MACROEPIDEMIOLOGY:

1. PUBLIC HEALTH RECORDS
2. POPULATION GENETICS AND FAMILIAL RISK
3. ENVIRONMENTAL EPIDEMIOLOGY
4. HUMAN PHYSIOLOGY AND GENETICS

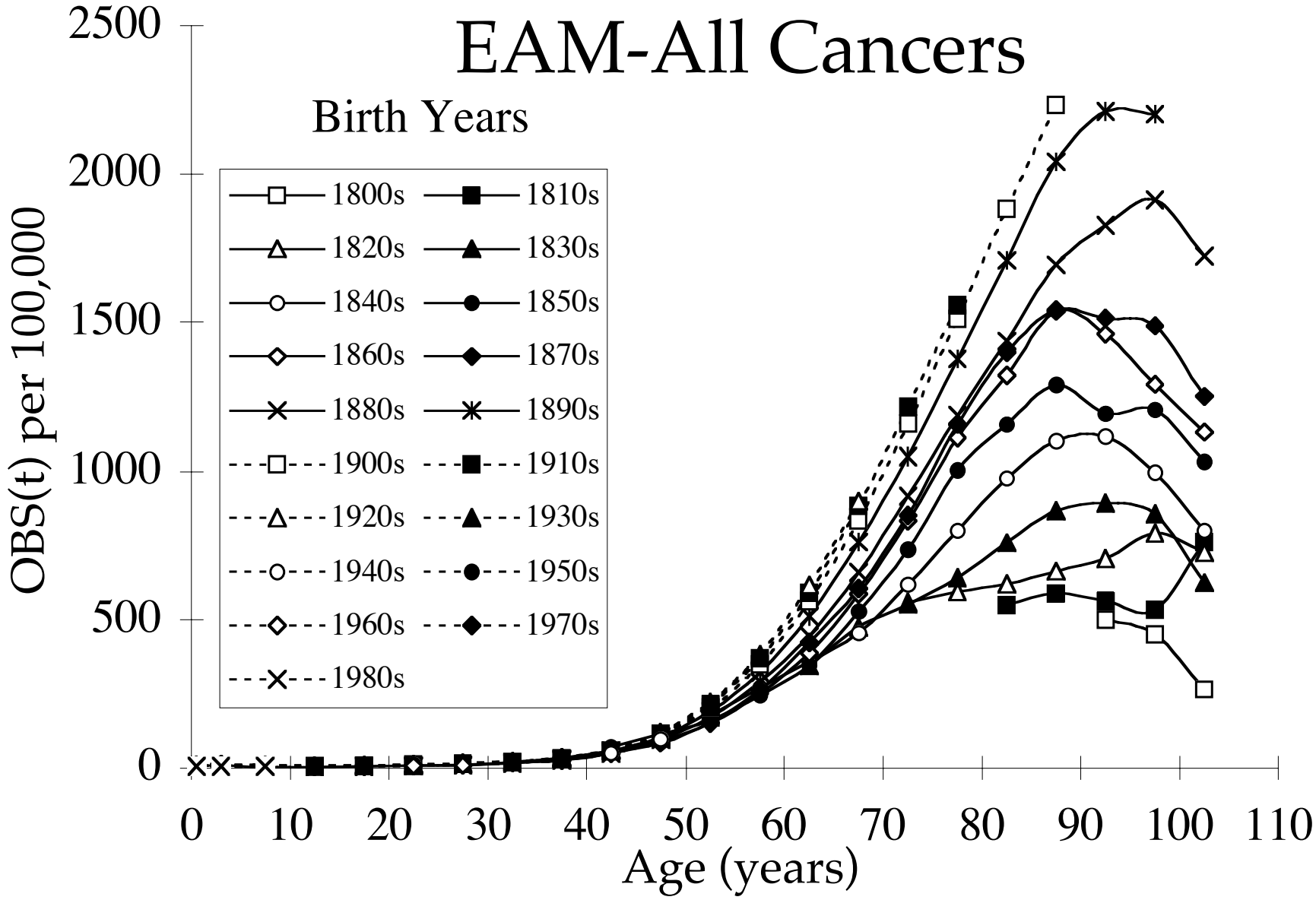
"*Eliminate the impossible, and whatever remains, however improbable, must be the truth.*"

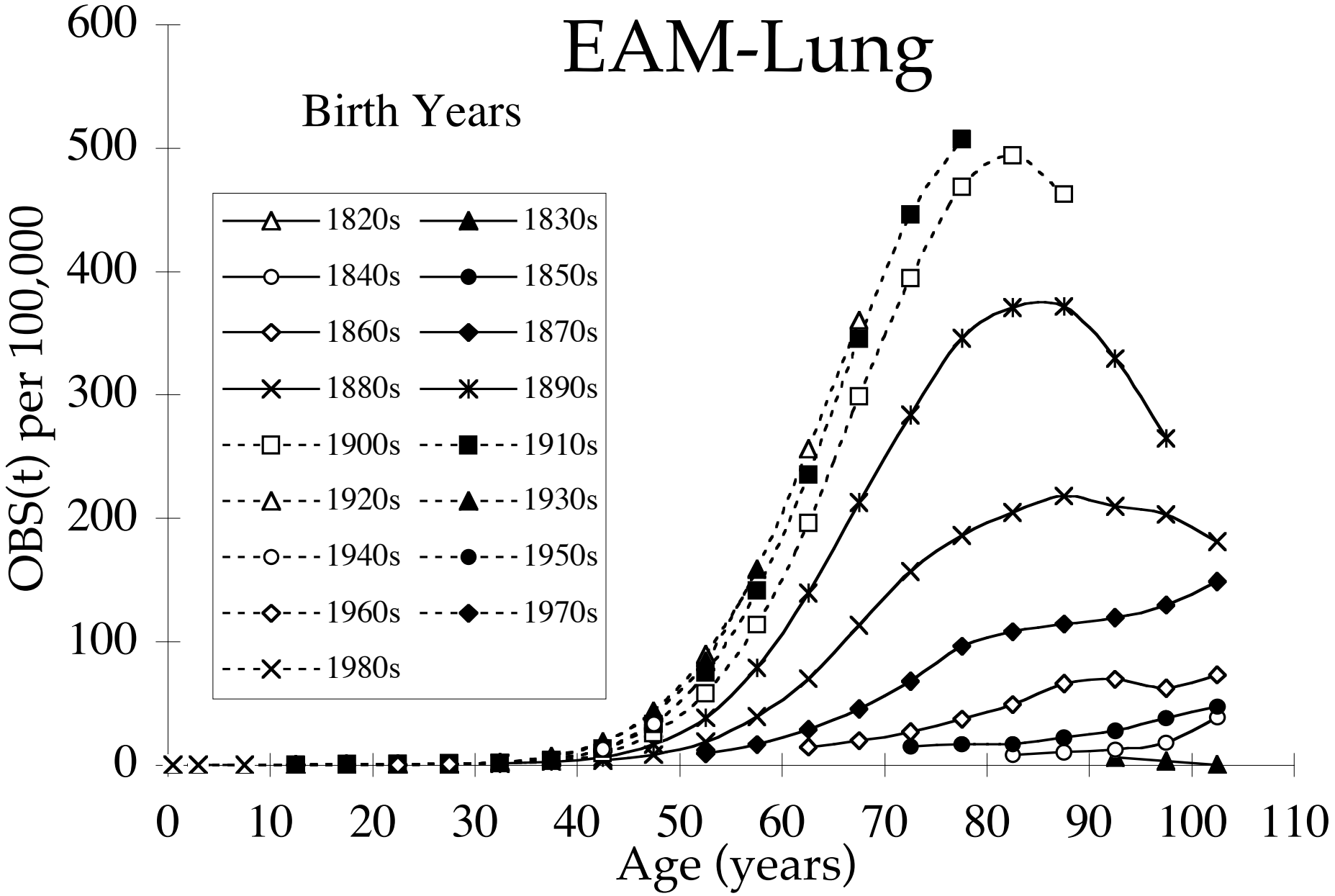
A.C. Doyle, M.D.

