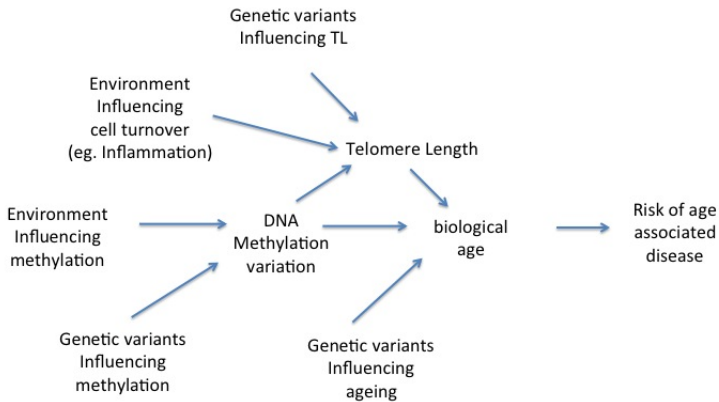


The Nordic Twin Cancer Study

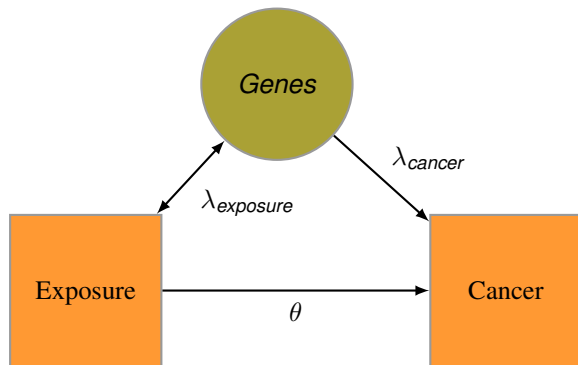
Dept. of Epidemiology and Biostatistics, SDU

Analysis of Twin Data in Health Science

17. maj 2018



Nordic Twin Cancer Study (2017)



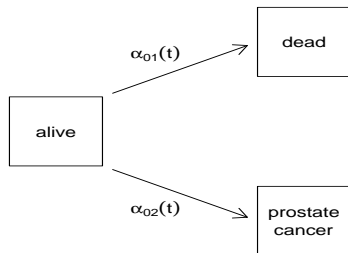
- (Exposures): Direct effect?
- (Genes): Genetic effect present and magnitude?
- (Interaction): Indication of genetic **modification** of exposure effect?

The Nordic Twin Cancer Study

HARVARD
SCHOOL OF PUBLIC HEALTH



	Denmark	Finland	Norway	Sweden	Total
Birth	1870-2004	1880-1957	1895-1979	1886-2008	
Cancer since	1943	1953	1953	1958	
Twins	110,482	24,438	26,470	136,822	298,212



Heredity of Cancer Elucidated by a Study of Unselected Twins

Bent Harvald, MD, and Mogens Hauge, MD, Copenhagen, Denmark

- **1963:** ~15.000 Danish twins, first study, less to conclude (JAMA).
- **2000:** ~90.000 Landmark paper, but wrong methodology (NEJM).
- **2016:** ~300.000 Most comprehensive of familial risks ever (JAMA).

Original Investigation

Familial Risk and Heritability of Cancer Among Twins in Nordic Countries

Lorelei A. Mucci, ScD, MPH; Jacob B. Hjelmborg, PhD; Jennifer R. Harris, PhD; Kamila Czene, PhD; David J. Havelick, ALM; Thomas Scheike, PhD; Rebecca E. Graff, ScD; Klaus Holst, PhD; Sören Möller, PhD; Robert H. Unger, BS; Christina McIntosh, SM; Elizabeth Nuttall, BA; Ingunn Brandt, MSc; Kathryn L. Penney, ScD; Mikael Hartman, MD, PhD; Peter Kraft, PhD; Giovanni Parmigiani, PhD; Kaare Christensen, MD, PhD; Markku Koskenvuo, MD, PhD; Niels V. Holm, MD, PhD; Kauko Heikkilä, PhLic; Eero Pukkala, PhD; Axel Skytthe, PhD; Hans-Olov Adami, MD, PhD; Jaakko Kaprio, MD; for the Nordic Twin Study of Cancer (NorTwinCan) Collaboration

