TWO HUNDRED YEARS OF CANCER RESEARCH

200 NEJM ANNIVERSARY ARTICLE

Vincent T. DeVita, Jr., MF., and Steven A. Rosenberg, M.D.,Ph.D.

NEJM 366;23 June 7 2012

R4 柯博伸

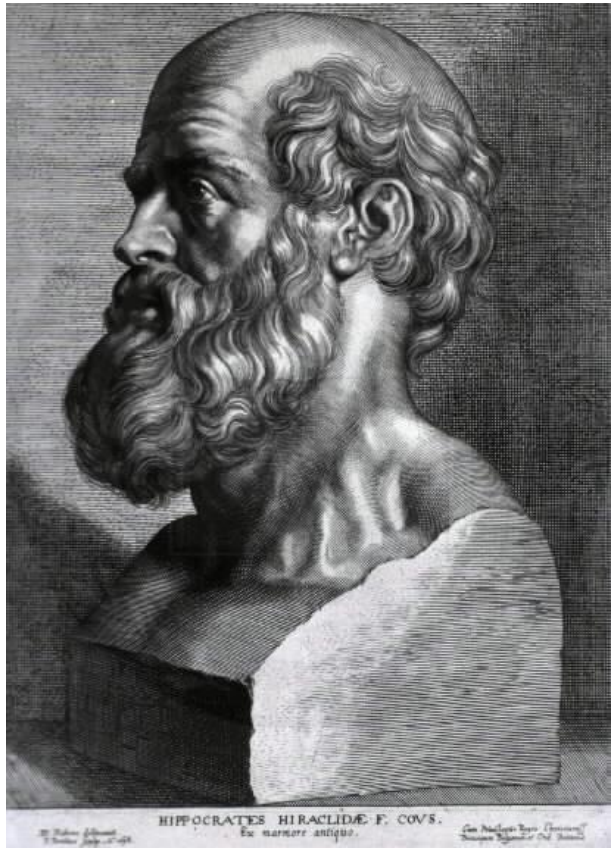
指導老師: 曾成槐主任

Outlines

- Singular Discoveries and Major Events in the Cancer Field
- Milestones in Cancer Treatment
- Cancer Prevention
- Survival Now and In the Future
- The Future

Hippocrates (c.460 BC – c. 370 BC)

- First to describe those visible cancer
  - Καρκίνος
    - Crab; solid-centered mass with branching
- Disease
  - Not punishment by God but product of environmental, factors, diet and living habits



Rudolf Virchow (1821-1902)
-The father of modern pathology

- German doctor, anthropologist, pathologist, biologist and politician
- Cited as the first to recognize leukemia cells
- "Cell division" in 1855
- "Cellular pathology based on physiological and compa -rative pathological histology" in 1863
- "Think microscopically"
- "Virchow's triad" in venous thrombus formation

Stephen Paget (1855-1926)

- English Surgeon
- Seed-and-soil hypothesis of metastatic disease
  - The distribution of secondary growths in cancer of the breast
    - Lancet 1889;1:571-3

Peyton Rous (1879-1970)

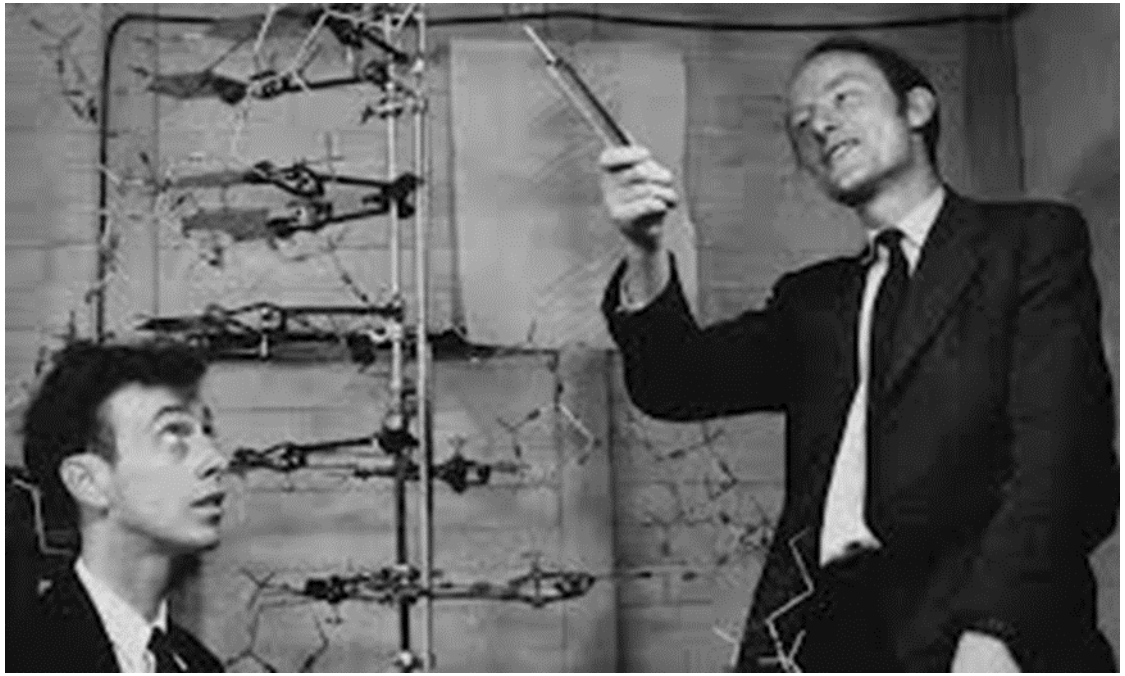
- United States
- Discover first oncovirus – Rous sarcoma virus
- Avian sarcoma could be transferred to another fowl simply by exposing the healthy bird to a cell-free extract of chicken tumor
- Awarded the Nobel Prize in Physiology or Medicine in 1966

Theodor Boveri (1862-1915)

- German biologist
- "Cancer can be triggered by chromosomal mutation" in 1914
  - "Cancerous tumor begins with a single cell in which makeup of its chromosome becomes scrambled, causing the cells to divide uncontrollably"
  - "Carcinogenesis was the results of aberrant mitoses and uncontrolled growth caused by radiation, physical or chemical insults or by microscopic pathogens."

Oswald Avery (1877-1955)

- Canadian-born American physician
- "Cellular information was transmitted not by proteins but by DNA." in 1944



- James Watson and Francis Crick
- Discovery of the structure of DNA by Watson and Crick in 1953

Marshall Warren Nirenberg (1927-2010)

- Found out genetic code
- Use short artificial RNA sequence in cell-free system with tRNA and ribosome
- Labeling one specific type of amino acid at a time, and then put the mixture through a Millipore filter

Seond letter

First letter	U	C	A	G	Third letter
U	UUU Phe UUC Phe UUA Leu UUG Leu	UCU Ser UCC Ser UCA Ser UCG Ser	UAU Tyr UAC Tyr UAA Stop UAG Stop	UGU Cys UGC Cys UGA Stop UGG Trp	U C A G
C	CUU Leu CUC Leu CUA Leu CUG Leu	CCU Pro CCC Pro CCA Pro CCG Pro	CAU His CAC His CAA Gin CAG Gin	CGU Arg CGC Arg CGA Arg CGG Arg	U C A G
A	AUU Ile AUC Ile AUA Ile AUG Met	ACU Thr ACC Thr ACA Thr ACG Thr	AAU Asn AAC Asn AAA Lys AAG Lys	AGU Ser AGC Ser AGA Arg AGG Arg	U C A G
G	GUU Val GUC Val GUA Val GUG Val	GCU Ala GCC Ala GCA Ala GCG Ala	GAU Asp GAC Asp GAA Glu GAG Glu	GGU Gly GGC Gly GGA Gly GGG Gly	U C A G

