Cancer Biology

Lecture 3

Fall 2018

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cancer progression

Normal cells

↓

Hyperplasia

↓

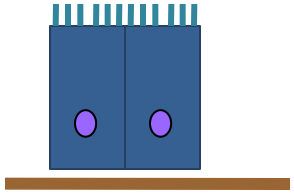
Dysplasia (Metaplasia)

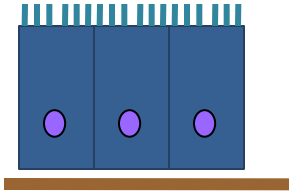
↓

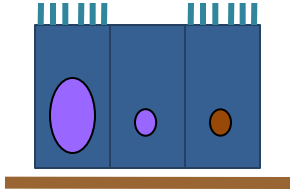
Neoplasia

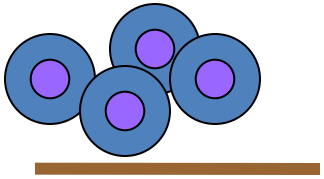
↓

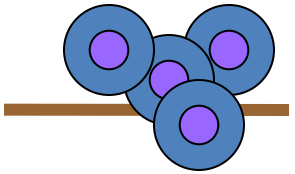
Metastasis











Cancer and environment

Cancer Epidemiology

Population studies

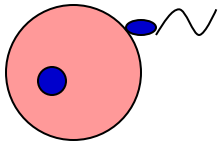
- Some cancers have similar risk/rates in all populations

