Genetic association studies in clinically important subtypes of breast and prostate cancer: lessons from BPC3

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Brief History of the Breast and Prostate Cancer Cohort Consortium (BPC3)

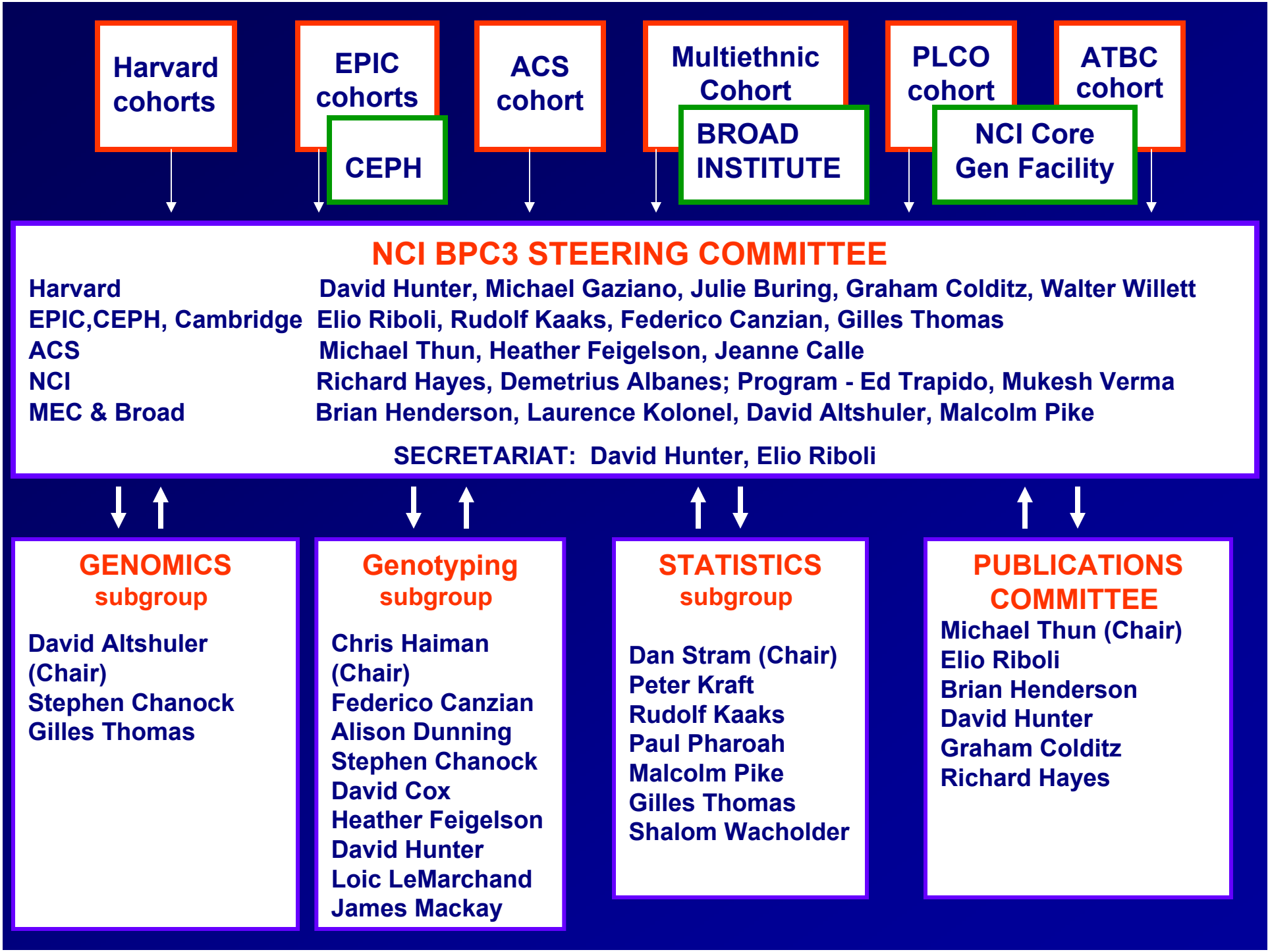
- Feb, 1999: Cancer Genetics Working Group – Epidemiology Subgroup Meeting
- May, 2000: Cohort Consortium Meeting (21 different cohorts)
- Oct, 2000: “proof of principle” study strategy was decided upon
- May, 2003: BPC3 was funded for up to 4 years, contingent on 2-year review

