National Cancer Institute

Clues From The Pathway-Driven Approach

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National Institutes of Health

Overview

- **Breast Cancer:**
  - Case-control and Cohort Breast Cancer Studies
  - Breast Cancer Association Consortium

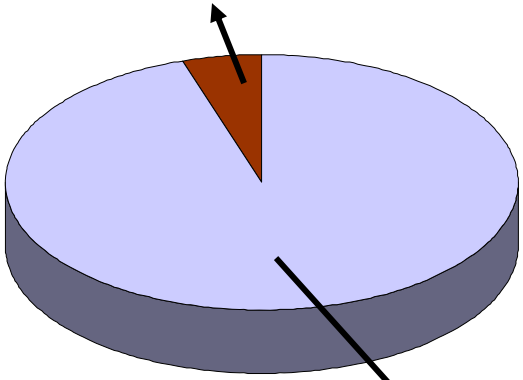
- **Bladder Cancer:**
  - Spanish Bladder Cancer Study
  - International Consortium of Case-control Studies of Bladder Cancer

Breast Cancer Etiology

Familial (5%)

High penetrance genes:
BRCA1, BRCA2, TP53, STK11, PTEN

Environmental exposures



"Sporadic" (95%)

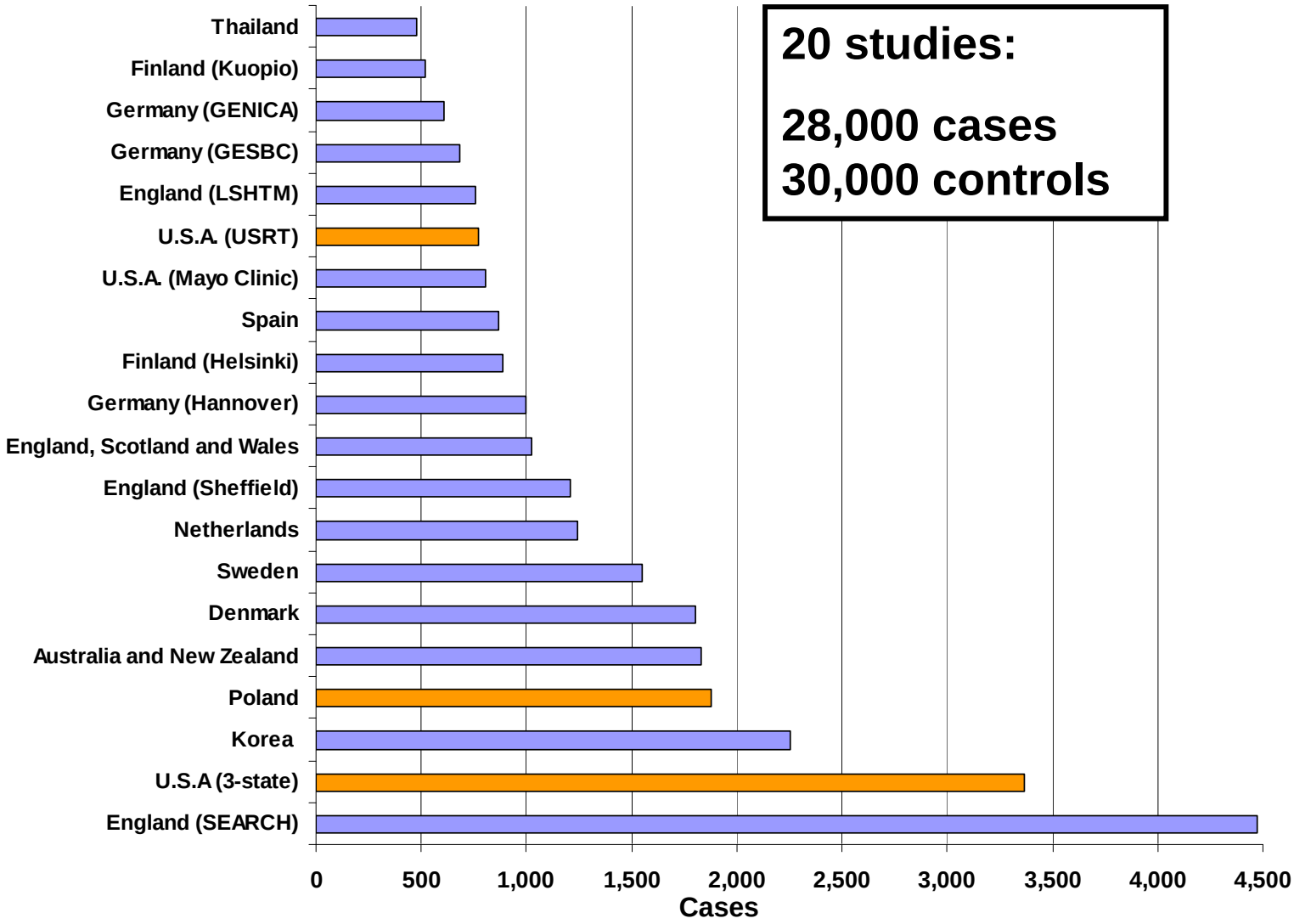
Environmental exposures:
- **Reproductive history**
- **Exogenous hormones**
- **Alcohol intake**
- **Obesity**
- **Physical activity**