- Others have very different rates in different populations

→identification of risk factors

1) Genetic
2) Environmental

Accuracy of replication



1 cell → more than 10^{16} cells

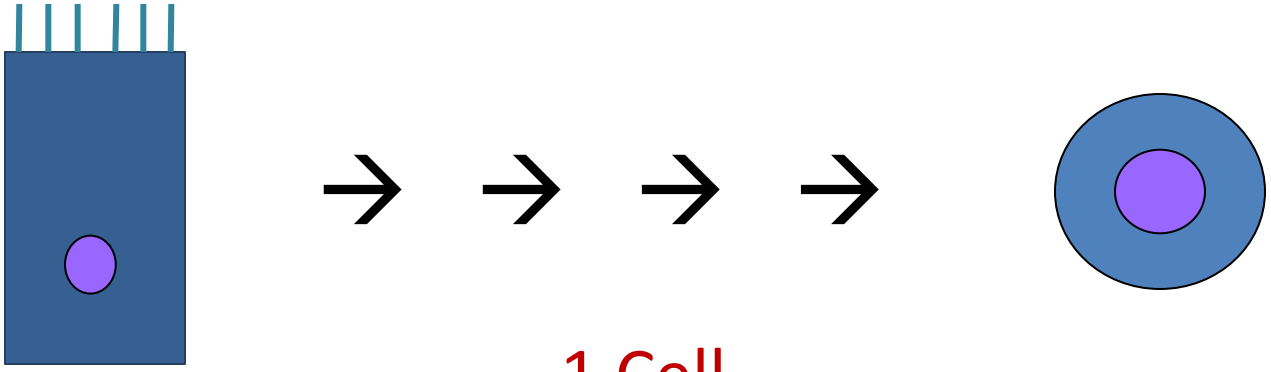
Human genome

= 3×10^9 nucleotides (letters) haploid

6×10^9 diploid

Need to copy ~ 10^{26} letters

Origin of cancer cell



1 Cell

Gene

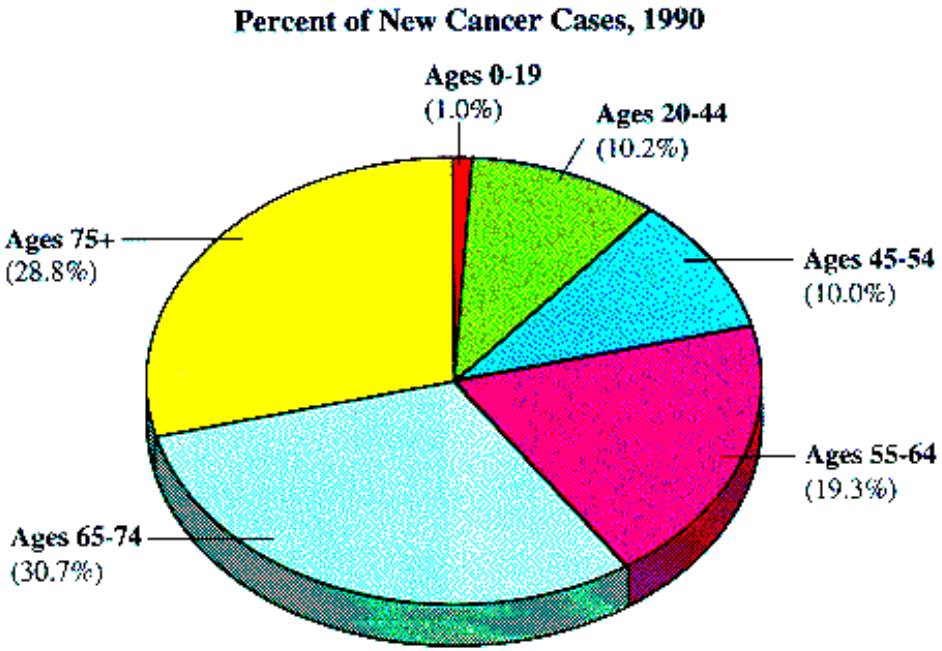
Environment

} Sources of error/damage

Epidemiology of Cancer Based on Age

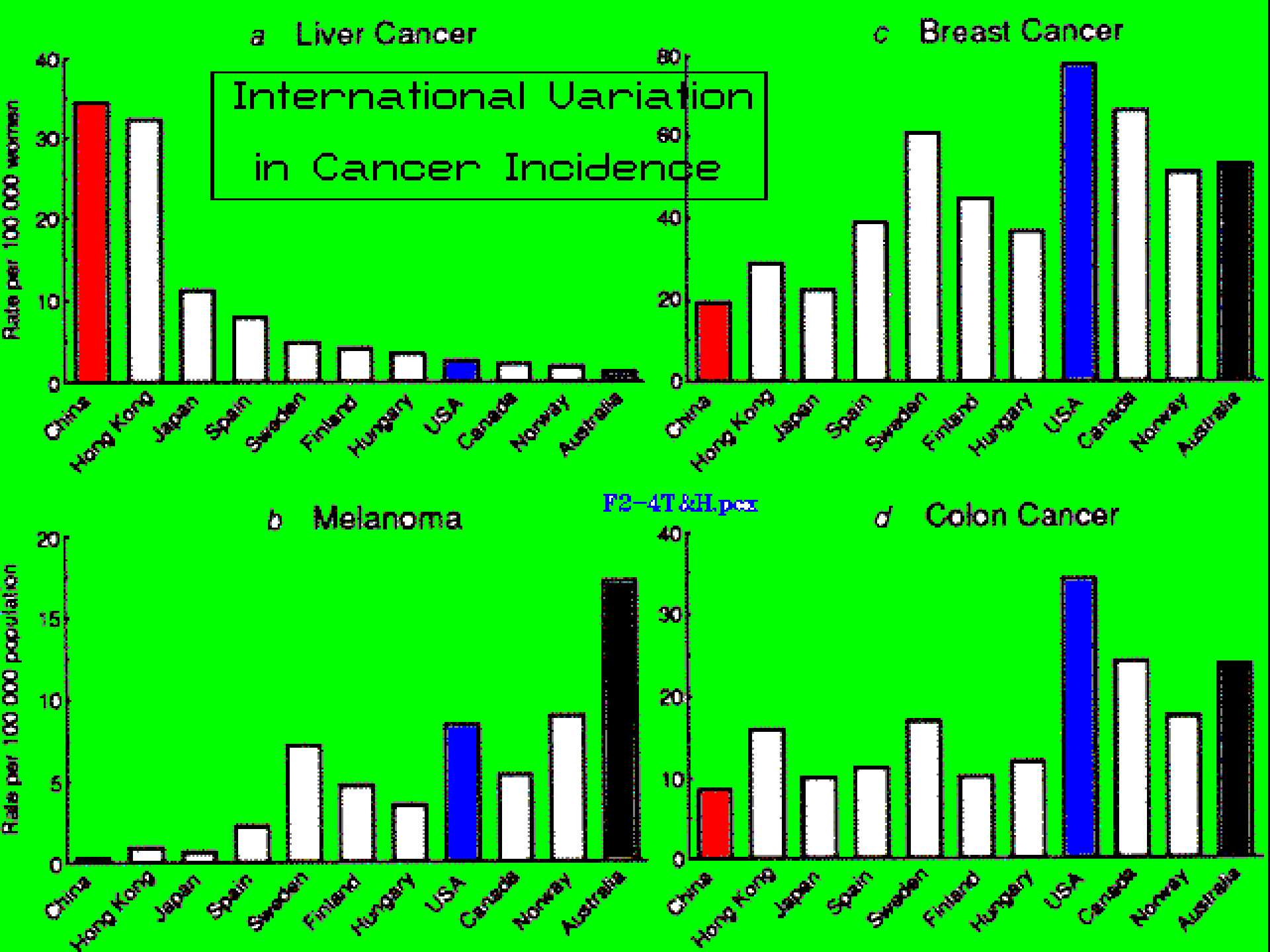
Cancer Incidence by Age

The contrast in cancer incidence by age is striking. Americans aged 65 and older face 10 times the risk of developing cancer compared with those under 65. The near-doubling in the annual number of new cancer cases for all ages – from an estimated 625,000 cases in 1970 to 1,170,000 cases in 1993 – is largely due to the increasing population size and especially the disproportionate increase in the older population.



Breast cancer incidence by age

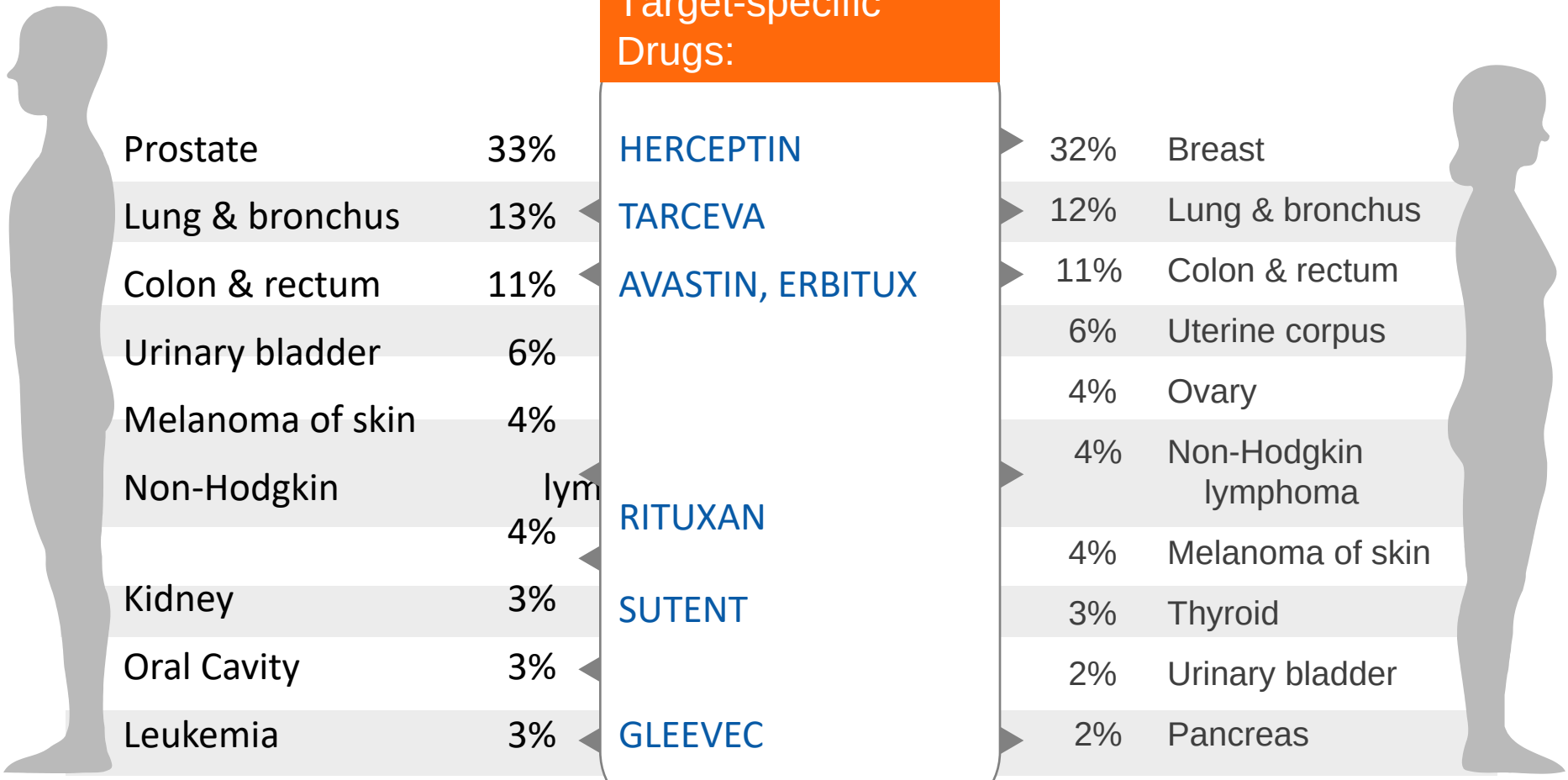
By age 25:	one in 19,608
By age 30:	one in 2,525
By age 35:	one in 622
By age 40:	one in 217
By age 45:	one in 93
By age 50:	one in 50
By age 55:	one in 33
By age 60:	one in 24
By age 65:	one in 17
By age 70:	one in 14
By age 75:	one in 11
By age 80:	one in 10
By age 85:	one in 9
Ever:	one in 8