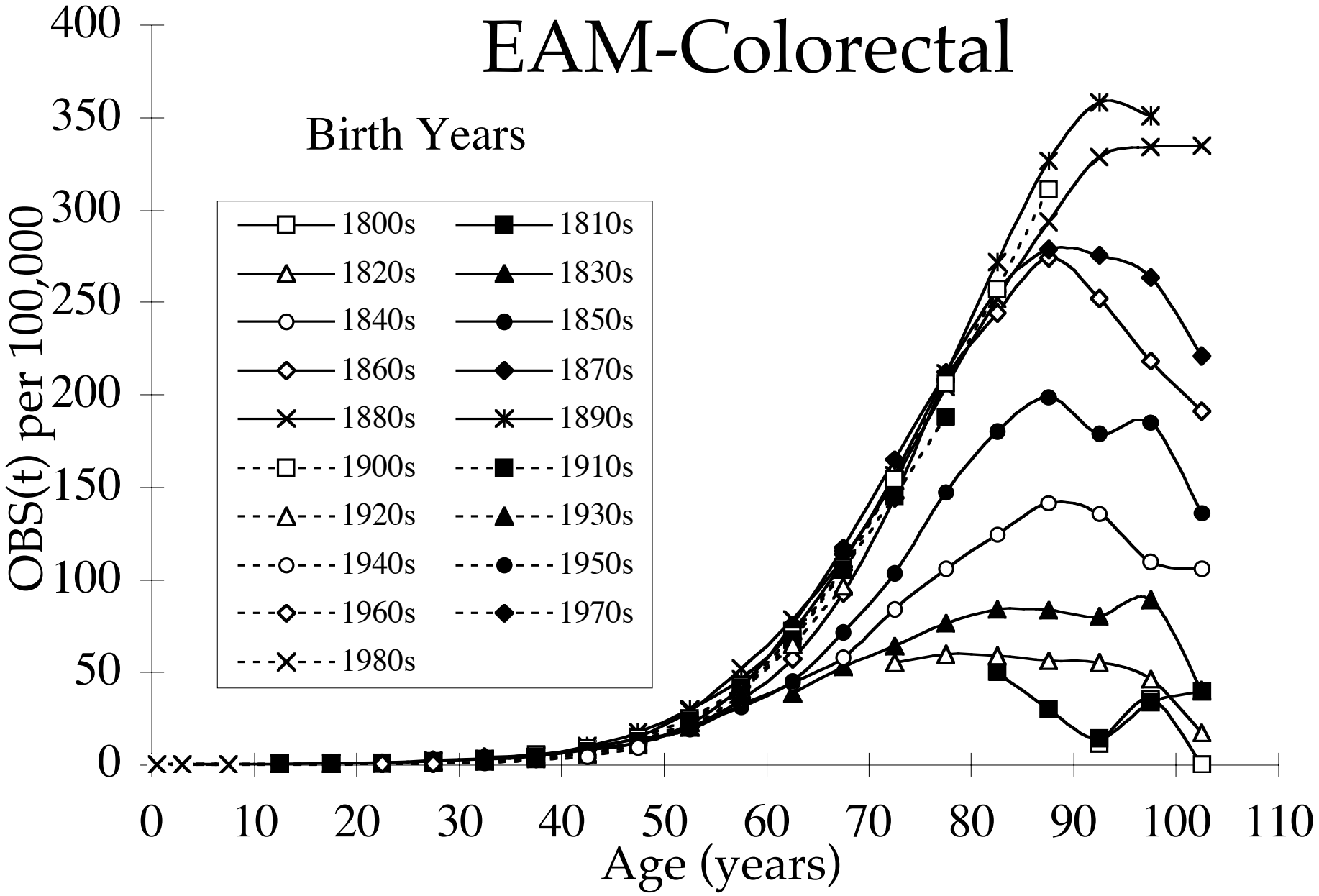
1. PUBLIC HEALTH RECORDS

http://epidemiology.mit.edu

http://epidemiology.mit.edu




EAM-Lung
Birth Years
1820s
1830s
1840s
1850s
1860s
1870s
1880s
1890s
1900s
1910s
1920s
1930s
1940s
1950s
1960s
1970s
1980s
OBS(t) per 100,000
600
500
400
300
200
100
0
0
10
20
30
40
50
60
70
80
90
100
110
Age (years)


EAM-Colorectal
Birth Years
1800s
1810s
1820s
1830s
1840s
1850s
1860s
1870s
1880s
1890s
1900s
1910s
1920s
1930s
1940s
1950s
1960s
1970s
1980s
OBS(t) per 100,000
0
50
100
150
200
250
300
350
400
0
10
20
30
40
50
60
70
80
90
100
110
Age (years)

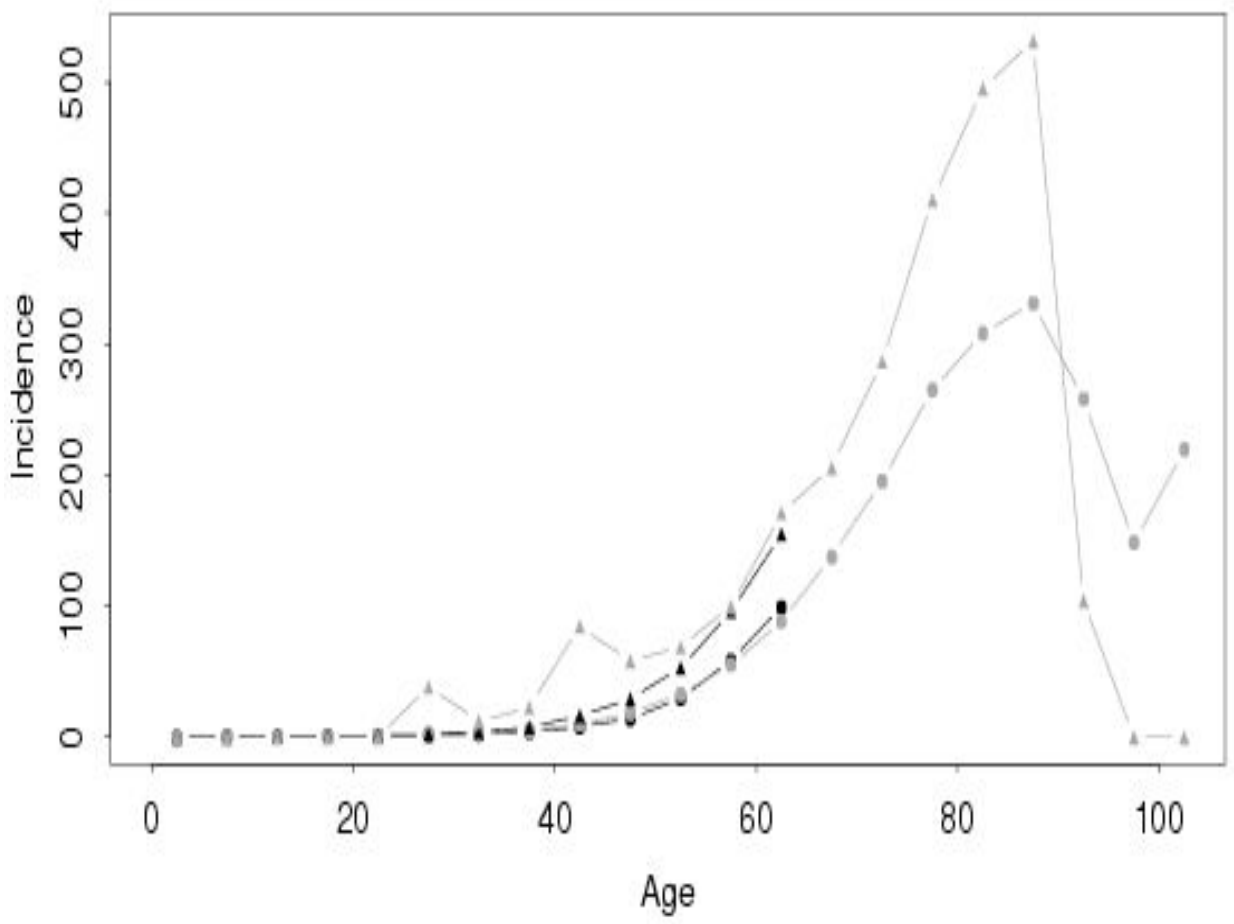
HISTORY OF AGE-SPECIFIC CANCER RATES (European Americans in the United States)

- Use of data through age 104 years reveals increased age-specific rates began with birth cohorts of the early 19th century.
- These age-specific rates reached ~stable values for birth cohorts by the late 19th century.

The concept that cancer rates rose in the most "developed" countries as a result of exposure to novel industrial chemicals during the 20th century is not supported by the historical data.

2. Population genetics and familial risk

Familial risk of late onset CRC = 2.5 +/- 0.2
(coincident cases 1958-2002)



Parent/child colorectal cancer in Sweden (K. Hemminki)

Community risk in the United States:
The distribution of colorectal cancer rates among communities is not significantly different from the distribution expected by chance. (1958-1995) Neither E nor G can be argued to vary among communities in this highly ethnically heterogeneous post-agrarian population. These data suggest that the value of E has reached a stable maximum with E approaching 1.0.
(Janice Watland, MIT)

Spousal risk in Sweden:
For parents living together for at least thirty years the relative risk of colorectal cancer is 1.0.
(Kari Hemminki, Deutches Krebs Forschung Zentrum, Heidelberg, Swedish Family Cancer Registry, 1933-2002)

Conclusions:
E =1 in post-agrarian communities for colon cancer.
Since F = G x E = 0.18-0.2, G= 0.18-0.2

Limitations on hypotheses genetic risk of colon cancer.

From familial data (Hemminki)

RR_G(colon) = ~ 2.5 +/- 0.2
RR_G ($A^{+/-}$ at risk) = 0.5/2pq
RR_G ($A^{-/-}$ at risk) = 1/q
u.s.w.

From U.S.data (MIT) and clinical data (Atkin)
G(colon) = ~ 0.18-0.2

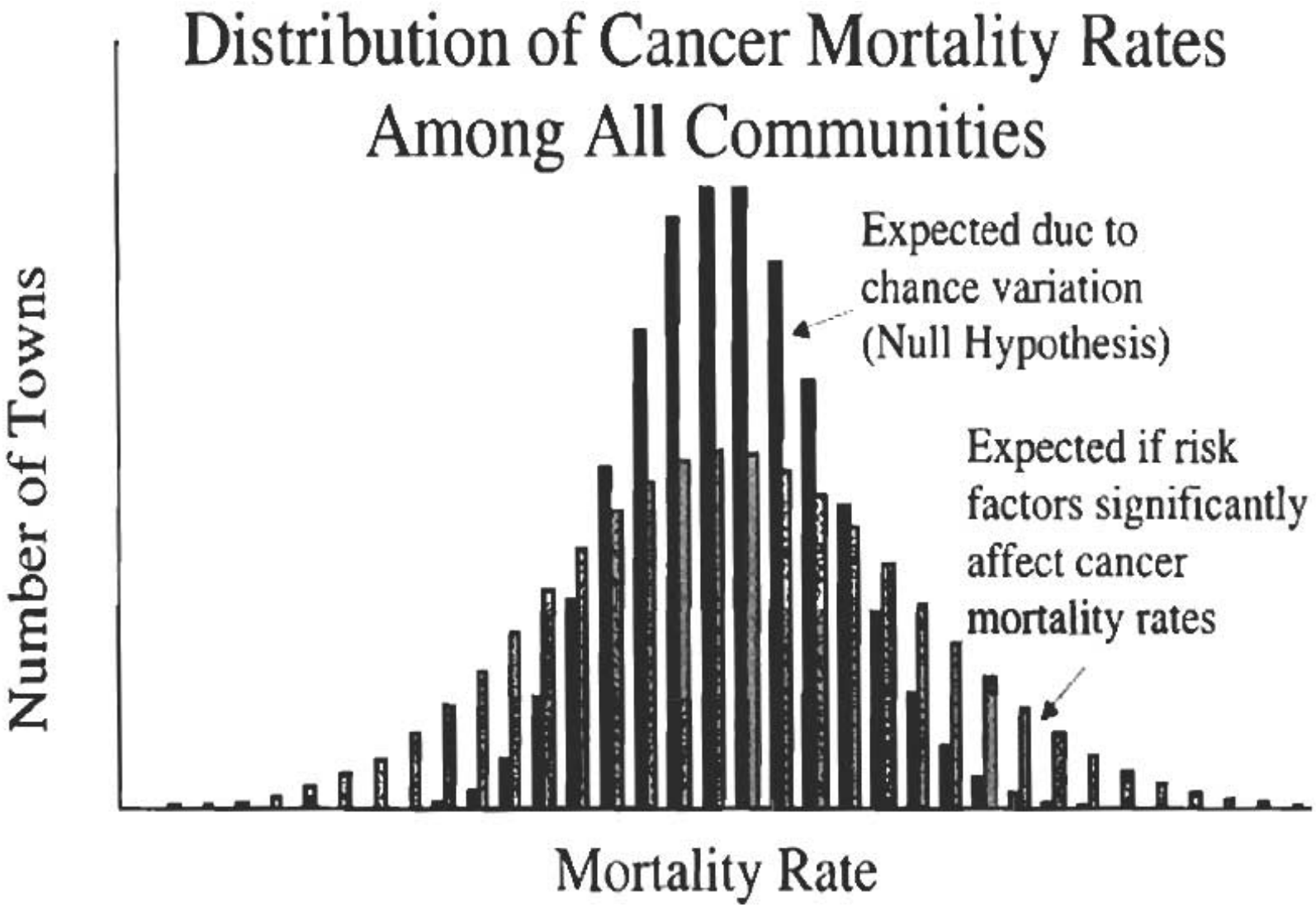
G ($A^{+/-}$ at risk) = 2pq
G ($A^{-/-}$ at risk) = q^2
u.s.w.

