Susceptibility to Tobacco Carcinogenesis: Genotypes Versus Phenotypes

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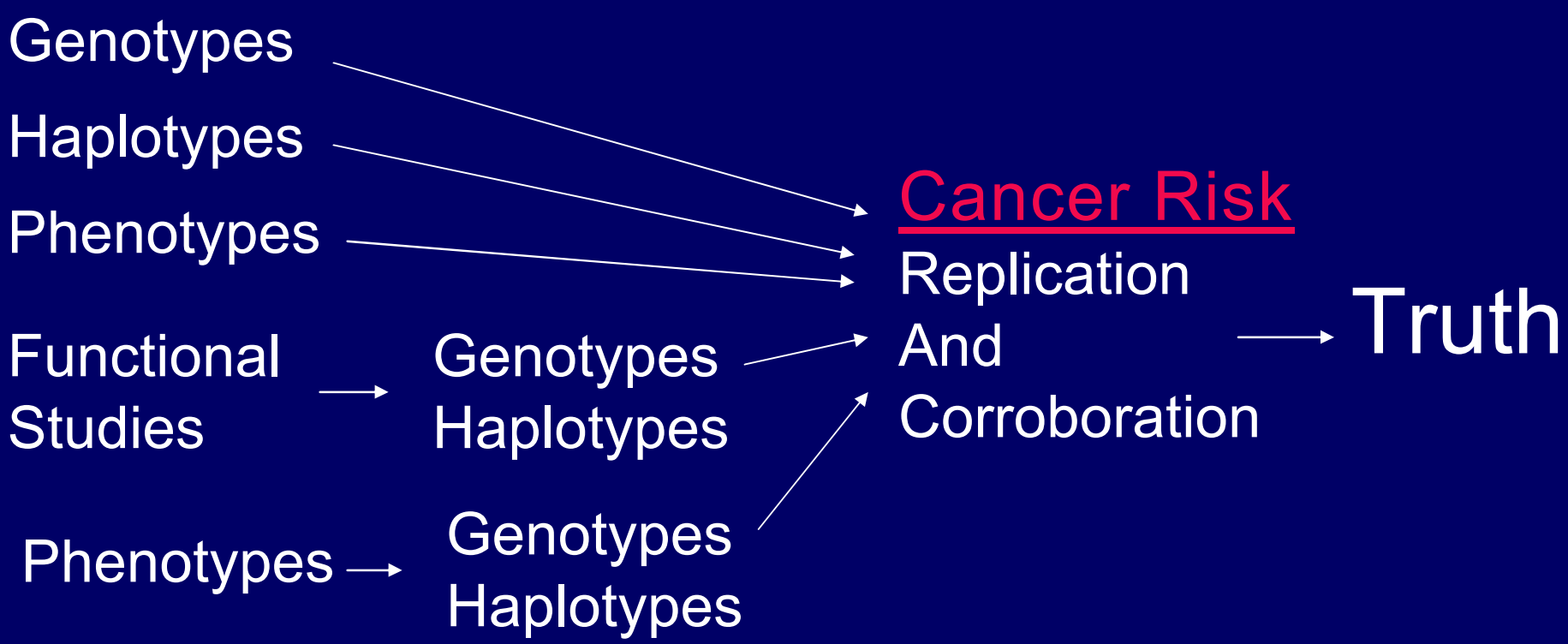
The Fast Track to Truth



What Are Phenotypes? I

How someone looks – molecular, microscopic, organ or whole body level

(a.k.a. intermediate or early detection markers)

Examples

(We can argue what is the appropriate classification but not whether the marker is a phenotype)

(Not all inclusive)

- Behavior – patterns of smokers, choice of cigarettes
- Exposure markers (macro and micro levels)
  - Metabolites and metabolic profiles
  - Expression profiles
- Biologically effective dose
  - Adducts

What Are Phenotypes? – More Examples

- Markers of harm (integrated susceptibility and exposure)
  - Mutations in cells that are morphologically normal or premalignant cells
  - Tissue activities
  - Cytogenetic studies
  - Methylation profiles in blood, epithelial cells
  - Imaging – spiral CT
- Markers of susceptibility
  - DNA repair capacity and other functional studies from groups of people

What Are Phenotypes? – Yet More Examples

- Markers of susceptibility
  - DNA repair capacity, teleromerase and other functional studies from groups of people
- Tumor phenotypes
- Clinical outcome – cancer prognosis
- Other tobacco-related disease or markers – COPD, lipids, white blood cells
  - Symptoms – cough or shortness of breath at early age
- Comorbid traits – drinking, depression

Genotyping and Phenotyping For Cancer Risk

Genotypes

- SNPs are predictive of how the host responds over a lifetime
- Inexpensive
- Useful in field and clinic
- Statistical power low for low penetrance, GE and gene-gene interactions
- Nonreplication issues - population, laboratory error, millions of SNPs

Phenotypes

- Represent complex genotypes
- Conceptually better predictive ability
- Less useful in field and clinic; the laboratory can be a challenge
- Nonreplication issues - population, laboratory error

Why Phenotypes? - I

- Complex genotypic trait
  - Includes unknown genes without a priori knowledge
  - Look at all genes in a pathway v. a priori rationale, because we can't get to all the genes – almost impossible task
  - Easier to understand which pathway and why
  - Increased odds of finding a moderately penetrant gene
  - Value added – we get risk factor data and provide mechanistic information
- Identify and validate genotypes
  - Helps identify which SNPS might be higher penetrant in the context of the pathway
  - Learn from extreme phenotypes – who gets sick from their first cigarette for adverse effects

