

Insights from the Breast & Prostate Cancer Cohort Consortium

NCI Epidemiology Leadership Workshop

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Objectives

- Briefly describe:
 - NCI Cohort Consortium
 - “Proof of principle” study: “Breast & prostate cancer and hormone-related gene variants”.
 - Lessons learned about large-scale collaborations during development of grant proposal and first year of funding.

Background of Cohort Consortium

- Started by NCI in 1999
- Objectives:
 - Establish a network of epidemiologists with existing cohort studies to study gene-environment interactions & cancer.
 - Foster interactions among epidemiologists, population geneticists, and statisticians to integrate rapid advances in genomic research into large-scale epidemiological studies.

“Proof of Principle” Study

- Collaboration involves 6 large cohorts (with multiple subcohorts) and 2 genome centers
- Focus on breast & prostate cancer
- Comprehensively survey candidate genes involved in steroid hormone metabolism, the IGF pathway, and their related receptors.
- Conduct parallel and pooled nested case control studies of putative functional SNPs (identified by resequencing) and haplotype tag SNPs associated with breast and prostate cancer.

Other Specific Aims

- In a subset of cohorts, assess the association of genetic variants with plasma hormones and IGF levels (and whether the associations vary by plasma level of hormones).
- Examine gene-environment interactions with known lifestyle and anthropometric risk factors.
- Demonstrate feasibility and benefit of this large-scale, multi-center, multidisciplinary collaboration.

Number of Cases from Each Cohort in “Proof of Principle” Study

Cohort	Breast (N)	Prostate (N)
CPS-II (ACS)	500	1200
ATBC (NCI)	-	1000
EPIC (IARC)	2050	900
Harvard Cohorts	1610	2100
MEC (Hawaii/USC)	1990	2400
PLCO (NCI)	-	1000
Total	6150	8600

Lessons Learned



Benefits of Participation In Cohort Consortium

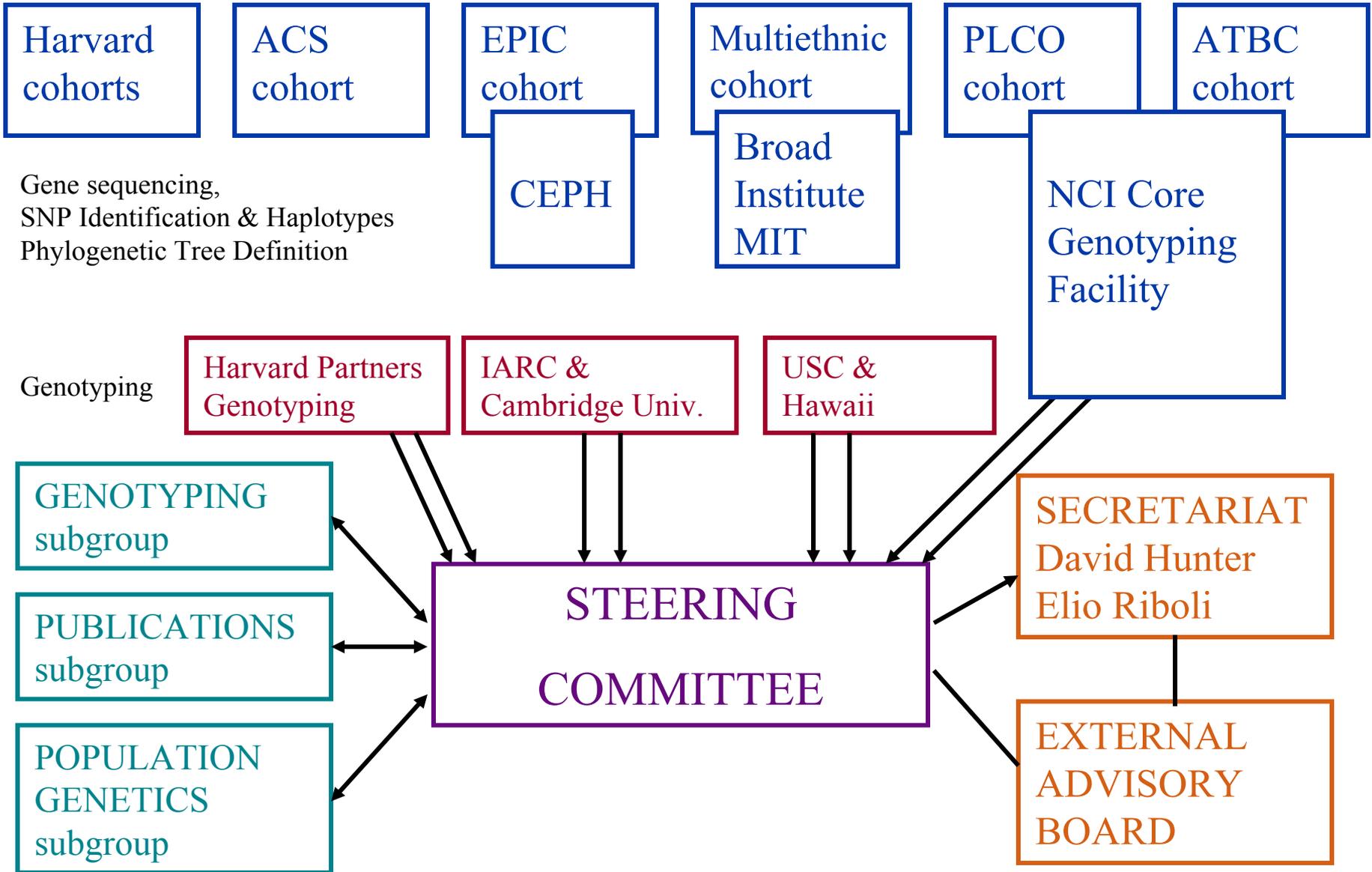
- Scientifically interesting & stimulating
- Potentially more informative than results from single, underpowered cohorts
- Decision not to participate may have costs
- If epidemiologists can't hang together, we may hang separately, especially in study of gene-gene & gene-environment interactions.