Specific Aims

1. Comprehensively survey candidate genes involved in steroid hormone and IGF pathways using resequencing and haplotype construction
2. Assess the association of putative functional SNPs and “tagging” SNPs (htSNPs) with breast and prostate cancer
3. Assess the association of these variants with plasma hormone and IGF-1 levels (in a subset of studies)
4. Examine gene-environment interactions

BPC3 Participating Cohorts

Study	Year started	Subjects with blood samples	Breast cancer cases	Prostate cancer cases
EPIC	1992	397,256	2,050	900
ACS CPS-II	1998	39,000	500	1,450
ATBC	1991	20,500	-	1,000
Harvard				
PHS	1982	20,000	-	1,500
NHS	1989	32,826	945	-
HPFS	1993	33,240	-	600
WHS	1993	28,263	675	-
MEC		100,000	1,990	2,400
PLCO	1993	75,000	~500	1,000
Total		797,085	6,660	8,850


Harvard cohorts
EPIC cohorts
CEPH
ACS cohort
Multiethnic Cohort
BROAD INSTITUTE
PLCO cohort
NCI Core Gen Facility
ATBC cohort
NCI BPC3 STEERING COMMITTEE
Harvard David Hunter, Michael Gaziano, Julie Buring, Graham Colditz, Walter Willett
EPIC,CEPH, Cambridge Elio Riboli, Rudolf Kaaks, Federico Canzian, Gilles Thomas
ACS Michael Thun, Heather Feigelson, Jeanne Calle
NCI Richard Hayes, Demetrius Albanes; Program - Ed Trapido, Mukesh Verma
MEC & Broad Brian Henderson, Laurence Kolonel, David Altshuler, Malcolm Pike
SECRETARIAT: David Hunter, Elio Riboli
GENOMICS subgroup
David Altshuler (Chair)
Stephen Chanock
Gilles Thomas
Genotyping subgroup
Chris Haiman (Chair)
Federico Canzian
Alison Dunning
Stephen Chanock
David Cox
Heather Feigelson
David Hunter
Loic LeMarchand
James Mackay
STATISTICS subgroup
Dan Stram (Chair)
Peter Kraft
Rudolf Kaaks
Paul Pharoah
Malcolm Pike
Gilles Thomas
Shalom Wacholder
PUBLICATIONS COMMITTEE
Michael Thun (Chair)
Elio Riboli
Brian Henderson
David Hunter
Graham Colditz
Richard Hayes

Progress to date (Funding ends 5/07)

- Comprehensively "tagged" 73 genes (goal was to examine 51 genes)
  - 59 genes completed by dense genotyping, the last 14 using HapMap data (phase II)
  - Nearly 6,000 markers genotyped
- 7 publications (several more in review)
- Tagging and assay information publicly available
- Established a mechanism for "rapid replication" of important results (e.g. 8q24)

