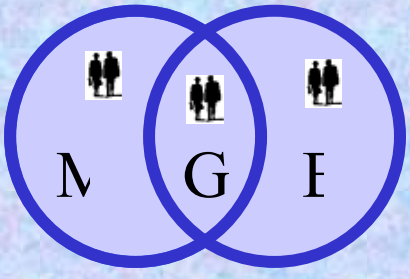


Genetic polymorphisms in the population and cancer risk

Kari Hemminki

German Cancer Research Center, Heidelberg
Family Medicine, Karolinska Institute, Huddinge

American Journal of
EPIDEMIOLOGY

Volume 161

Number 9

May 1, 2005

Sponsored by the Society for Epidemiologic Research
Published by Oxford University Press

SPECIAL ARTICLE

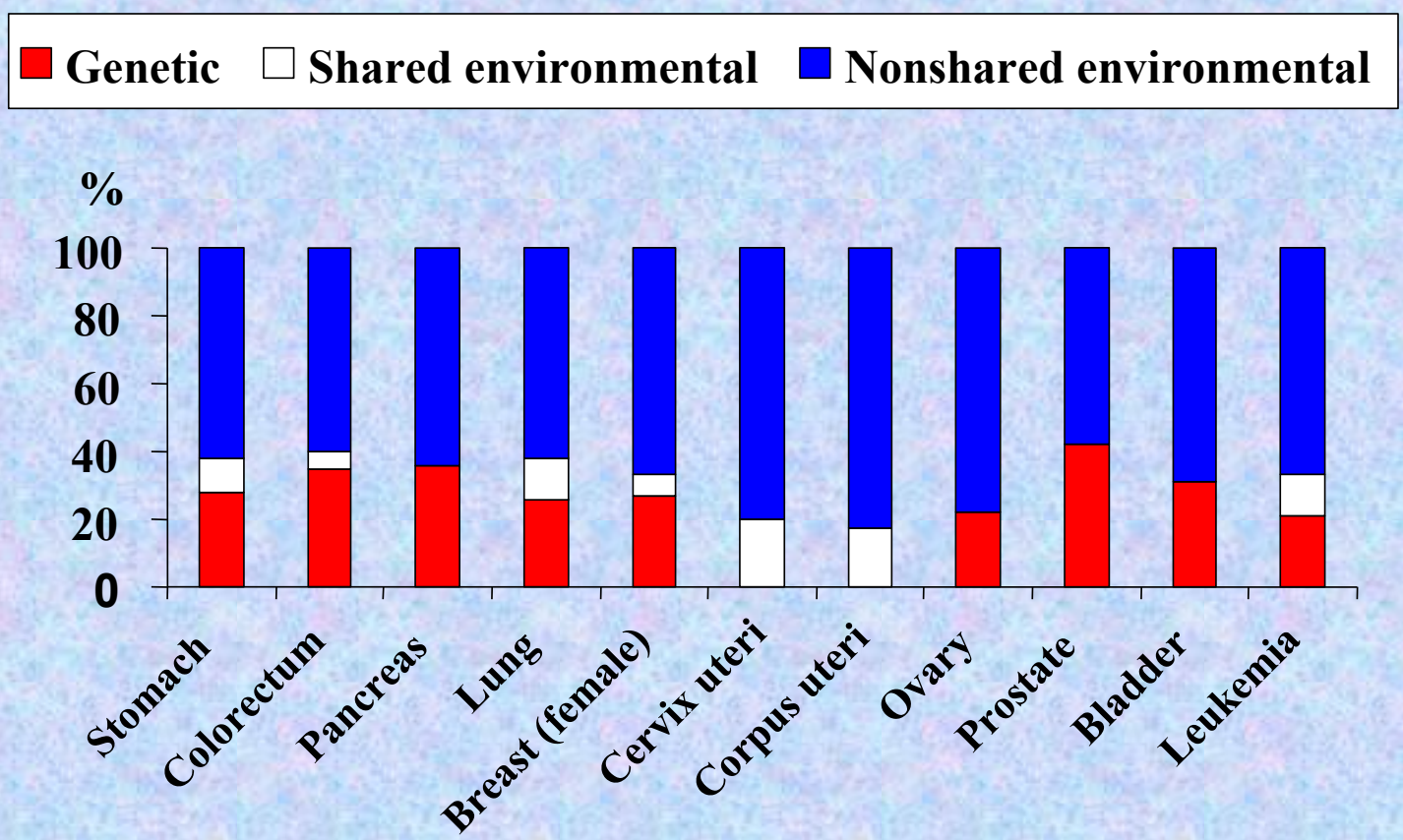
Do We Need Genomic Research for the Prevention of Common Diseases with Environmental Causes?

