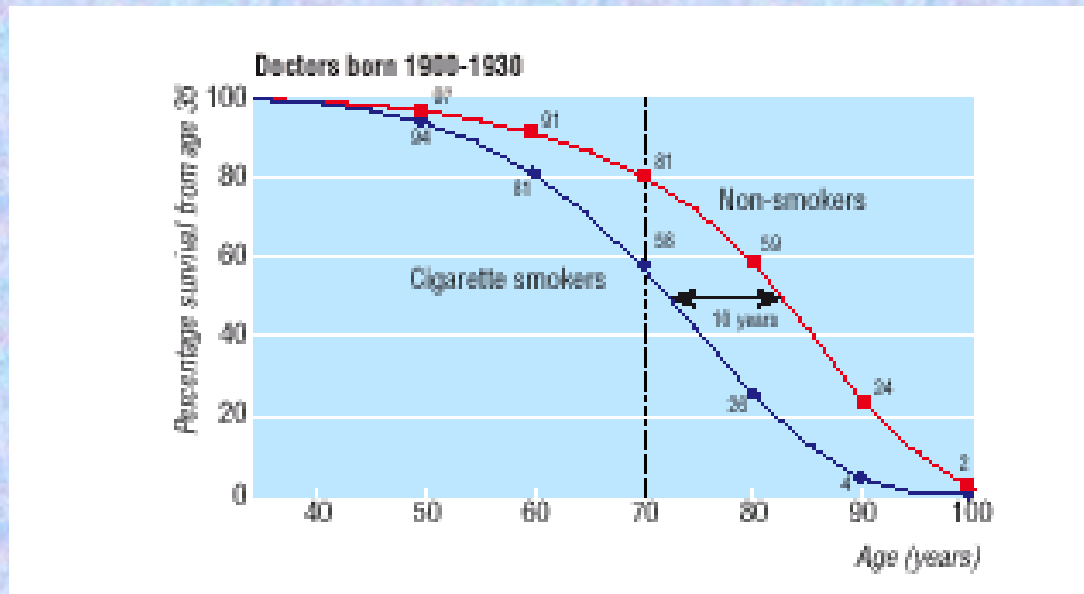
Percentage of Variance Cancer in Sweden, Denmark and Finland

■ Genetic □ Shared environmental ■ Nonshared environmental



Conclusions from the twin study

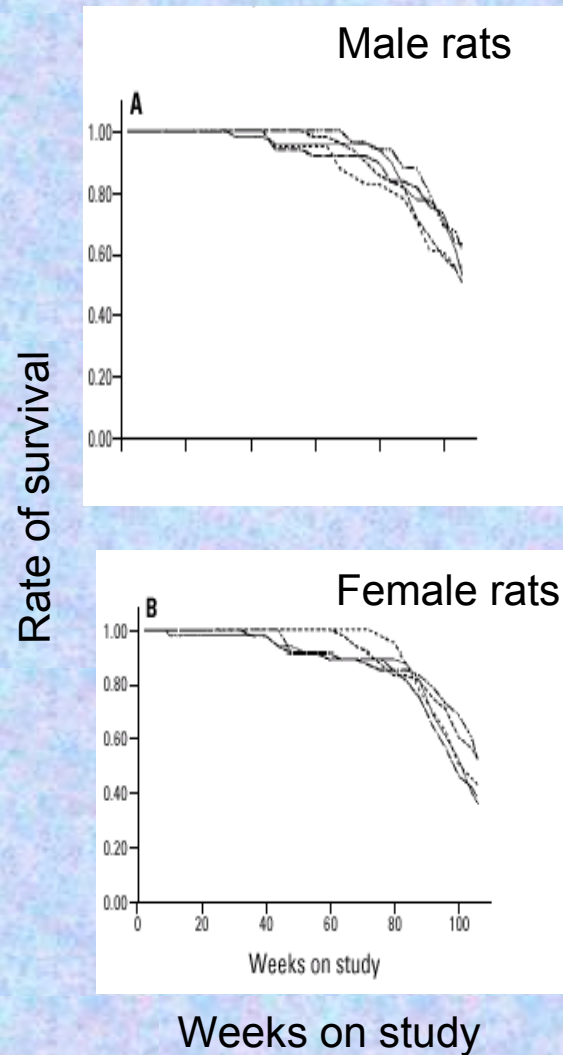
- Random environment most important cause for all cancer
- Breast cancer heritability 24%
- Colorectal cancer heritability 35%
- Prostate cancer heritability 42%



Survival from age 35 for continuing cigarette smokers and lifelong non-smokers among UK male doctors born 1900 – 1930, with percentages alive at each decade of age

Richard Doll et al., BMJ 2004 (328)

Fumonisin B1 Bioassay



Strategies for identifying disease genes

Single genes

High risk

Intermediary risk

Low risk

Linkage/pedigrees

Whole-genome association?

