National Cancer Institute

Pre-Consortium Challenges: Bladder Cancer Consortium

Nathaniel Rothman, MD, MPH, MHS

Occupational and Environmental Epidemiology Branch,

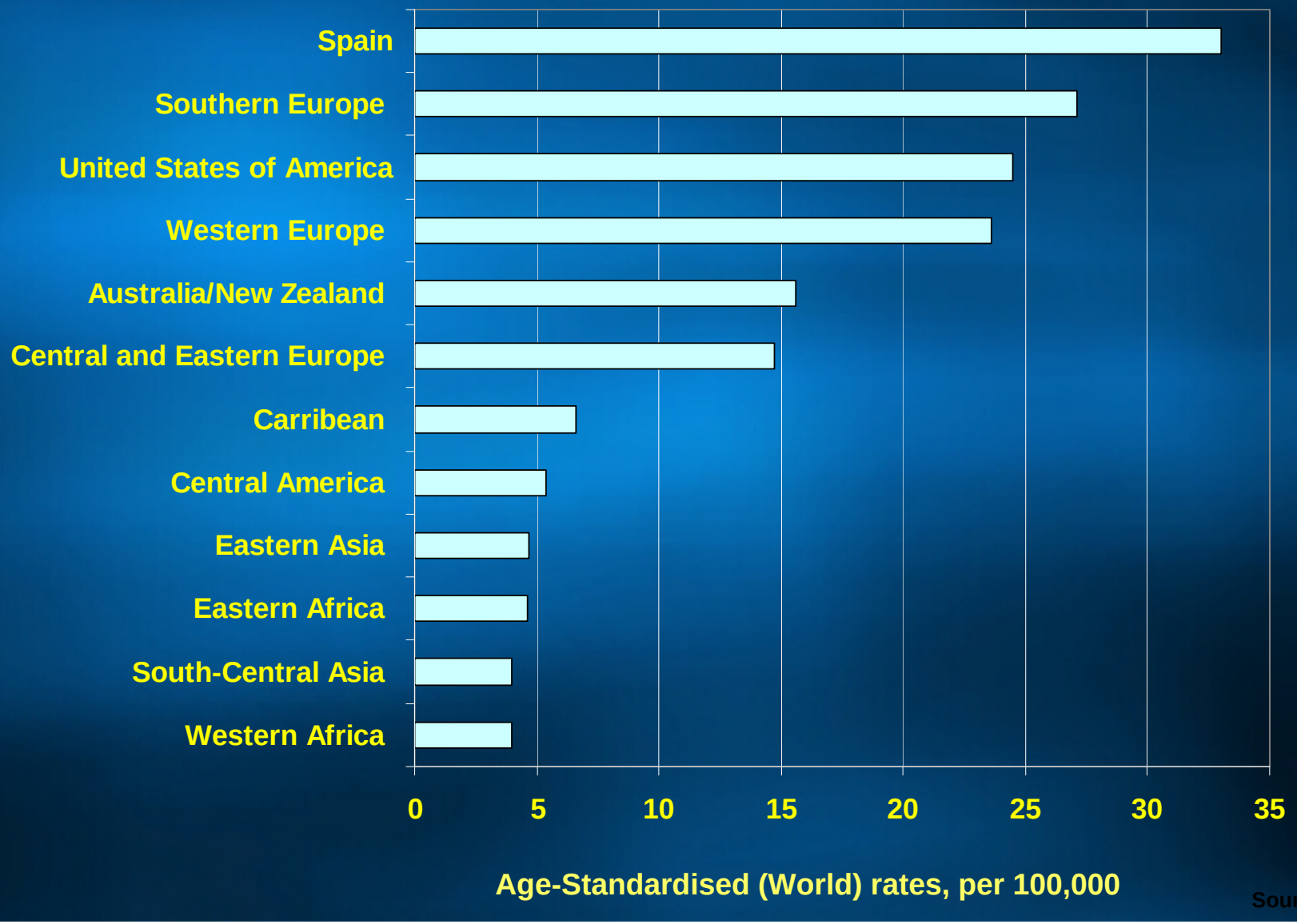
Division of Cancer Epidemiology and Genetics,

NCI, NIH, DHHS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Bladder Cancer Incidence Rates



Source: Globocan 2002

Pre-Consortium History
AACR, 2000

- Interest among a few investigators in bladder cancer research to share information re: ongoing research
- Informal meeting of investigators doing etiologic research in bladder cancer, in San Francisco, at AACR 2000
- Each person gave a summary of research activities
- Interest in research on genetic and other risk factors
- New generation of large studies were still in the field
- Not exactly sure what to do next!