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

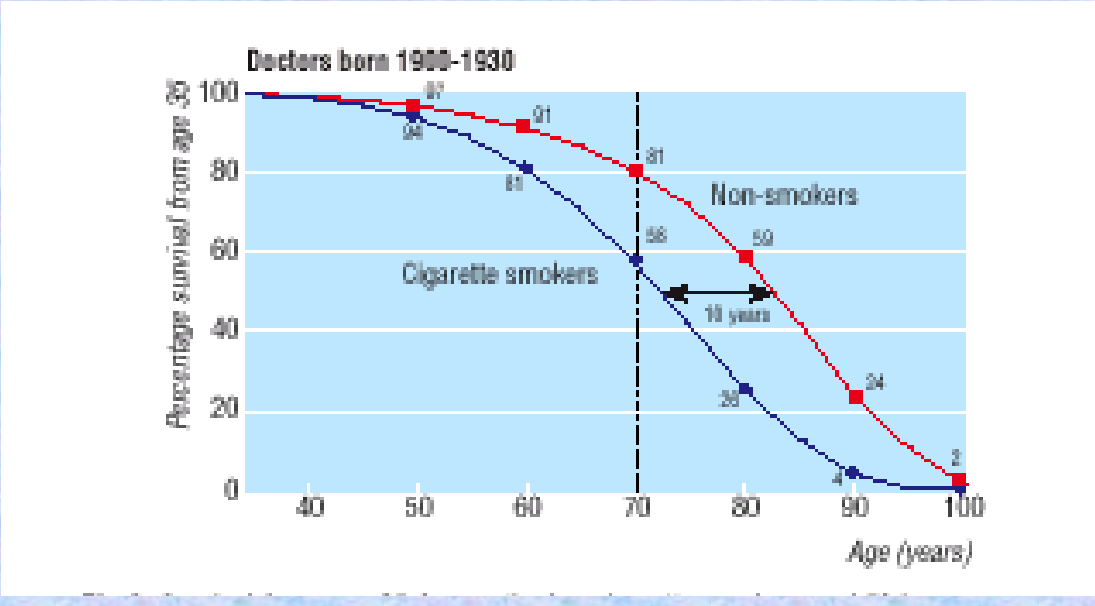
Cancer in Sweden, Denmark and Finland



Lichtenstein et al, *NEJM (2000)*

Conclusions from the twin study

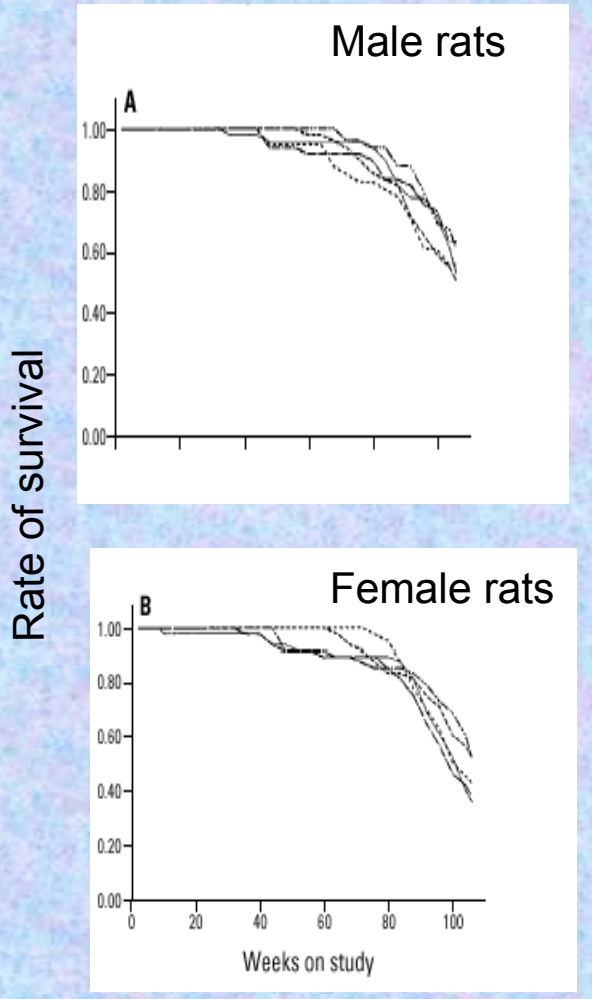
- Random environment most important cause for all cancer
- Breast cancer heritability 24%
- Colorectal cancer heritability 35%
- Prostate cancer heritability 42%