Association

Interactions

Gene-gene

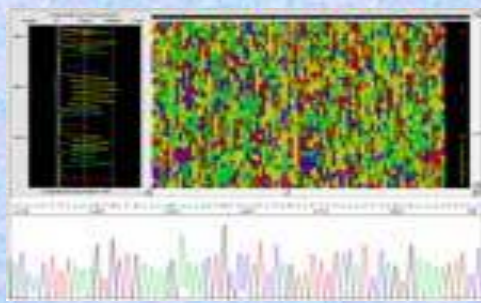
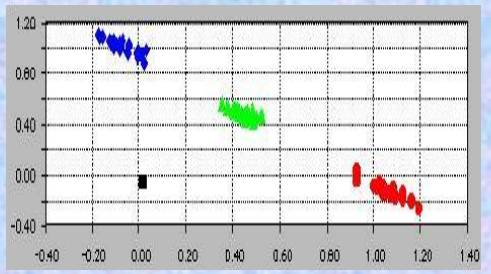
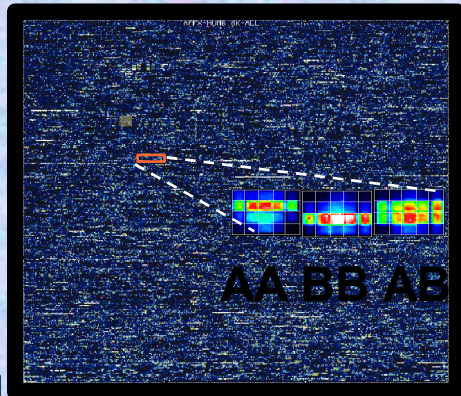
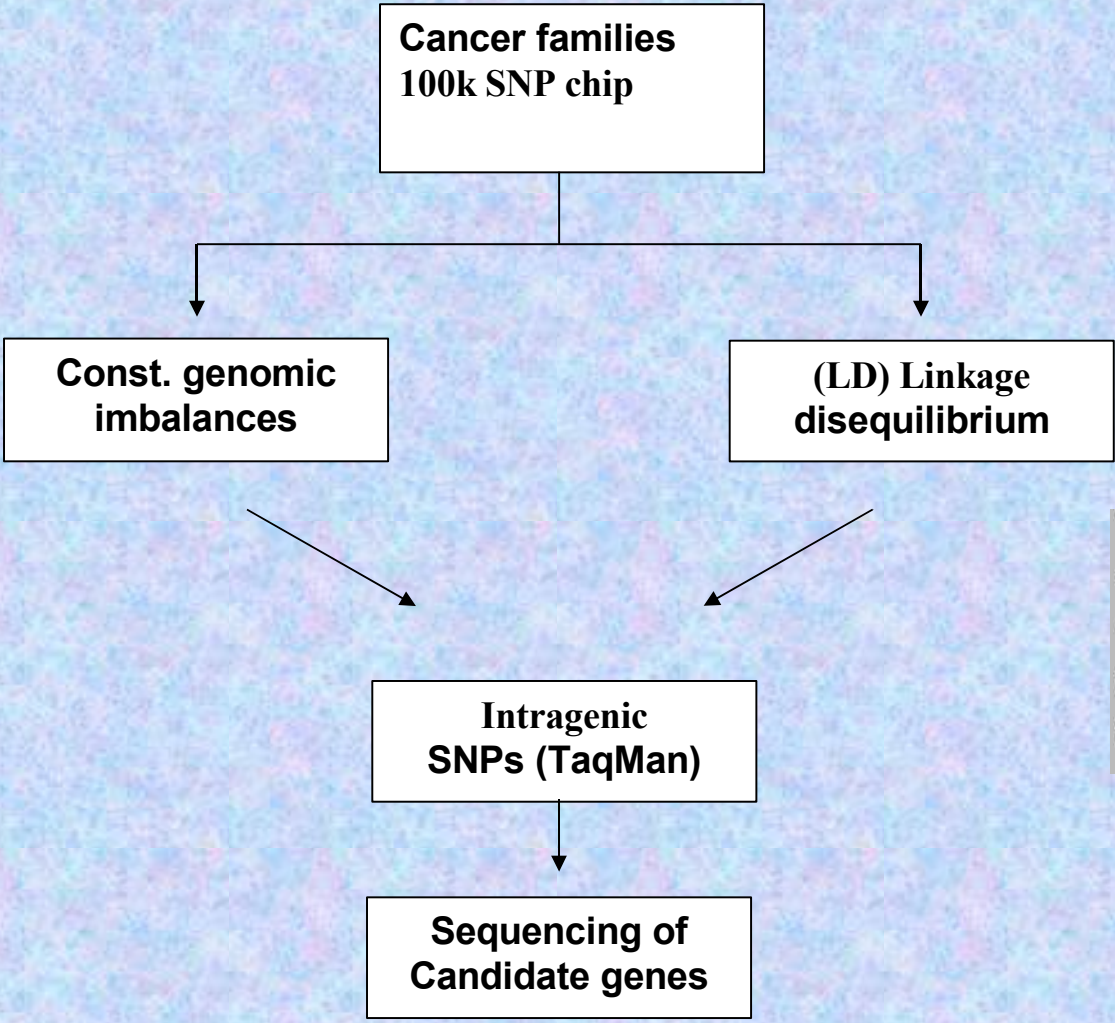
Gene-environment

