

Historical Perspectives on the Evolution of Cancer Epidemiology

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*Trends in 21st Century:
From Scientific Discoveries to
Population Health Impact*

Formal Cancer Epidemiology: The Early Years

Studies

Relative Risk

Smoking and Lung Cancer

Richard Doll & A. Bradford Hill
(*Brit Med J* Sept 1950)

14

Ernest L. Wynder & Everts A. Graham
(*JAMA* May 1950)

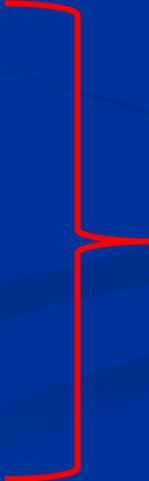
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Alcohol – Upper GI Cancers

Radiation – Leukemia

Tobacco – Other Cancers

18 specific chemical or industrial processes
(*IARC* 1979)



Ranging from
4 to several
hundred

Epidemiology - Then

- **Small, simple studies**
- **Small study teams**
- **PI did virtually everything**

Epidemiology - Now

- **Large, complex studies**
- **Large, multidisciplinary teams**
- **Specialization**

Why the Differences?

- **Major changes in the goals of Classical Epidemiology**
- **Introduction of, and major shift to, Molecular Epidemiology**

Classical Epidemiology

Then

Large Risks

Evident Exposures

Main Effects

Now

Low-level Risks

Difficult to measure exposures

Effect Modification

Molecular Epidemiology: Opportunities

- **Overcome Some Weaknesses of Classical Approaches**
 - **Measure Exposures**
 - **Measure Outcomes**
 - **Assess Susceptibility**
 - **Mechanistic Studies**
 - **Assess larger numbers of markers simultaneously**

Hormone Therapy (HT) for Menopause and Cancer

**Pooled Analysis:
4 follow-up studies of
all cancers**

HT Exposed N = 1130

Cases: Observed = 7
Expected = 74

**Relative Risk (RR) of Breast
Cancer by Duration of HT use**

Duration of ERT (yrs.)	RR	95% CI
< 1		
1 - 4	} 0.9	0.5 - 1.5
5 - 9	1.2	0.6 - 2.0
10 - 14	1.3	0.6 - 2.4
15+	2.0	1.1 - 3.4
P for trend		0.02
# of exposed cases		49

Relative Risk (RR) of Breast Cancer: Never Users, Recent Users, and Past Users

RR for Recent Users for ≥ 5 Years

<u>Weight</u>	<u>BMI</u>
$\leq 65 \text{ kg} = 1.65$	$\leq 25.0 = 1.52$
$\geq 65 \text{ kg} = 1.06$	$\geq 25.0 = 1.02$
$P_{\text{trend}} \quad 4 \times 10^{-3}$	1×10^{-4}

Genetic Epidemiology

➤ 1980s onward: Mendelian Inheritance

- Genome-wide linkage
- High-risk families

➤ 1990s onward: Susceptibility Genes

- RFLP + other technologies
- Candidate genes

Genomics – A Lost Decade

- Thousands of candidate genes
- Pursued “to extinction” in tens of thousands of studies
- Tiny fraction of reported associations ever replicated
 - Even fewer GxE interactions