Why Phenotypes? - II

- There is very good statistical power in these studies
  - There are several phenotypic markers that show consistent results with small numbers of cases in cohorts and case-control studies (e.g., DNA adducts, mutagen sensitivity)
- Provides information about the host's response to exposure in context of ongoing exposures
  - Enhance exposure assessment (low dose exposures in low risk populations)
  - Identify risks for single agents within complex exposures
  - Estimate total exposure for multiple sources
- Can quantitate response (genotypes only approximate quantitative response, but may be for different disease)
- Can study target tissue (sputum, urine)

Mutagen Sensitivity Assay

Organ	Cases/Controls	OR (95% CI)	Reference
Liver	28/110	5.6 (2.3, 13.8)	Wu, 1998
Secondary Oral and lung cancers	28/250	2.7 (1.2, 5.8)	Spitz 1994
Lung – Afr. Amer.	90/119	3.7 (1.4, 9.4)	Spitz, 1997
Familial Oral Ca.	17/14	P<0.001	Ankathal, 1996
Triple primary Ca.	18/18	P=0.44 (NQO p=0.07)	Miller, 1998
Oral Cavity	60/112	2.4 (1.2, 4.8)	Wang, 1998
Upper aerodig.	67/81	4.8 (3.4, 9.8)	Wu, 1998
Head and neck	313/224 (pooled)	P trend <0.01 up to 19.2	Cloos, 1996
Lung	33/96	6.5 (3.7, 11.4)	Wei, 1996
Glioma	219/238	2.1 (1.4, 3.1)	Bondy, 2001

Why study susceptibilities in the context of smoking?

- We need more people to stop smoking
- We need to understand risks in former smokers and those exposed to ETS
- We need to understand risks for new tobacco company products
- Guide chemoprevention and early detection
- Provides mechanistic understanding (prevention trials in lung cancer have failed [except for smoking cessation!])
- Predictor for treatment response, cure, and survival

Priorities - I

1. Definitively identify the most susceptible
   - Behavior to clinical outcome paradigm
   - Lung and other smoking-related cancers
   - Provide information useful to tobacco control efforts

Priorities

2. Identify and validate better phenotypic markers for lung and other cancers
   - Validate – reproducibility, reliability, sensitivity, and specificity
   - Validate in context of pathways and measures
   - High throughput
   - Inexpensive
   - Less tissue
   - Less time
   - Accessible tissues, or reduce morbidity for tissue collection
   - Useful in cohorts
   - Markers for morphologically normal and abnormal cells
   - Early markers of disease that lead to theurapuetic intervention
   - Develop prioritization scheme

Priorities

3. Identify and validate targeted phenotypic markers for not only lung, but other cancers
   - Exposure
   - Harm
   - Clinical outcome
4. Potential reduction exposure products (PREPs)
   - Canary in the mine
   - Recognize that there have been a lot of recent recommendations

Priorities

6. Develop risk assessment model
   - Develop quantitative phenotypes
   - Use of multiple phenotypes
   - Include covariates and comorbidities
7. Studies to identify the SNPs behind the phenotypes
   - Use of extreme phenotypes
   - Prioritization scheme for studying SNPs
   - Sequencing of genes within pathways for phenotypes – multiple gene approaches (Not amenable to genome-wide scans yet)

Priorities

8. Validate surrogate tissue use for target tissues (lung and non-lung cancers)
9. Studies that understand tobacco smoke exposure, in addition to constituent analysis
   - Complex mixture studies
   - Inflammatory, irritant, and immune response
   - Studies that consider carcinogens other than TSNs and PAHs
   - What enzymes get induced by tobacco smoke or other product exposure

Priorities

10. Studies of tobacco products other than cigarettes
    - Smokeless tobacco
11. Family studies for lung cancer
    - Better analysis about tracking the smoking patterns
    - Better understanding of risk by histology
    - Identify key genes
12. Understand importance and usefulness of lesions that regress
    - Better predictive phenotypes
13. Studies that apply and validate phenotypic markers in smoking cessation trials and for former smokers

Priorities

14. Studies focusing on specific histologies and smoking behaviors
    - Why is histology incidence changing?
    - Bronchial alveolar cancer
    - Impact of regulation and changes in workplace smoking
15. Studies of former smokers
    - 40+ million of them; remain at high risk
    - Studies that lead to chemoprevention or other prevention strategies
    - Regressing lesions – better predictive phenotypes
    - Effect modification

Priorities

16. Risks for cancers other than lung
    - Phenotypes for easily accessible tissue
      - Bladder and oral cavity
    - Second primaries
17. Environmental tobacco smoke
    - Studies that show functional outcomes
    - Study markers of harm
    - Broad carcinogen exposure
      - other than PAH and TSNs
    - Focus on lung
    - Expression profiles
    - Recognize that these individuals are the most susceptible

Resource Needs (Needs Work!)

1. Develop phenotype panels for scanning genotypes
   - Phenotypes that represent different pathways
   - Validated
   - Well-characterized population
   - (How many people in set?)
2. Mechanism for following controls to become cohorts
   - Phenotype studies do not need to be large
3. More cohort studies to use repeated measures over time
4. Same interview measures for smoking across studies
5. Studies that allow for better communication of results
   - What are best ways to explain phenotypes and smoking?

Resource Needs
(Needs Work!)

6. Better ETS exposure assessment methodology
7. Partnerships with health care providers (i.e., dentists, community docs, nonacademic hospitals)
8. Cohorts need to anticipate the role of phenotype studies

Thank you!