BEST FIT: [$A^{+/-}$] = $RISK_G$

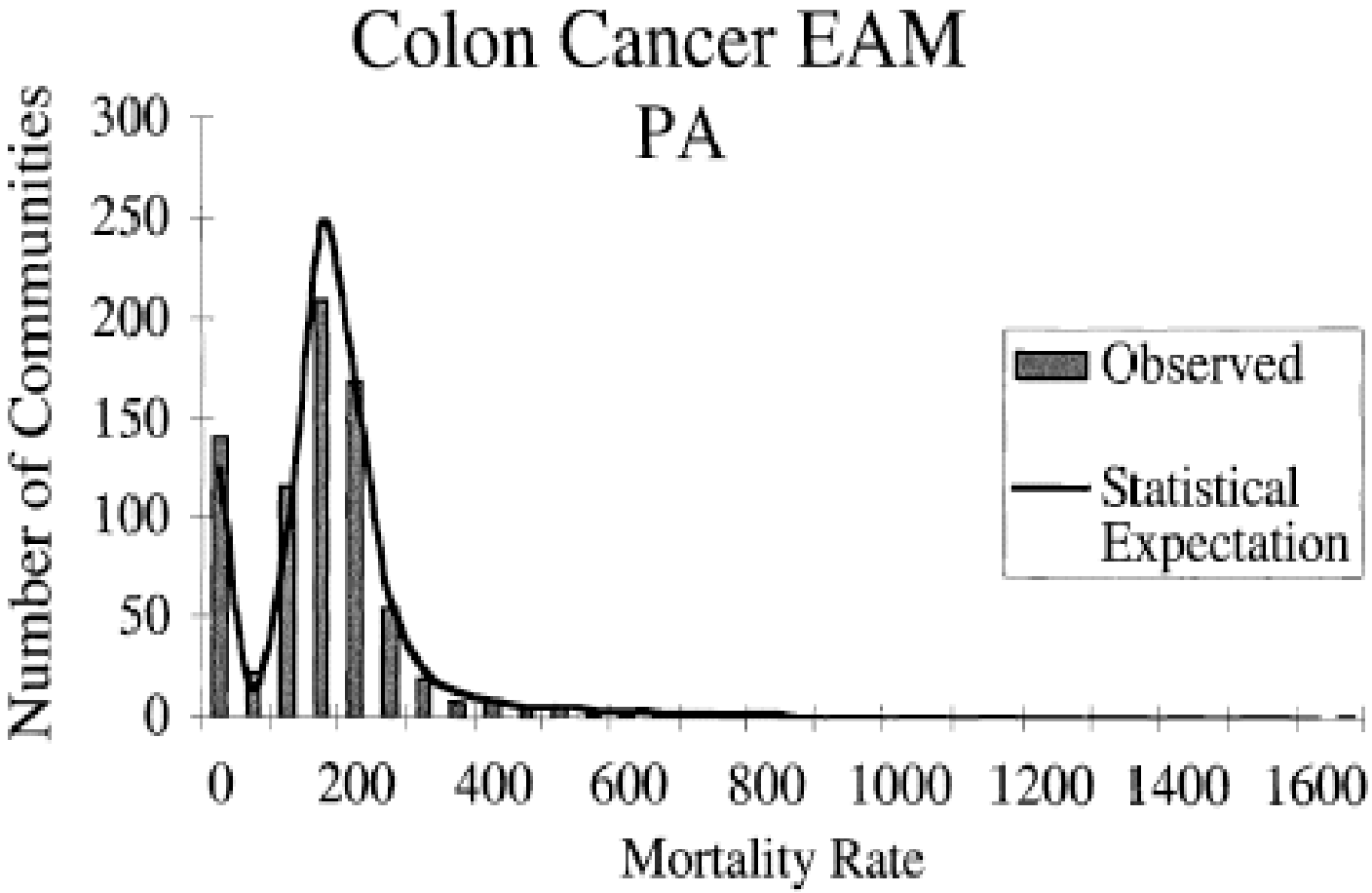
q= ~0.1

which is, coincidentally, the average value of q for all known genes carrying non-deleterious inactivating mutations

3. Environmental epidemiology

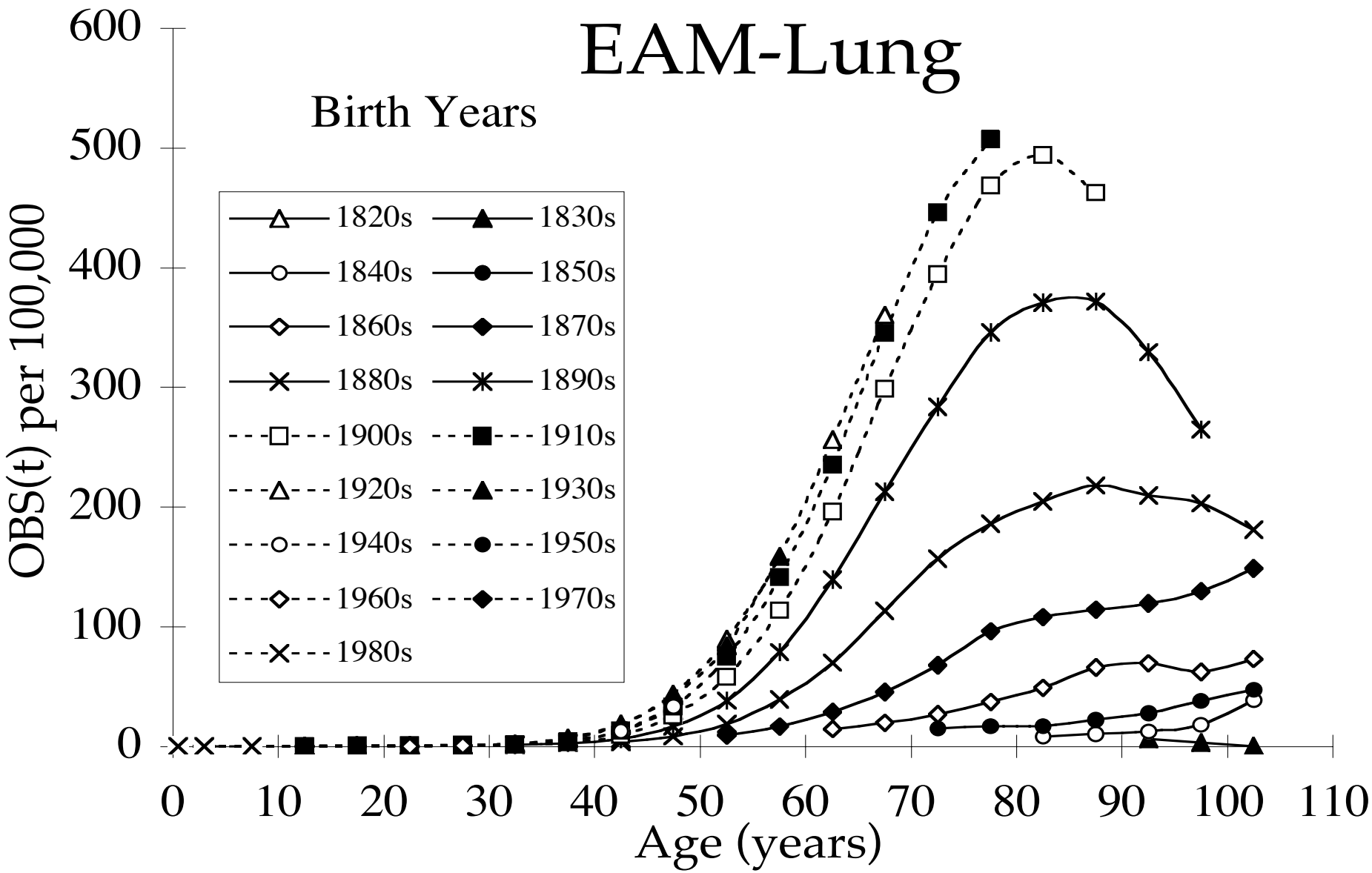

Distribution of Cancer Mortality Rates
Among All Communities
Number of Towns
Expected due to
chance variation
(Null Hypothesis)
Expected if risk
factors significantly
affect cancer
mortality rates
Mortality Rate