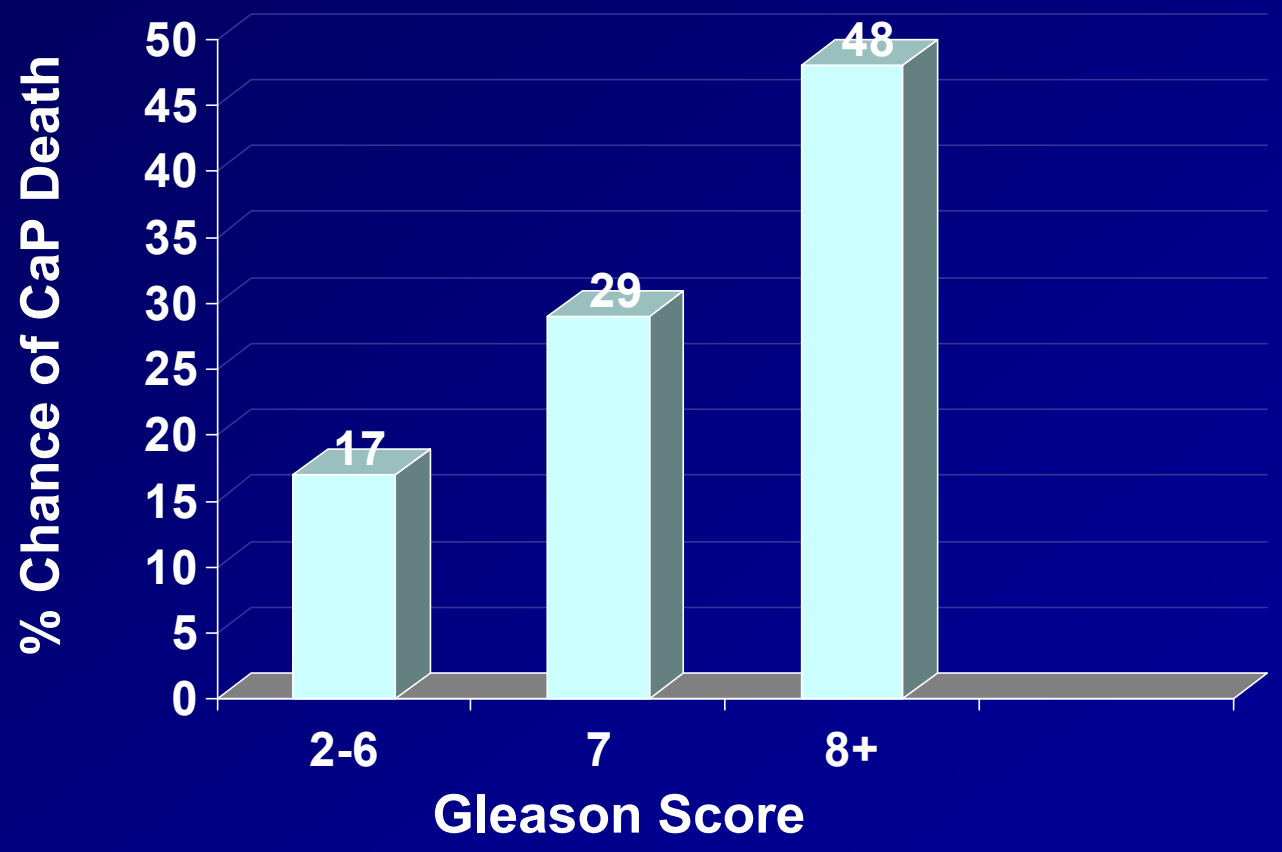
Renewal: planning for the future

- Considerations:
  - Take advantage of large size and recent innovations in genomics
  - Address NCI priorities to study rare and fatal cancers
- Concept:
  - ER negative breast cancers and advanced, aggressive prostate cancers are relatively uncommon phenotypes with poor prognosis
  - Limited knowledge about the etiology of these subtypes
  - Current scans, planned or underway, are underpowered to examine these subtypes

Advanced and Aggressive Prostate Cancer

- Advanced CaP (stage C/D) accounts for approximately 7% of all cases
  - 6% of CaP among whites
  - 10% of CaP among African Americans
  - Older men (>65) more likely to have advanced CaP than younger men
- High Gleason score associated with mortality
- Some evidence from epi studies that risk factors may differ for advanced/aggressive cases