Genetic Epidemiology

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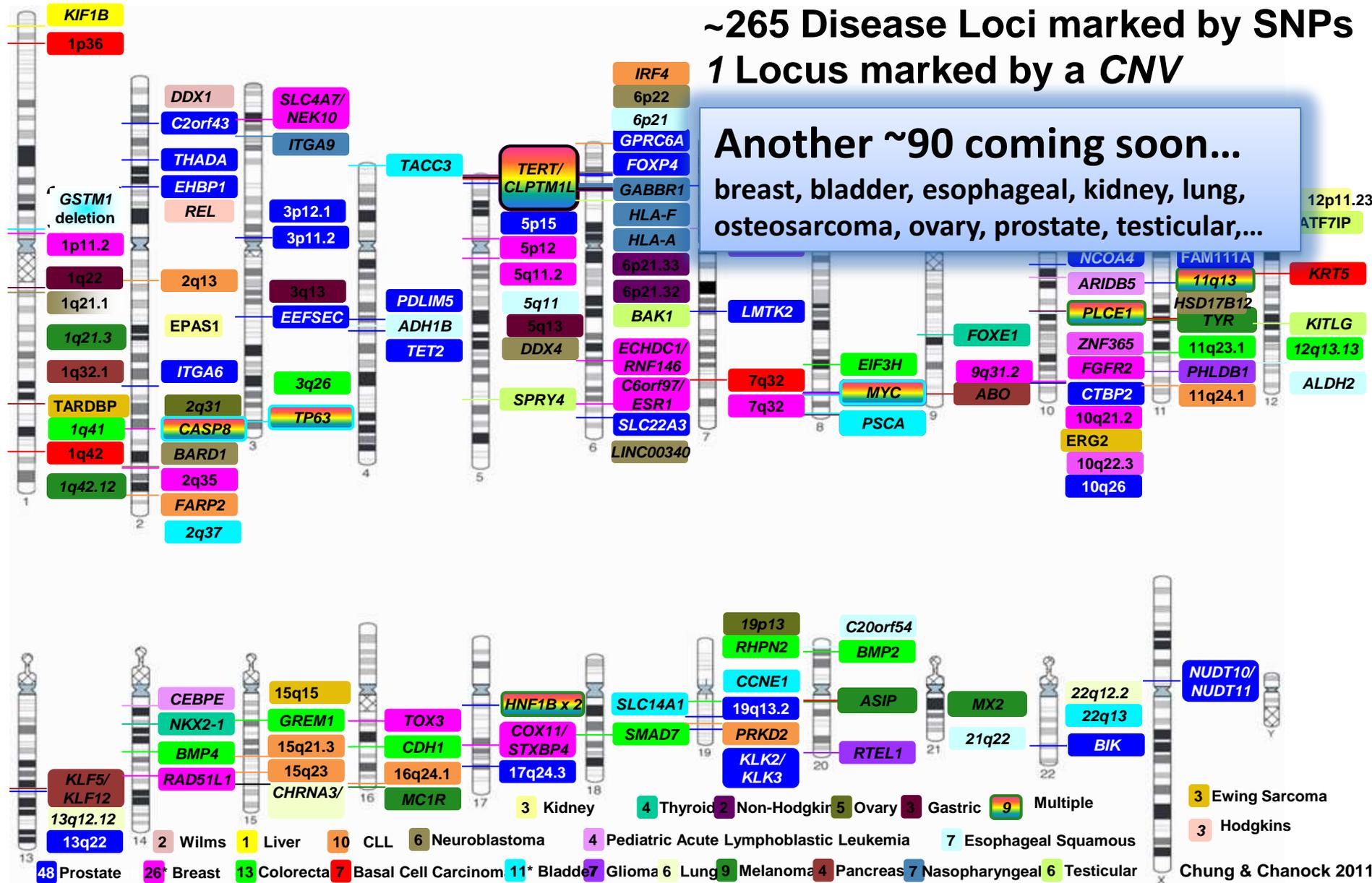
➤ 1990s onward: Susceptibility Genes

- RFLP + other technologies
- Candidate genes

➤ 2006 onward: Susceptibility Genes

- Database + SNP chip
- Agnostic search

Published Cancer GWAS Etiology Hits: 10.18.12



Early Established Susceptibility Loci for Breast Cancer

Loci	m.a.f*			OR het	OR hom	Population Attributable Risk
	Eur	As	Afr			
CASP8	0.13	0.00	0.21	0.89	0.74	20
FGFR2	0.38	0.30	0.50	1.23	1.63	19
TNRC9	0.25	0.60	0.53	1.23	1.39	10
MAP3K1	0.28	0.54	0.35	1.13	1.27	7
8q24	0.40	0.56	0.58	1.06	1.18	6
LSP1/H19	0.31	0.14	0.12	1.06	1.17	4
2q35	0.50	0.15	0.69	1.20	1.40	19

*minor allele frequencies

Pharoah P. *N Engl J Med* 2008;358:2796-803.