International Variation
in Cancer Incidence
a Liver Cancer
Rate per 100 000 women
0
10
20
30
40
China
Hong Kong
Japan
Spain
Sweden
Finland
Hungary
USA
Canada
Norway
Australia
c Breast Cancer
0
20
40
60
80
b Melanoma
Rate per 100 000 population
0
5
10
15
20
d Colon Cancer
0
10
20
30
40

Cancer type	Highest rate	Lowest rate	Ration H/L
Skin (Melanoma)	Australia (Queensland)	Japan	**155:1**
Lip	Canada (Newfoundland)	Japan	**151:1**
Nasopharynx	Hong Kong	United Kingdom	**100:1**
Prostate	US (African American)	China	**70:1**
Liver	China (Shanghai)	Canada (Nova Scotia)	**49:1**
Penis	Brazil	Israel (Ashkenaz Jews)	**42:1**
Cervix (Uterus)	Brazil	Israel (Non-Jews)	**28:1**
Stomach	Japan	Kuwait	**22:1**

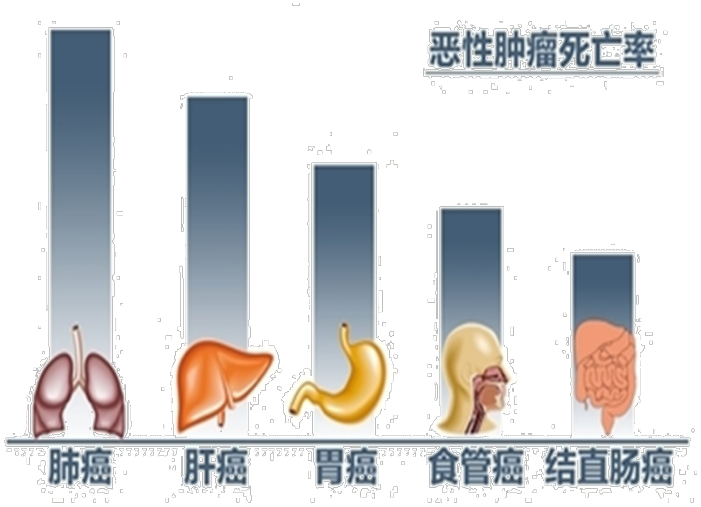
Age adjusted death rate at 60 from a certain type of cancer. (Muir et al 1987)