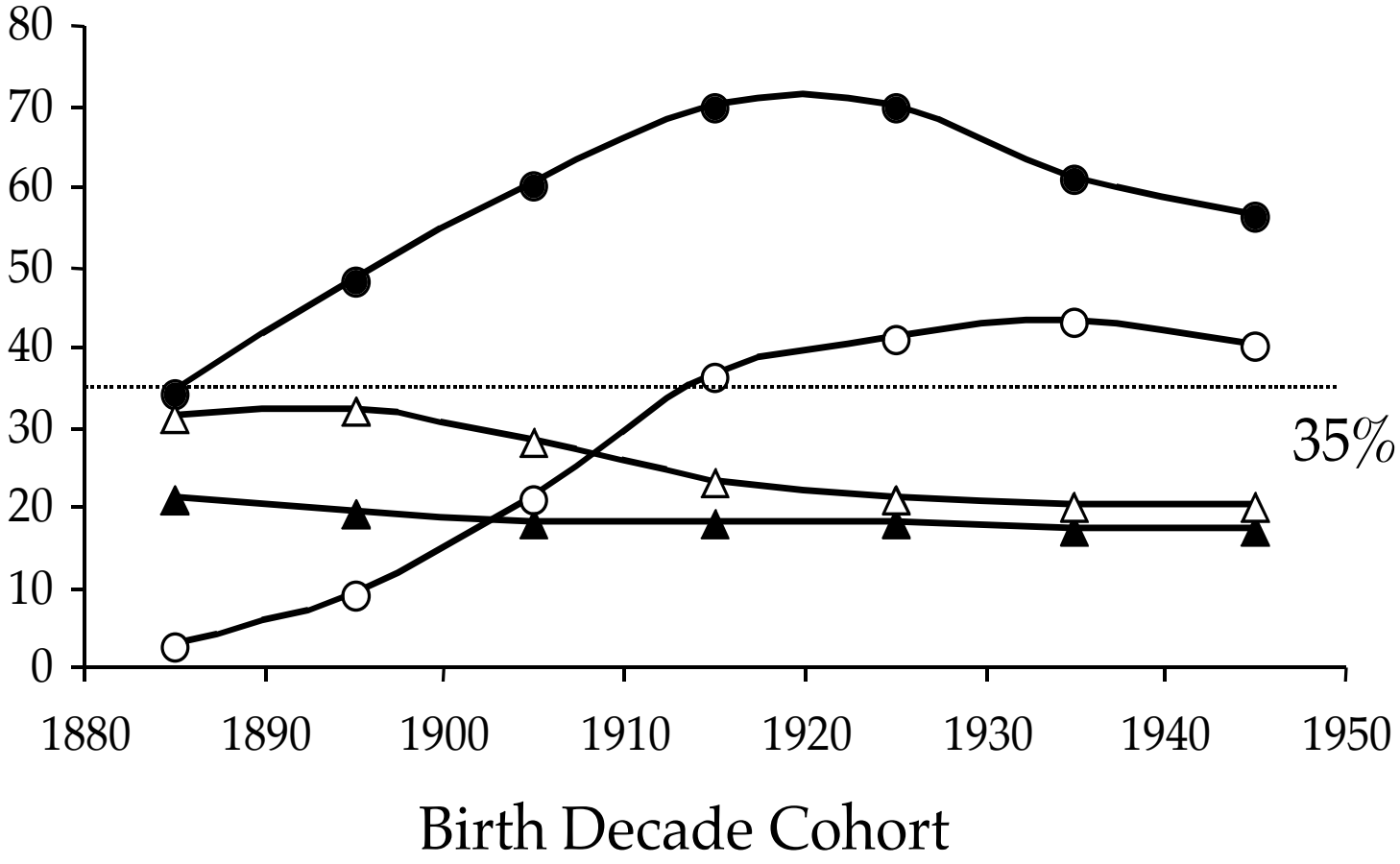
MODERN CANCER RATES AMONG U.S. COMMUNITIES DISTRIBUTE ACCORDING TO THE NULL HYPOTHESIS