Challenges of Participating In Cohort Consortium

- Team process inherently more cumbersome
- Larger cohorts that have already developed separate studies may jeopardize their own funding or scientific investment.
- Concern that younger and non-tenured investigators may be invisible in team science, harming career advancement.
- Trust and respect are honorable and desirable, but require structures that ensure fairness and maximize opportunities.

The Process Is Complex

Breast and Prostate Cancer Risk and Hormone-Related Gene Variants



Organizational Structure

Must be clearly defined on paper

- Section “H” in the Breast & Prostate Protocol
- Should communicate that the organizational structure has been developed.

This must reflect reality

- Essential if the study is to succeed

Protocol Development

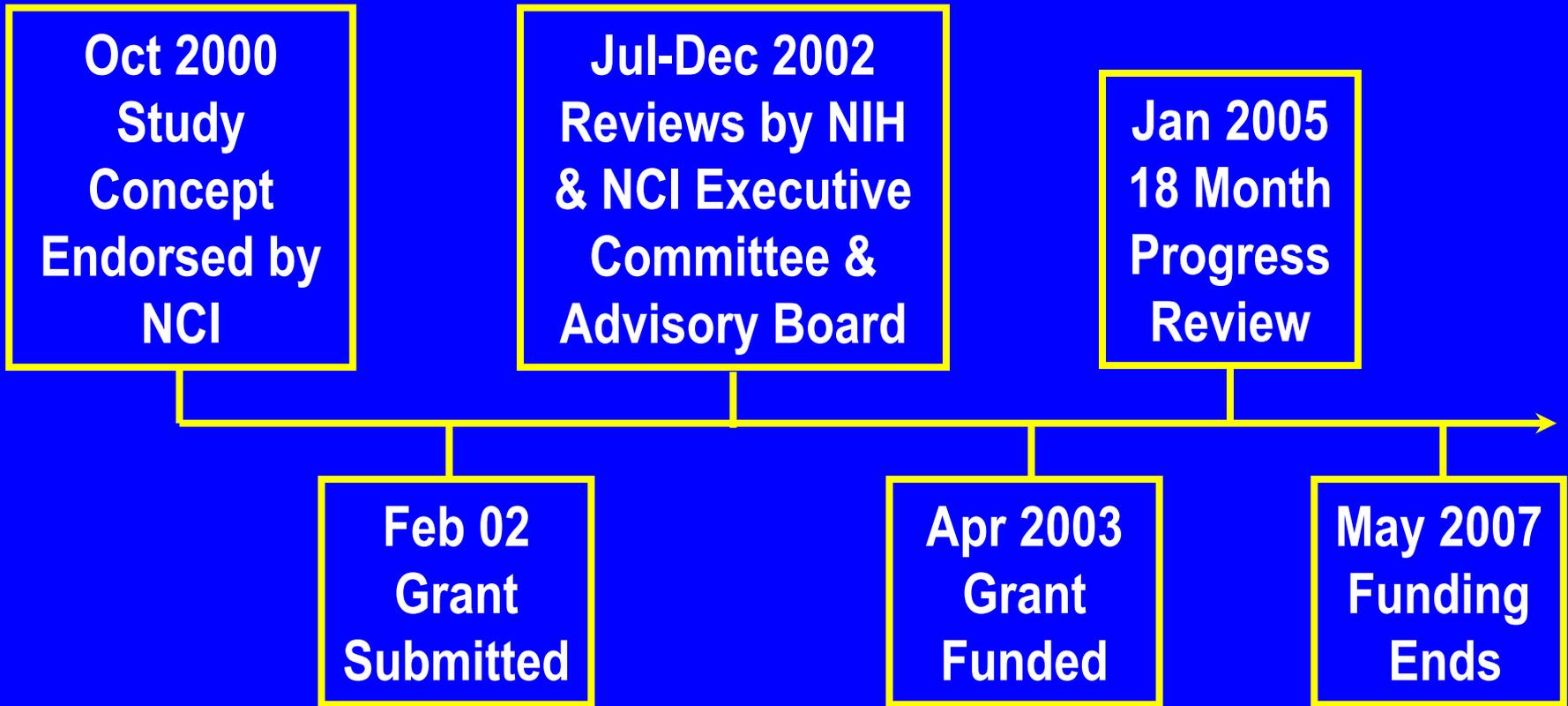
- Clearly define responsibilities & leadership roles
- A few people will do the heaviest lifting, but work can be divided by topic:
 - Pathways
 - Genetic variants (Resequencing or *in silico*)
 - Haplotype construction
 - Genotyping
 - Phenotype analyses
 - Analytic approach & statistical issues
 - Cohort descriptions

Protocol Development (2)

- Rationale for cohort consortium strongest when:
 - Prospective design essential
 - Other approaches cannot provide adequate sample size within a reasonable time frame
 - Costs can be reduced by using existing cohorts and collective buying laboratory reagents .

Time flys

Timeline- Breast & Prostate Study



Other issues

- Most of the work gets done in small working groups
- Large conference calls are useful mostly for updates and communication across working groups
- Busy schedules and long-distance communication complicate decision-making.

Other issues (2)

1. Proposal can be strengthened through genuine involvement of population geneticists
2. In this study, the population geneticists introduced :