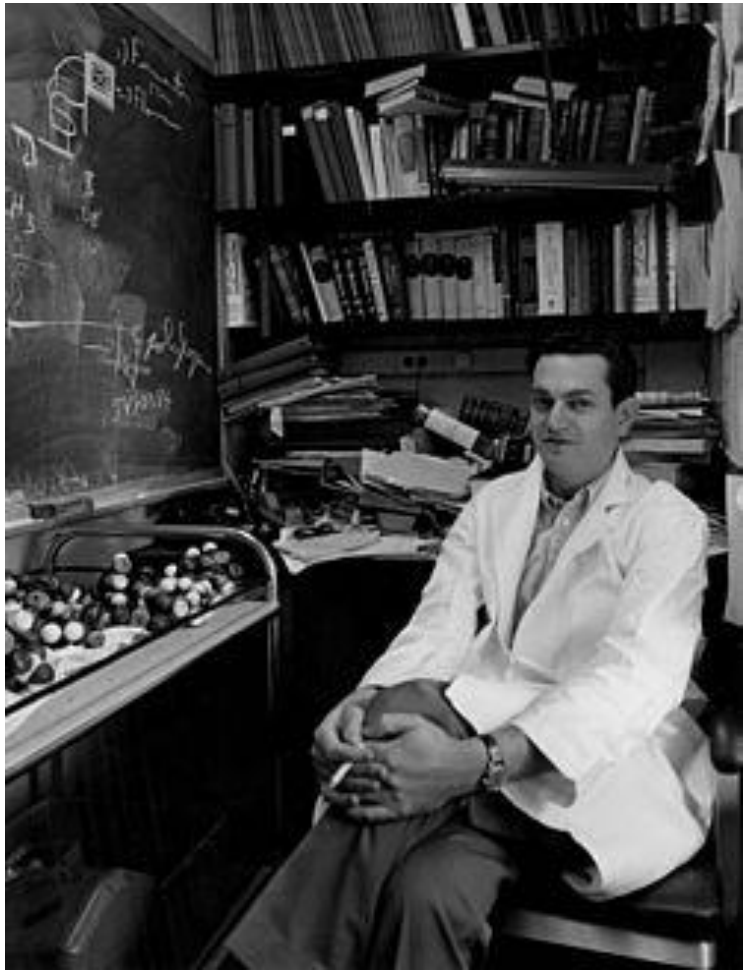


Table 1. Singular Discoveries and Major Events in the Cancer Field and Changing Relative Survival Rates for Patients with Cancer in the United States, 1863–2006.*

Year	Discovery or Event	Relative Survival Rate
1863	Cellular origin of cancer (Virchow)	
1889	Seed-and-soil hypothesis (Paget)	
1914	Chromosomal mutations in cancer (Boveri)	
1937	Founding of NCI	
1944	Transmission of cellular information by DNA (Avery)	
1950	Availability of cancer drugs through Cancer Chemotherapy National Service Center	
1953	Report on structure of DNA	35%
1961	Breaking of the genetic code	
1970	Reverse transcriptase	

National Cancer Institute

- The first disease-oriented agency, a part of NIH established by U.S Congress
- 2/3 anti-cancer drugs approved by FDA till 1995 were NCI-sponsored investigational new drugs

Alkylating agents .

- Chlorambucil (Leukeran) (1957)
- Cyclophosphamide (Cytoxan) (1959)
- Thiotepa (1959)
- Melphalan (Alkeran) (1959) (IV in 1993)
- Streptozotocin (Zanosar) (1982)
- Ifosfamide (Ifex) (1988)

Antimetabolites

- Mercaptopurine (1953)
- Methotrexate (1953)
- Thioguanine (1966)
- Cytosine arabinoside (Ara-C) (1969)
- Floxuridine (FUDR) (1970)
- Fludarabine phosphate (1991)
- Pentostatin (1991)
- Chlorodeoxyadenosine (1992)

Plant alkaloids and antibiotics

- Vincristine (Oncovin) (1963)
- Actinomycin D (Cosmegen) (1964)
- Mithramycin (Mithracin) (1970)
- Bleomycin (Blenoxane) (1973)
- Doxorubicin (Adriamycin) (1974)
- Mitomycin C (Mutamycin) (1974)
- L-Asparaginase (Elspar) (1978)
- Daunomycin (Cerubidine) (1979)
- VP-16-213 (Etoposide) (1983)
- VM-26 (Teniposide) (1992)
- Taxol (Paclitaxel) (1992)

Synthetic drugs

- Hydroxyurea (Hydrea) (1967)
- Procarbazine (Matulane) (1969)
- O, P'-DDD (Lysodren, Mitotane) (1970)
- Dacarbazine (DTIC) (1975)
- CCNU (Lomustine) (1976)
- BCNU (Carmustine) (1977)
- Cis-diamminedichloroplatinum (Cisplatin) (1978)
- Mitoxantrone (Novantrone) (1988)
- Carboplatin (Paraplatin) (1989)
- Levamisole (Ergamisol) (1990)
- Hexamethylmelamine (Hexalen) (1990)
- All-trans retinoid acid (Vesanoid) (1995)
- Porfimer sodium (Photofrin) (1995)

Hormones and steroids

- DES (1950)
- Prednisone (1953)
- Fluoxymesterone (Halotestin) (1958)
- Dromostanolone (Drolban) (1961)
- Testolactone (Teslac) (1970)
- Methyl prednisolone
- Prednisolone
- Zoladex (1989)

Biologicals

- Alpha interferon (Intron A, Roferon-A) (1986)
- BCG (TheraCys, TICE) (1990)
- G-CSF (1991)
- GM-CSF (1991)
- Interleukin 2 (Proleukin) (1992)

National Cancer Act

- "To support research and the application of the results of research to reduce the incidence, morbidity and mortality from cancer"

President Nixon signs the National Cancer Act in 1971.
Photo courtesy of the National Cancer Institute.

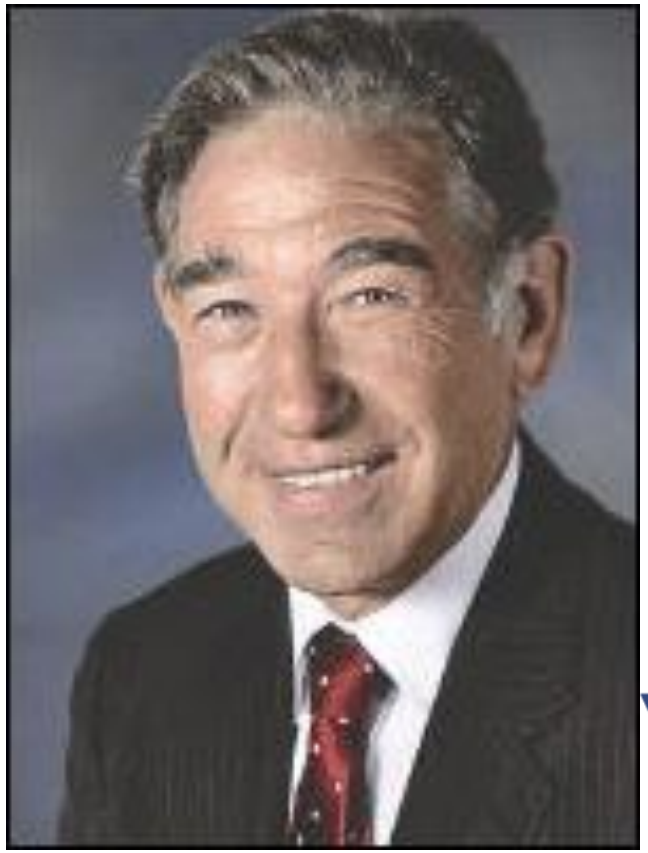
- December 23, 1971
- In 1980s, NCI accounted 23% budget of NIH
- Actually, 85% funds went to support basic research

1971	Restriction enzymes Passage of National Cancer Act	
1975	Hybridomas and monoclonal antibodies Tracking of cancer statistics by SEER program	50%
1976	Cellular origin of retroviral oncogenes	

Stanley Cohen (1922-)

- American biochemist
- Discover EGFR in 1979

  (Nobel Prize in Medicine)

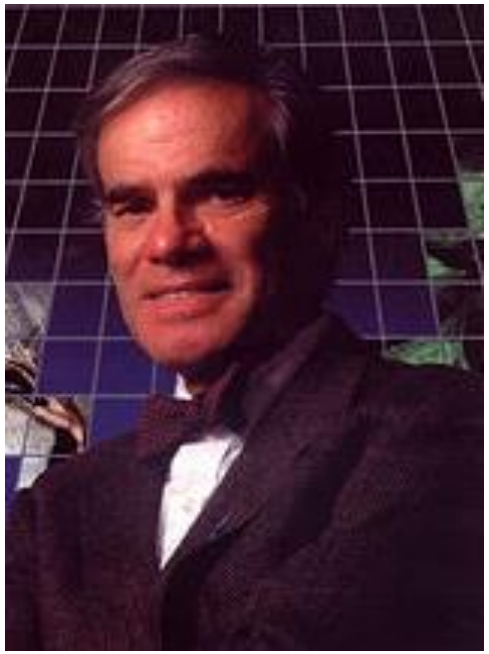


1979	Epidermal growth factor and receptor
1981	Suppression of tumor growth by p53
1984	G proteins and cell signaling
1986	Retinoblastoma gene
1990	First decrease in cancer incidence and mortality
1991	Association between mutation in APC gene and colorectal cancer