520 Pennsylvania communities 1958-1995 (Dr. Janice Vatland)

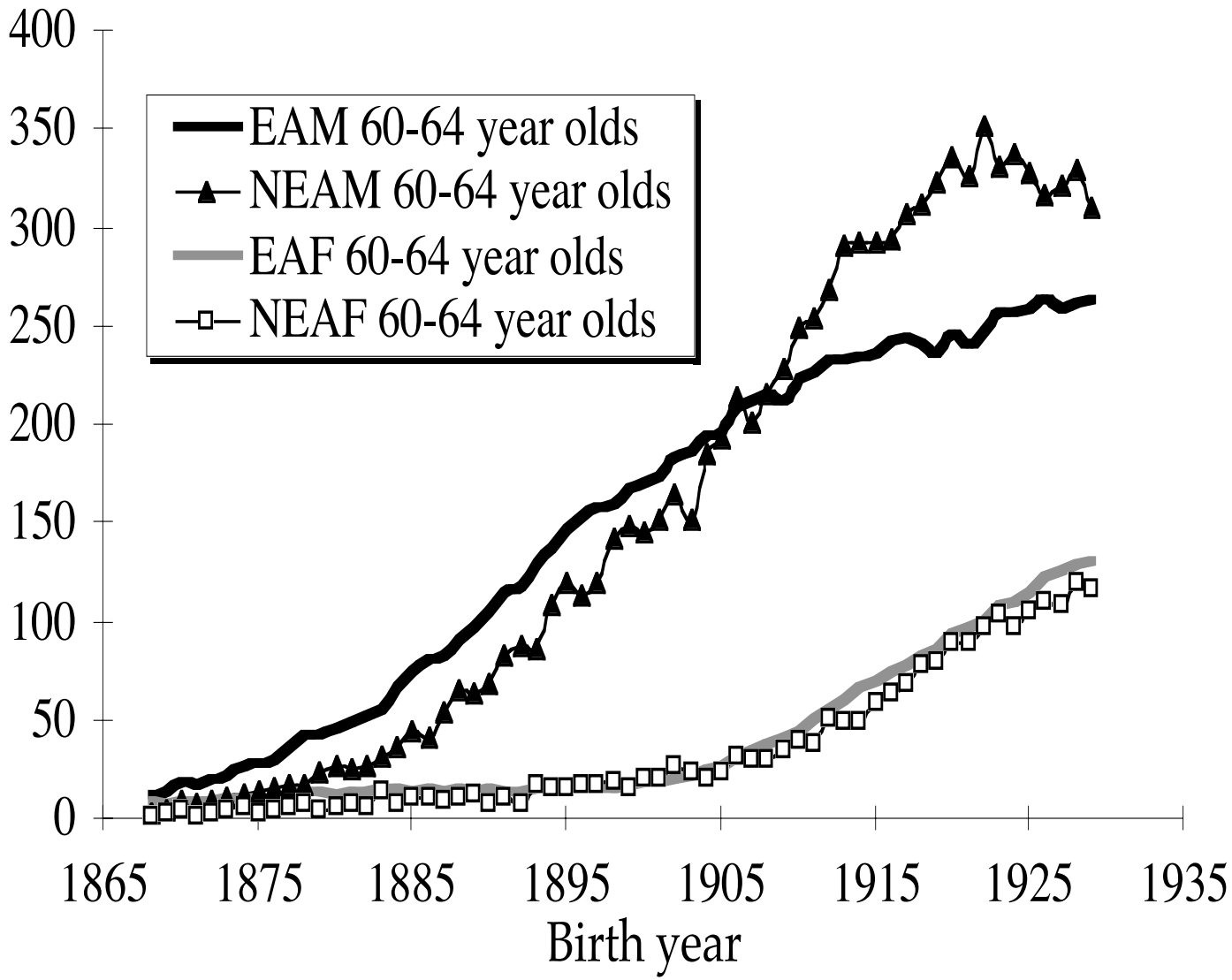
European American Males Lung Cancer

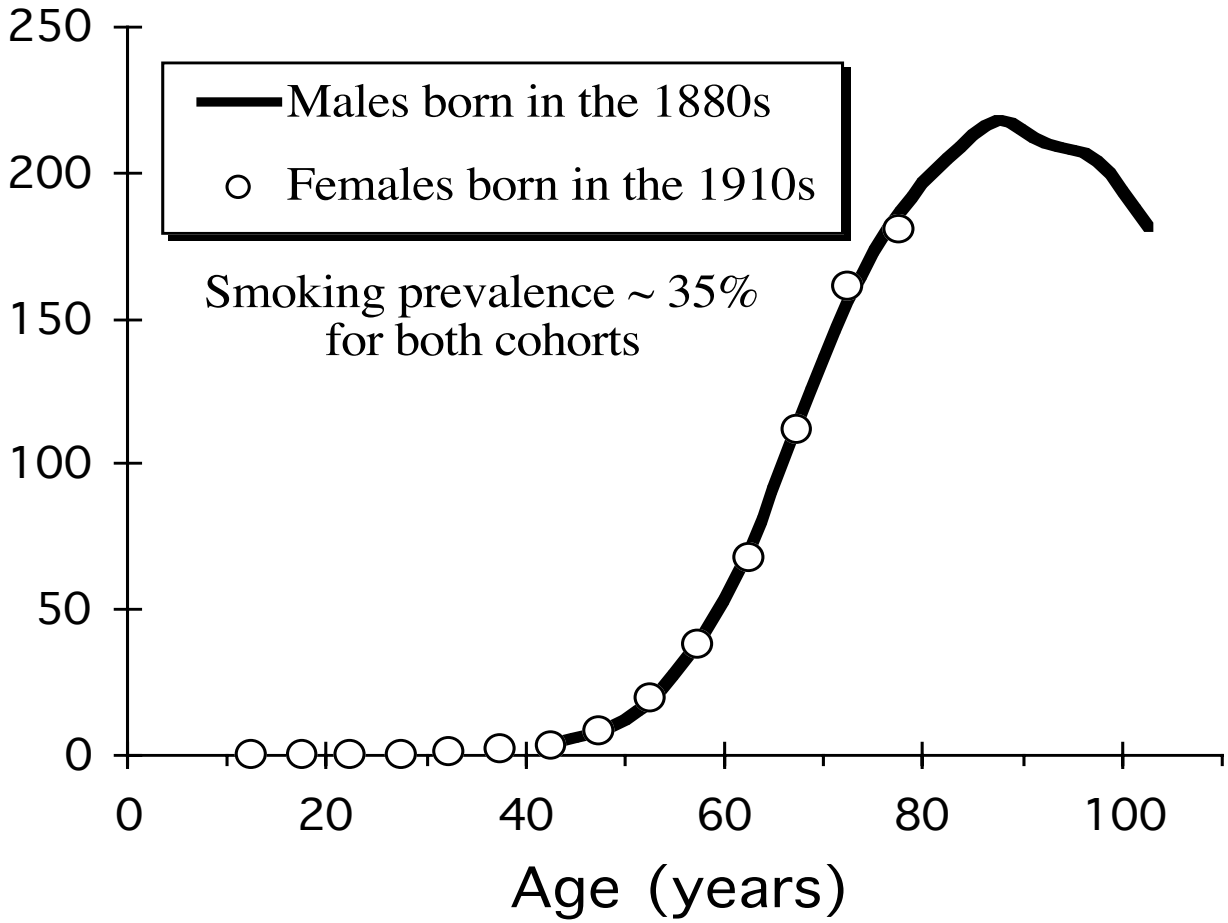




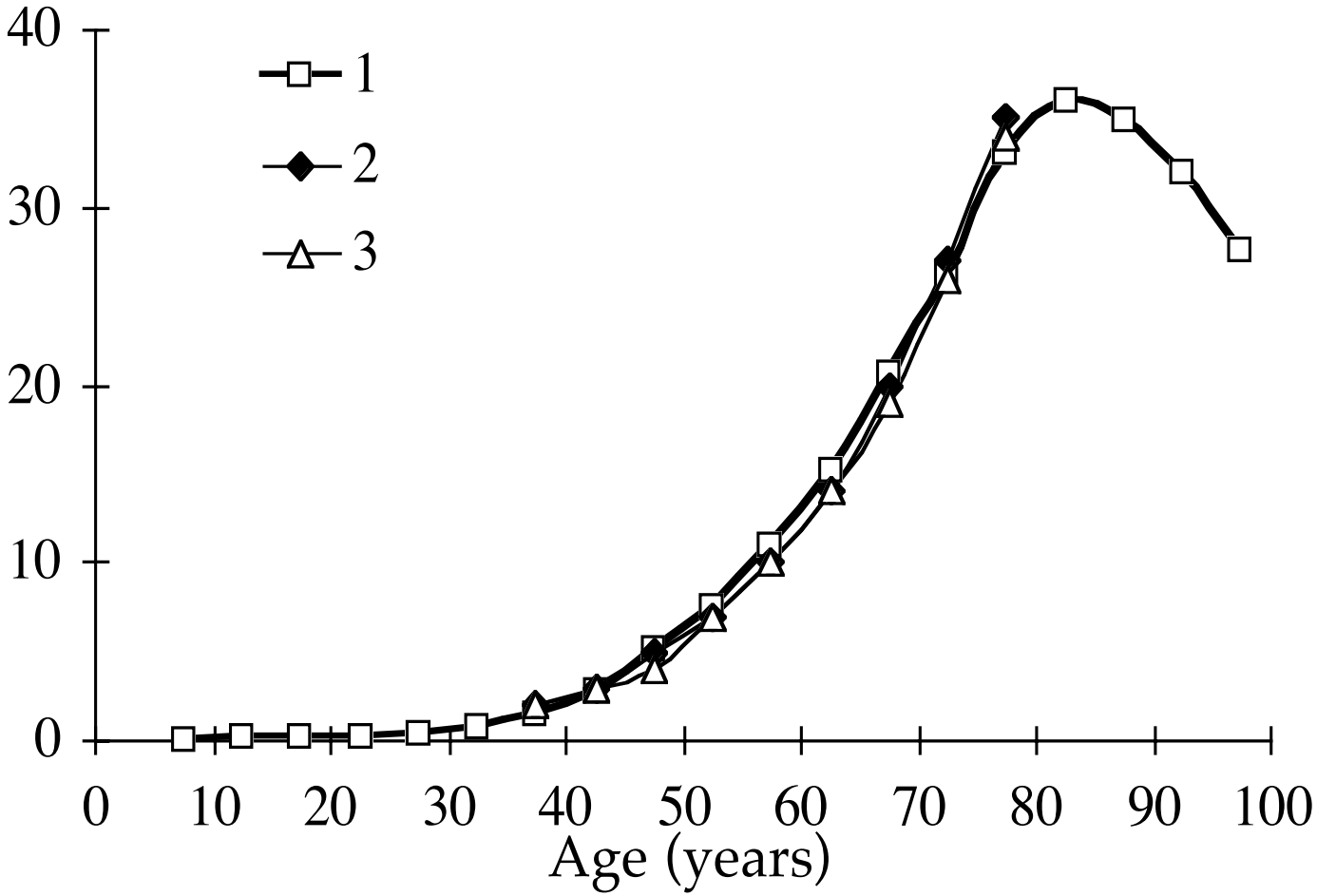
Prevalence (USA) and starting age of smoking.

Solid symbols, males; open symbols, females.


400
350
300
250
200
150
100
50
0
EAM 60-64 year olds
NEAM 60-64 year olds
EAF 60-64 year olds
NEAF 60-64 year olds
1865
1875
1885
1895
1905
1915
1925
1935
Birth year



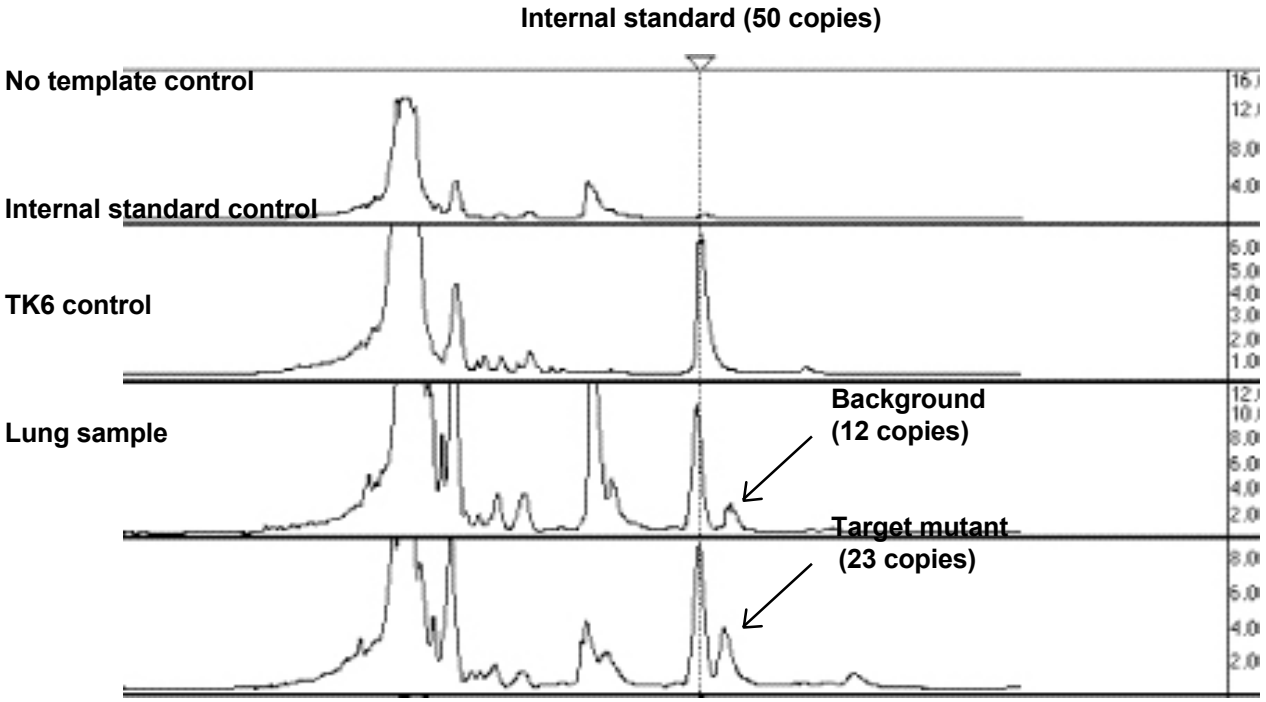
Males and female smokers apparently have identical age specific lung cancer death rates despite significantly different lung cell numbers.



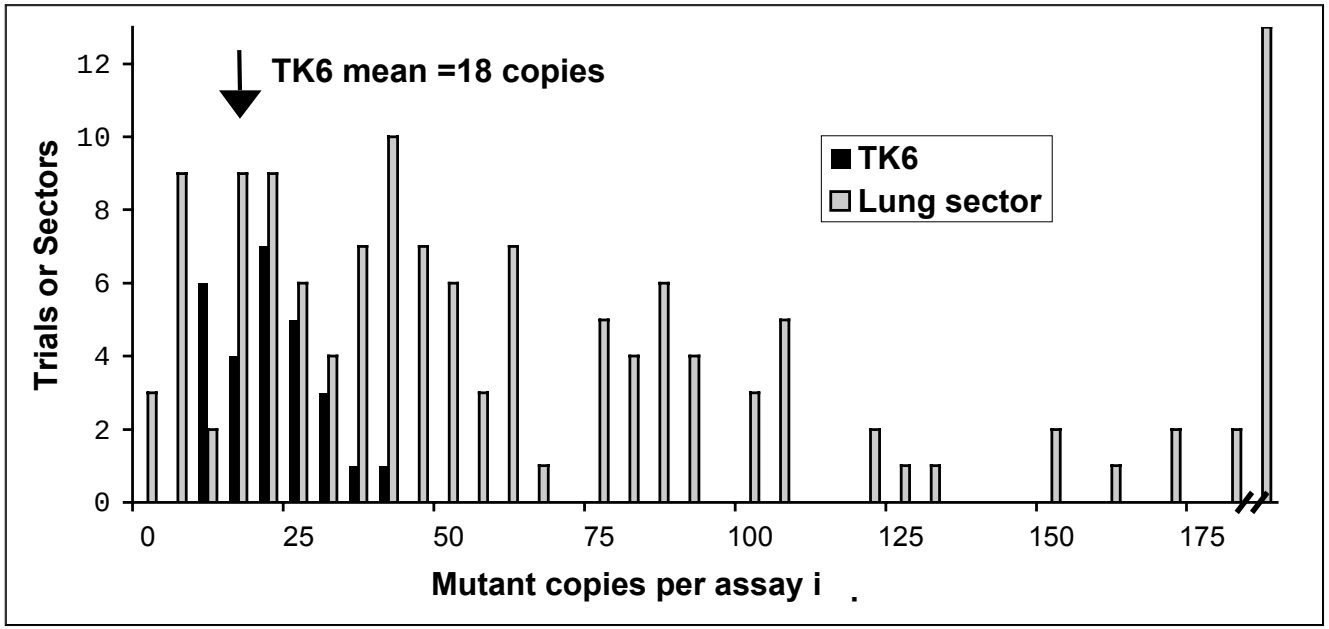
OBS(h,t) for male and female nonsmokers (2,3) and all females born before 1900 (1).