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

Richard Doll et al., BMJ 2004 (328)

Fumonisin B1 Bioassay



Howard PC et al., Environ Health Perspect 2001 (109)

Strategies for identifying disease genes

<u>Single genes</u>	
High risk	Linkage/pedigrees
Intermediary risk	Whole-genome association?
Low risk	Association
<u>Interactions</u>	
Gene-gene	Association?
Gene-environment	Association?

Paradigms of gene hunt

- Mendelian: rare, many disease alleles

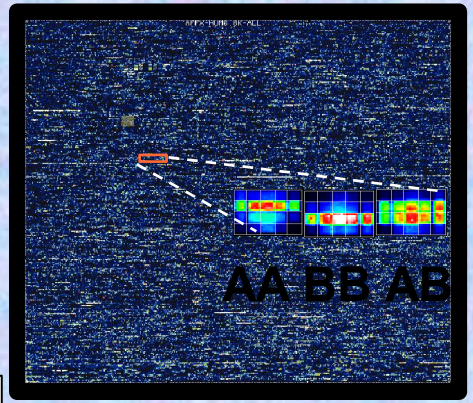
  Low LD! Pedigrees/families

- Technocrat: common disease – common variant (CDCV)

  High LD! Use all patients

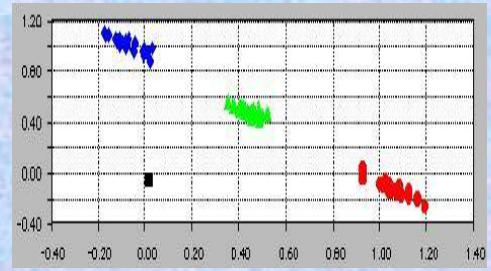
- Confirming: cadidate gene approach

Cancer families
100k SNP chip

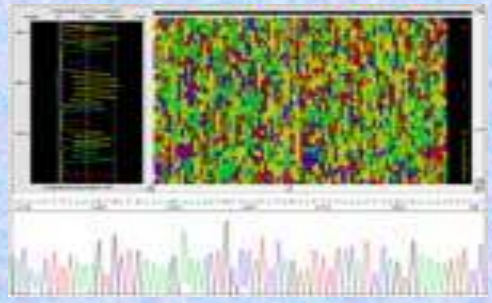


Const. genomic imbalances

(LD) Linkage disequilibrium

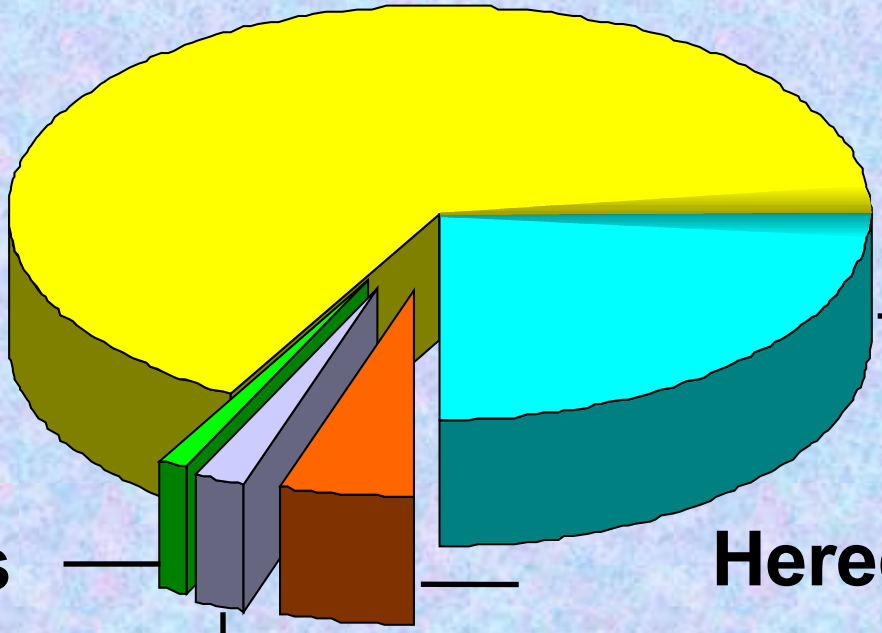


Intragenic SNPs (TaqMan)



Sequencing of Candidate genes

Causes of Hereditary Susceptibility to colorectal cancer



Burt RW et al. *Prevention and Early Detection of CRC*, 1996

Human Molecular Genetics, 2004, Vol. 13, Review Issue 2 **R177–R185**
doi:10.1093/hmg/ddh247

An update on the genetics of colorectal cancer

Zoe Kemp[1], Cristina Thirlwell[1], Oliver Sieber[1], Andrew Silver[2] and Ian Tomlinson[1,2,*]

[1]Molecular and Population Genetics Laboratory, London Research Institute, Cancer Research UK, 44 Lincoln's Inn Fields, London WC2A 3PX, UK and [2]Colorectal 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	*APC*	Inhibition of wnt signalling; ?chromosome segregation	Linkage analysis
HNPCC	*MLH1*	DNA mismatch repair	Linkage analysis
	MSH2	DNA mismatch repair	Linkage analysis
	MSH6	DNA mismatch repair	Candidate gene
	PMS2	DNA mismatch repair	Candidate gene
MAP	*MYH*	Base excision repair	Somatic mutation screening
Peutz–Jeghers	*LKB1*	Serine threonine kinase; ?cell polarity	CGH and linkage analysis
Juvenile polyposis	*SMAD4*	TGF-beta signalling	Candidate linkage analysis
	ALK3	TGF-beta + BMP signalling	Linkage analysis
Cowden's	*PTEN*	Phosphatase, inhibition of AKT signalling	Somatic screening, linkage analysis