Cancer site	Cumulative risk ¹ (%)	N Twin pairs concordant/ discordant		Familial risk ² (95% CI) – MZ twins	Familial risk (95% CI) – DZ twi
		MZ	DZ		
Overall cancer	32.4%	1383/5887	1933/11461	45.9% (44.1%-47.7%)	37.1% (35.7-38.4)
Head and neck ³	0.8%	5/191	6/361	6.0% (2.4-14.4%)	5.1% (2.2-11.3%)
Esophagus	0.4%	0/87	0/183	--	--
Stomach	1.6%	14/338	15/648	6.8% (3.9-11.4%)	4.4% (2.6-7.3%)
Small intestine	0.1%	0/32	0/59	--	--
Colon	2.9%	30/577	31/1156	10.9% (7.4-15.8%)	7.9% (5.4-11.4%)
Rectum and anus	1.9%	14/440	13/771	6.6% (3.7-11.4%)	5.8% (3.4-9.7%)
Liver	0.5%	0/124	2/208	--	--
Gallbladder, extrahepatic bile duct	0.5%	1/110	1/187	0.5% (0-4.7%)	0.3% (0-1.0%)
Pancreas	1.1%	4/234	6/508	4.3% (1.5-11.6%)	3.7% (1.5-8.6%)
Nose, sinuses	0.1%	0/21	0/36	--	--
Larynx	0.2%	2/53	1/113	8.4% (2.3-26.4%)	2.7% (1.1-6.1%)
Lung, trachea and bronchus	3.2%	50/682	74/1366	17.5% (13.4-22.5%)	13.4% (10.8-16.6)
Pleura	0.1%	1/22	0/38	--	--
Bone	0.1%	0/20	0/35	--	--
Melanoma of skin	1.2%	11/342	6/585	19.6% (11.5-31.3%)	6.1% (2.7-13.2%)
Skin, non-melanoma	3.0%	16/395	10/618	14.5% (7.5-26.2%)	4.6% (2.4-8.6%)
Connective and soft tissues	0.2%	0/57	0/110	--	--
Breast	9.4%	124/1175	141/2223	28.1% (23.9-32.8%)	19.9% (17.0-23.2)
Cervix uteri	1.0%	1/210	3/324	--	--
Corpus uteri	2.2%	9/272	6/481	7.0% (3.4-14.0%)	3.6% (1.6-8.0%)
Uterus, other	0.1%	0/24	0/36	--	--
Ovary	1.6%	6/234	4/427	8.7% (4.0-17.9%)	2.9% (1.1-7.4%)
Other female genital organs	0.4%	0/47	1/84	--	--
Penis and other genital organs	0.1%	0/15	0/34	--	--
Prostate	10.5%	197/807	148/1719	38.0% (33.9-42.2%)	22.0% (18.8-25.7)
Testis	0.5%	5/90	3/123	13.8% (5.7-29.6%)	6.0% (1.9-16.9%)
Kidney	0.8%	5/196	2/374	6.7% (2.8-15.1%)	1.8% (0.4-6.8%)
Bladder, other urinary organs	2.2%	18/471	13/870	9.9% (6.2-15.5%)	5.5% (3.1-9.7%)
Eye	0.1%	2/30	0/64	--	--
Brain, central nervous system	0.9%	1/343	3/522	1.7% (0.5-6.2%)	1.8% (0.3-12.0%)
Thyroid	0.2%	0/85	1/132	--	--
Hodgkin's disease	0.1%	0/57	0/69	--	--
Multiple myeloma	0.4%	0/114	0/174	--	--
Non-Hodgkin lymphoma	0.7%	1/254	3/466	--	--
Leukemia, acute	0.3%	0/77	0/139	--	--
Leukemia, other	0.6%	5/128	3/259	15.2% (6.1-33.2%)	4.1% (1.3-11.9%)

Politiken and US media January 2016

Kræftrisiko for ...

Din kræftrisiko stiger, hvis du har en kræftramtvillingebror eller -søster

... almindelig person

... person med kræftsyg enægget tvilling

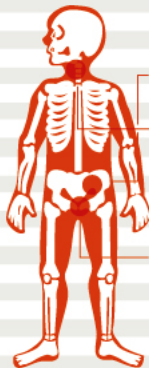
... person med kræftsyg tveægget tvilling