Low penetrance genes:
- ***CHEK2, ATM,*** **others?**

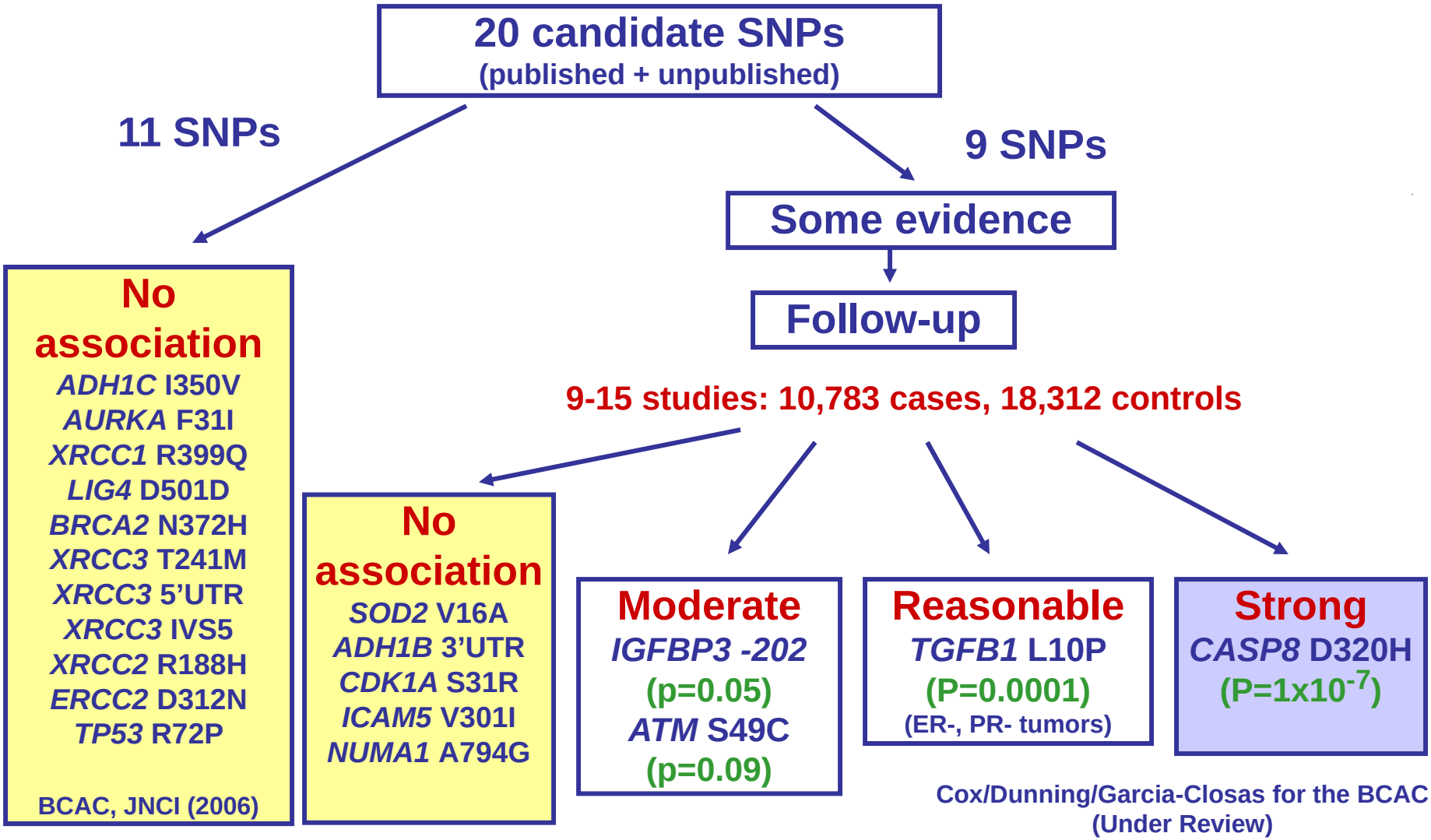
Pathways of Interest in Breast Cancer

- Established or possible risk factors:
  - Hormone biosynthesis, metabolism, and action
  - Obesity
  - Alcohol metabolism
  - Carcinogen metabolism
  - Inflammation
- Carcinogenic processes:
  - DNA repair, cell cycle control, and apoptosis
  - Cell signaling pathways
  - Telomere length
- Gene expression studies
- Somatic mutations