Association?

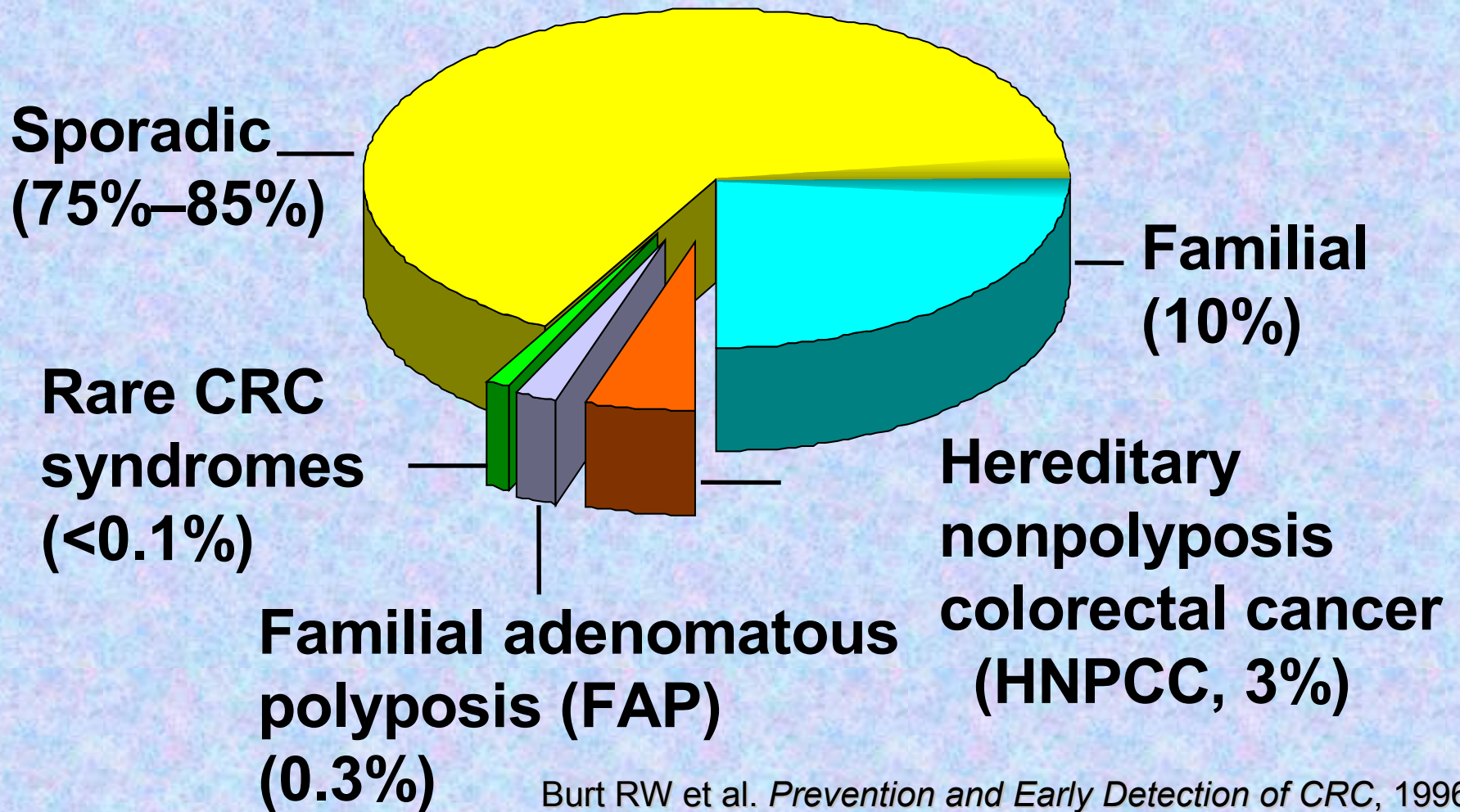
Association?