Pre-Consortium History 2000-2005

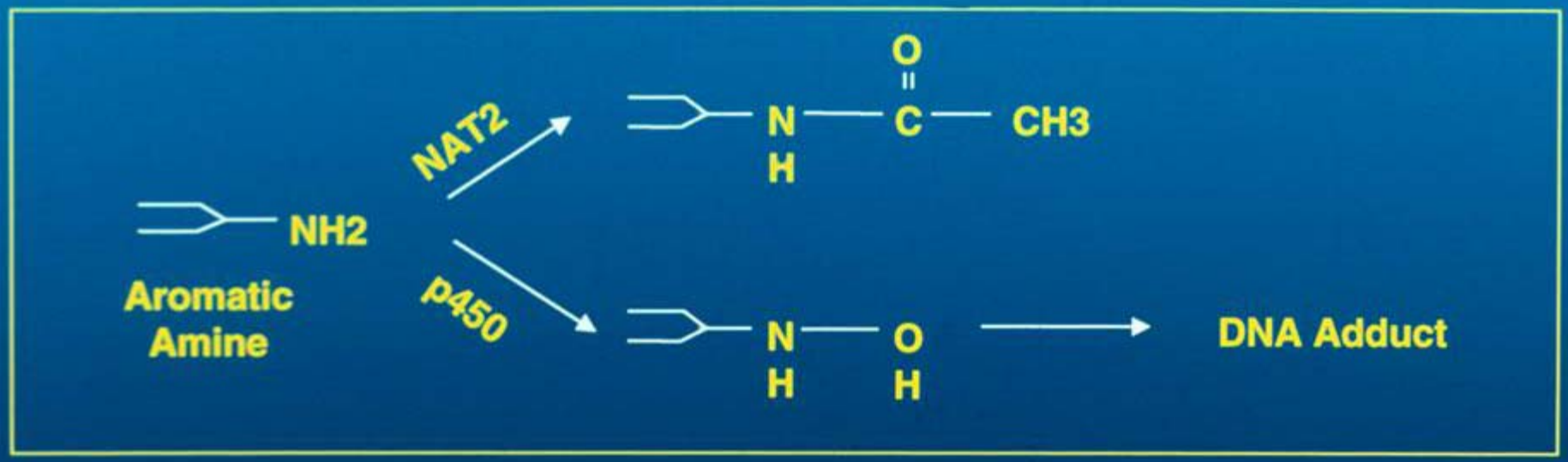
- Relatively large case-control studies with between 500 to 1200 cases and controls, with biologic samples, were completed

Pre-Consortium History

Meta and pooled genetic analyses: 2000-2005

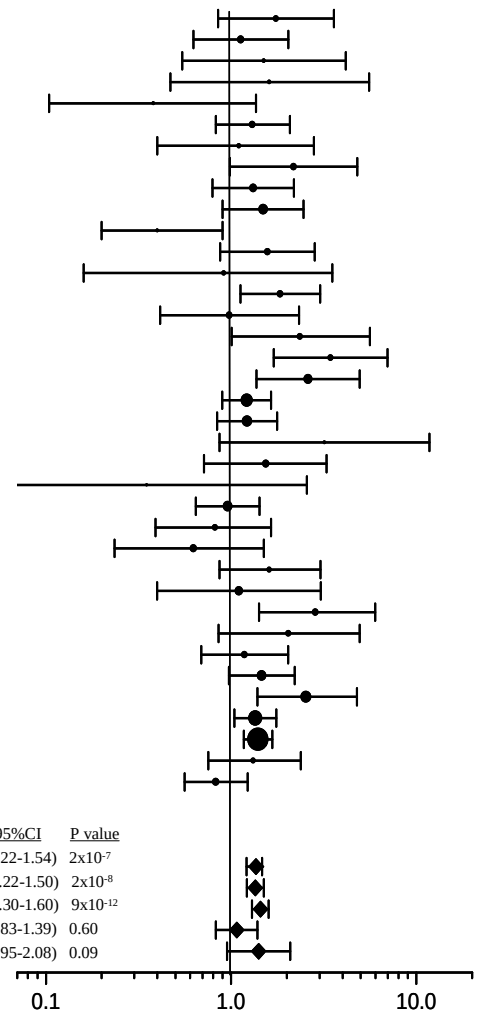
- **Series of meta-analyses and pooled analyses published on *NAT2* , *GSTM1* and bladder cancer showing strong, consistent main effects, with evidence of NAT2-smoking interaction**