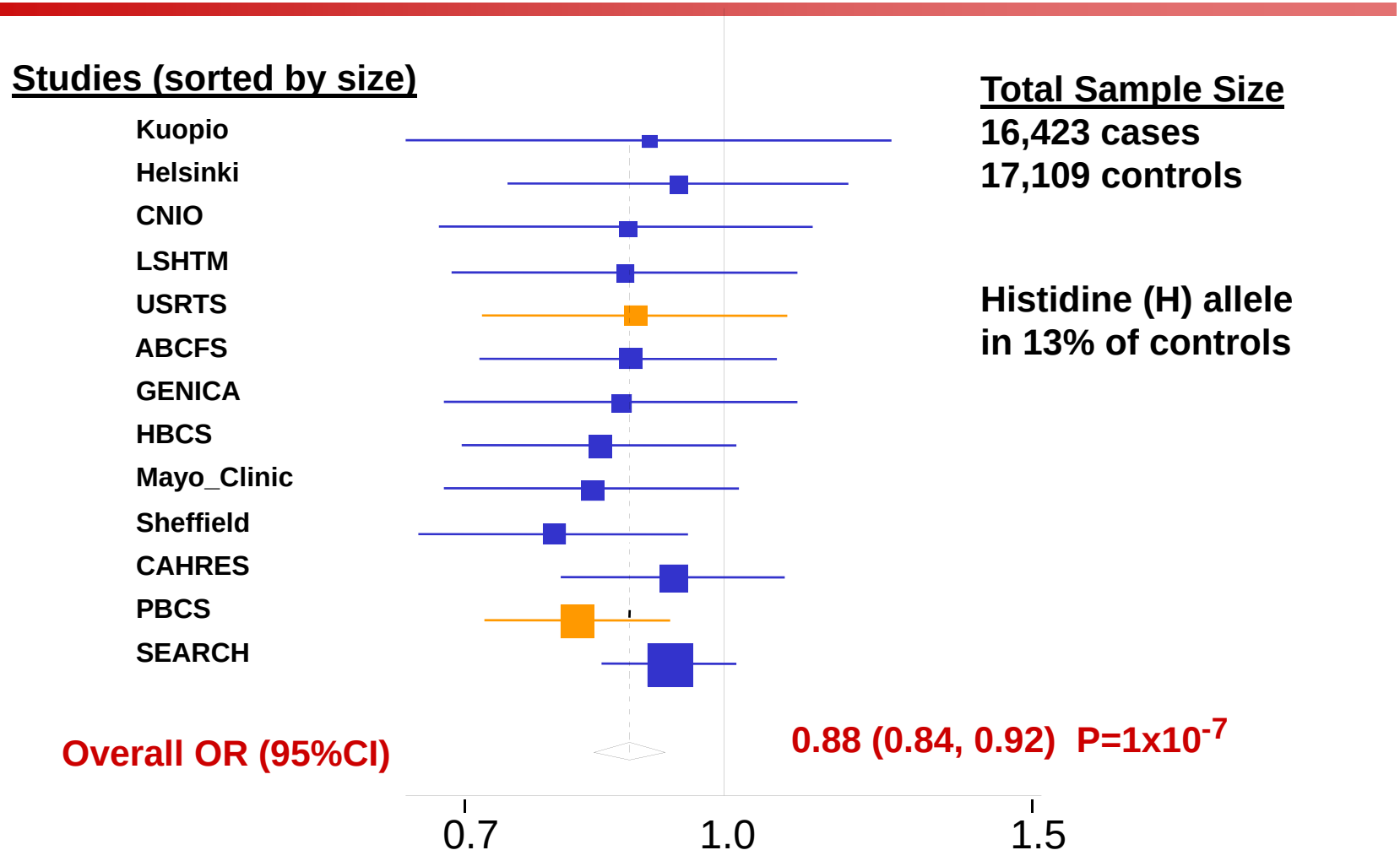
Breast Cancer Association Consortium



Breast Cancer Association Consortium: Findings to Date



Caspase 8 *(CASP8)* D302H Variant Decreases Breast Cancer Risk



Total Sample Size
16,423 cases
17,109 controls

Histidine (H) allele in 13% of controls

Cox A/Dunning A/Garcia-Closas M for the BCAC (Under Review)*
* in alphabetical order