Prostate cancer death increases with Gleason Score



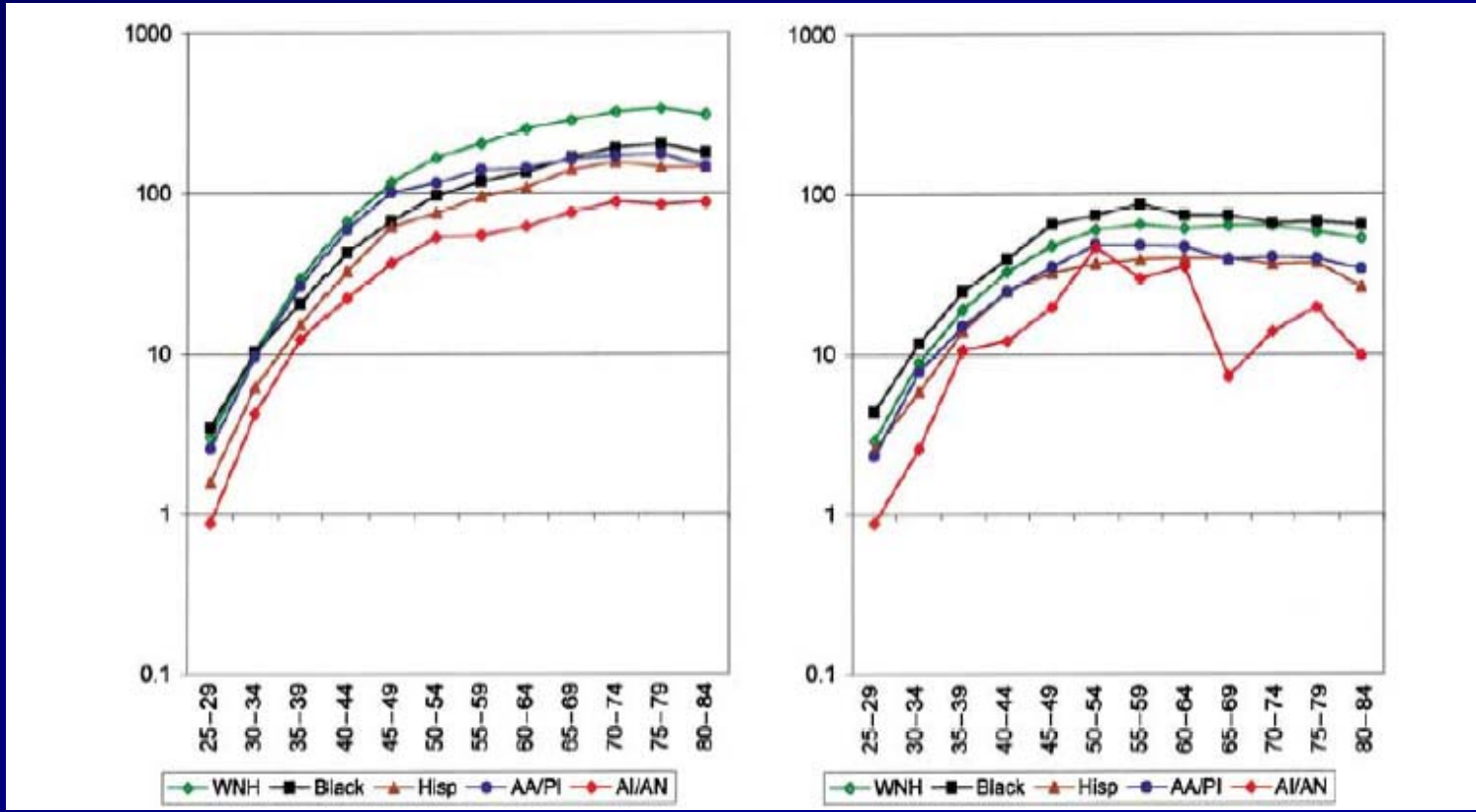
ER- breast cancer

- ER- tumors ~15-20% of breast cancer among white women and 40% of breast cancer in black women
- ER- cancers have different age-incidence pattern than ER+ cancers
- Most ER- tumors are histologic grade 3 or 4 at diagnosis; most ER+ tumors are diagnosed at grade 2
- ER- tumors have poorer prognosis and often do not respond to hormonal treatment modalities
- Common risk factors differ by ER status:
  - circulating steroid hormone levels, parity, alcohol consumption, CHRT, postmenopausal obesity
- In the BCAC GWAS, several novel loci associated with risk of ER+ breast cancer were not associated with ER- breast cancer (Easton D, personal communication)

Five-year age-specific incidence rates for ER+ and ER- breast cancers by ethnicity (1992-1998)

ER+ Breast Cancer Incidence

ER- Breast Cancer Incidence



Chu and Anderson, Br Cancer Res Treat, 2002

ER- breast and advanced prostate cancer significantly contribute to cancer burden