4. Human physiology and genetics

A

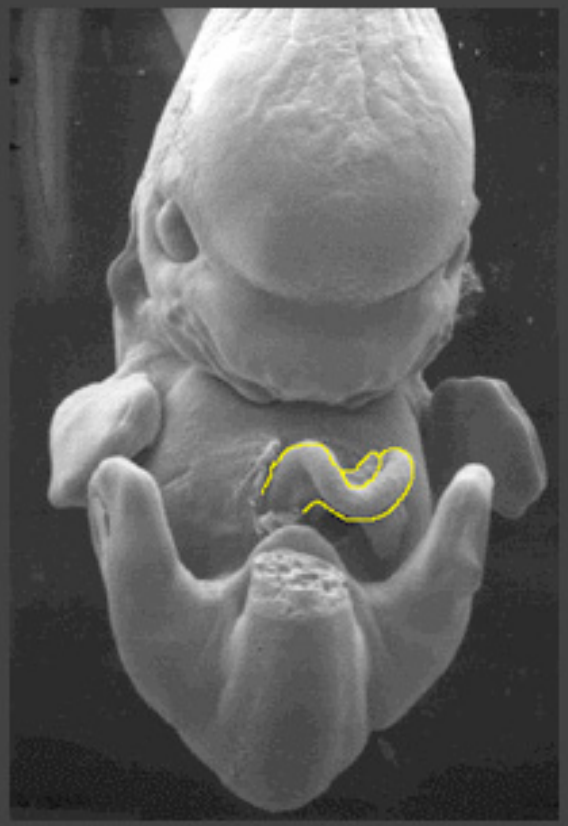

Internal standard (50 copies)
No template control
Internal standard control
TK6 control
Lung sample
Background
(12 copies)
Target mutant
(23 copies)
Volts

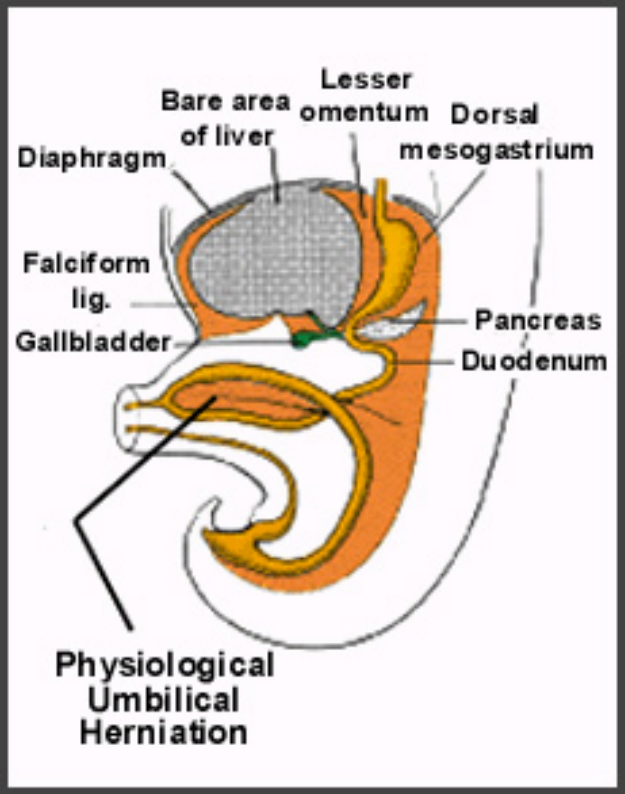
B


TK6 mean =18 copies
TK6
Lung sector
Trials or Sectors
Mutant copies per assay
0
2
4
6
8
10
12
0
25
50
75
100
125
150
175

Colon embryology and carcinogenesis.

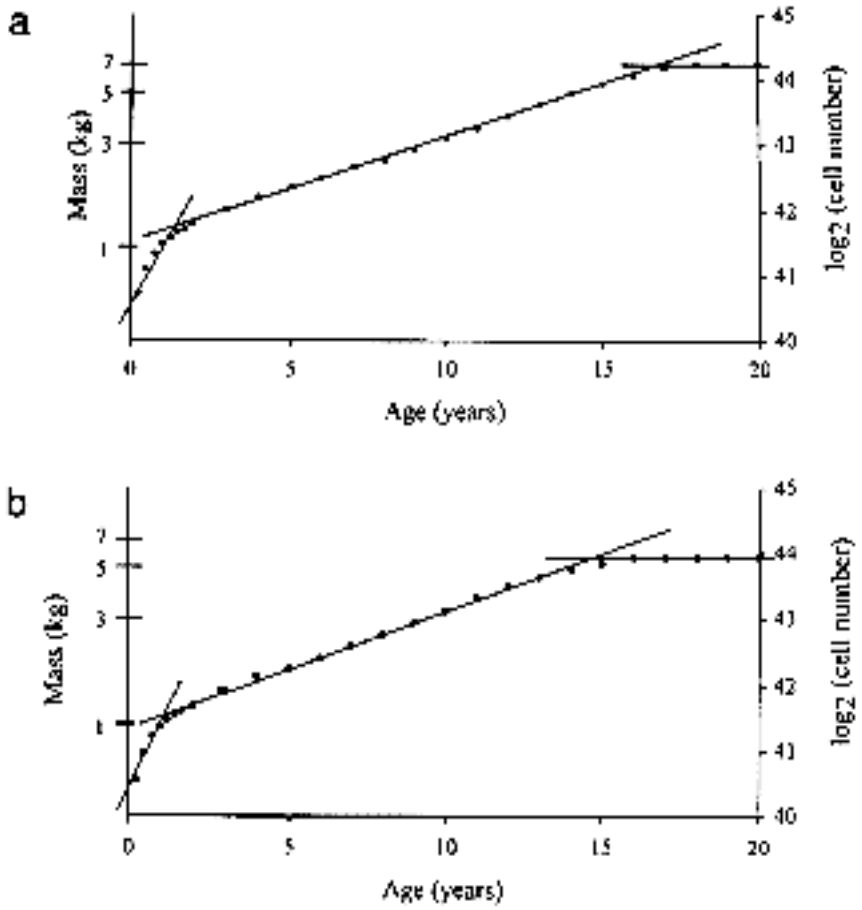
Digestive system of human fetus between 5 and 7 weeks age of gestation



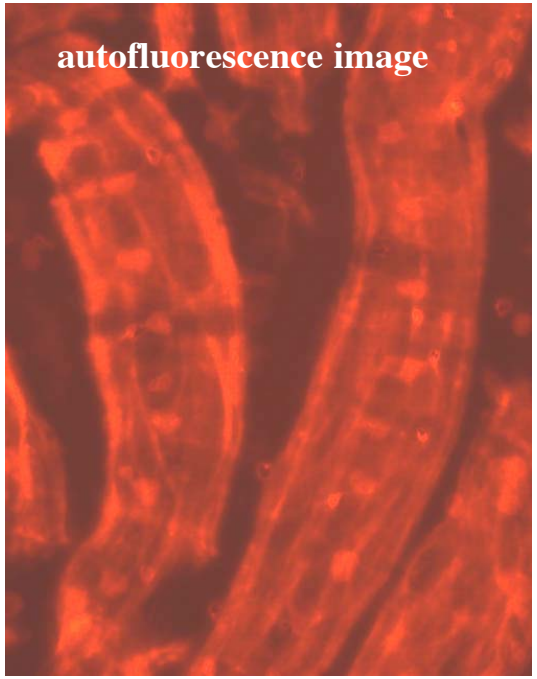


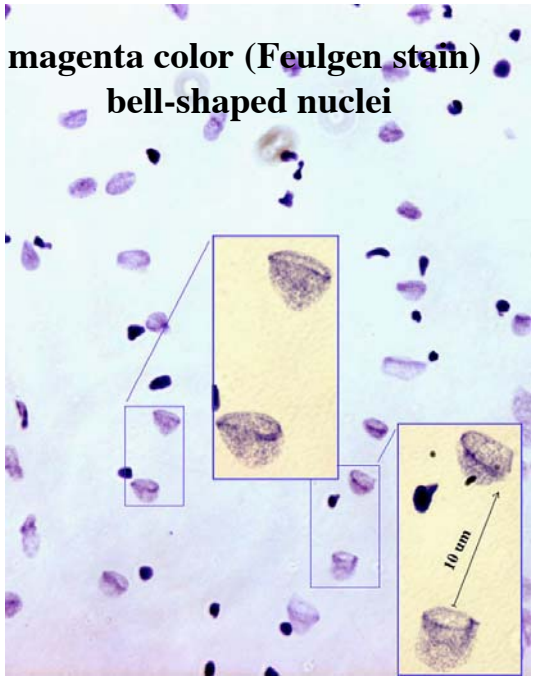
The midgut elongates rapidly and during the sixth week of development it extends beyond the body wall in the umbilical cord (physiological umbilical herniation).

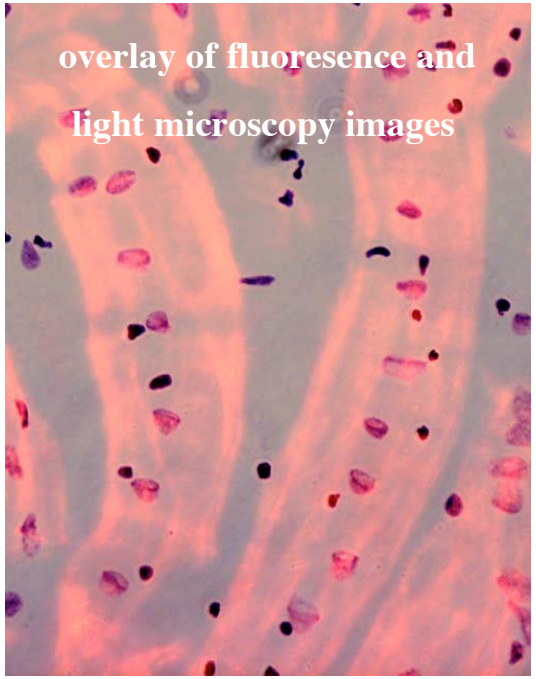
Exponential Growth of Human Juveniles

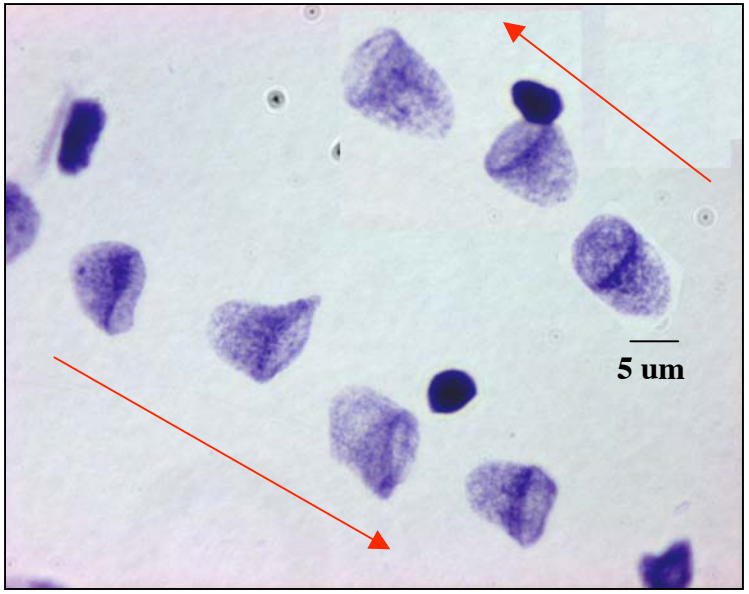


(a) Mass of males as a function of age [31]. (b) Mass of females as a function of age [31].