Paradigms of gene hunt

- Mendelian: rare, many disease alleles
Low LD! Pedigrees/families
- Technocrat: common disease – common variant (CDCV)
High LD! Use all patients
- Confirming: candidate gene approach



Causes of Hereditary Susceptibility to colorectal cancer



An update on the genetics of colorectal cancer

Zoe Kemp¹, Cristina Thirlwell¹, Oliver Sieber¹, Andrew Silver² and Ian Tomlinson^{1,2,*}

¹Molecular and Population Genetics Laboratory, London Research Institute, Cancer Research UK, 44 Lincoln's Inn Fields, London WC2A 3PX, UK and ²Colorectal Cancer Unit, Cancer Research UK, St Mark's Hospital, Watford Road, Harrow HA1 3UJ, UK

Received July 23, 2004; Revised and Accepted July 27, 2004

Genes responsible for known polyposis and CRC syndromes

Syndrome	Gene	Function	Method of discovery
FAP	<i>APC</i>	Inhibition of wnt signalling; ?chromosome segregation	Linkage analysis
HNPCC	<i>MLH1</i>	DNA mismatch repair	Linkage analysis
	<i>MSH2</i>	DNA mismatch repair	Linkage analysis
	<i>MSH6</i>	DNA mismatch repair	Candidate gene
	<i>PMS2</i>	DNA mismatch repair	Candidate gene
MAP	<i>MYH</i>	Base excision repair	Somatic mutation screening
Peutz–Jeghers	<i>LKB1</i>	Serine threonine kinase; ?cell polarity	CGH and linkage analysis
Juvenile polyposis	<i>SMAD4</i>	TGF-beta signalling	Candidate linkage analysis
	<i>ALK3</i>	TGF-beta + BMP signalling	Linkage analysis
Cowden's	<i>PTEN</i>	Phosphatase, inhibition of AKT signalling	Somatic screening, linkage analysis

Summary of polymorphisms tested for CRC

Gene	Name	Polymorphism	Rating
<i>ADH3</i>	Alcohol dehydrogenase	Codon 350	**
<i>APC</i>	Adenomatous polyposis coli	E1317Q	**
<i>APOE</i>	Apolipoprotein E	ϵ 2/3	**
<i>BLM</i>	Bloom syndrome	BLM ^{Ash}	**
<i>CBS</i>	Cystathionine beta-synthase	ins68bp x8	*
<i>CCDN1</i>	Cyclin D1	A870G	**
<i>CDH1</i>	E-cadherin	-347 insA (promoter)	**
<i>CHEK2</i>	Checkpoint kinase 2	del1100C	*
<i>COX1</i>	Prostaglandin H synthase 1	R8W	*
		L15 Δ	**
		P17L	*
<i>COX2</i>	Prostaglandin H synthase 2	L237M	*
		V511A	*

*No evidence of association; **some reports of association, but early data or unconfirmed evidence; ***good evidence of association.