Summary of polymorphisms tested for CRC

Gene	Name	Polymorphism	Rating
ADH3	Alcohol dehydrogenase	Codon 350	**
APC	Adenomatous polyposis coli	E1317Q	**
APOE	Apolipoprotein E	ε2/3	**
BLM	Bloom syndrome	BLM^{Ash}	**
CBS	Cystathionine beta-synthase	ins68bp x8	*
CCDN1	Cyclin D1	A870G	**
CDH1	E-cadherin	−347 insA (promoter)	**
CHEK2	Checkpoint kinase 2	del1100C	*
COX1	Prostaglandin H synthase 1	R8W	*
		L15Δ	**
		P17L	*
		L237M	*
COX2	Prostaglandin H synthase 2	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
CYP1A1	Cytochrome P450 1A1	I462V	*
		nt 6235 T > C	*
EPHX	Epoxide hydrolase (microsomal)	Y113H	*
		H139R	*
GCPII	Glutamate carboxypeptidase	H475Y	*
GSTM1	Glutathione *S*-transferase mu1	Null alleles	*
GSTP1	Glutathione *S*-transferase pi1	I101V	*
		A114V	*
GSTT1	Glutathione *S*-transferase theta1	Null alleles	*
HRAS1	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
IL6	Interleukin 6	−174 G > C	**
IL8	Interleukin 8	−251 T > A	**
IRS1	Insulin receptor substrate 1	G972R	**
IRS2	Insulin receptor substrate 2	G1057D	*
MLH1	MutL homologue (MMR)	D132H	**
MLH3	MutL homologue (MMR)	P844L	*
		S845G	*
MMP1	Matrix metalloproteinase 1	2G	**
MMP3	Matrix metalloproteinase 3	6A	**
MSH2	MutS homologue 2 (MMR)	nt 2006 C > T	*
MTHFD1	MTHF dehydrogenase	R653Q	*
MTHFR	MTHF reductase	C677T	***
		A1298C	***
MTR	Methionine synthase	A66G	**
		A2765G	*
MTRR	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
NAT1	*N*-Acetyltransferase 1	Multiple alleles, e.g. *10	*
NAT2	*N*-Acetyltransferase 2	Rapid acetylator alleles	***
PAI1	Plasminogen activator inhibitor 1	Ins G promoter	*
PLA2G2A	Secretory phospholipase A2	nt 964 C > G	*
		nt 1073 G > C	*
PPARG	Peroxisome proliferator activated receptor	P10A	**
SHMT	Serine hydroxymethyltransferase	L474F	*
TGFB1	Transforming growth factor beta1	L10P	*
TGFBR1	TGF beta receptor 1	$del(Ala)_3$	**
TNFA	Tumour necrosis factor alpha	−308 G > A	**
TNFB	Tumour necrosis factor beta	−238 G > A	*
TP53	p53	R72P	*
TS	Thymidylate synthase	2R/3R promoter	**
		1494del6	*
VDR	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:

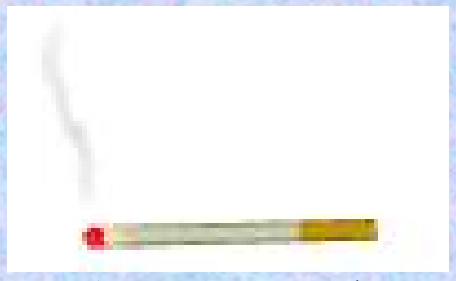
- ~ 2500 CRC consecutive cases
  ~ 2500 controls

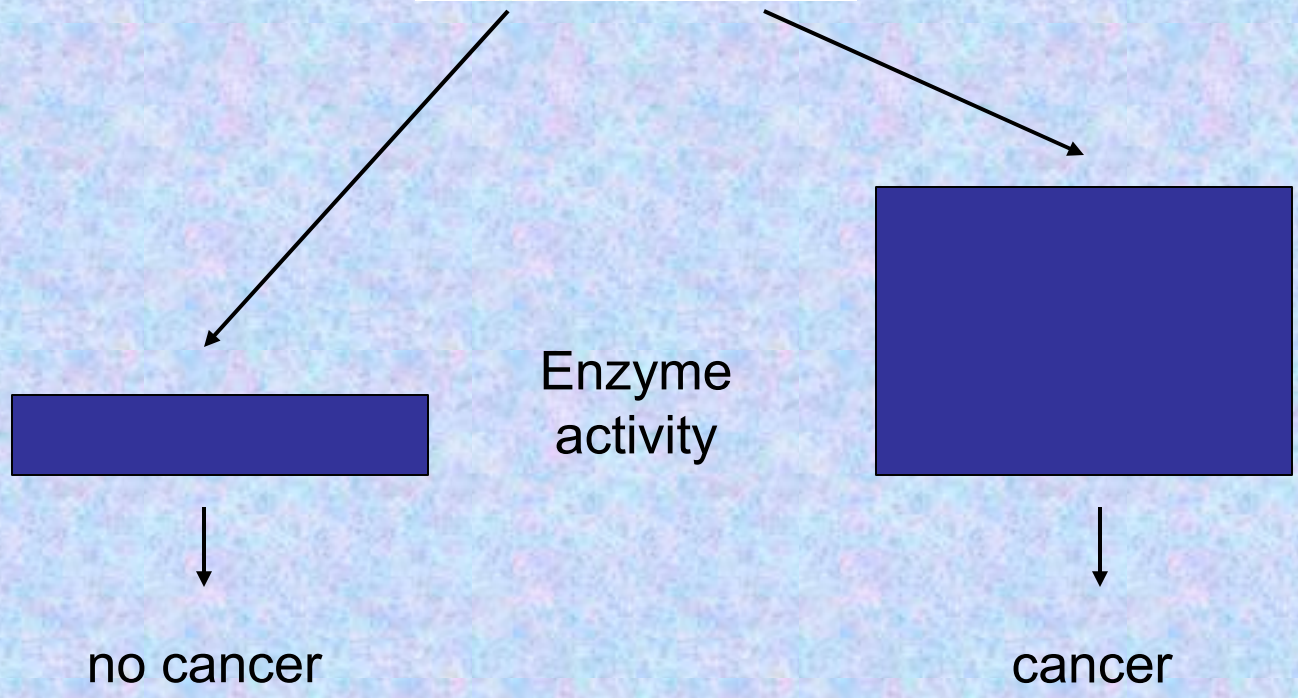
- Most positive results to be repeated on 650 samples by the German HNPCC Consortium (non-HNPCC) at DKFZ