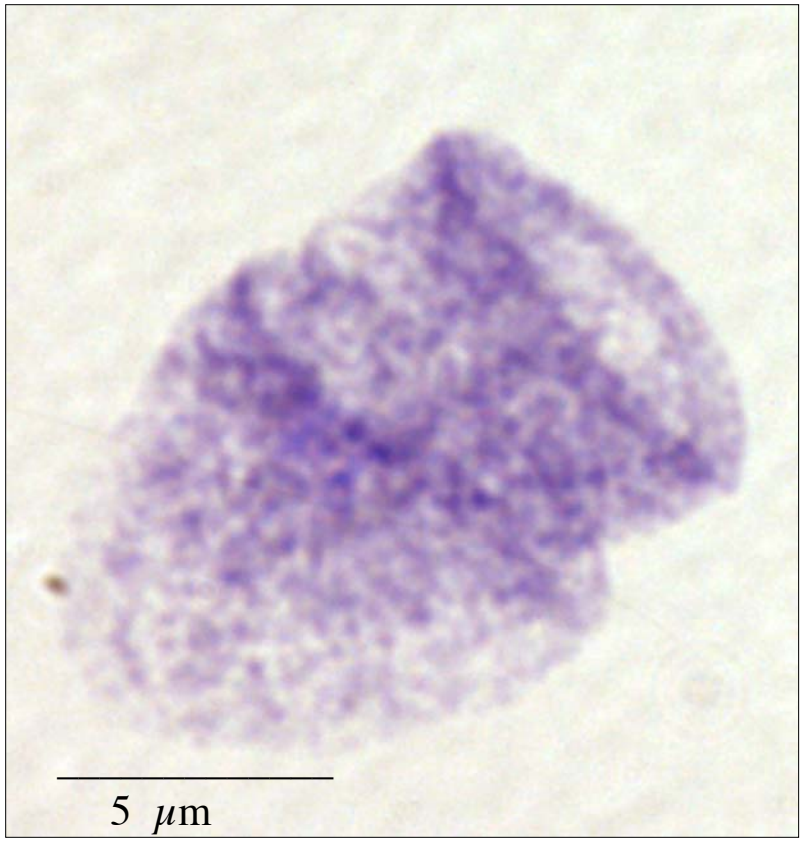


The 'head to toe' orientation of the bells is preserved in all embryonic tubes but tubes snake backwards and for wards such that parallel tubes may have locally anti-parallel bell-shaped nuclei orientation.

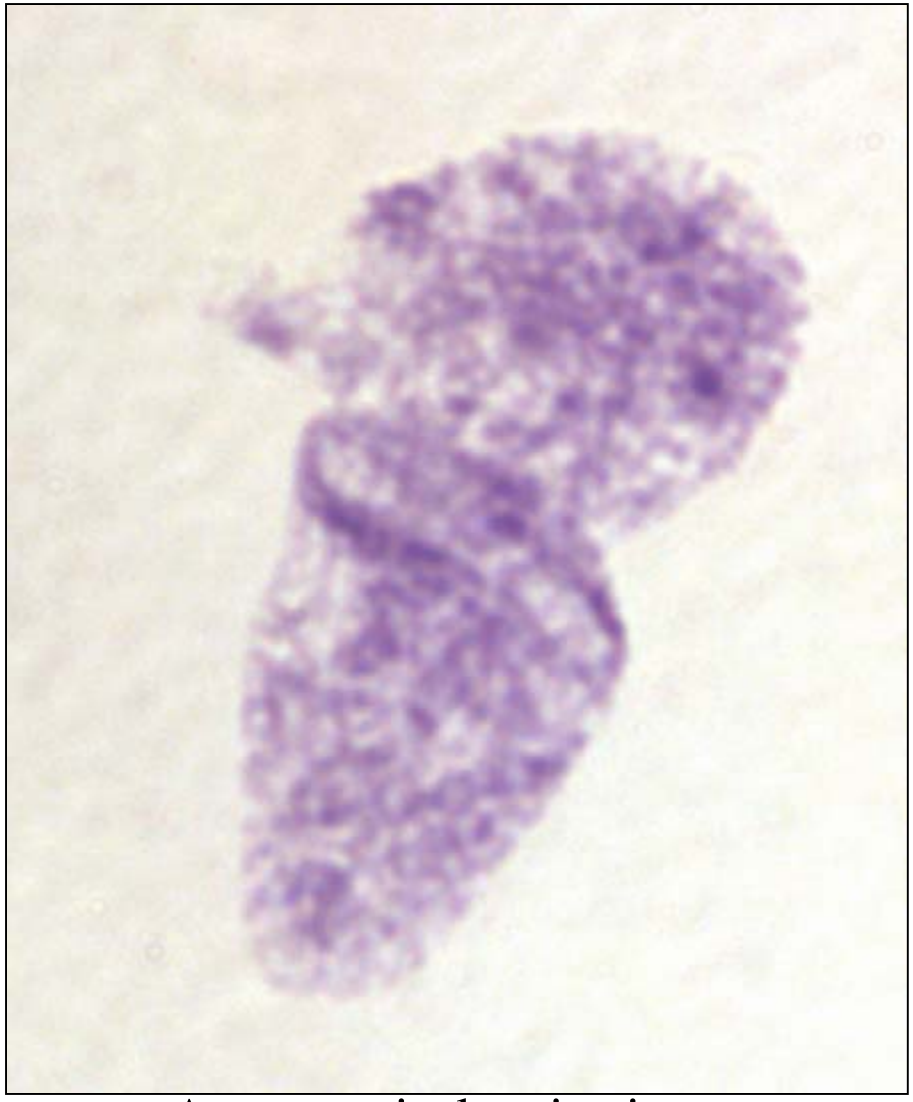
Divisions of bell-shaped nuclei in human embryonic midgut

Direct cell division by simple cleavage of the nucleus without spindle formation or the appearance of chromosomes:

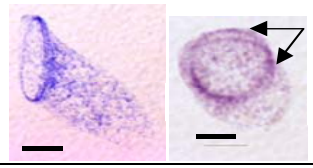
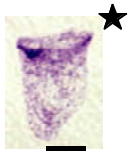
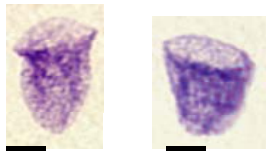
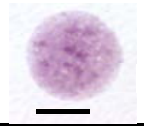
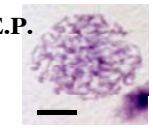
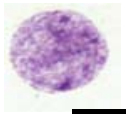
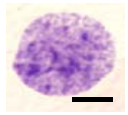
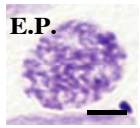
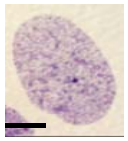
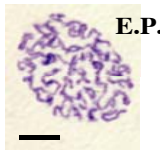
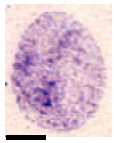
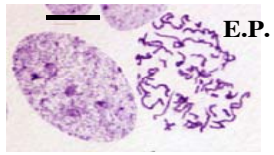
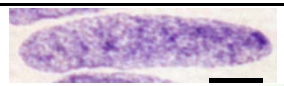
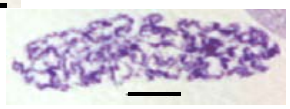
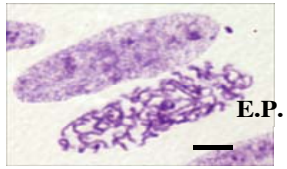
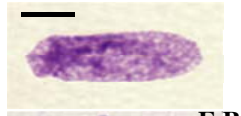
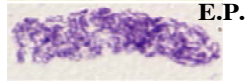
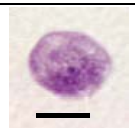
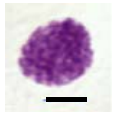
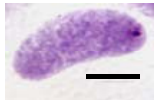
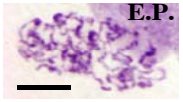
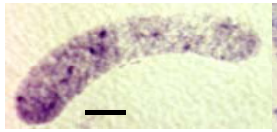
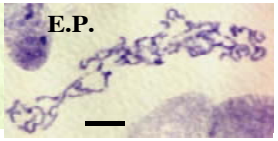
Amitosis



Symmetrical amitosis



Asymmetrical amitosis

Nuclei morpho-types	Embryonic hindgut	Adult normal colon	Adenoma, adenocarcinoma
Bell-shaped nucleus	 Early prophase not observed		
Spherical nucleus	 E.P. 		 E.P. 
Oval-shaped nucleus	 E.P. 		 E.P.
'Cigar'-shaped nucleus	 E.P. 	not observed	 E.P.
'Bullet'-shaped nucleus	not observed	not observed	 E.P. 
Condensed spherical nucleus	 	not observed	not observed
'Bean'-shaped nucleus	 E.P. 	not observed	not observed
'Sausage'-shaped nucleus	 E.P. 	not observed	not observed

The data are consistent with Cohnheim's contention that tumors are simply embryonic organs growing in adults.