Detoxification of Aromatic Amines by N-Acetylation



Meta-Analysis of Case-Control Studies of *NAT2* Slow Acetylation and Bladder Cancer

Study	Year	Country	Cases
Lower	1979	Denmark	71
Lower	1979	Sweden	115
Lower	1979	USA	34
Woodhouse	1982	UK	30
Miller	1983	USA	26
Evans	1983	UK	100
Cartwright	1984	Portugese	47
Hanssen	1985	Germany	105
Ladero	1985	Spain	130
Mommsen	1985	UK	228
Karakaya	1986	Turkey	23
Kaisary	1987	UK	98
Horai	1989	Japan	51
Roots	1989	Germany	102
Lee	1994	Korea	98
Ishizu	1995	Japan	71
Dewan	1995	India	77
Risch	1995	UK	189
Brockmoller	1996	Germany	374
Okkels	1997	Denmark	254
Su	1998	Taiwan	27
Peluso	1998	Italy	114
Taylor (Black)	1998	USA	15
Taylor (Whites)	1998	USA	215
Hsieh	1999	Taiwan	74
Kim	2000	Korea	112
Jaskula-Sztul	2001	Poland	56
Kontani	2001	Japan	149
Giannakopoulos	2002	Greece	89
Hao	2004	China	69
Mittal	2004	India	101
Hung	2004	Italy	201
Tsukino	2004	Japan	325
Gu	2005	USA	504
Garcia-Closas	2005	Spain	1134
McGrath (NHS)	2006	USA	63
McGrath (HPFS)	2006	USA	124



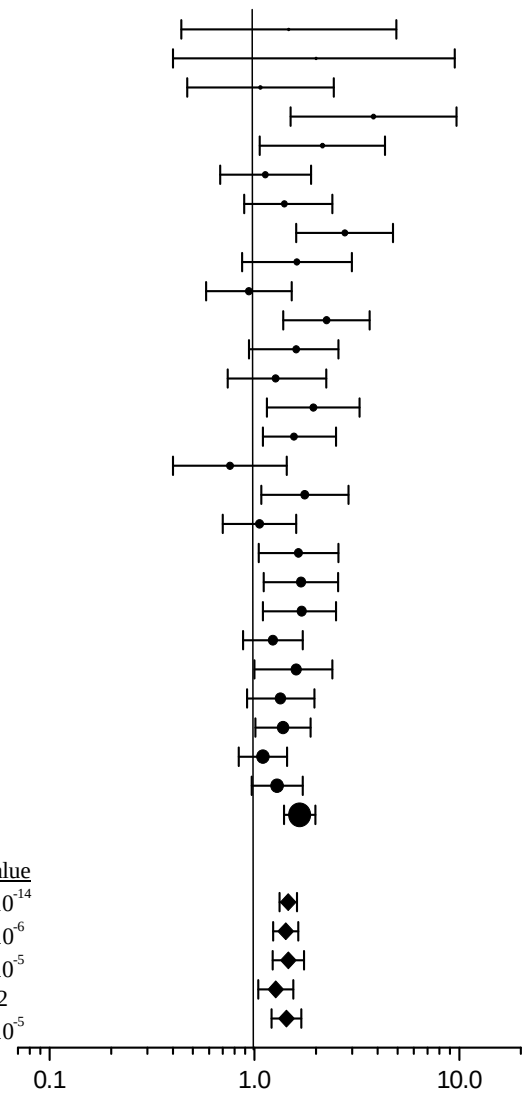
	Cases	OR 95%CI	P value
All studies (N=36)	5594	1.37 (1.22-1.54)	$2x10^{-7}$
Studies of Caucasian (N=24)	4403	1.35 (1.22-1.50)	$2x10^{-8}$
Europe (N=18)	3437	1.44 (1.30-1.60)	$9x10^{-12}$
USA (N=6)	966	1.07 (0.83-1.39)	0.60
Studies of Asians (N=9)	975	1.41 (0.95-2.08)	0.09