Caspase 8 and Breast Cancer: Plausibility and Significance of Findings

- ***CASP8*** **D302H is the first common variant with convincing evidence of an association with breast cancer.**

- **Caspase 8 is a critical initiator of death receptor mediated apoptosis.**

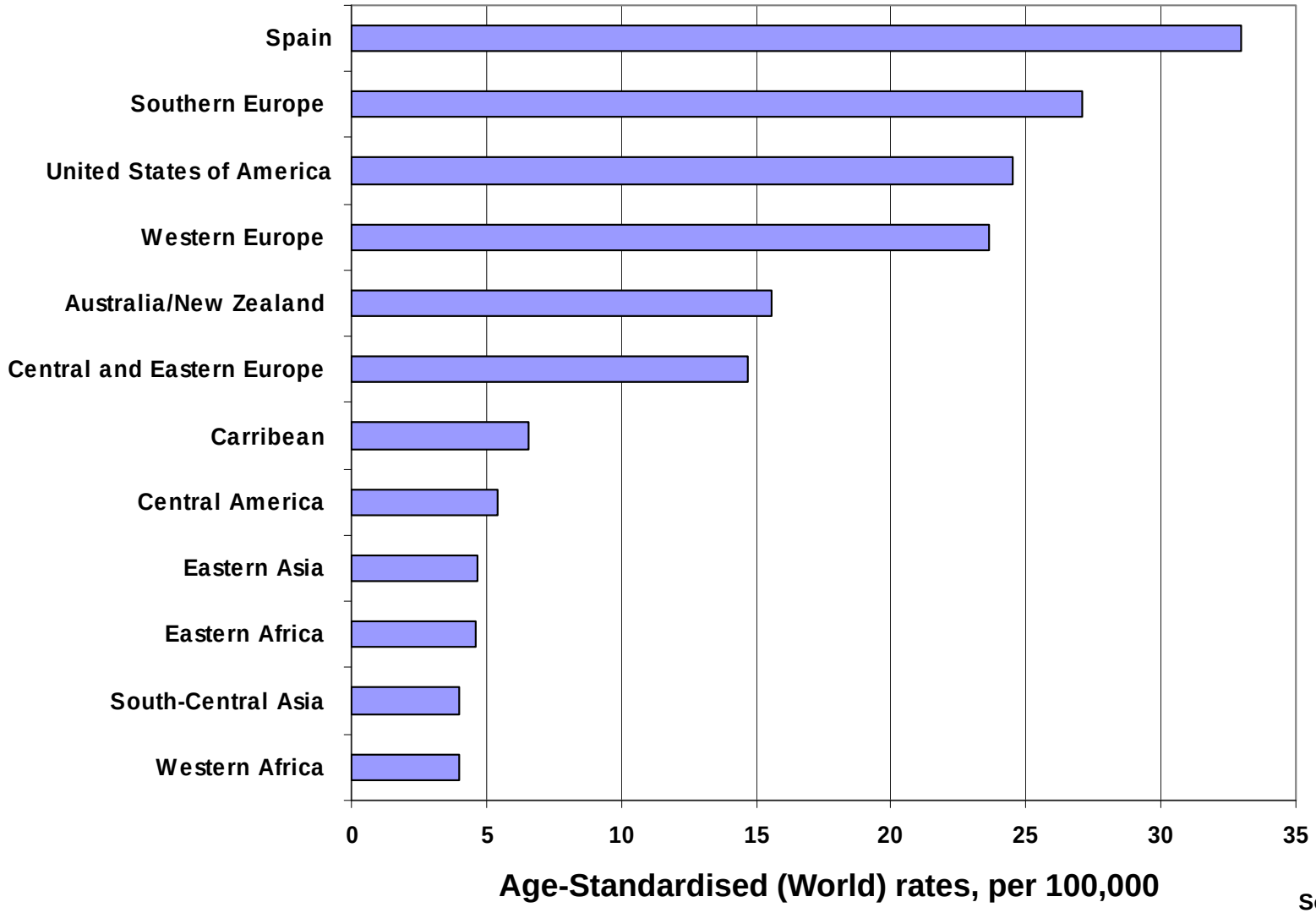
- **Follow-up:**
  - **Fine mapping to dissect genetic variants in *CASP8.***
  - **Functional significance of variants.**