Estimated new cancer cases – 2007

Male	Female
Prostate 218,890 (29%)	Breast 178,480 (26%)
Lung & bronchus 114,760 (15%)	Lung & bronchus 98,620 (15%)
Colon & rectum 79,130 (10%)	Colon & rectum 74,630 (11%)
Urinary bladder 50,040 (7%)	Uterine corpus 39,080 (6%)
Non-Hodgkin lymphoma 34,200 (4%)	Non-Hodgkin lymphoma 28,990 (4%)
Melanoma of the skin 33,910 (4%)	Melanoma of the skin 26,030 (4%)
Kidney & renal pelvis 31,590 (4%)	Thyroid 25,480 (4%)
Leukemia 24,800 (3%)	Ovary 22,430 (3%)
Oral cavity & pharynx 24,180 (3%)	Kidney & renal pelvis 19,600 (3%)
Pancreas 18,830 (2%)	Leukemia 19,440 (3%)
All sites 766,860 (100%)	All sites 678,060 (100%)

ER- Breast

25% of all Br Ca = 44,600 new cases

Advanced CaP

7% of all CaP = 15,300 new cases

~ Esophagus, CML

Cancer Facts & Figures, 2007

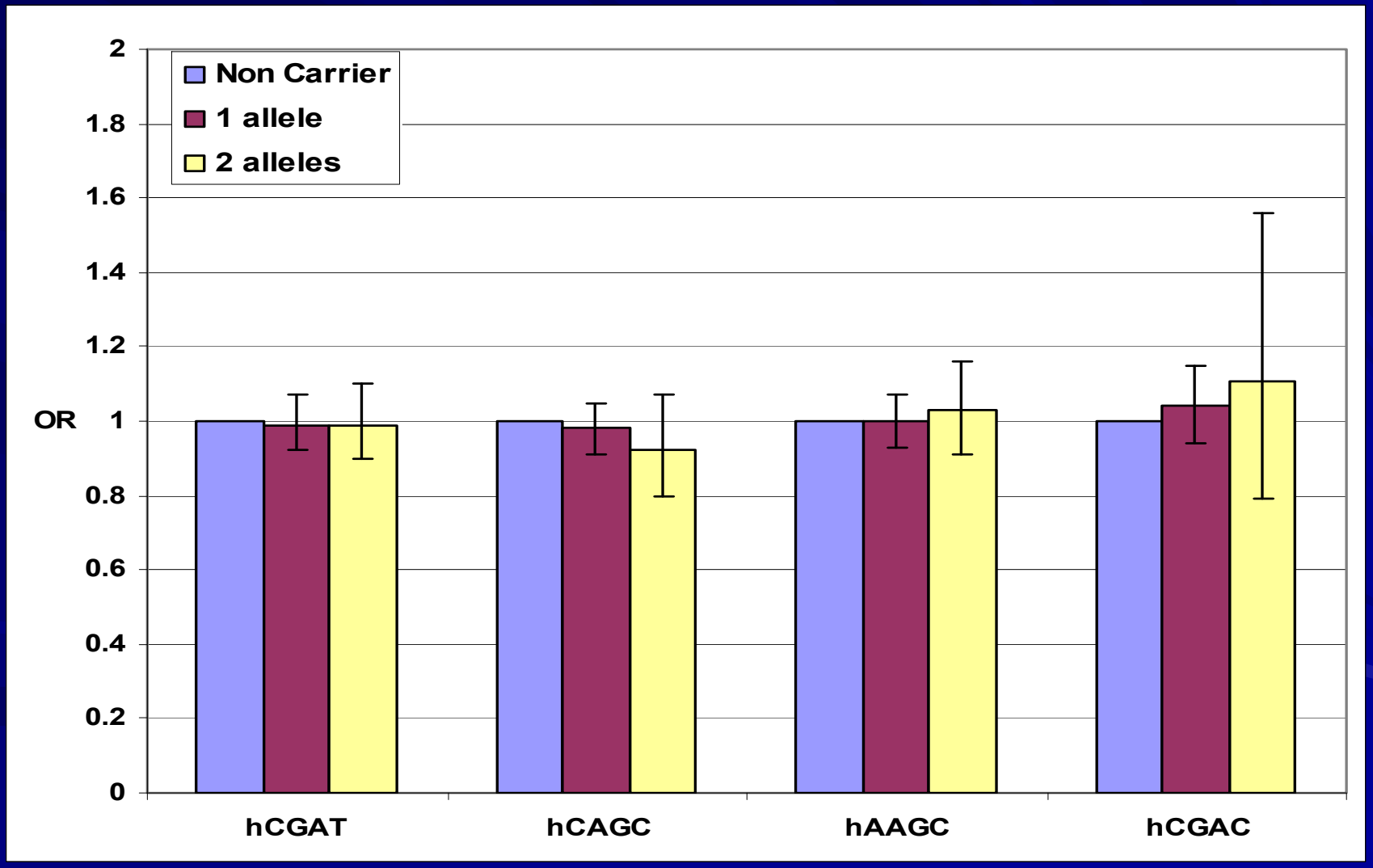
A Cautionary Tale:

Haplotype Analysis of the *HSD17B1* Gene and Risk of Breast Cancer: A Comprehensive Approach to Multicenter Analyses of Prospective Cohort Studies

Feigelson et al, Cancer Research, 2006; 66:2468-75

No main effect associations observed with Common Haplotypes (≥ 5%) in HSD17B1

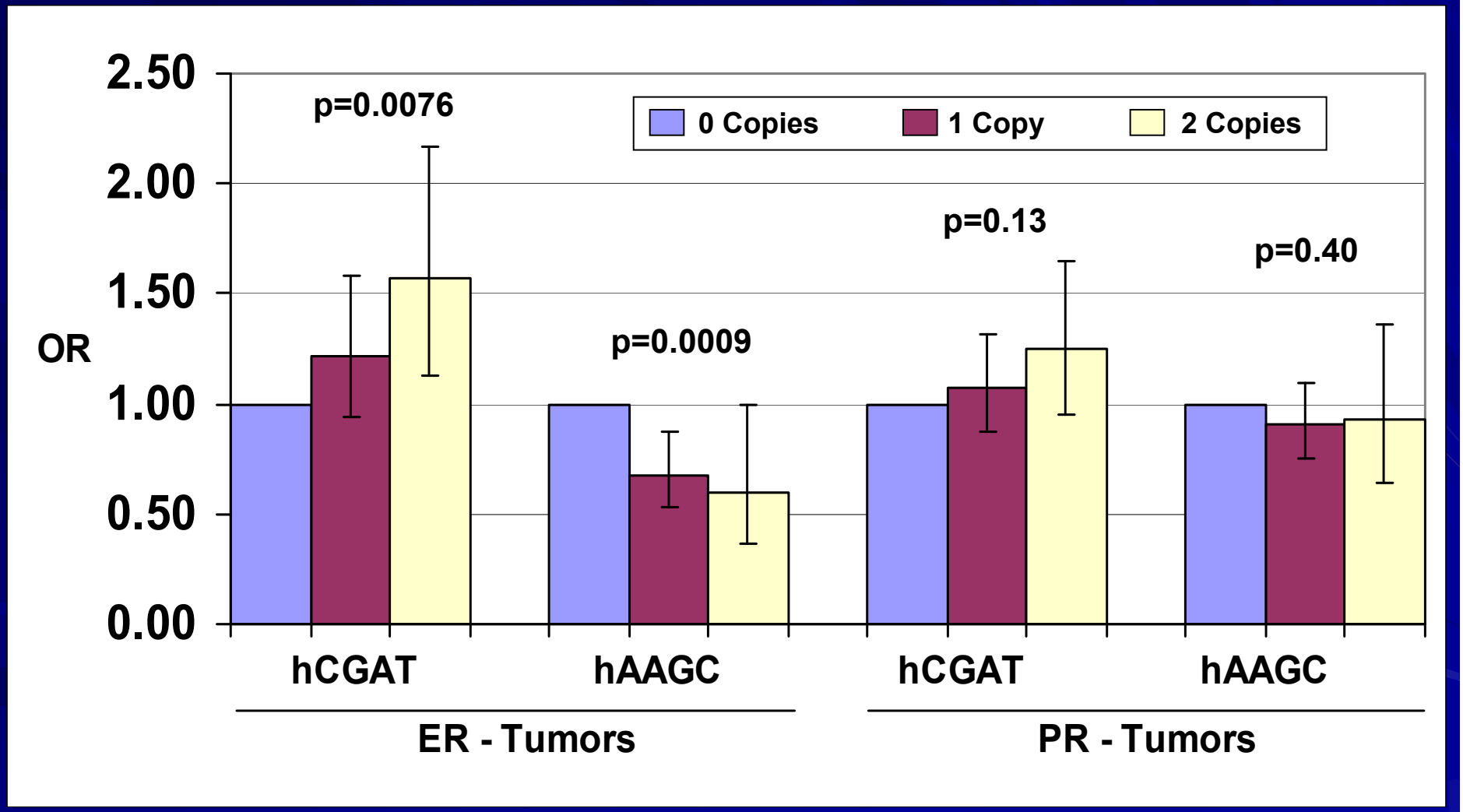
N=5,370 cases, 7,480 controls



Unexpected Finding in Analysis by ER and PR status

- Data on receptor status were available for 4 of the 5 cohorts (ACS, NHS, WHS, MEC)
  - 1737 ER+ tumors
  - 354 ER- tumors
  - 1486 PR+ tumors
  - 545 PR- tumors

HSD17B1 Haplotypes Associated with ER- and PR- Breast Cancer



HSD17B1 and Breast Cancer

- Main effects and interactions null
- Unexpected association in ER- tumors
  - Replication needed to confirm this finding

- This finding has *not* been replicated in a large case control study (M. Garcia-Closas, personal communication)

"Lessons Learned"

>> Big studies are not big enough for rare subtypes

>> Replication is essential

BPC3 Renewal: Estimated sample size

Cohort	Br Ca Cases	ER- Cases	CaP Cases	Aggr CaP
ATBC	--	--	1526	510
CPS-II	2353	210	2477	663
EPIC	6271	500	2001	300
HPFS	--	--	1419	270
NHS1	1410	203	--	--
NHS2	219	39	--	--
WHS	790	123	--	--
MEC	2589	417	3632	928
PHS	--	--	2370	529
PLCO	1275	178	2900	399
TOTAL	14907	1670	16325	3599
TOTAL (WHITES)	13363	1336	14103	2823

Renewal: Specific Aims (4 of 6 total aims)