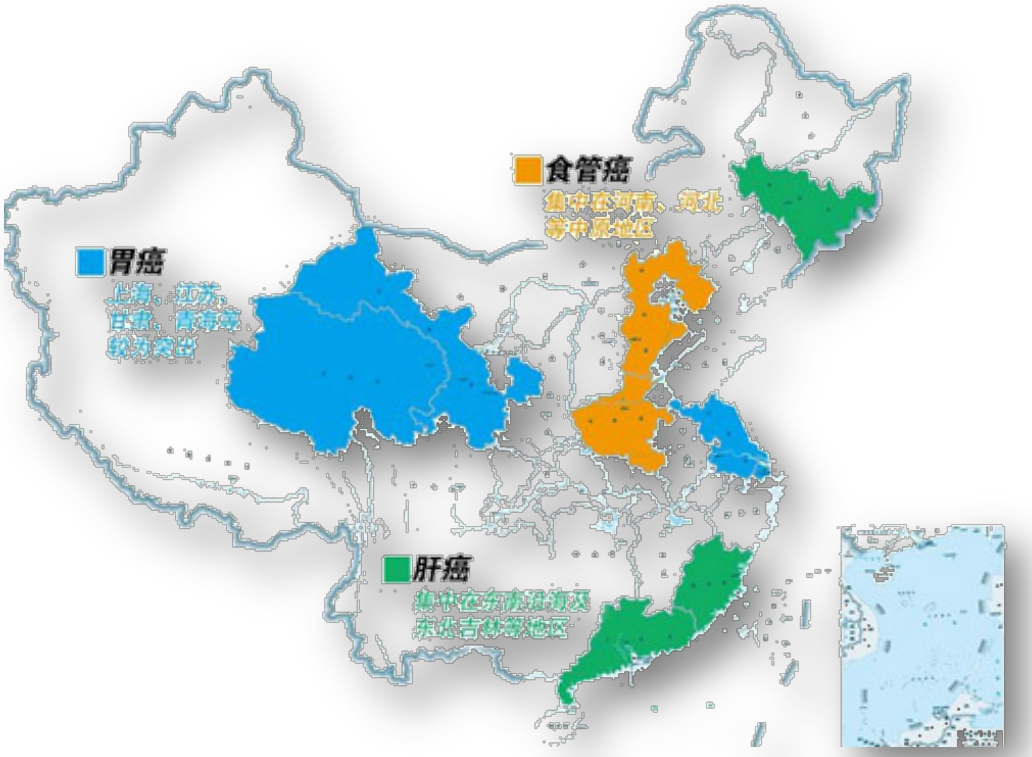
Knowing Cancer Origin Informs Therapy



Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2004.

更令人关注的是，2012年中国新增癌症病例高居世界第一位，肝癌和食管癌患者约占全球一半，死亡分别占全球的51%和49%；胃癌症例和死亡均占全球40%；鼻咽癌80%发生在中国。





全国肿瘤登记中心发布的《2012中国肿瘤登记年报》

全国肿瘤登记中心发布的《2012 中国肿瘤登记年报》显示，

我国每年新发肿瘤病例约为

$$\frac{3120000\text{例}}{365\text{天}} \approx 8550\text{例/天}$$

每分钟有6人被诊断为癌症，

有5人死于癌症，

其中，肺癌、胃癌、肝癌成为发病与死亡率最高的癌症，而乳腺癌、结直肠癌、宫颈癌使女性健康受到威胁，这些高发癌症与不健康的生活方式息息相关。

肺癌
lung cancer

高发地区

黑龙江、吉林、辽宁、云南

东北和云南的矿产业比较集中，严重污染的空气让大量致癌物质侵蚀人们的肺部，诱发癌症。

诱发肺癌的罪魁祸首：吸烟

10个死于肺癌的患者

9个是烟民

除了主动吸烟的人，受害更深的是那些经常被迫吸“二手烟”的人，他们发生肺癌的几率也相对较高。

而日益恶劣的环境因素，如尾气、阴霾天、工业污染等因素，拉近了人们与肺癌间的距离。

专家支招

- 公共场所要全面禁烟
- 45 岁以上有吸烟史的人每年做 1 次体检
- 通过肺部低剂量螺旋 CT 筛查出早期肺癌

肝癌

Liver cancer

高发地区

浙江、广西、江苏等沿海地区，内蒙古、吉林

从肝癌的地区分布特点来看，华东、华南和东北明显高于西北、西南和华北，沿海高于内地。

诱发肝癌的罪魁祸首：

病毒性肝炎和黄曲霉素

这些沿海等高发地区同时符合这两个条件：

① 沿海地区气候炎热、潮湿，为致癌物黄曲霉素的滋生创造了条件，增加了患肝癌的风险。

② 沿海地区病毒性肝炎的感染率相对较高。

此外对于东北来说，爱喝酒是导致肝癌的一个重要诱因，长期饮酒会使肝细胞反复发生脂肪变性、坏死和再生，导致肝硬化，最终转化为肝癌，而由肝硬化转化成肝癌的比例高达70%。

专家支招

由于肝癌发病的特定性，预防肝癌要从以下3方面做起

- 接种肝炎疫苗
- 少饮用沟塘水
- 以深井水和自来水替代
- 改变饮食习惯，少喝酒，不吃霉变食物，如花生、玉米等。

宫颈癌

Cervical cancer

高发地区

内蒙古、 山西、陕西、湖北、湖南、江西

中国目前每年新发宫颈癌病例有10万人，占全球病例的1/5

我国宫颈癌高发区主要集中在中西部地区，农村略高于城市。宫颈癌发病高低与生活水平、卫生和受教育程度相关。

最大病因：人乳头瘤病毒（HPV）感染

诱发宫颈癌的罪魁祸首：

- 过早开始性生活
- 多个性伴侣
- 经期不注意卫生
- 性传播疾病导致的宫颈炎症对宫颈的长期刺激
- 吸烟
- 长期口服避孕药等。

专家支招

预防宫颈癌最有效的方法是

- 接种宫颈癌疫苗
- 防止不洁性行为
- 积极治疗慢性宫颈疾病。

食管癌

Esophageal cancer

高发地区

河南、河北、山西

诱发食管癌的罪魁祸首：

遗传 & 饮食等因素

但饮食因素是可控的。长期吃得过快、过粗、过烫或饮酒，都可能反复灼伤或损伤食管黏膜，从而诱发癌变。

诱发食管癌的罪魁祸首：

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专家支招

- 有家族史的人要定期体检
- 食物温度要在 40 度以下。

胃癌

Gastric cancer

高发地区

辽宁、山东、甘肃、江苏、福建

胃癌早期症状不明显，七成患者确诊时已经到了中晚期，这也是其死亡率居高不下的一个原因。

在胃癌的发病群体中，中年男性是“主力”。

诱发胃癌的罪魁祸首：

- 暴饮暴食
- 饮酒过度
- 饮食习惯

爱吃高盐、腌制的食品，特别是没腌透的食品，其中含有较高的致癌物亚硝酸盐。

专家支招

- 预防胃癌要多吃绿、黄色蔬菜
- 少吃咸、腌、干硬、发霉的食物
- 限酒
- 40 岁以上的男性、有家族史、慢性胃病史，并合并幽门螺杆菌感染的人，应定期去检查。