Summary of polymorphisms tested for CRC

Gene	Name	Polymorphism	Rating
<i>CYP1A1</i>	Cytochrome P450 1A1	I462V	*
		nt 6235 T > C	*
<i>EPHX</i>	Epoxide hydrolase (microsomal)	Y113H	*
		H139R	*
<i>GCPII</i>	Glutamate carboxypeptidase	H475Y	*
<i>GSTM1</i>	Glutathione S-transferase mu1	Null alleles	*
<i>GSTP1</i>	Glutathione S-transferase pi1	I101V	*
		A114V	*
<i>GSTT1</i>	Glutathione S-transferase theta1	Null alleles	*
<i>HRAS1</i>	Harvey rat sarcoma virus 1	VNTR rare alleles	***

*No evidence of association; **some reports of association, but early data or unconfirmed evidence; ***good evidence of association.

Summary of polymorphisms tested for CRC

Gene	Name	Polymorphism	Rating
<i>IL6</i>	Interleukin 6	-174 G > C	**
<i>IL8</i>	Interleukin 8	-251 T > A	**
<i>IRS1</i>	Insulin receptor substrate 1	G972R	**
<i>IRS2</i>	Insulin receptor substrate 2	G1057D	*
<i>MLH1</i>	MutL homologue (MMR)	D132H	**
<i>MLH3</i>	MutL homologue (MMR)	P844L	*
		S845G	*
<i>MMP1</i>	Matrix metalloproteinase 1	2G	**
<i>MMP3</i>	Matrix metalloproteinase 3	6A	**
<i>MSH2</i>	MutS homologue 2 (MMR)	nt 2006 C > T	*
<i>MTHFD1</i>	MTHF dehydrogenase	R653Q	*
<i>MTHFR</i>	MTHF reductase	C677T	***
		A1298C	***
<i>MTR</i>	Methionine synthase	A66G	**
		A2765G	*
<i>MTRR</i>	Methionine synthase reductase	A66G	*

*No evidence of association; **some reports of association, but early data or unconfirmed evidence; ***good evidence of association.

Summary of polymorphisms tested for CRC

Gene	Name	Polymorphism	Rating
<i>NAT1</i>	<i>N</i> -Acetyltransferase 1	Multiple alleles, e.g. *10	*
<i>NAT2</i>	<i>N</i> -Acetyltransferase 2	Rapid acetylator alleles	***
<i>PAI1</i>	Plasminogen activator inhibitor 1	Ins G promoter	*
<i>PLA2G2A</i>	Secretory phospholipase A2	nt 964 C > G	*
		nt 1073 G > C	*
<i>PPARG</i>	Peroxisome proliferator activated receptor	P10A	**
<i>SHMT</i>	Serine hydroxymethyltransferase	L474F	*
<i>TGFB1</i>	Transforming growth factor beta1	L10P	*
<i>TGFBRI</i>	TGF beta receptor 1	del(Ala) ₃	**
<i>TNFA</i>	Tumour necrosis factor alpha	-308 G > A	**
<i>TNFB</i>	Tumour necrosis factor beta	-238 G > A	*
<i>TP53</i>	p53	R72P	*
<i>TS</i>	Thymidylate synthase	2R/3R promoter	**
		1494del6	*
<i>VDR</i>	Vitamin D receptor	M1T	**
		intron 8 BsmI	*
		I352I C > T	*
		3'-UTR polyA short/long	**

*No evidence of association; **some reports of association, but early data or unconfirmed evidence; ***good evidence of association.