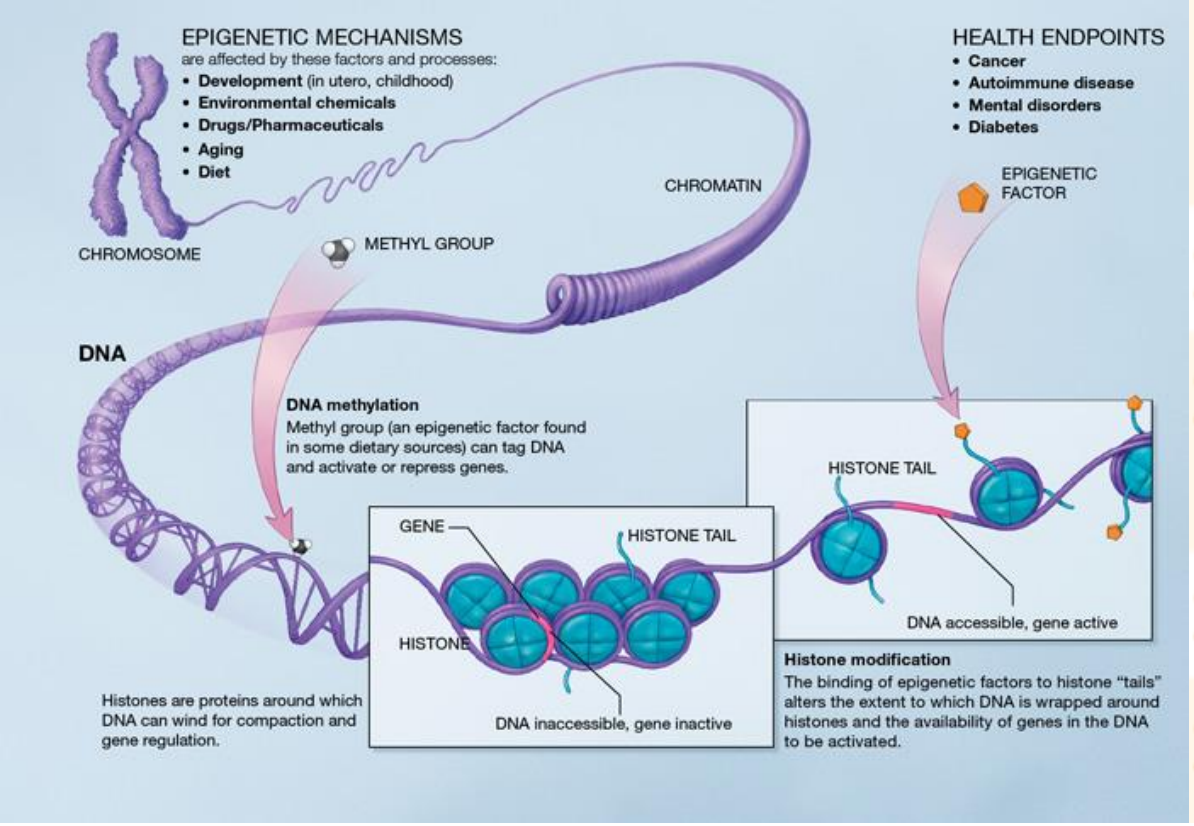
Martin Rodbell & Alfred G. Gilman

- U.S biochemist
- GTP involved in cell signaling in 1960s

- U.S biochemist
- Discover the protein interacted with GTP to initiate signaling cascades in 1984



1994
Nobel Prize in
Physiology or Medicine



1994 Genetic cancer syndromes
Association between *BRCA1* and breast cancer

2000 Sequencing of the human genome

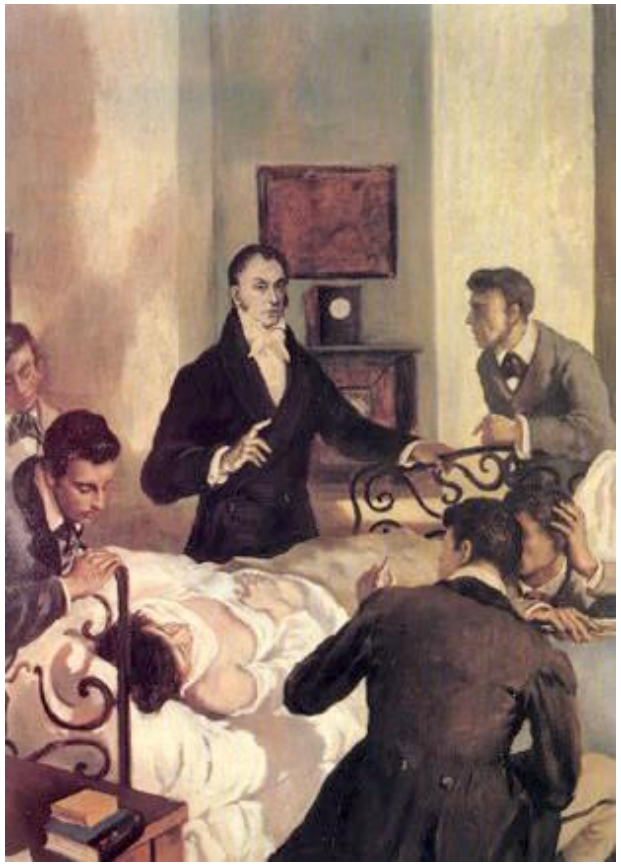
2002 Epigenetics in cancer
MicroRNAs in cancer

2005 First decrease in total number of deaths from cancer

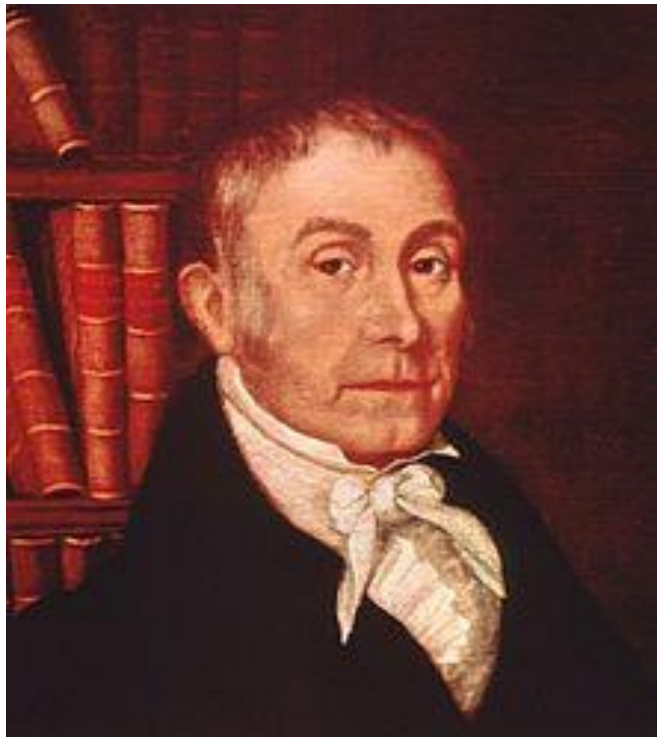
2006 Tumor stromal interaction

The first abdominal surgery in U.S

In 1809



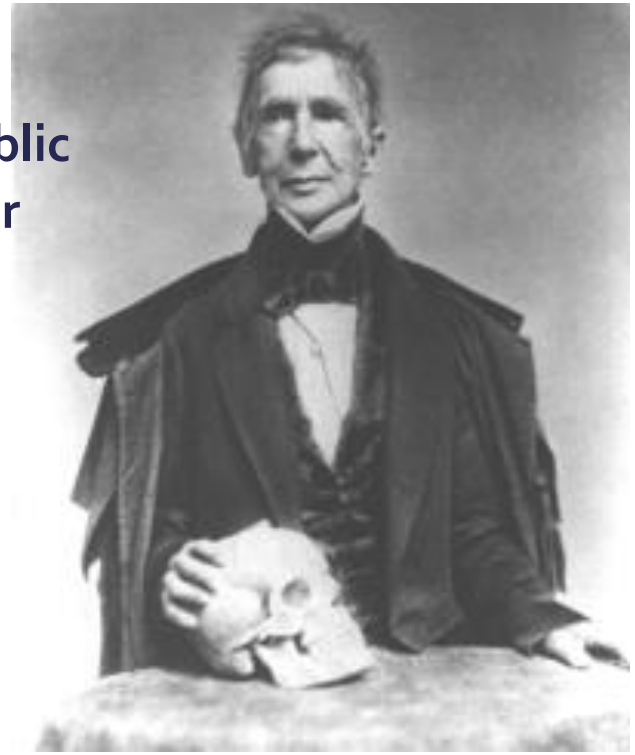
Ephraim McDowell (1771-1830, US)



Great work for paving way for surgery

John Collins Warren (1778-1856)