结直肠癌

Colorectal cancer

高发地区

辽宁、山东、甘肃、江苏、福建

近两年，浙江、上海、江苏等省市的结直肠癌（大肠癌）发病率增速已远超西方国家。

诱发结直肠癌癌的罪魁祸首：

- 常年高脂肪饮食
- 缺少膳食纤维摄入
- 久坐少动
- 不按时排便等不良生活习惯

专家支招

- 控制饮食
- 少吃油炸、煎炸、腌制食品
- 适量增加运动量
- 促进肠道蠕动
- 养成定时排便的习惯
- 多吃粗粮、果蔬等富含纤维素的食物。

另外，即便得了结直肠癌，如果能在病变早期就发现它，通过手术等方式治疗，几乎不会影响寿命。

乳腺癌

Breast cancer

高发地区

所有城市

我国女性乳腺癌发病的平均年龄为 48.7 岁，比西方国家提早了 10 年。在女性高发癌症中，乳腺癌已经超越过去的肺癌成为第一。

城市女性之所以容易得乳腺癌，

诱发乳腺癌的罪魁祸首：

- 与长期工作压力大
- 生活不规律
- 晚婚晚育
- 频繁吃避孕药
- 久坐不动
- 缺少锻炼有关

专家支招

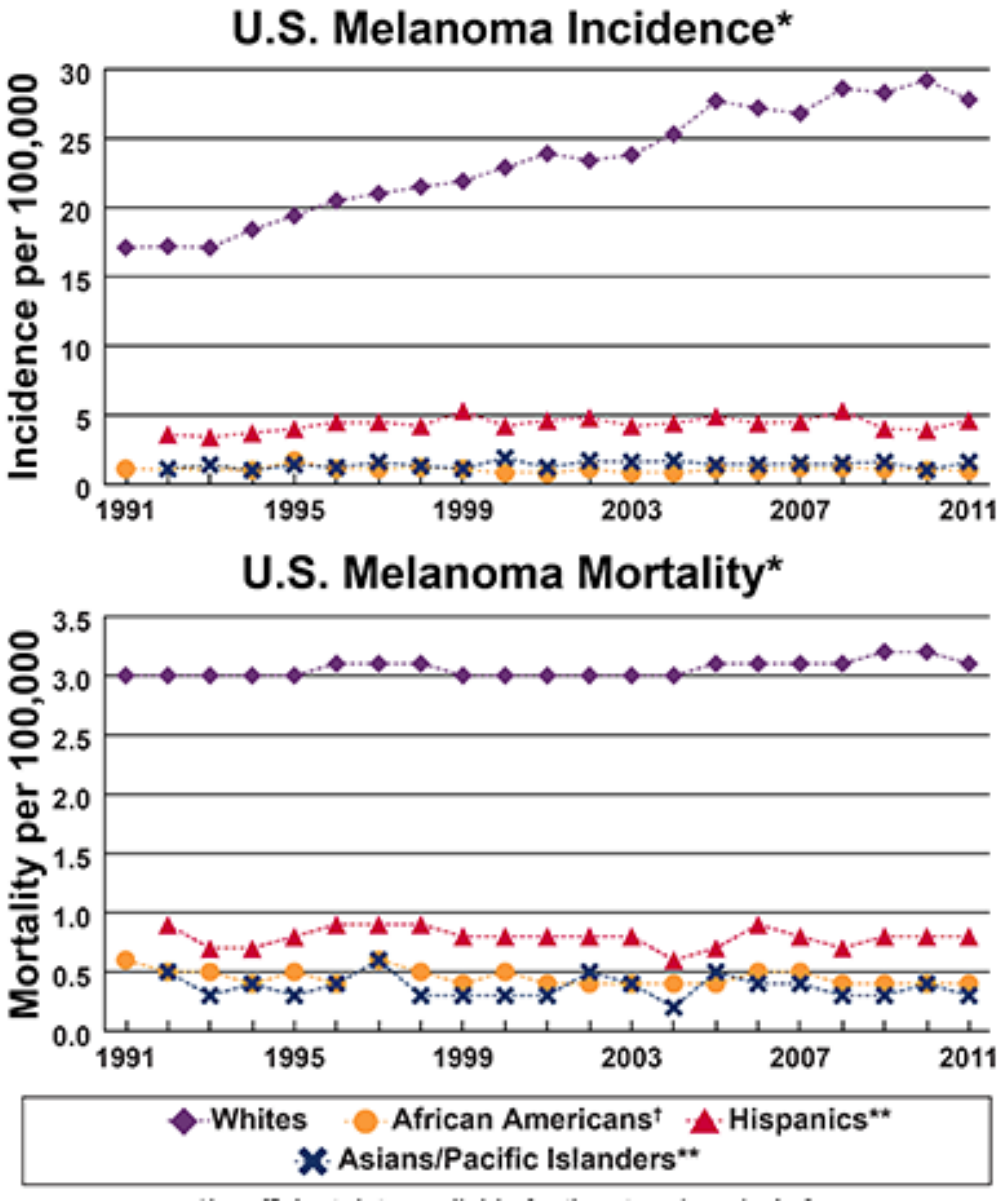
- 化妆品、洗涤剂、塑料用品等要慎用
- 女性最好要哺乳
- 有乳癌家族史、40 岁以上未孕、过度肥胖的女性应定期体检和早期筛查。

Epidemiological Data can also sometimes provide clues about the biological mechanisms underlying certain types of cancers.

Malignant Melanoma
(Solar radiation exposure)

Burkitt's Lymphoma
(Co-infection with virus transmitted by mosquitos also transmitting malaria)

Trends in melanoma incidence in the U.S.



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Malignant Melanoma
(Solar radiation exposure)

Burkitt's Lymphoma
(Co-infection with virus transmitted by mosquitos also transmitting malaria)

Incidence of Burkitt's Lymphoma in Relation to Infectious Disease Etiology: Aedes simpsoni mosquito transmission vector for malaria and Epstein Barr Virus co-infection