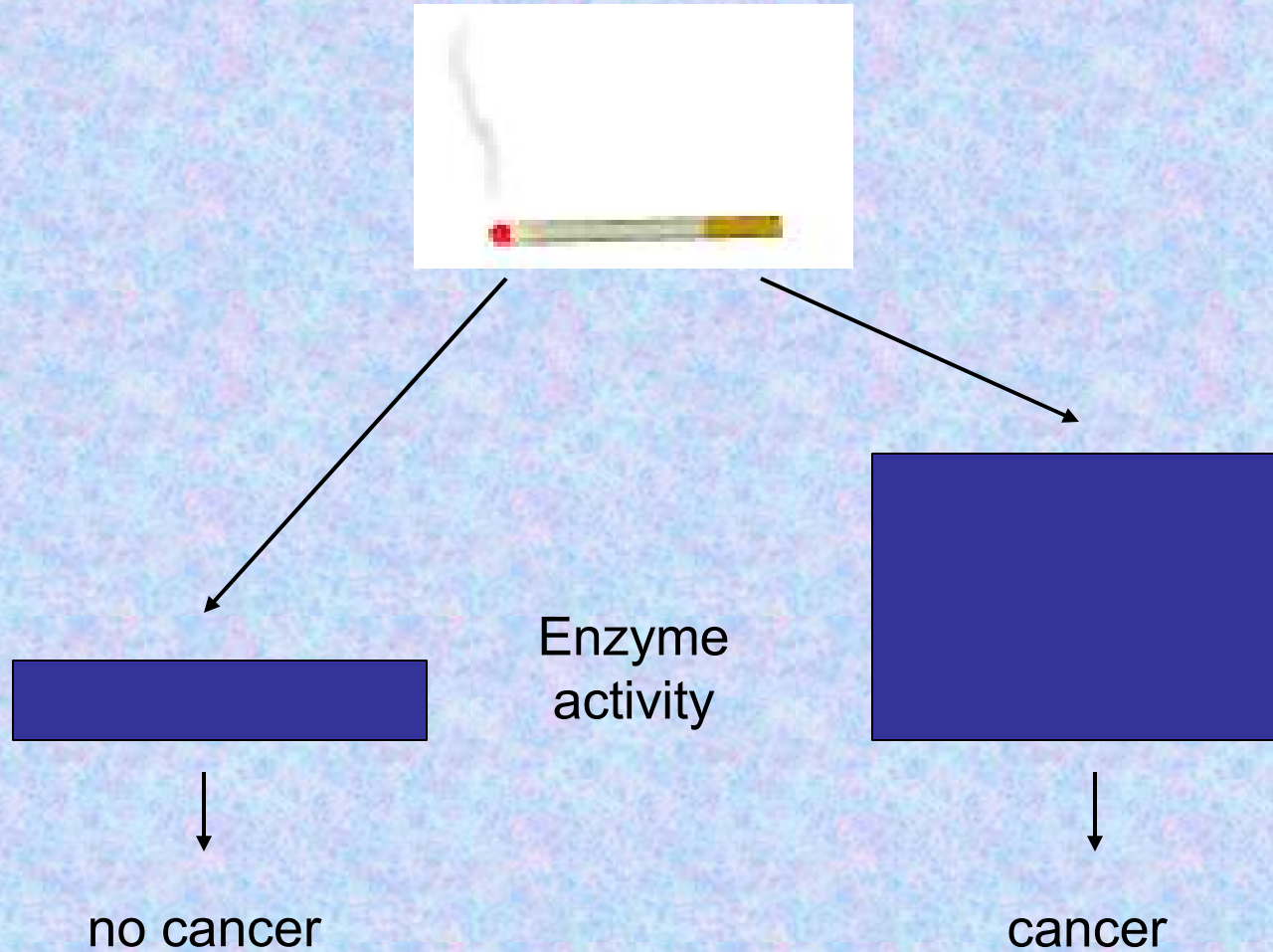
Large-scale UK association study on 1500 non-synonymous SNPs (Illumina platform) by Dr. R. Houlston and coworkers:

- ~ 2500 CRC consecutive cases
~ 2500 controls
- Most positive results to be repeated on 650 samples by the German HNPPC Consortium (non-HNPPC) at DKFZ

Comparison of association studies

Gene	Results	
	UK (N = 2500)	DKFZ (N = 650)
1	+	-
2	+	-
3	+	-
4	+	-
5	+	-
6	+	-
7	+	-
8	+	-
9	+	-
10	+	-

Gene-environment interaction



Genetic study

1000 cases, 1000 controls
20 genes with SNPs

Result:

Genes A, B risk ($p < 0.05$)

Genes C,D protection

Number of comparisons:

20 x 3 genotypes = 60

Gene-environment study

Same populations and SNPs

Associations with 5 potential risk factors (dichotomized)

Result:

Gene E – genotype aa ($p < 0.05$)

Gene F – genotype Aa

Gene G – genotype AA

etc.