Bladder Cancer

Excellent model to evaluate genetic susceptibility and gene-environment interactions:

- **Relatively homogenous histology.**
- **Well-known non-genetic causes:**
  - **Tobacco smoking**
  - **Occupational exposure to aromatic amines**
- **Good understanding of genetic variation in carcinogen metabolism.**
- **Familial association not yet explained.**

Bladder Cancer Incidence Rates



Source: Globocan 2002

Spanish Bladder Cancer Study

Hospital-based case-control study

in 5 areas of Spain (1998-2001)

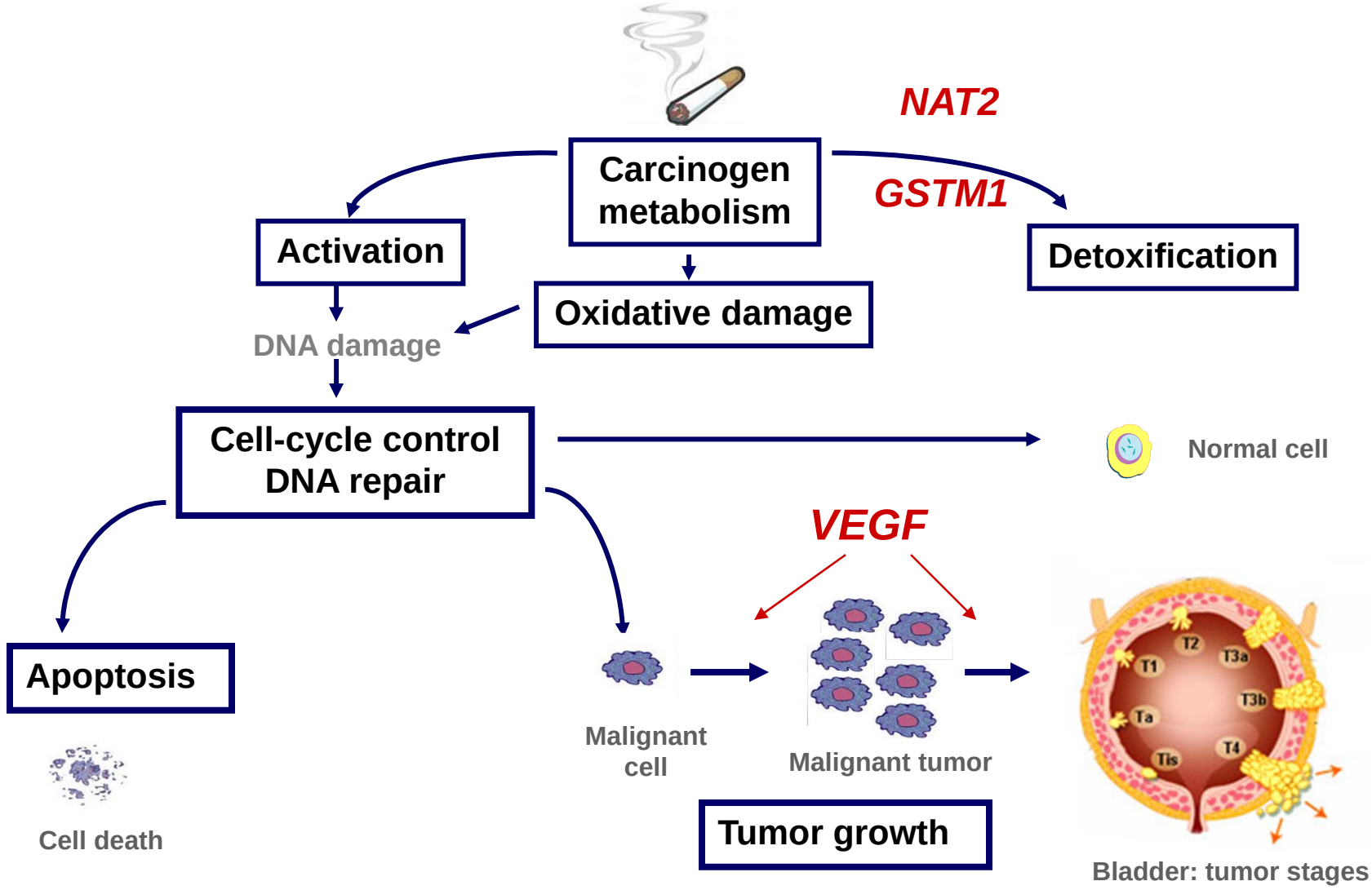
1219 cases (85% of eligibles)