- GWAS of ER- breast cancer (whites only)
  - 1300 cases and controls from BPC3 cohorts
  - Confirm highly associated SNPs in 2500 ER- c/c in the Breast Cancer Association Consortium (BCAC)
- GWAS of aggressive prostate (whites only)
  - Aggressive defined as: Stage C/D or Gleason 8+
  - 1300 cases and controls from BPC3 cohorts
  - Confirm findings with add'l 1300 c/c in BPC3
- Assess the generalizability of these findings in non-white women and men from the MEC
- Assess GxE with SNPs identified in these and other scans with prospectively collected questionnaire data

Power for GWAS (two-stage design): Detectable RR estimates per copy of risk allele at 90% power

	Breast (N=3800)		Prostate (N=2600)	
Risk Allele Frequency	Globally Significant[1]	Suggestive[2]	Globally Significant[1]	Suggestive[2]
0.05	1.66	1.57	1.71	1.64
0.10	1.46	1.38	1.50	1.45
0.20	1.35	1.29	1.37	1.33
0.50	1.28	1.24	1.30	1.27
0.80	1.38	1.33	1.41	1.37
0.90	1.57	1.48	1.62	1.55

[1]Type 1 error rate 9×10^{-8}; [2]Type 1 error rate 9×10^{-6}

Possible criticism

"Scan in older, white men and women may not detect important alleles for the rare cancer phenotypes that are more common among African Americans"

- Recent identification of 8q24 susceptibility allele in an Icelandic populations suggest this is not the case
  - Locus identified is more common among individuals of African descent
  - RR is similar, PAR is greater in African Americans