Number of comparisons:

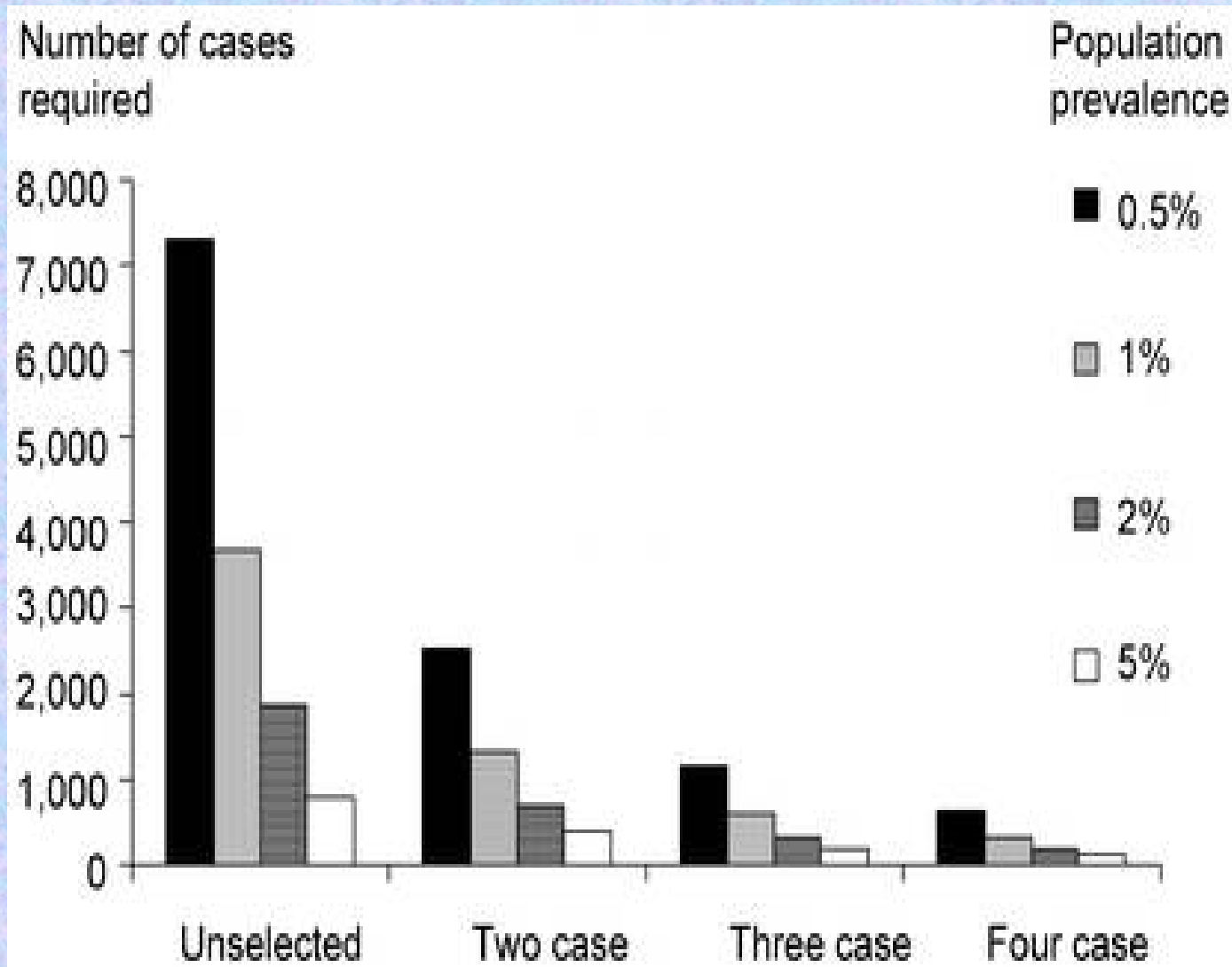
20×3 (genotypes) \times 5 (exposures) \times 2 = 600

Gene-environment study

- + gene-environments important (perhaps)
- multiple comparisons
- heritable component small