1271 controls (88% of eligibles)

Why Spain?

- **Higher incidence rates**
- **Higher prevalence of tobacco and occupational exposures**
- **Higher participation rates, lower cost**

Candidate Pathways for Bladder Cancer



NAT2 and *GSTM1:* Strong Candidate Genes for Bladder Cancer

- **Metabolism of bladder carcinogens.**
- **Meta-analyses of previous studies:**
  - **Suggested associations with bladder cancer risk**
  - **Relatively small studies (23 to 374 cases)**
  - **Concerns about publication bias and heterogeneity**
- **Interactions with cigarette smoking:**
  - **Strong biological rationale for *NAT2***

NAT Slow Acetylation and *GSTM1* Null Genotypes Increase Bladder Cancer Risk

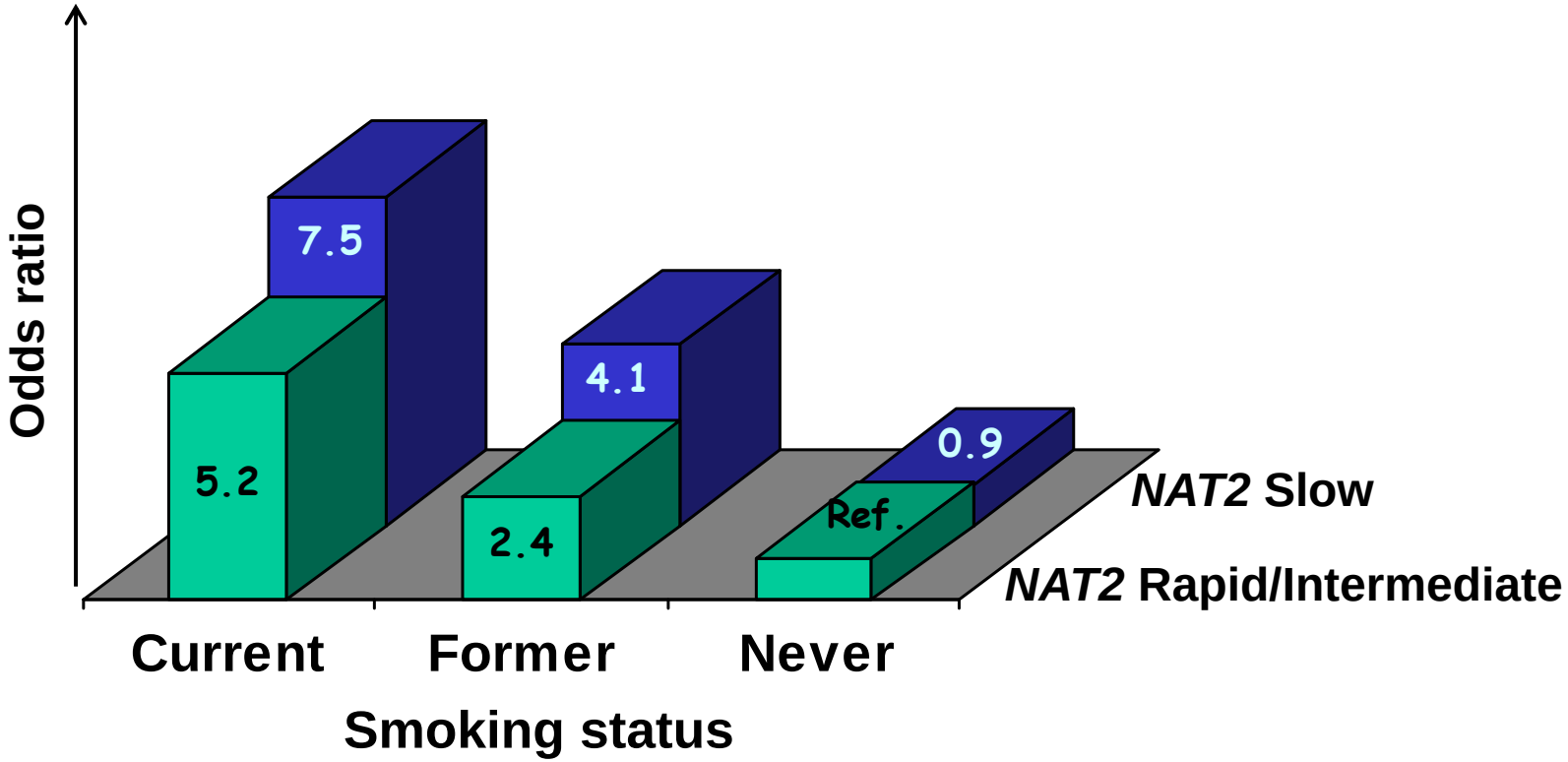
Spanish Bladder Cancer Study

	Phenotypes*	Cases	Controls	OR	95%CI	p-value
NAT2	Rapid/Intermediate	406	493	1.0		