Kræft generelt

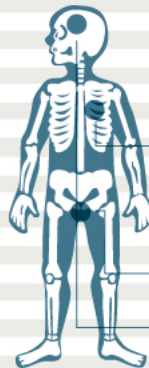
Hoved-og hals	0,8 %
Mave	1,1 %
Tarm	2,9 %
Endetarm	1,9 %
Bugspytkirtel	1,1 %
Strubehoved	0,2 %
Lunge	3,2 %
Modermærke	1,2 %
Hud	1,9 %
Bryst	9,4 %
Livmoder	2,0 %
Æggestok	1,6 %
Prostata	10,5 %
Testikel	0,5 %
Nyre	0,8 %
Blære	2,2 %
Hjerne	0,9 %
Blod	0,6 %



32,4 %



45,9 %



37,1 %

Special sites

- **Opposite versus same sexed twin pairs** Ahrenfeldt, Christensen et al, CEBP (2014)
- **Prostate cancer**, Hjelmberg, Kaprio et al., CEBP (2014)
- **Prostate cancer - response**, Hjelmberg, CEBP (2015)
- **Breast cancer**, Möller, Christensen, Hjelmberg et al, CEBP (2015).
- **All cancer sites**, Mucci, Hjelmberg, Kaprio et al. JAMA (2016)
- **Lung cancer in smokers** Hjelmberg, Korhonen et al, Thorax (2017)
- **Cancer immunization** McIntosh, Adami et al, 2016, in progress
- **Colon and rectal cancers** Graff, Hjelmberg et al, 2017, CGH.

Biostatistics - Methodology

- *Estimating heritability for cause specific mortality based on twin studies*; Scheike, Holst and Hjelmberg; *LIDA* (2013).
- *Estimating twin concordance for bivariate competing risks twin data*; Scheike, Holst and Hjelmberg; *Stat Med* (2014)
- *Measuring early or late dependence for bivariate lifetimes of twins* Scheike, Holst and Hjelmberg; *LIDA* (2014).
- *Estimating Twin Pair Concordance for Age of Onset* Scheike, T. H., Hjelmberg, J. B. and Holst, K. K.: *Behavior Genetics*. (2015)

R.A. Fisher (1890-1962)



- R.A. Fisher (1918): Biometrical Genetics.

Biometrical Genetics

XV.—The Correlation between Relatives on the Supposition of Mendelian Inheritance. By R. A. Fisher, B.A. Communicated by Professor J. ARTHUR THOMSON. (With Four Figures in Text.)

(MS. received June 15, 1918. Read July 9, 1918. Issued separately October 1, 1918.)

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Model??

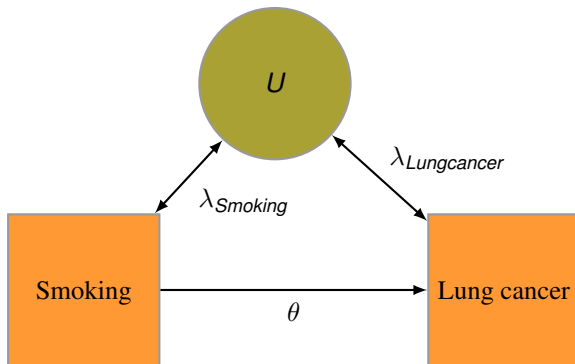
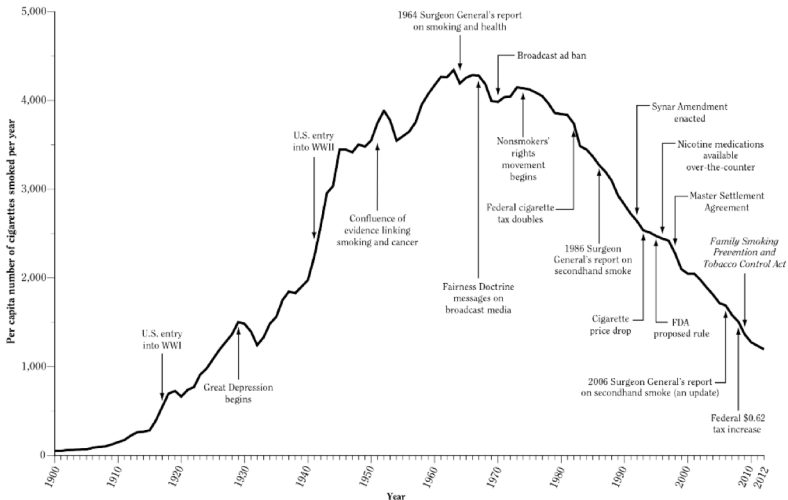