Cigarette Smoking, NAT2 Phenotype, and Breast Cancer Risk in Two Large Consortial Analyses

		<u>NAT</u>	<u>Smoking (pack years)</u>		
			Never	≤ 20	> 20
Ambrosone, et al.	Rapid*		1	1.07	1.04 (0.9 - 1.3)
	Slow		1	1.21	1.44 (1.2 - 1.9)
Cox, et al.	Rapid**		1	1.13	1.24 (1.1 - 1.4)
	Slow		1	1.08	1.25 (1.1 - 1.4)

* p(interaction) = 0.03

** p(interaction) = 0.87

Ambrosone, et al. *Cancer Epidemiol Biomarkers Prev* 2008; 17(1)

Cox, et al. *Am J Epidemiol* 2011; 174(11)

Genomics History as Lesson for Future

Two major caveats:

- **Importance of High Quality Epidemiologic Methods**
- **Assay Development**

Lessons for the Future - #1

- **We are not as smart as we wish we were**
 - **Less a-priori, more listening to data**
 - **Mandatory Corollary: Replication, Replication, Replication**

Lessons for the Future - #2

- **Remarkable opportunities from new science and technologies**
 - **Classical Epidemiology: Internet, environment, and lifestyle monitoring tools, linked datasets**
 - **Molecular Epidemiology: All of the “omics”**
 - **Mandatory Corollaries:**
 - **Work with lab to bring to “primetime”**
 - **Best epidemiologic methods**

Lessons for the Future - #3

➤ **Bigger, Better, Sooner**

- **Many of the important, contemporary questions in biology and public health can only be addressed by aggregating large amounts of high quality epidemiologic data.**

Lessons for the Future

1. Listen to the Data
2. Remarkable opportunities from new science and technologies
3. Bigger, Better, Sooner
4. Much faster and better at adapting methods to meet scientific needs and opportunities as they emerge

Formidable, but surmountable, obstacles to implementing “Lessons for the Future”

- **Appropriate “credit” for participating in team science and consortial efforts**
- **Role for junior investigators**
- **Relative value and timing of individual vs. pooled analyses**
- **Cultural differences between disciplines**
- **Rapid changes in state-of-the-art technologies**
- **Study subject participation, cooperation, and consent**
- **Rapid and broad data-sharing**
- **Funding for necessary infrastructure**
- **Inadequacy of traditional grant mechanisms for funding broad “discovery” efforts**
- **ETC, ETC, ETC...**

General Trends Over Time, NOT Dogma

Then

- **“Big Science” studies did exist**
 - CPS1, Dorn, British physician cohorts
 - International Breast Cancer and National Bladder Cancer Case-control Studies

- **Interdisciplinary studies did exist**
 - Hepatitis B and liver cancer

General Trends Over Time, NOT Dogma

Now

- Still an important role for relatively small, innovative studies
- Still will be high-risk risk factors
- Many things will not be well-assessed by biomarkers

Ever Use of Artificial Sweeteners and Bladder Cancer Risk in 632 Cases and 632 Controls

	<u>RR</u>	<u>P-Value</u>
Men	1.6	0.018
Women	0.6	N.S.

Bladder Cancer and Ever Use of Artificial Sweeteners in 3,000 Cases and 5,766 Controls

	<u>RR</u>	<u>95% CI</u>
Men	0.99	(0.89-1.10)
Women	1.07	(0.89-1.29)
Both Sexes	1.01	(0.92-1.11)

“As a general rule of thumb, we are looking for a relative risk of three or more [before accepting a paper for publication].”

Marcia Angell
Editor, *New Engl J Med*
1995

*Advances will be accelerated by
“Collective Intelligence”*

*“I not only use all of the brains
I have, but all I can borrow”*

Woodrow Wilson

Breast Cancer and Candidate Genes

Search Study:

**170 SNPs in 120 Candidate Genes
in 4400 cases and 4400 controls**

- **None significant after control for population stratification and multiple testing.**

Cigarette Smoking, Genotype, and Breast Cancer

- Since 1995, 50 studies have examined this relationship in relation to a total of 11 susceptibility genes
- “literature is complicated by methodologic limitations, ... which likely contributed to the inconsistent findings. These methodologic issues should be addressed in future studies.”