Comparison of association studies

	Results	
Gene	**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:

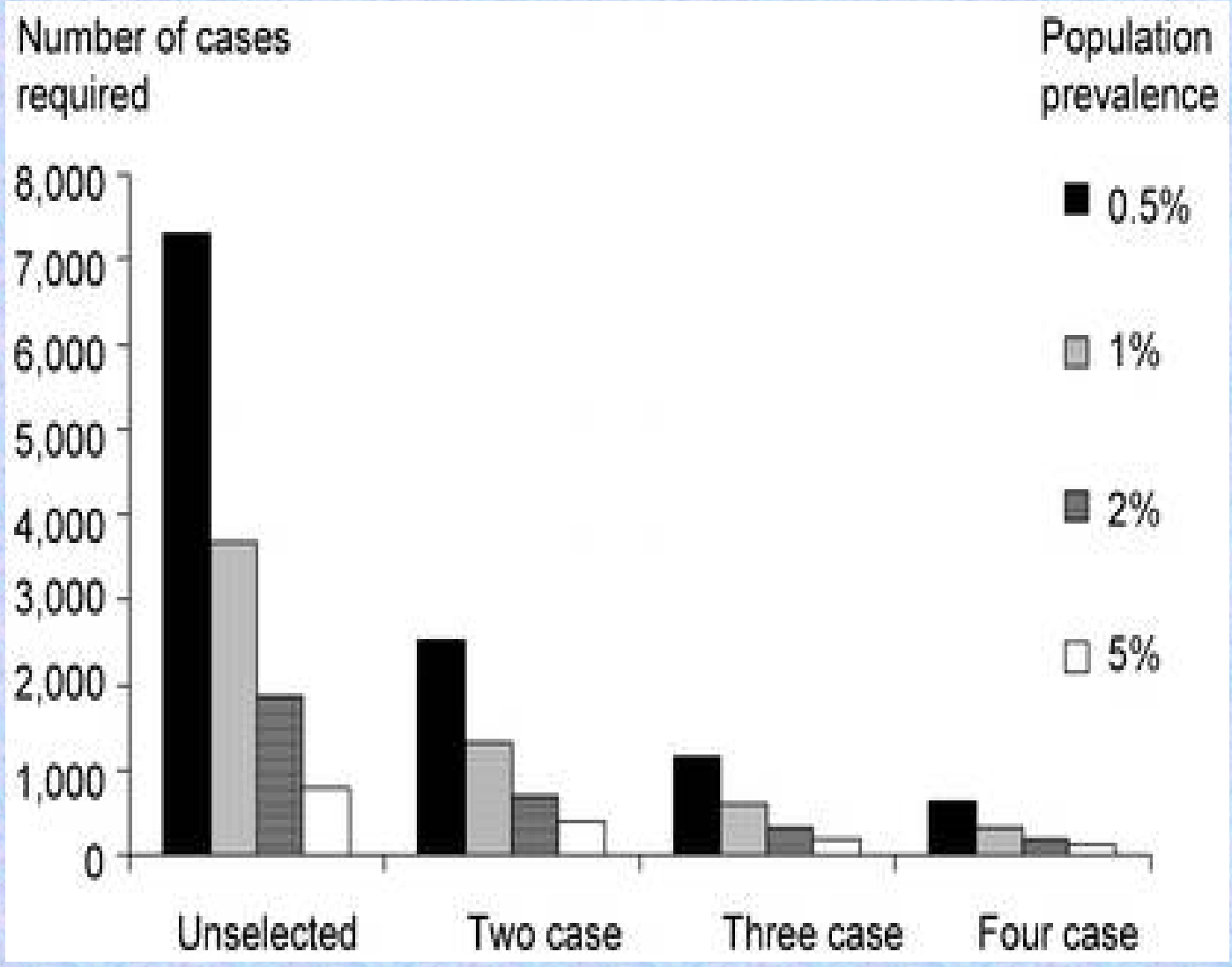
- Gene E – genotype aa ($p < 0.05$)
- Gene F – genotype Aa
- Gene G – genotype AA
- etc.