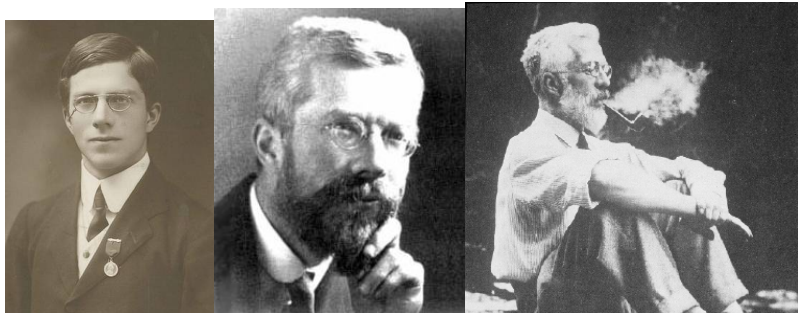
Figure 2.1 Adult* per capita cigarette consumption and major smoking and health events, United States, 1900–2012



Sources: Adapted from Warner 1985 with permission from Massachusetts Medical Society, ©1985; U.S. Department of Health and Human Services 1989; Creek et al. 1994; U.S. Department of Agriculture 2000; U.S. Census Bureau 2013; U.S. Department of the Treasury 2013.

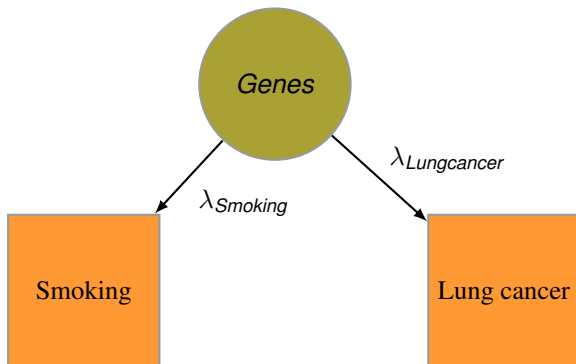
*Adults ≥18 years of age as reported annually by the Census Bureau.

R.A. Fisher (1890-1962)

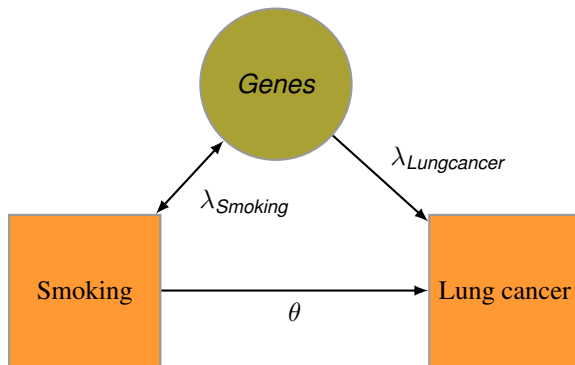


- (1918): Biometrical Genetics.
- (1935): Randomization negates the effect of confounders.
- (1950): 'correlation does not imply causation'.

Model by R.A.Fisher (1950)

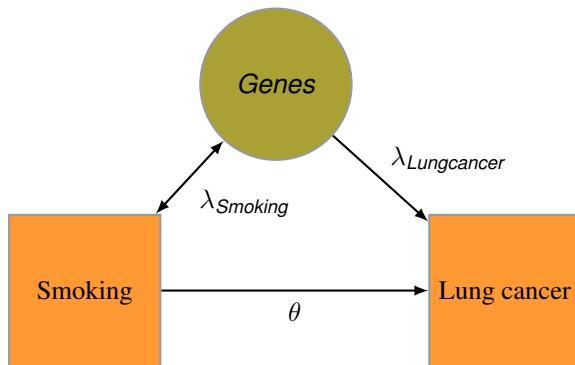


Nordic Twin Cancer Study (2017)



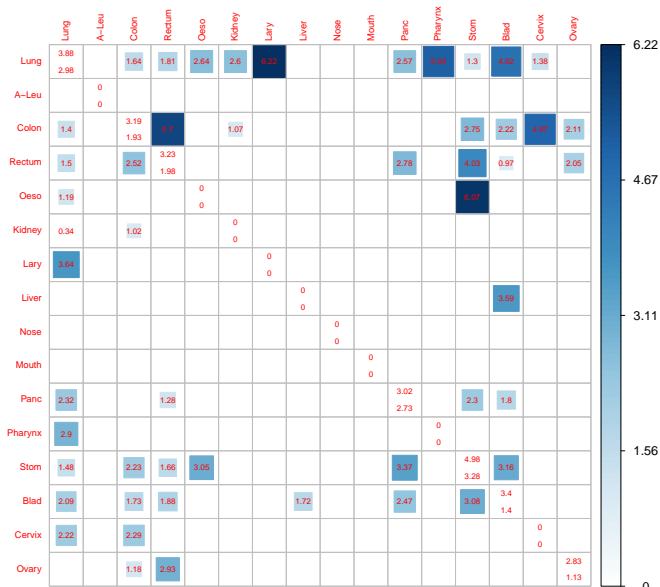
- (Smoking): Direct effect.
- (Genes): Genetic effect present and may be **mediated** through smoking.
- (Interaction): No indication of genetic **modification** of smoking effect.