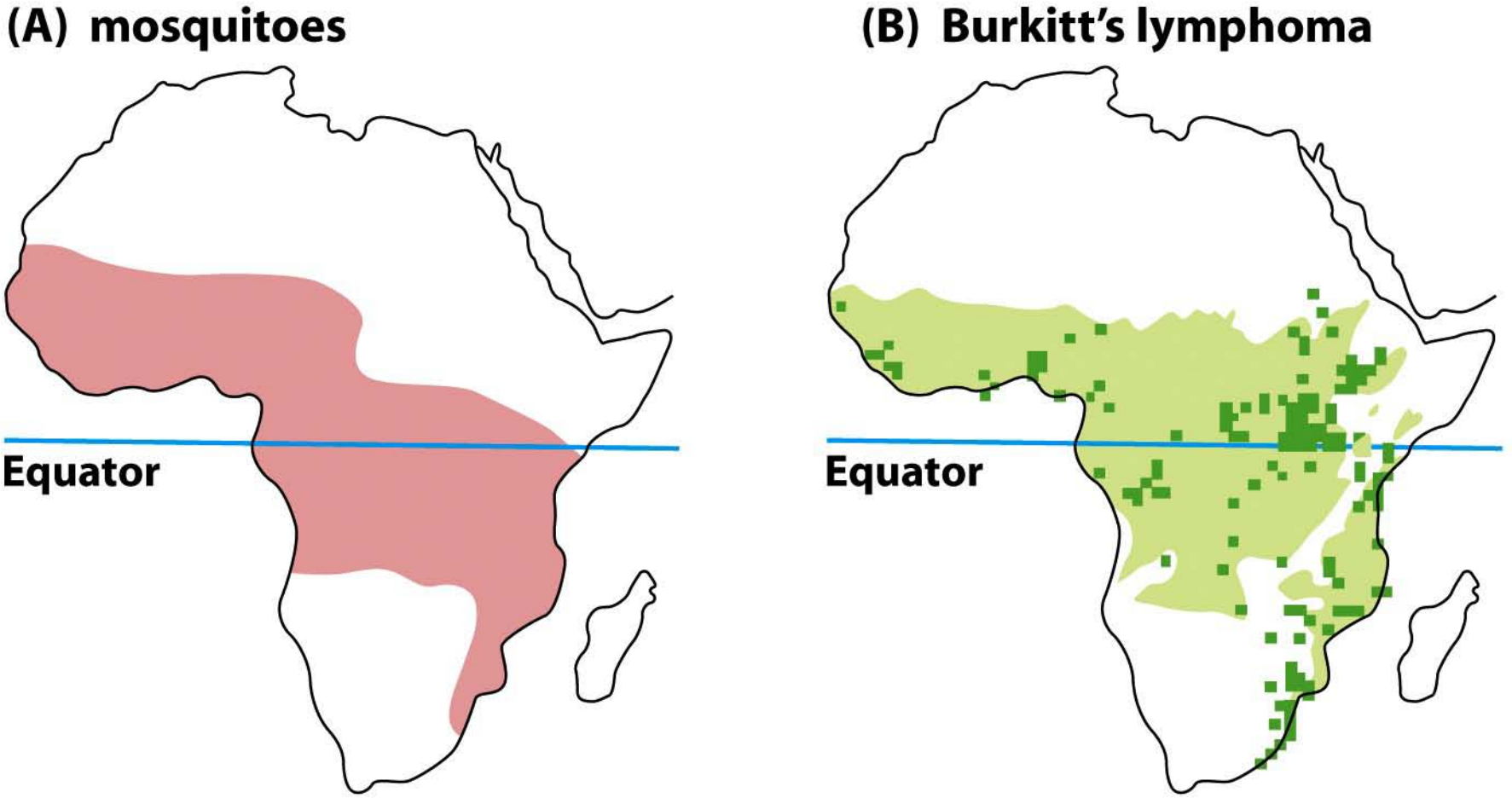


Figure 4.12 *The Biology of Cancer* (© Garland Science 2007)

Examples of environmental risk factors

- Lung cancer: 31% males, 25% females
- **1st** cancer death
  - Doll and Hill, 1950
  - Most recent number of cigarettes smoked per day before the onset of lung cancer

Cigarettes /day	0	1-4	5-14	15-24	25 or more
Life time risk	1x	**8x**	**12x**	**14x**	**27x**