Anesthesia in public
with sulphuric ether
In 1846

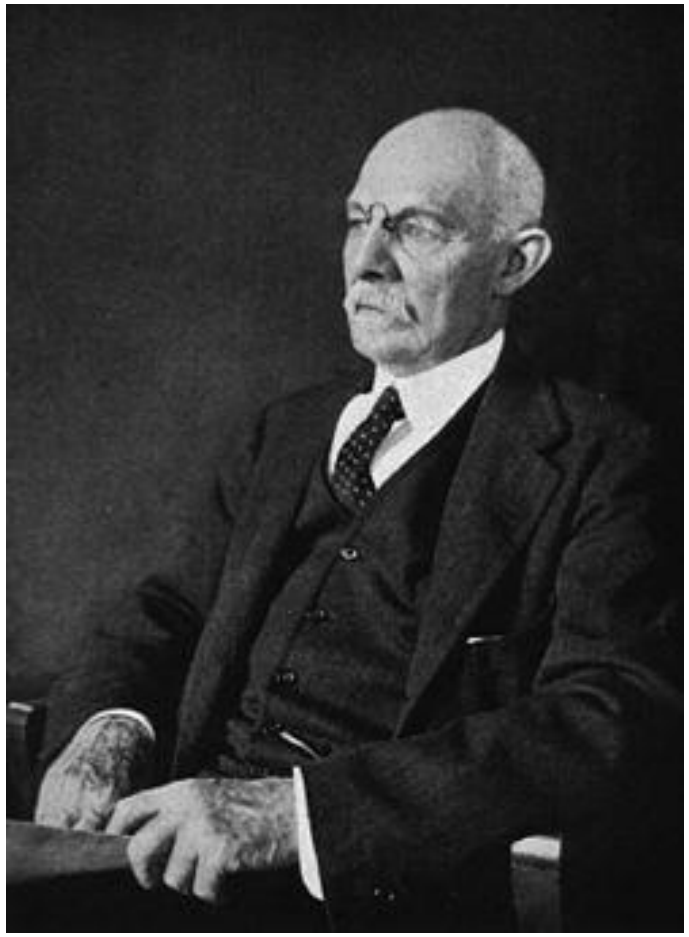


Joseph Lister (1827-1912)

Introduction of
Antisepsis
In 1867

William Halsted (1852-1922)

- American Surgeon
- Radical mastectomy in 1894
- "Breast cancer spread in a centrifugal fashion from the primary tumor to adjacent structures"
- En bloc resection, even the head of the humerus

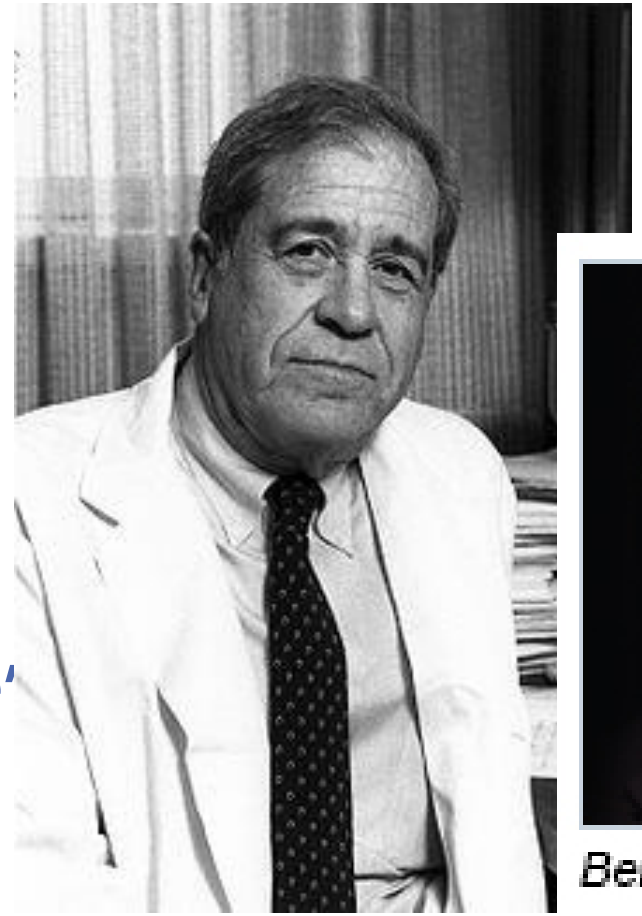


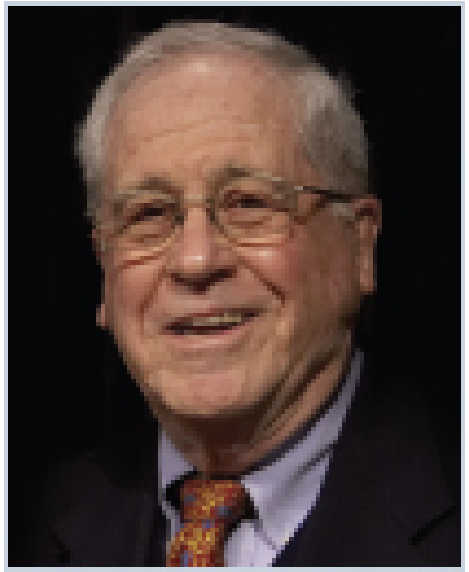
Bernard Fisher (1918-)

- American scientist
- In 1958, inspired after a meeting in NIH which evaluated systemic therapy following radical mastectomy (Thiotepa)
- Then in 1968 wiyh hypothesis :

"Breast cancer can early be a systemic disease'

- Ended the "too much and too little" -standard practice of the Halsted radical mastectomy
- Lumpectomy rather than radical mastectomy, if supplemented by chemotherapy, radiation therapy or both.





Bernard Fisher, MD

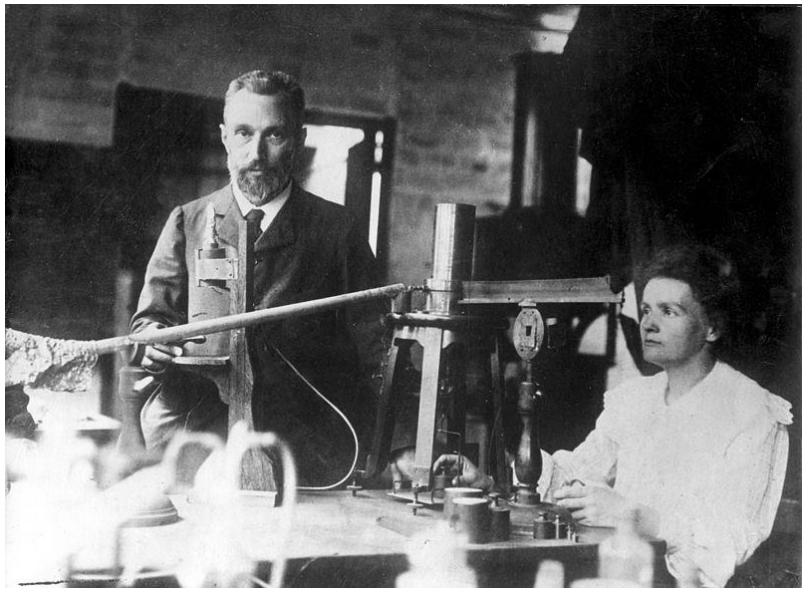
The era of radiation treatment

Wilhelm Rontgen (1845-1923, German)