Rothman et al., IJE, 2007

Meta-Analysis of *GSTM1* Null Genotype and Bladder Cancer

Study		Country	Cases
Romkes	Unpublished	USA	13
Bell (blacks)	1993	USA	16
Heckbert	1992	USA	29
Daly	1993	UK	53
Mungan	2000	Netherlands	61
Šalagovic	1999	Slovakia	76
Lin (whites)	1994	USA	89
Georgiou	2000	Greece	89
Chern	1994	UK	95
Zhong	1993	UK	97
Aktas	2001	Turkey	103
Srivastava	2004	India	106
Moore	2004	Argentina	114
Törüner	2001	Turkey	121
Jeong	2003	Korea	126
Peluso	2000	Italy	130
Steinhoff	2000	Germany	135
Schnakenberg	2000	Germany	157
Kang	1999	Korea	174
Hung	2004	Italy	201
Bell (whites)	1993	USA	213
Kim	2002	Korea	216
Lee	2002	Korea	232
Okkels	1996	Denmark	234
Tsukino	2004	Japan	325
Karagas	2005	USA	354
Brockmöller	1996	Germany	374
García-Closas	Current	Spain	1139

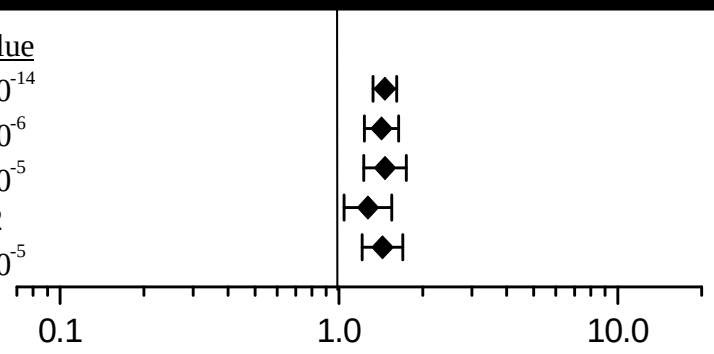
	Cases	OR 95% CI	P value
All studies (N=28)	5072	1.5 (1.3-1.6)	$2x10^{-14}$
Studies of white populations(N=18)	3539	1.4 (1.2-1.6)	$1x10^{-6}$
Europe (N=13)	2841	1.5 (1.2-1.7)	$2x10^{-5}$
USA (N=5)	698	1.3 (1.1-1.5)	0.02
Studies of Asian populations (N=6)	1073	1.4 (1.2-1.7)	$3x10^{-5}$



Garcia-Closas et al., Lancet, 2005

Meta-Analysis of *GSTM1* Null Genotype and Bladder Cancer

	Cases	OR 95% CI	P value
All studies (N=28)	5072	1.5 (1.3-1.6)	$2x10^{-14}$
Studies of white populations(N=18)	3539	1.4 (1.2-1.6)	$1x10^{-6}$
Europe (N=13)	2841	1.5 (1.2-1.7)	$2x10^{-5}$
USA (N=5)	698	1.3 (1.1-1.5)	0.02
Studies of Asian populations (N=6)	1073	1.4 (1.2-1.7)	$3x10^{-5}$



Bladder Cancer

Excellent model to evaluate susceptibility and gene-environment interactions

- Relatively homogeneous histology, but with important heterogeneity at the molecular level
- Major causes well described
  - Tobacco smoking; Occupational exposures
  - Water contaminants (chlorinated by-products, arsenic)
  - Family history
- Consistent, highly significant candidate gene associations (*NAT2*, *GSTM1*) and important findings with functional assays
- Awareness of false positive problem with low prior risk factors, and sample size needs to detect GXE
- Important clinical applications of genomic data with regard to recurrence and survival