Cancer risk: Gene vs. Environment

Japanese
immigrants in US

Japanese in Japan

stomach cancer
colon cancer

1st Generation

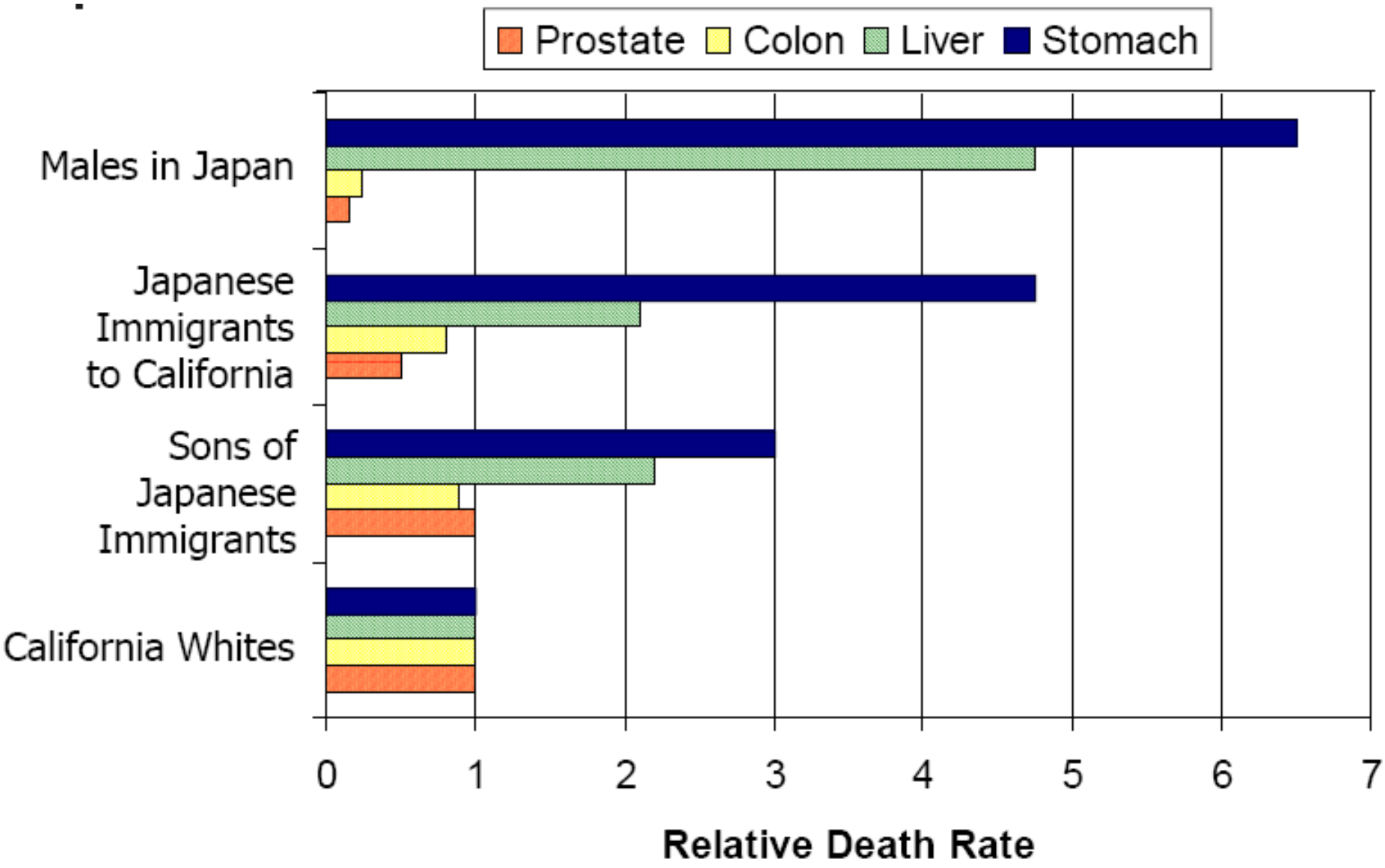
2nd Generateion

?

Caucasian in US

stomach cancer
colon cancer

Migration and cancer rate



Cancer risk: Gene vs. Environment

Japanese in Japan

stomach cancer

colon cancer

Japanese immigrants in US

1st Generation

2nd Generateion

Caucasian in US

stomach cancer

colon cancer

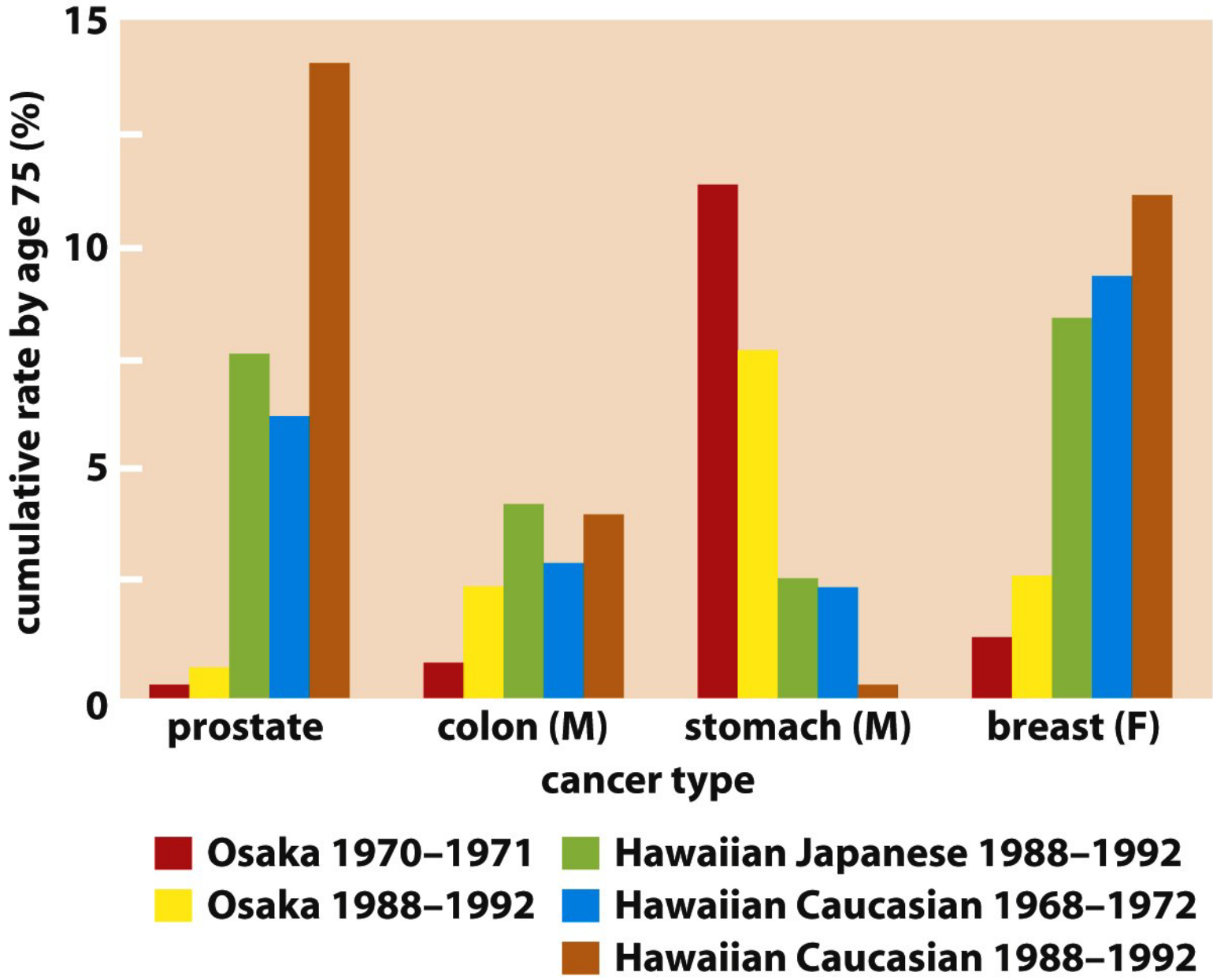


Figure 2.20 *The Biology of Cancer* (© Garland Science 2007)

Introduction

- What is cancer?
- **What causes cancer?**
  - **Chemicals**
  - **Virus**
- How do we deal with cancer?