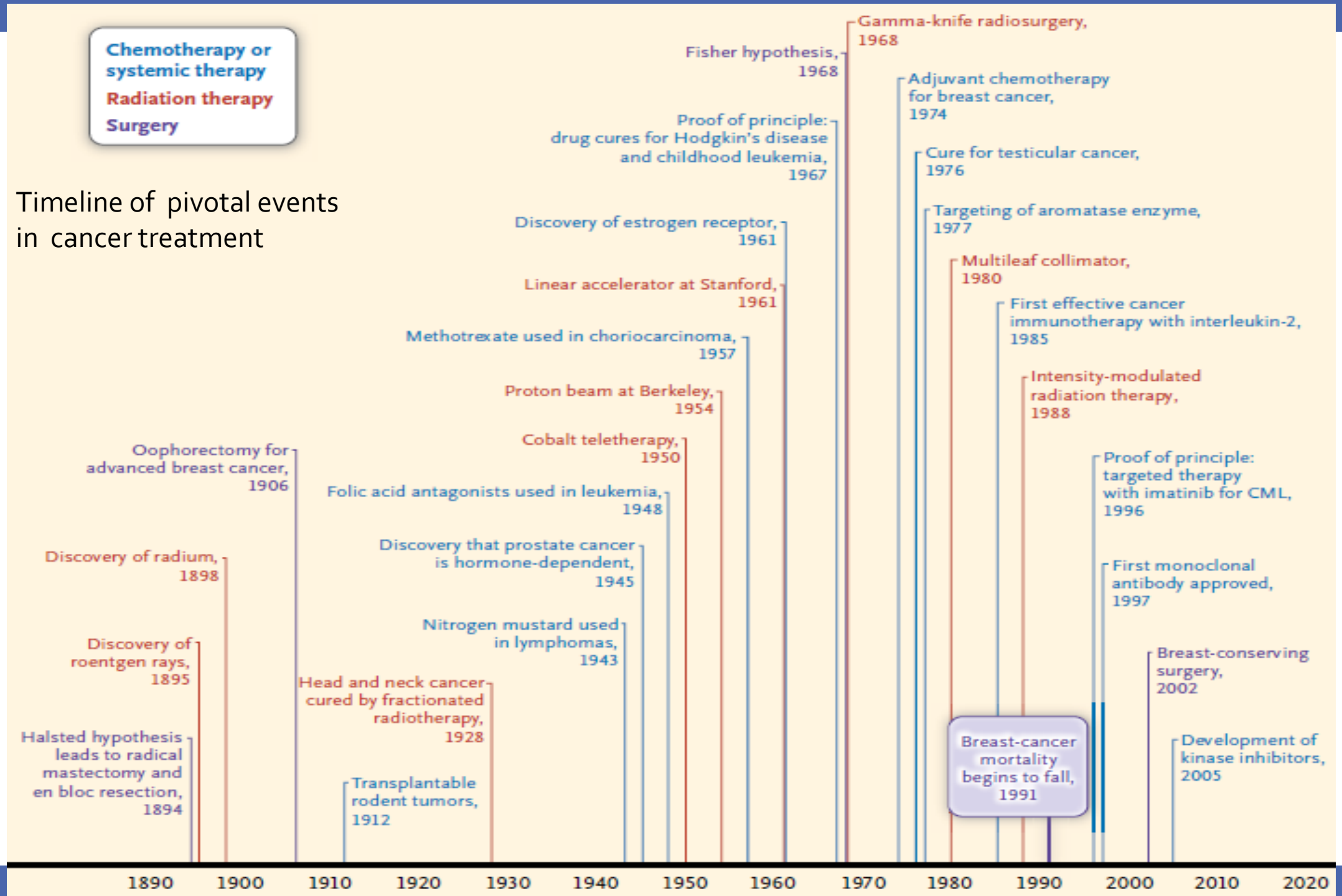
- X rays in 1985
- Nobel Prize in Physics in 1901

Pierre and Marie Curie (Poland)

- Discover Radium and Polonium
- Nobel Prize in Physics in 1903



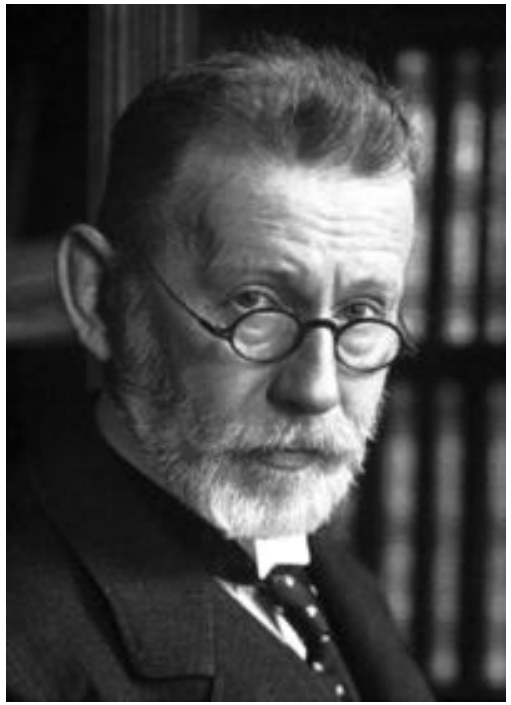
Timeline of pivotal events in cancer treatment



"Chemotherapy"

Paul Ehrlich (1854-1915, German)

- Coin the word "chemotherapy"



- In the early 20th century, researchers devoted the first half of the century to establishing screening systems that would reliably predict antitumor activity in human on the basis of data from murine models.
- Part of the problems was the limited capability for testing new agents in humans.
- Frustrating till…

Mustard Therapy in 1943

- Mustard gas
- German introduction during World War I

Alfred Gilman

Louis S. Goodman

Nitrogen mustard

Nitrogen Mustard Therapy

Sinking of SS John Harvey's secret cargo of mustard gas bombs

Dr. Stewart Francis Alexander

Lymphoid and myeloid suppression

- after exposure by investigating the autopsies of the victims

- Goodman and Gilman: Mustine tor treat a patient with HL
- A dramatic reduction in tumor mass

Landmark Article
Sept 21, 1946
(*JAMA* 1946;132:126-132)

Hodgkin's disease	27
Lymphosarcoma	13
Chronic myelocytic leukemia	7
Acute and subacute myeloblastic leukemia	4
Chronic lymphocytic leukemia	5
Subacute lymphoblastic leukemia	3
Miscellaneous diseases*	8
Total	67

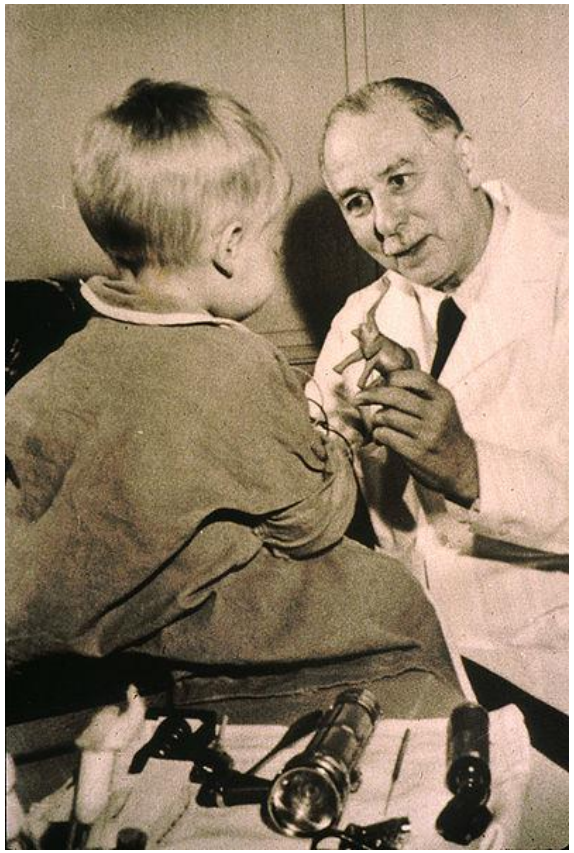
Nitrogen Mustard Therapy

Use of Methyl-Bis(Beta-Chloroethyl)amine Hydrochloride and Tris(Beta-Chloroethyl)amine Hydrochloride for Hodgkin's Disease, Lymphosarcoma, Leukemia and Certain Allied and Miscellaneous Disorders

Folic acid antagonist in 1948

Sidney Farber (1903-1973; U.S)

- Use Aminopterin (4-amino analog of folic acid) in ALL child
- Result in brief remissions in 10/16 cases



The New England
Journal of Medicine

Copyright, 1948, by the Massachusetts Medical Society

Volume 238 JUNE 3, 1948 Number 23

TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

Sidney Farber, M.D.,† Louis K. Diamond, M.D.,‡ Robert D. Mercer, M.D.,§
Robert F. Sylvester, Jr., M.D.,¶ and James A. Wolff, M.D.‖

Folic acid antagonist

- Methotrexate induced remission in breast cancer in 1951
- First to demonstrate use of drug in solid tumors

- MTX alone cure choriocarcinoma in 1957

Jane. C. Wright(1919-2013)

李敏求 (1919-1980)

blood 1965 26: 642-656

The Effectiveness of Combinations of Antileukemic Agents in Inducing and Maintaining Remission in Children with Acute Leukemia

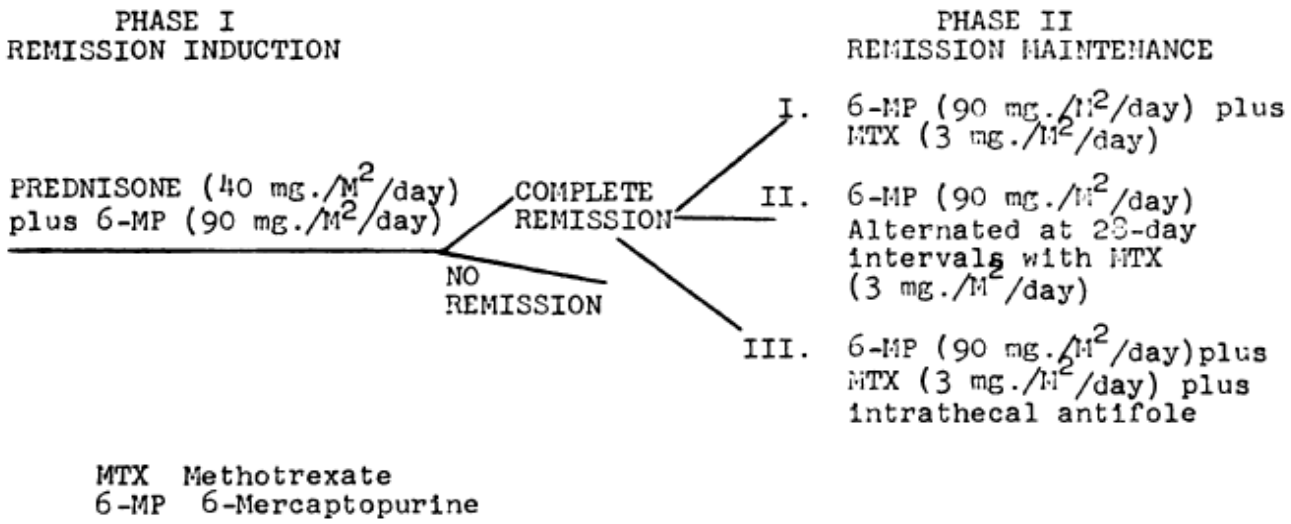


Fig. 1.—Experimental design.