	Slow	728	637	1.4	(1.2-1.7)	0.0002
GSTM1	Present	786	561	1.0		
	Null	716	571	1.7	(1.4-2.0)	$1x10^{-8}$

* Inferred from genotype data

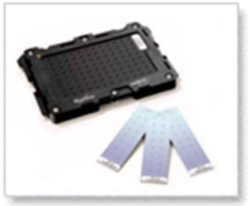
Garcia-Closas M et al. *Lancet,* 2005; 366: 649-658.

Stronger Effect of Smoking on Bladder Cancer Risk for *NAT2* Slow Acetylators



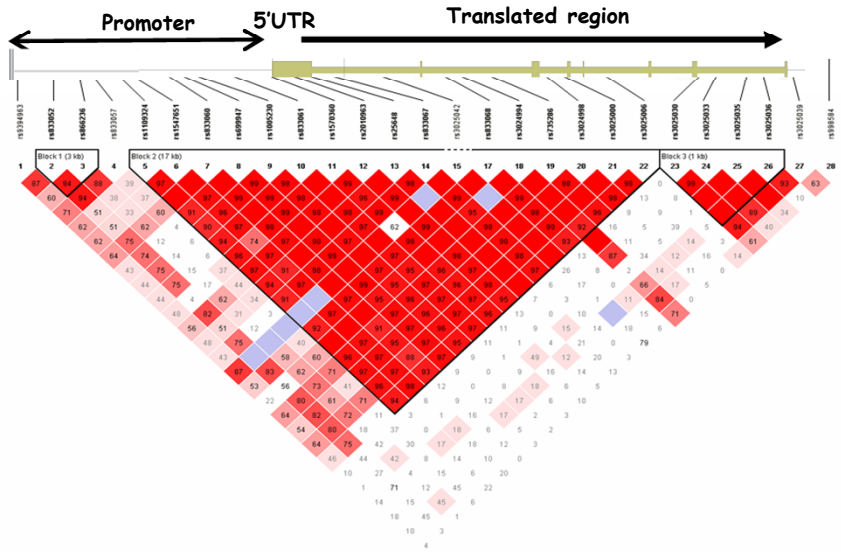
Garcia-Closas M et al. *Lancet,* 2005; 366: 649-658.

Large-scale Evaluation of Candidate Genes for Bladder Cancer



- 1,433 SNPs within or near 386 genes.
- Most notable finding for a 5'UTR variant in the vascular endothelial growth factor (*VEGF*) gene:
  - Major role in angiogenesis.
  - VEGF tumor and urinary levels related to bladder cancer recurrence and progression.
  - Variants associated with VEGF plasma levels, promoter activity, bladder cancer aggressiveness.