Number of comparisons:
20 x 3 (genotypes) x 5 (exposures) x 2 = 600

Gene-environment study

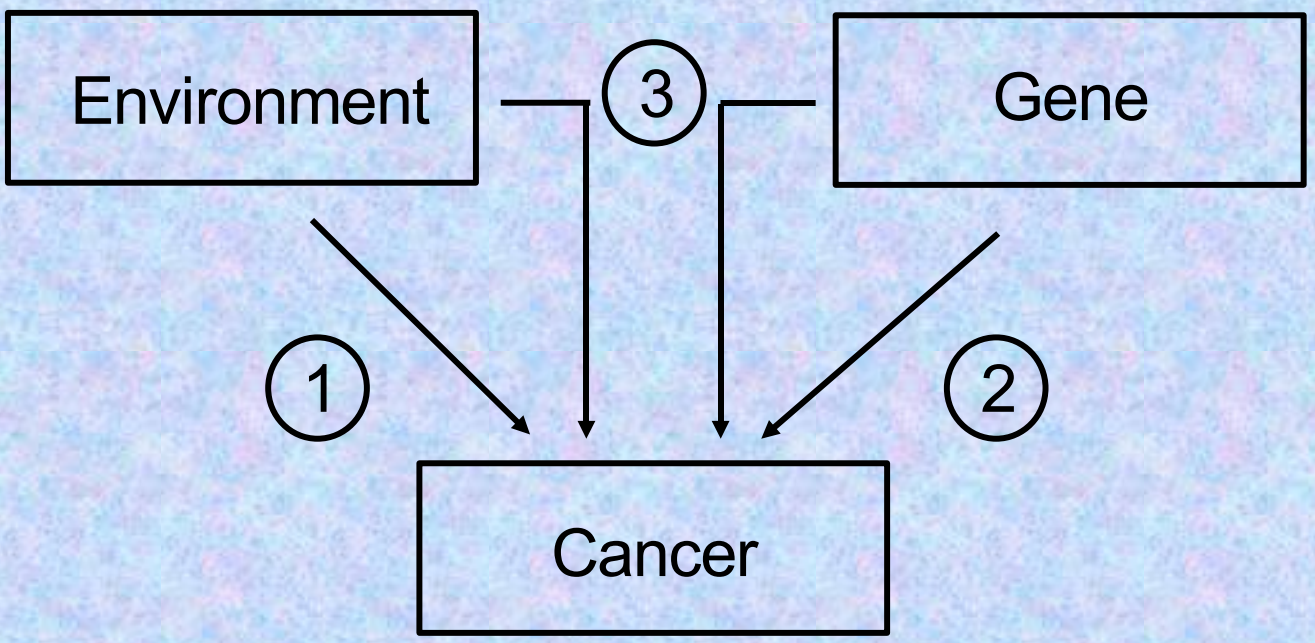
+ gene-environments important (perhaps)
– multiple comparisons
– heritable component small

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)?

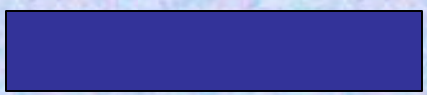
Possibly, but almost impossible to demonstrate

Gene-environment interaction

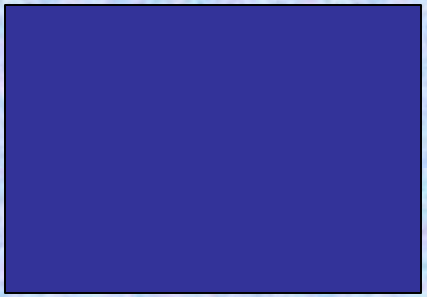
CURSE

OR

PROMISE



Enzyme activity

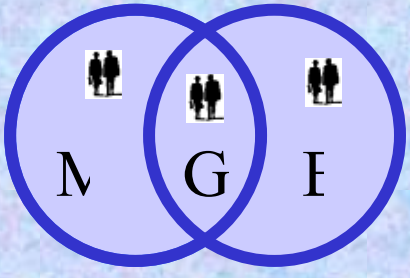


no cancer

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