Table 2.—*Response in Phase I: Remission Induction with Combination 6-MP and Prednisone*

Total number of patients	154
No. achieving complete remission*	127 (82%)
No. achieving partial remission*	13 (9%)
No response	14 (9%)
Death in phase I	8 (5%)

1. Combination chemotherapy →an addictive increase in CR
2. Intrathecal antifolate ↓ occurrence of meningeal leukemia
3. In maintainance chemotherapy, 6-MP+ MTX not prolonged longer remission than 6-MP alone

Vincent Theodore DeVita, Jr (1935-)

1967

Cancer Research

Intensive Combination Chemotherapy and X-irradiation in Hodgkin's Disease

John H. Moxley III, Vincent T. De Vita, Kirkland Brace, et al.

Ann Intern Med 1970;73:881-95.

- M(or cyclophosphamide)OPP
- ↑ response rate and probably the survival of patients with Hodgkin's disease

Mid-1970s, 2 landmark of adjuvant chemotherapy in breast cancer

- L-phenylalanine mustard (L-PAM) as adjuvant chemotherapy for LN(+) improve DFI, and overall survival

NEJM 1975

L-PHENYLALANINE MUSTARD (L-PAM) IN THE MANAGEMENT OF PRIMARY BREAST CANCER

An Update of Earlier Findings and a Comparison with Those Utilizing L-PAM Plus 5-Fluorouracil (5-FU)

Bernard Fisher, MD, Andrew Glass, MD, Carol Redmond, ScD, Edwin R. Fisher, MD, Bruce Barton, MS, Emillie Such, RN, Paul Carbone, MD, Steven Economou, MD, Roger Foster, MD, Robert Frelick, MD, Harvey Lerner, MD, Martin Levitt, MD, Richard Margolese, MD, John MacFarlane, MD, David Plotkin, MD, Henry Shibata, MD, Herbert Volk, MD (and other cooperating investigators)*

- CMF (Cyclophosphamide, MTX, and fluorouracil) developed by NCI but performed in Italy
  - Gianni Bonadonna et al. NEJM 1976

- By 1991, morality from breast cancer in USA ↓ 34%
  - Availability of multiple effective chemotherapeutic agents and hormone treatments
  - Improved diagnostic tools for early diagnosis
  - Clinical trails
- Permissive effect on the use of drugs in the postoperative treatment of other major cancers, such as colorectal cancers.
  - Mortality from colorectal cancer40% during the past four decades.

For cancer treatment…

Target therapy
Immunotherapy

Paradigmatic change…

- 2006, Brian J. Druker (1955-)
  - Gleevec (Imatinib) for CML patients at 60 months
    - 87% complete cytogenetic response
    - 89% overall survival rate

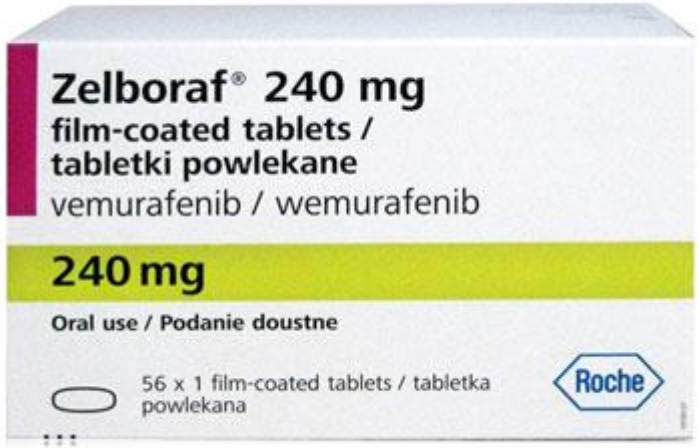
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia

As for Metastatic melanoma…

- 2011, Vemurafenib (PLX4032) V.S Dacarbazine
  - Improve overall and progression-free survival for those with BRAF V600E mutation



The NEW ENGLAND JOURNAL of MEDICINE

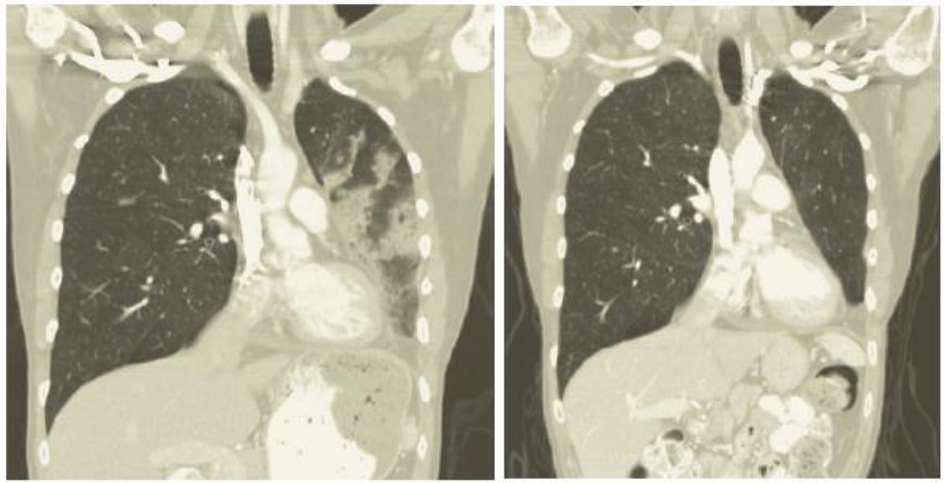
ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

As for lung cancer…

- Crizotinib approved in 2011 by FDA for
- Non-small-cell lung cancer , EML4-ALK fusion gene(+) in 2-7%, never or light smokers
- Mean treatment duration 6.4 months in 82 patients
  - Overall response rate 57% ; Stable disease 33%
  - Grade 1 or 2 GI side effects

B CT before and after Crizotinib



As for immunotherapy…

- Antibodies were described in 1880s
- G. Köhler & C. Milstein et al. Produced monoclonal antibodies
  - By fusing cultured myeloma cells with normal B cells from immunized donor mouse
    - Nature 1975: Continuous cultures of fused cells secreting antibody of predefined specificity
  - The Nobel Prize in Physiology or Medicine in 1984

Era of therapeutic antibody since 1997

- Initially for relapsed low-grade NHL or follicular lymphoma approved by FDA in 1997

blood

1997 90: 2188-2195

IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphoma

David G. Maloney, Antonio J. Grillo-López, Christine A. White, David Bodkin, Russell J. Schilder, James A. Neidhart, Nalini Janakiraman, Kenneth A. Foon, Tina-Marie Liles, Brian K. Dallaire, Ken Wey, Ivor Royston, Thomas Davis and Ronald Levy

Other advances in Immunotherapy

- Till early 1960s, Cellular rather than humoral immunity was known to play a major role in the immune destruction of experimental cancers
- Till 1976s, T-cell growth factor (the "IL-2") was described from successfully cultured T cells from bone marrow in conditioned medium
- Administration of LAK cells (1.8- 1.8 x 10^{10} autologous) plus interleukin-2 (up to 90 doses) to patient with advanced metastatic cancer in 25 patients
  - 10 patients had partial response (melanoma, CRC, RCC and lung adenoCa.)
  - 1 patient (metastatic melanoma) had complete response and sustained for 10 months