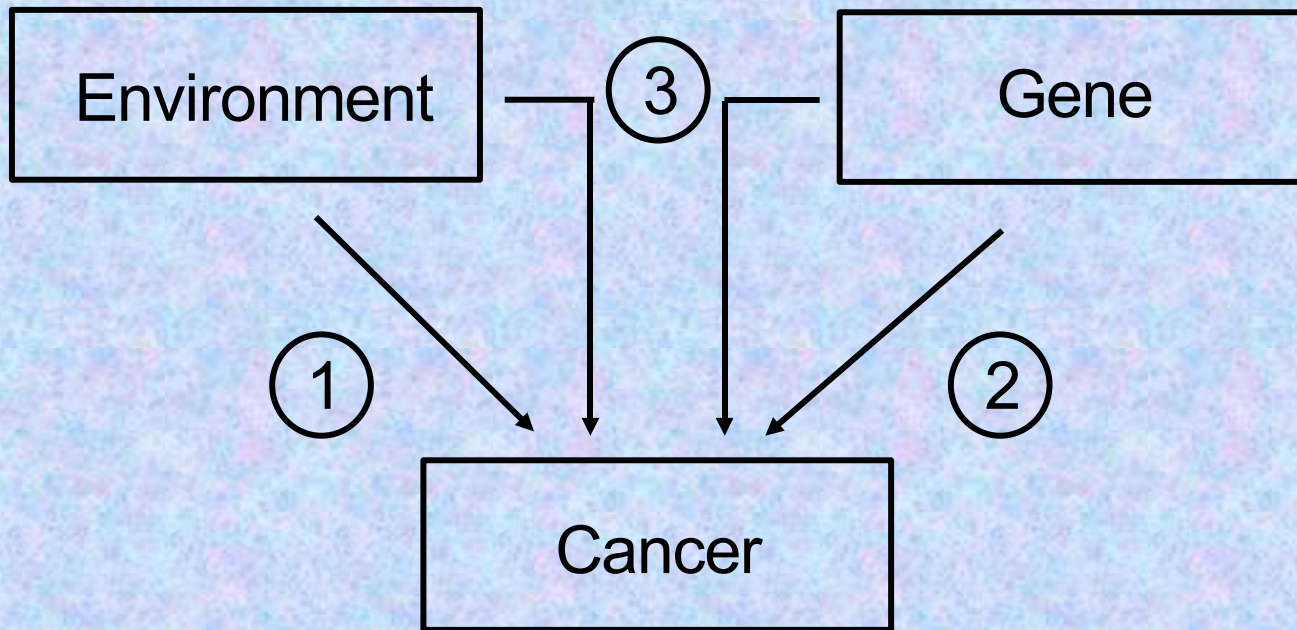
If you are not sure what you do, do something that you are sure about.

No fishing expeditions!



Houlston and Peto, Hum Genet (2003)

Sample sizes required to detect an allele conferring a RR of 2.0 with 95% power ($P=0.01$) under a range of population prevalence, for affected individuals from different types of family and two controls per case



Is 3) possible without 1) and 2)?

Possibly, but almost impossible to demonstrate

Gene-environment interaction

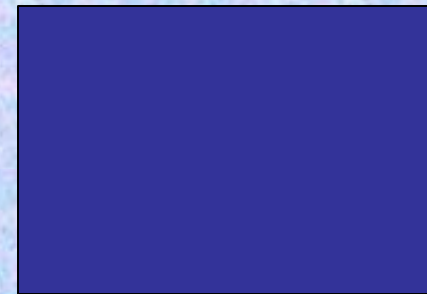
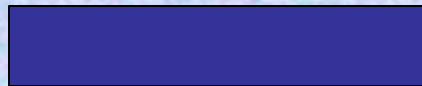


CURSE

PROMISE

OR

Enzyme
activity

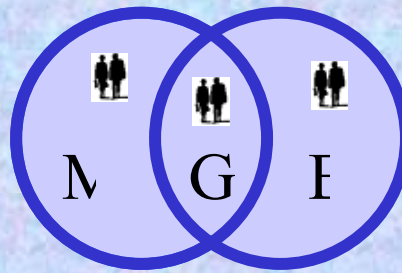


no cancer

cancer

Past and future of gene hunt

- Linkage analyses
 - *BRCA1* and *BRCA2*, progress since 1994?
- Association studies
 - Reproducibility? Credibility?
 - Familial cases, large sample size
 - Relevant SNPs and/or haplotypes
 - Array technologies



Team members

Asta Försti

Kerstin Wagner

Barbara Burwinkel

Michael Wirtenberger

Bernd Frank

Rajiv Kumar