Nordic Twin Cancer Study (2017)



- (Smoking): Direct effect.
- (Genes): Genetic effect present and may be **mediated** through smoking.
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Relative recurrence Risks - Tobacco cancers



Peto Mack Hypothesis

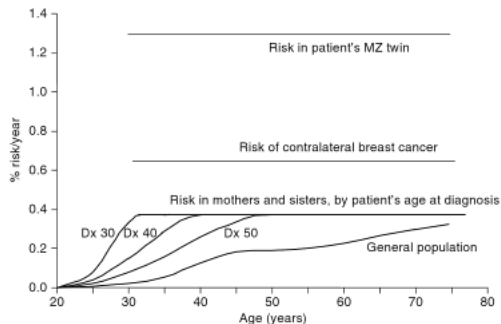
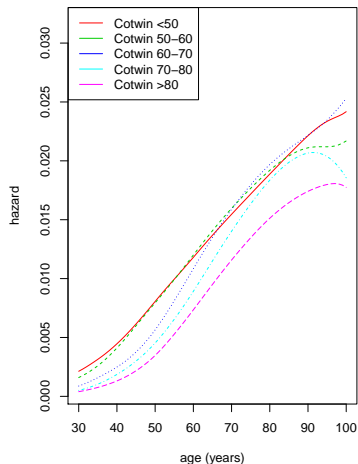
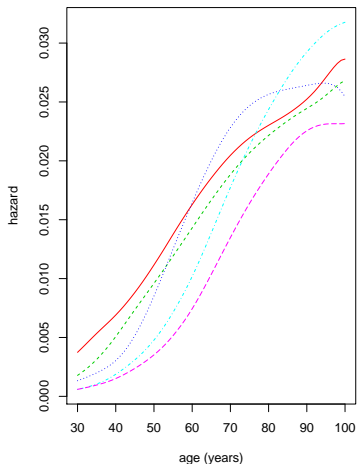


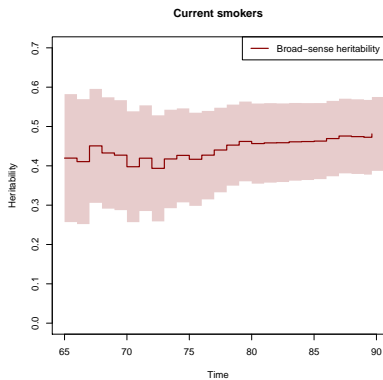
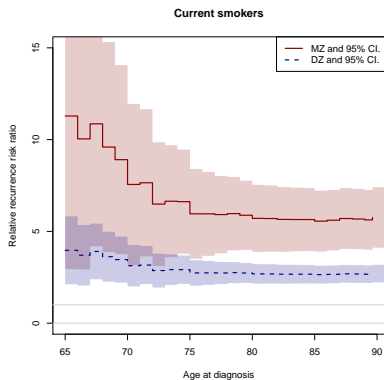
Figure 17.1 Incidence of breast cancer in the general population and in patient's relatives. Dx, age at diagnosis of breast cancer.

Peto Mack Hypothesis - All Cancer

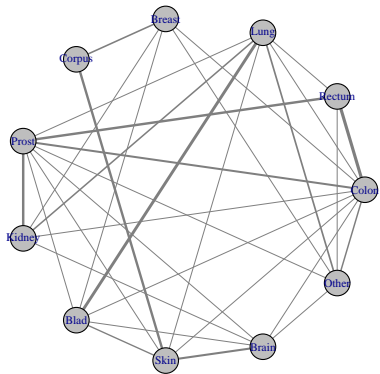


Forecasting Cancer Incidence

- Constant force of cancer suggests Gompertz-law of incidence.
- How about forecasting lung cancer incidence given exposure and constant force of cancer?



Heritability



collaborators

University of Southern Denmark

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