The heterogeneity of *at least* nuclear morphotypes must be addressed in studies of mRNA and protein

COMMON THEORETICAL STRUCTURES

1. Clonal expansion models
2. Cell/function mortality models.

"Two-(Rate-Limiting)-Stage" Model
Armitage & Doll, 1957

INITIATION **PROMOTION**

NORMAL -"**n**" events-> PRENEOPLASIA- "**m**" events->NEOPLASIA CELLS

We extended the basic model by positing that there is a subfraction, F, of the subpopulation that is at lifetime risk and a subfraction (1-F) that is not.

For the multi-parametric equations describing the model we created a computer program, CancerFit©.

Cancer Data--->Carcinogenesis Model

$$\frac{OBS(h,t)}{[1-SUR(h,t)\ REP(h,t)\ (1-TOT(h,t)]} = \frac{F\ P_{OBS}(h,t)}{F + (1-F)\ e^{1/f \int (0,\ t) POBS(h,t)\ dt}}$$

where $P_{OBS}(h,t) = [1 - e^{-V_{OBS}(h,t)}]$

$$V_{OBS}(h,t) = \mathbf{Cinit}\,(n)\int_{0}^{t} a\,N_a \frac{d\left(1 - e^{\left(\mathbf{Cprom(m)}\ 2^{(\mu)(t-a)}\right)}\right)}{d\,(t - a)}\,da$$

INITIATION PROMOTION

NORMAL CELLS ->“n” events-> **PRENEOPLASIA**-> “m” events->**NEOPLASIA**

“zero” = adult growth rate

μ = preneoplastic growth rate

BioFit.Fit

Tue 3:22 PM

Bio Fit Version 1.3 – Sweden colon cancedr parents2 copy.rtf

File Settings

Find Fits | Single Fits | Graph Single Fit

Quick Alpha-Beta View | Set Parameters

T Squared View | Log Linear View | Alpha-Beta View

Definitions | Data File | Data File 2 | Quick View | Cum of Obs

Please select the parameter list you want to fit better.

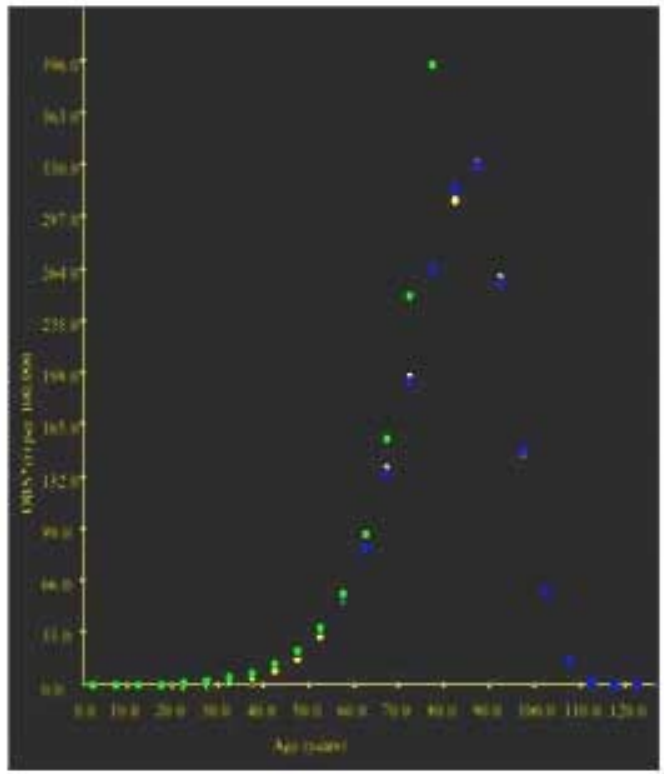
Click Plot to view the line. UnPlot to remove the last line you added.

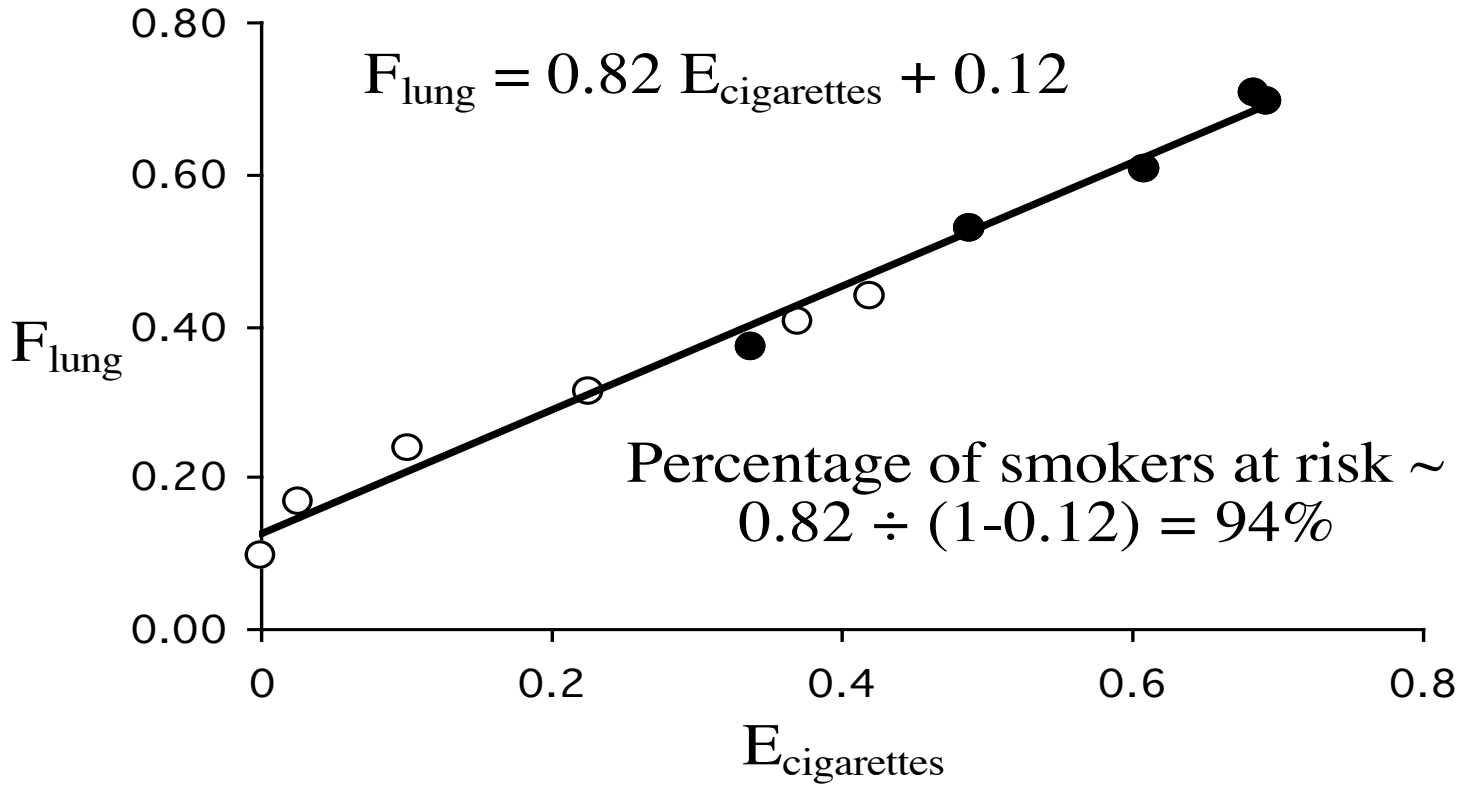
F	f	Cinit	Alph...	Beta	rA	Dista...	X	Area
0.0601	0.84...	0.022	0.143	0.0	5.68E-5	1.28E-8	0.92...	0.0973
0.0601	0.84...	0.018	0.145	0.0	6.19E-5	1.32E-8	0.88...	0.0975
0.0601	0.84...	0.019	0.143	0.0	6.44E-5	1.36E-8	0.89...	0.0975
0.0601	0.84...	0.021	0.144	0.0	5.68E-5	1.35E-8	0.91...	0.0973
0.0601	0.84...	0.022	0.142	0.0	5.93E-5	1.31E-8	0.92...	0.0974
0.0601	0.84...	0.023	0.141	0.0	5.93E-5	1.38E-8	0.93...	0.0974
0.0601	0.84...	0.023	0.142	0.0	5.68E-5	1.38E-8	0.93...	0.0973
0.0726	0.68...	0.018	0.142	0.0	5.93E-5	1.31E-8	0.88...	0.0976
0.0726	0.68...	0.022	0.14	0.0	5.43E-5	1.41E-8	0.92...	0.0975
0.0726	0.68...	0.014	0.145	0.0	6.44E-5	1.39E-8	0.82...	0.0978
0.0851	0.57...	0.012	0.144	0.0	6.95E-5	1.43E-8	0.76...	0.0980
0.0977	0.49...	0.011	0.144	0.0	6.7E-5	1.30E-8	0.72...	0.0974
0.0977	0.49...	0.012	0.142	0.0	6.7E-5	1.39E-8	0.76...	0.0974
0.1102	0.43...	0.012	0.141	0.0	6.19E-5	1.36E-8	0.76...	0.0976
0.1102	0.43...	0.009	0.144	0.0	6.7E-5	1.37E-8	0.67...	0.0977
0.1102	0.43...	0.011	0.141	0.0	6.95E-5	1.45E-8	0.72...	0.0976
0.1227	0.38...	0.008	0.144	0.0	6.95E-5	1.43E-8	0.62...	0.0978
0.1227	0.38...	0.009	0.141	0.0	6.95E-5	1.46E-8	0.67...	0.0978
0.1227	0.38...	0.009	0.142	0.0	6.7E-5	1.45E-8	0.67...	0.0977
0.1478	0.31...	0.008	0.14	0.0	6.95E-5	1.43E-8	0.62...	0.0977

<< Re-Run Find Fits | Plot | UnPlot | Plot Pobs

Save Results | Show Data

Data Plot





Fraction of cigarette smokers, F, at lifetime risk of lung cancer mortality is greater than 94% of maximum fraction smoking cigarettes, E, for males and females.

Genetic risk is close to 100%.

Cumulative mortality for smokers that quit at ages shown.

Symbols from Peto et al., 2000.

Black lines: hypothesis that smoking reversibly increases preneoplastic growth rates in all smokers.

We are encouraged.