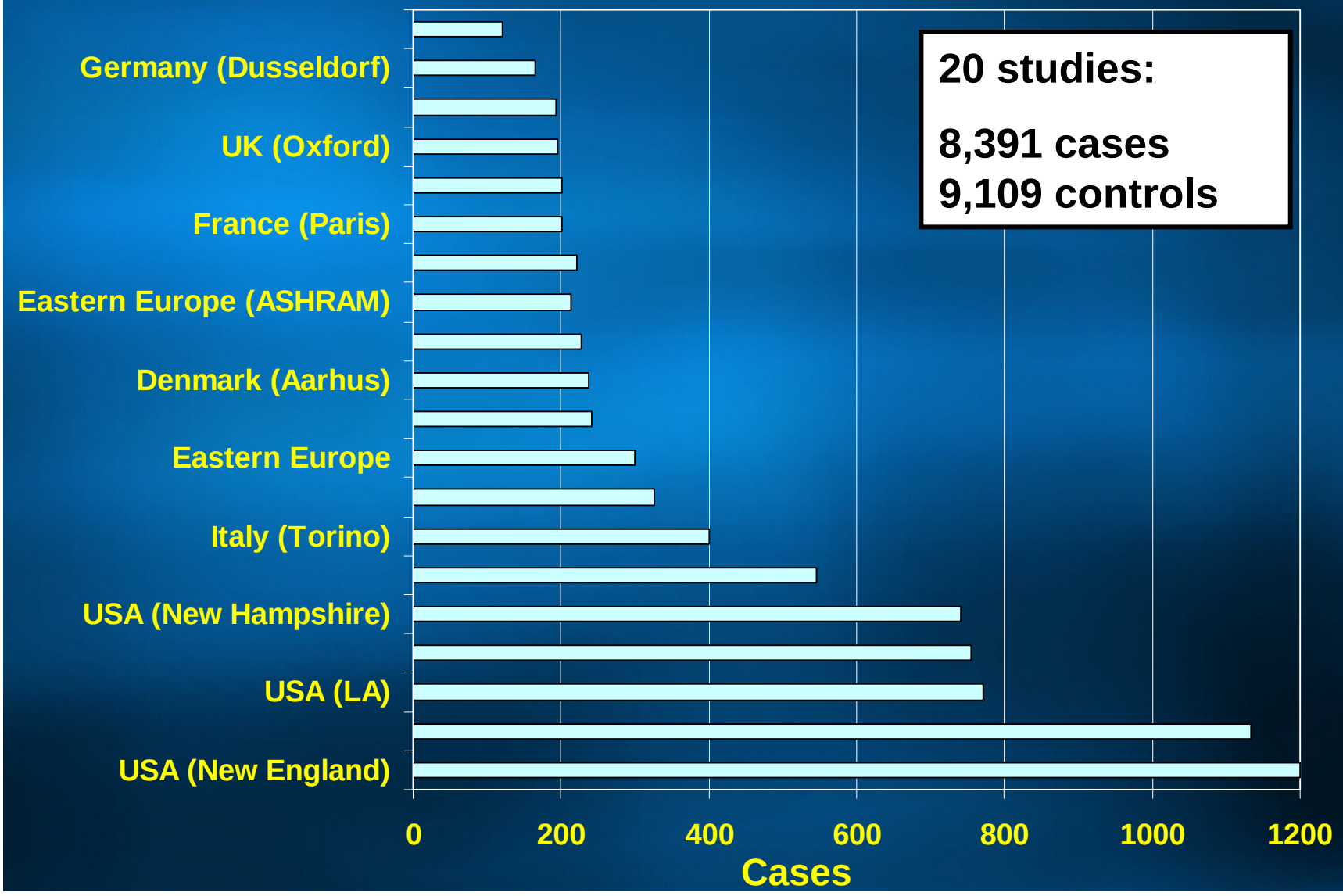
First Formal Meeting, AACR, 2005

- Paradigm of consortia had been established (Cohort consortium, InterLymph)
- Investigators of several relatively large studies communicated with each other about starting a bladder cancer consortium
- Agree to contact all known investigators in the field and invite to a side-meeting at AACR annual meeting
- Investigators met and shared information about status of studies
- Agreement to set up working groups, and to meet formally on a regular basis (second meeting at AACR, 2006)

Investigator Web Portal

Bladder Cancer Consortium

International Consortium of Case-Control Studies of Bladder Cancer



20 studies:

8,391 cases
9,109 controls

Working Groups

EXPOSURES

Hair dyes, NSAIDS, Occupation, Environment, Diet, Gender differences, Family history

GENES

Candidate gene pathways (e.g., metabolism, DNA repair, inflammation), Genome-Wide scans, functional assays

TUMORS

Pathologic criteria, genetic and epigenetic alterations

CLINICAL OUTCOMES

Investigator Web Portal

Bladder Cancer Consortium

International Consortium of Case-Control Studies of Bladder Cancer

First free-standing meeting to be held in Barcelona, June 18-19, 2007

Initial pooling projects have been established

Key Questions in Early Stages of a Consortium

- What is its purpose?
- Who will help to lead/coordinate it initially?
- How will it be funded?
- What should its first projects be?
- Challenge with regard to initial pooling projects of published, vs. unpublished, data

Issues in Coordinating Genetic Studies Without a Core Source of Funding – Profound Impact of Technology

- **TaqMan**

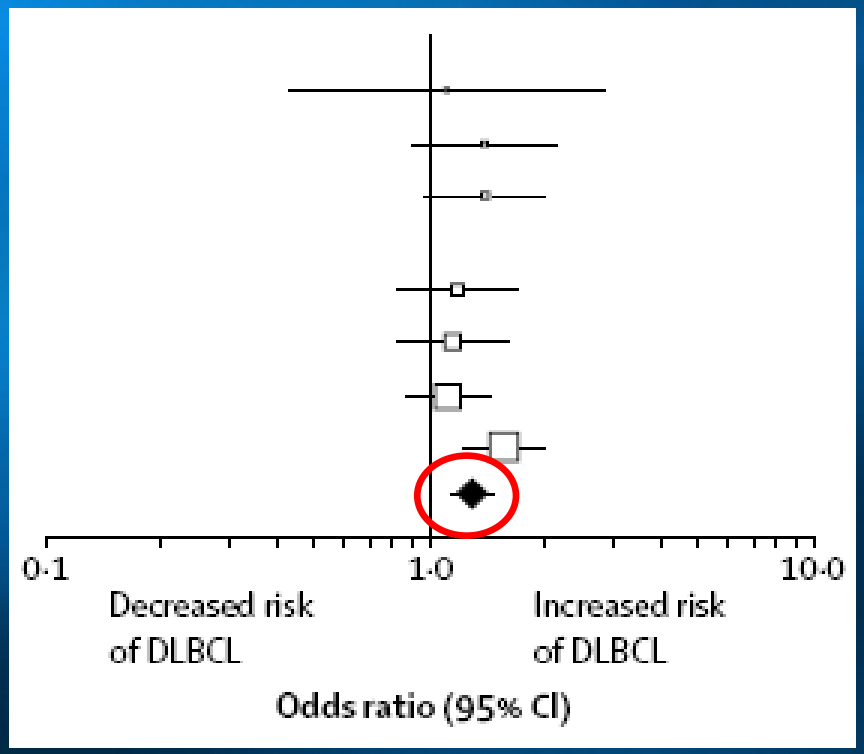
  Enhances ability to agree to pool limited unpublished data from a few candidate genes (example of InterLymph)

- **Illumina GoldenGate**

- **GWAS platforms**

TNF G-308A and Diffuse Large B-Cell Lymphoma

Pooled Analysis From Seven Studies in InterLymph



OR = 1.35 (additive model)

p-trend = 0.000055

Rothman et al., Lancet Oncology, 2006

Issues in Coordinating Genetic Studies Without a Core Source of Funding – Profound Impact of Technology

- **TaqMan**

- **Illumina GoldenGate**

  Less willingness to do TaqMan assays;

  Greater inclination to publish papers with many genes in one pathway, or entire "OPA"

- **GWAS platforms**

  Worthwhile to develop consortial plans

  Whoever gets funding first will lead the effort, but up front involvement of all studies that will play a role in replication efforts, and GXE analyses, critical

Acknowledgements

- **Coordinating Committee**

  Montse Garcia-Closas (NCI)

  Margaret Karagas (Dartmouth)

  Manolis Kogevinas (IMIM)

  Xifeng Wu (MD Anderson)

- **PIs, co-investigators of 20 participating studies!**