- Rosenberg SA et al. N Engl J Med 1985

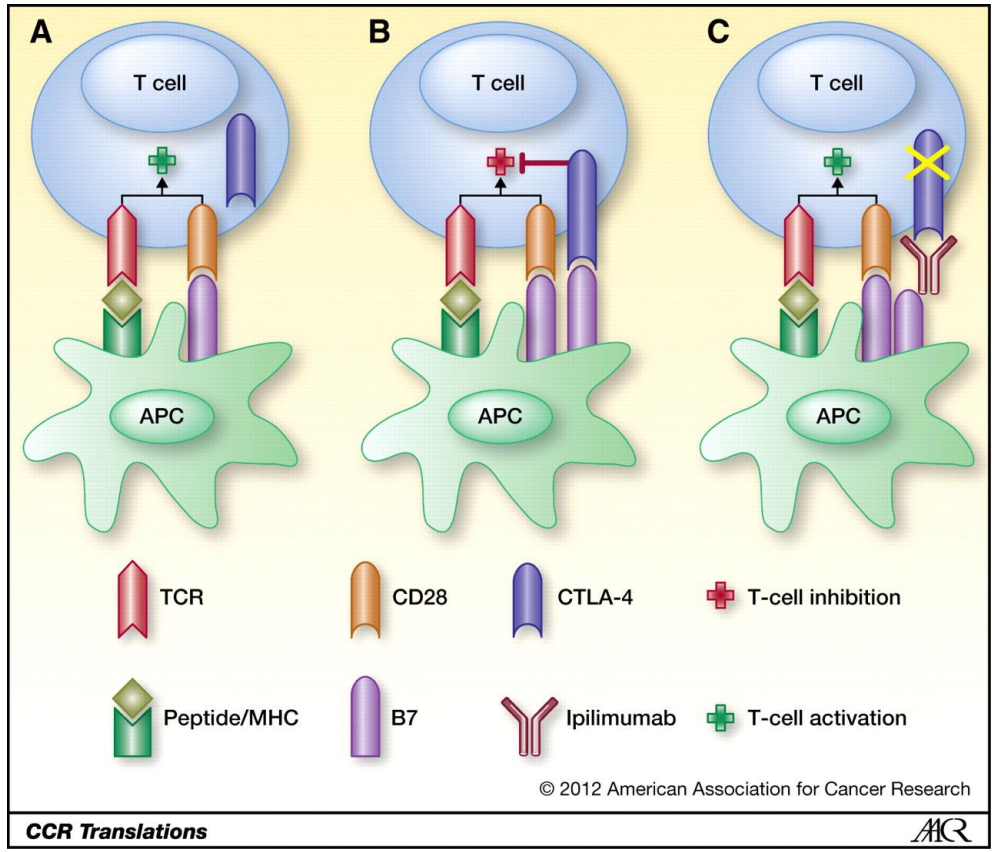
Immunotherapy

- IL-2 iapproved for the treatment of metastatic renal cancer in 1992 and metastatic melanoma in1998
- Ipilimumab
  - Approved by FDA in March 2011
  - Unrescetable metastatic melanoma
  - failed /not tolerate other systemic Tx

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma



Immunotherapy-Development of cell-transfer therapy

- Dudley ME et al .

Patient	Age/sex	Treatment*				Sites of evaluable metastases	Response duration‖ (months)	Autoimmunity
		Cells infused† ($\times 10^{-10}$)	CD8/CD4 phenotype‡ (%)	Antigen specificity§	IL-2 (doses)			
1	18/M	2.3	11/39	Other	9	Lymph nodes (axillary, mesenteric, pelvic)	PR¶ (24+)	None
2	30/F	3.5	83/15	MART-1, gp100	8	Cutaneous, subcutaneous	PR (8)	Vitiligo
3	43/F	4.0	44/58	gp100	5	Brain, cutaneous, liver, lung	NR	None
4	57/F	3.4	56/52	gp100	9	Cutaneous, subcutaneous	PR (2)	None
5	53/M	3.0	16/85	Other	7	Brain, lung, lymph nodes	NR-mixed	None
6	37/F	9.2	65/35	Other	6	Lung, intraperitoneal, subcutaneous	PR (15+)	None
7	44/M	12.3	61/41	MART-1	7	Lymph nodes, subcutaneous	NR-mixed	Vitiligo
8	48/M	9.5	48/52	gp100	12	Subcutaneous	NR	None
9	57/M	9.6	84/13	MART-1	10	Cutaneous, subcutaneous	PR (10+)	Vitiligo
10	55/M	10.7	96/2	MART-1	12	Lymph nodes, cutaneous, subcutaneous	PR¶ (9+)	Uveitis
11	29/M	13.0	96/3	MART-1	12	Liver, pericardial, subcutaneous	NR-mixed	Vitiligo
12	37/F	13.7	72/24	MART-1	11	Liver, lung, gallbladder, lymph nodes	NR-mixed	None
13	41/F	7.7	92/8	MART-1	11	Subcutaneous	NR	None

Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. Science 2002; 298:850-4

Cancer prevention

- The role of tobacco in cancer
- The connection between viruses and cancer
- Chemoprevention

The role of tobacco

- 1912, smoking might be related to lung cancer.
- In the 1950s, epidemiologic evidence became solid
- In 1964, Surgeon General's report on smoking and cancer

The New City Times

JANUARY 11, 1964 PRICE: FIVE CENTS

SURGEON GENERAL SAYS:

STUDIES SHOW SMOKING KILLS!

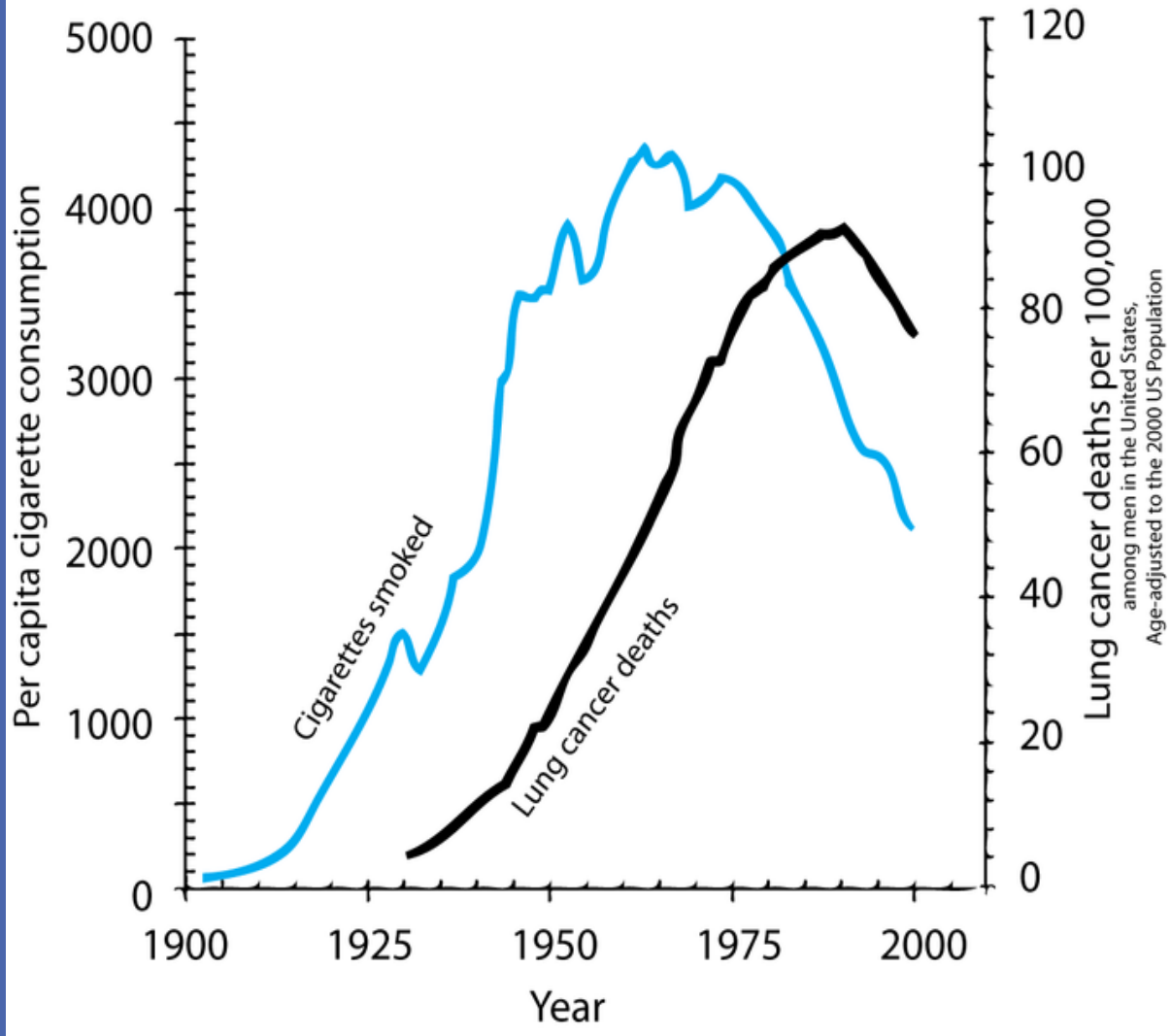
We got proof, kids, that smoking is bad news.