Detailed Characterization of *VEGF* Variants in the Spanish Bladder Study



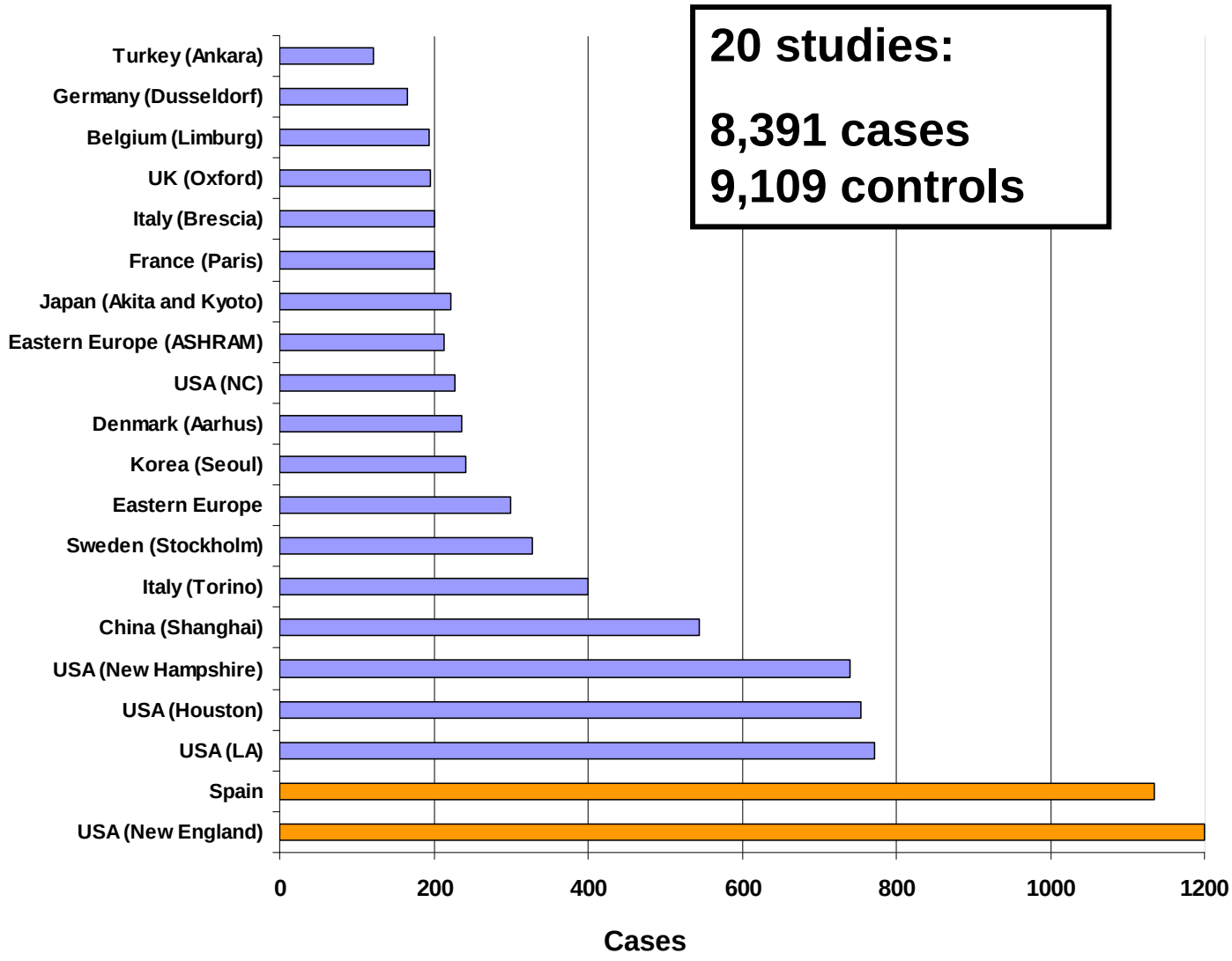
	Location	MAF	Heterozygous OR (95%CI)	Homozygous OR (95%CI)	P
rs833052	Promoter	0.12	1.1 (0.9-1.4)	2.5 (1.1-6.0)	0.04
rs1109324	Promoter	0.14	1.1 (0.9-1.4)	2.7 (1.3-6.0)	0.01
rs1547651	Promoter	0.14	1.1 (0.9-1.4)	3.0 (1.4-6.6)	0.006
rs25648	5'UTR	0.14	1.1 (0.9-1.4)	5.1 (2.3-11.2)	0.00005

Garcia-Closas M et al. (Under Review)

Bladder Cancer Consortium

Investigator Web Portal

International Consortium of Case-Control Studies of Bladder Cancer



Concluding Remarks

- **Starting to identify associations with genetic variants unlikely to be false positives:**
  - **Large, good quality individual studies**
  - **Collaborative efforts through consortia**
  - **Robust and affordable genotyping technology**

- **From candidate pathways based on current understanding of etiology to genome-wide scans.**

Collaborative Research Program

Breast Cancer Studies
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Bladder Cancer Study
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