 - A plan for haplotype analyses when this was still novel
 - Extensive resequencing of candidate genes (exons, promotor regions, and regions of mouse-human homology)
 - Standardized criteria for quality control of the genotyping data

Other issues (3)

- Can genotyping be centralized, or will many centers wish to use their own genotyping facilities?
- Can the researchers agree to publish pooled analyses as soon as these are completed, or will publication be delayed until individual centers have published?

Publication Issues

- The Breast & Prostate study has evolving Publication Guidelines.
- These currently apply to the 1st seven publications (an overview paper and main effects papers for three genes and two cancers).
- Guidelines revisited approximately every two months at this point.

Publication Issues (2)

- Criteria for authorship defined broadly (to be inclusive rather than exclusive).
- Must fulfill the criteria of the International Committee of Medical Journal Editors
- All authors and their organizations will be listed at end of paper.
- All who qualify as authors will listed in Pub Med
- Byline under title will state “From the Breast and Prostate Cancer Cohort Consortium” and have footnote directing readers to author list.

Demonstrating Feasibility is Part of “Proof of Principle”

- * Demonstrate the feasibility of studying gene-environment interactions by systematically collecting and pooling data from existing cohort studies.
- * Promote collaboration involving population geneticists, biostatisticians and epidemiologists at all phases of the study.
- * Determine whether “the whole is greater than the sum of the parts”

Conclusions

- I don't have a crystal ball to predict the future of the cohort consortia.
- But, the approach has enormous potential.
- Realizing this potential will require adapting individual and institutional behavior to this new research environment.