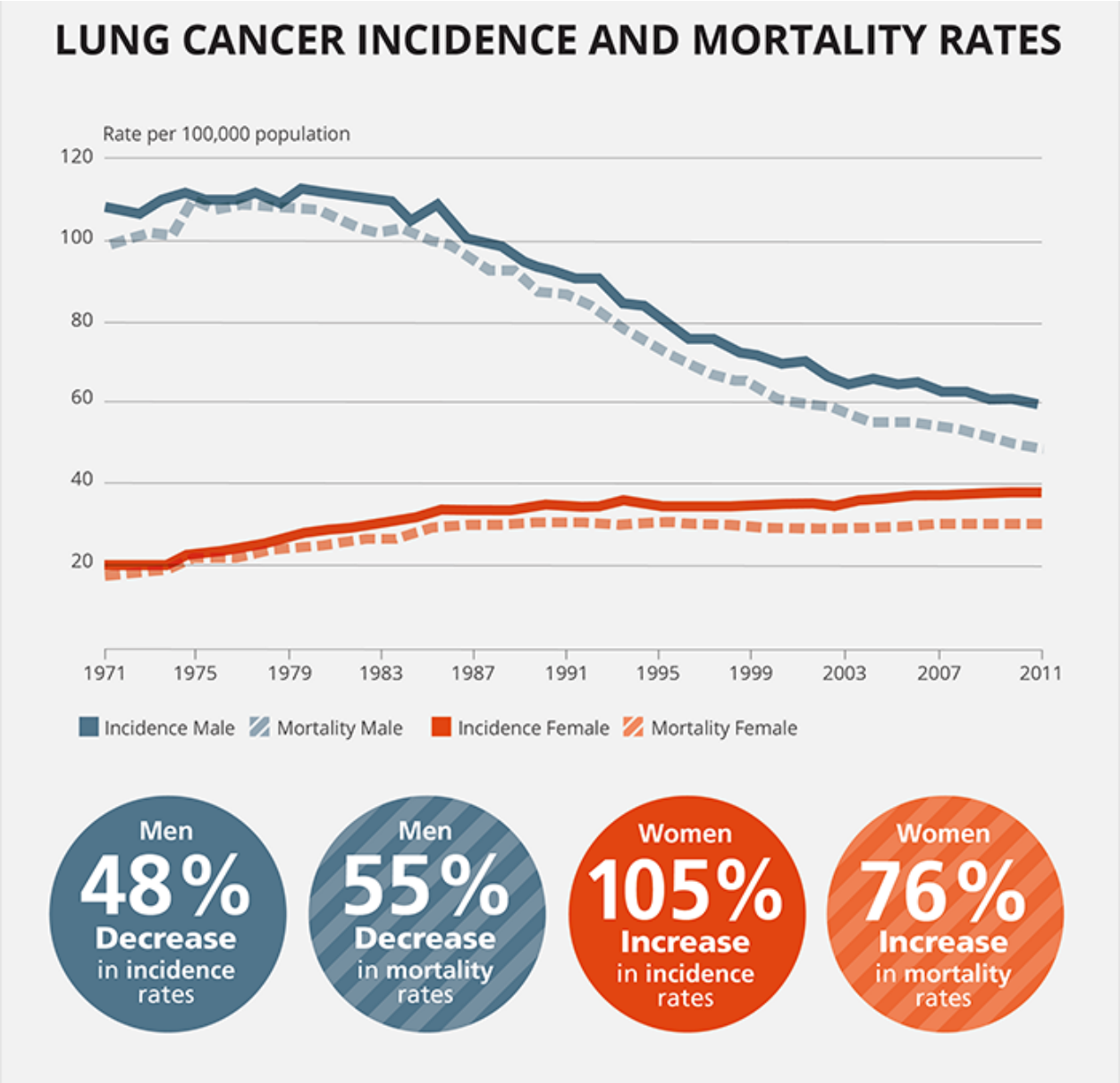
Cigarettes behind cancer and other diseases

The U.S. Surgeon General, on advice from the Centers for Disease Control and Prevention (CDC), announced today that smoking cigarettes can be deadly. Using the science of epidemiology, the CDC studied 7,000 reports and briefed the Surgeon General that smoking can cause cancer and other serious diseases. In his landmark 387-page report, the Surgeon General and his Advisory Committee briefed White House officials in a closed-in meeting at the State Department early Saturday morning.

1965, warning labels on packages

1970, ban on tobacco advertising


Per capita cigarette consumption
5000
4000
3000
2000
1000
0
Cigarettes smoked
Lung cancer deaths
120
100
80
60
40
20
0
Lung cancer deaths per 100,000
among men in the United States,
Age-adjusted to the 2000 US Population
1900
1925
1950
1975
2000
Year


LUNG CANCER INCIDENCE AND MORTALITY RATES
Rate per 100,000 population
120
100
80
60
40
20
1971
1975
1979
1983
1987
1991
1995
1999
2003
2007
2011
Incidence Male
Mortality Male
Incidence Female
Mortality Female
Men
48%
Decrease
in incidence
rates
Men
55%
Decrease
in mortality
rates
Women
105%
Increase
in incidence
rates
Women
76%
Increase
in mortality
rates

The connection between viruses and cancer

- HPV (Human papillomavirus)
- Discovered in 1907
- Linked to cervical cancer in 1976
- Vaccine to prevent infection approved by FDA in 2000

- HBV (Hepatitis virus B)
- Discovered in 1967
- Linked to liver cancer in 1974
- Vaccine prevent hepatitis B and liver cancer since 1984

Chemoprevention

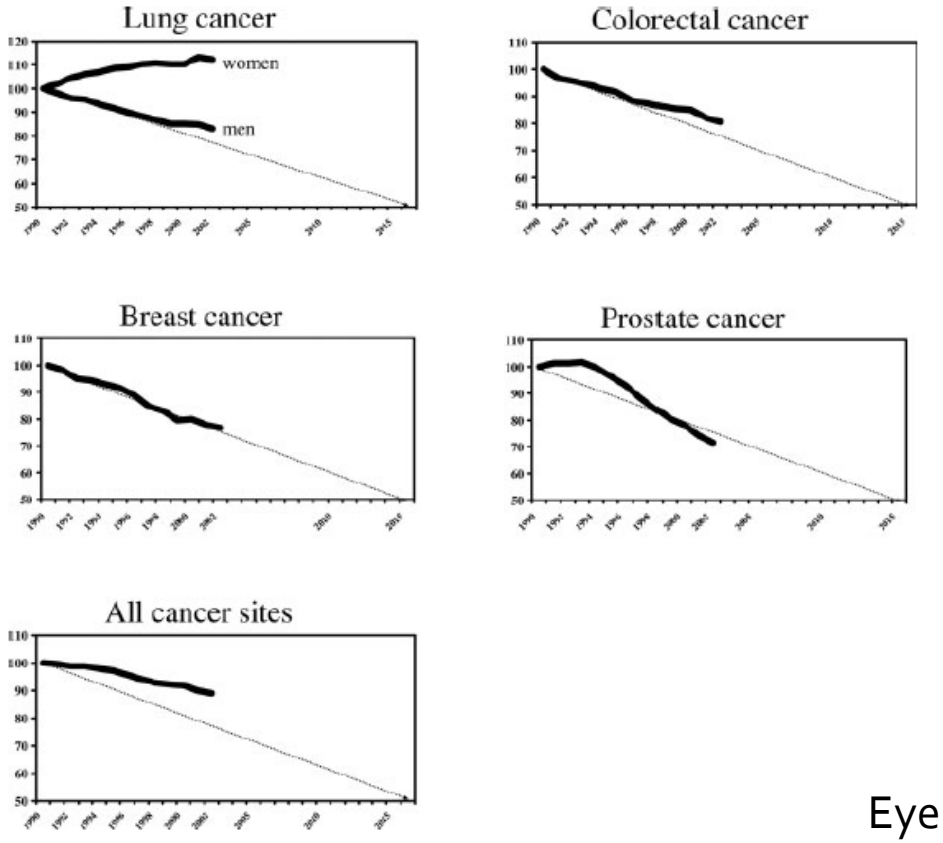
- Antiestrogens
- Finasteride
- Aspirin

- Breast cancer
- Prostate cancer
- Colorectal cancer

Not widely used because large numbers of otherwise normal persons would need to be exposed to potentially toxic materials in order to prevent some cancers.

Survival now and in the future

- 5-yr relative survival rate for all cancer
  - 38% in late 1960s
  - 68% in 2012
  - 80% estimated till 2015,
- Mortality for all cancer
  - Decreased 24% since 1990
  - 38% estimated till 2015



Eyers T et al.
Cancer 2006; 107: 396-405

The Future

- To foresee a time when a person's individual genome can be sequenced for as little as $100 in a routine laboratory test
- To identify genome which has increased risk for developing cancer by comparing normal, premalignant and malignant tissue
- To detect abnormalities and targets for drug therapies
- To convert cancer into curable or chronic disease at least
- To face gratifying or daunting economic and social consequences
- This overview of 200 years of the cancer field provides support for the principle of the value of patience and investment in research!!

Thanks for your attention