Carcinogen

- 1775: chimney sweep and scrotal (阴囊）carcinoma.

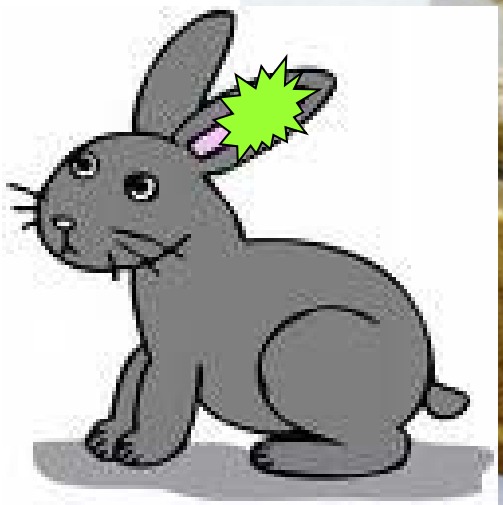
Sir Percivall Pott (1714-1788)

Carcinogen test

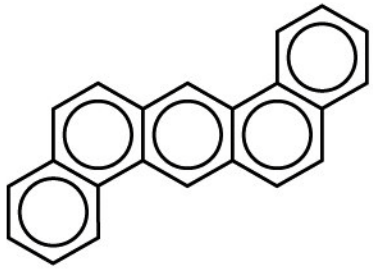
Katsusaburo Yamagiwa, 1915
Japan

660 days
Coal Tar
(焦油)

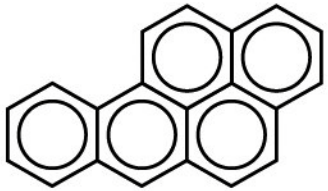
Skin
carcinoma



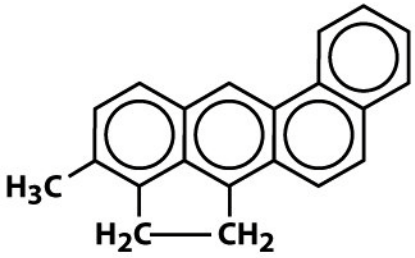
Carcinogens in tar



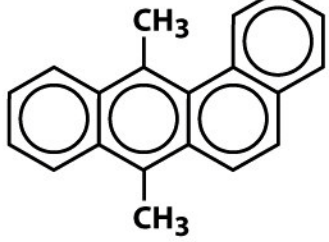
dibenz[*a*,*h*]anthracene



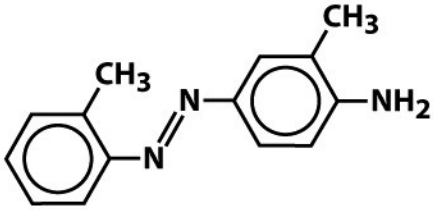
benzo[*a*]pyrene



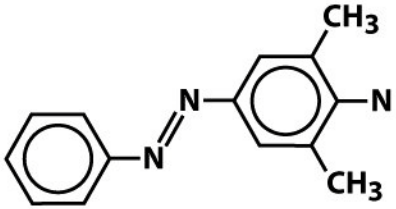
3-methylcholanthrene



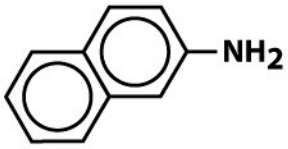
7,12-dimethylbenz[*a*]-anthracene



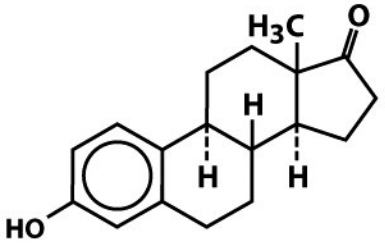
2·,3-dimethyl-4-amino-azobenzene



N,*N*-dimethyl-4-amino-azobenzene



2-naphthylamine



estrone

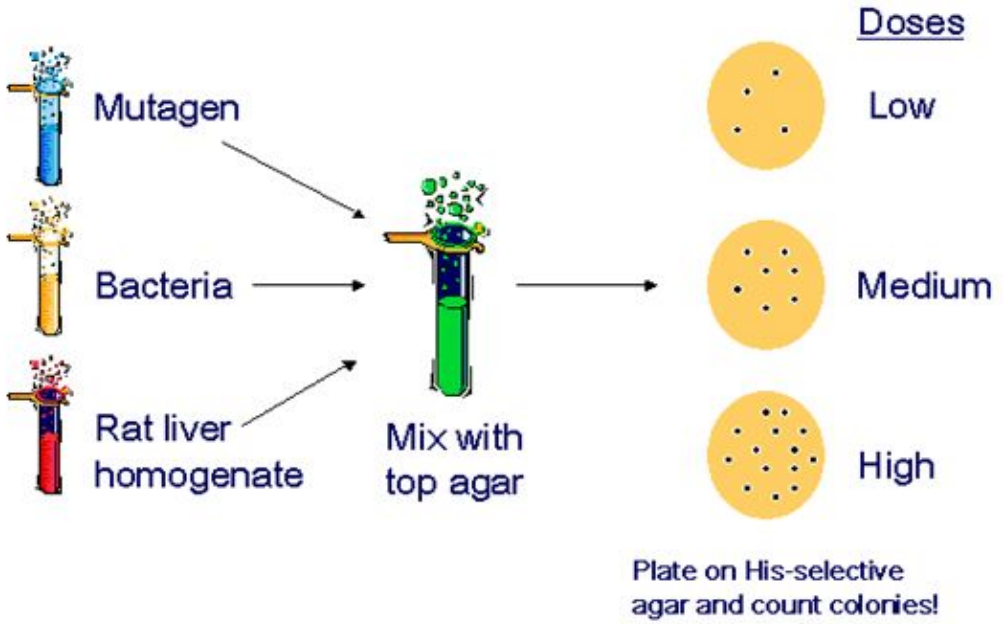
Figure 2-22 The Biology of Cancer (© Garland Science 2007)

How to test for carcinogens?

How do we know if a Compound is Carcinogenic?

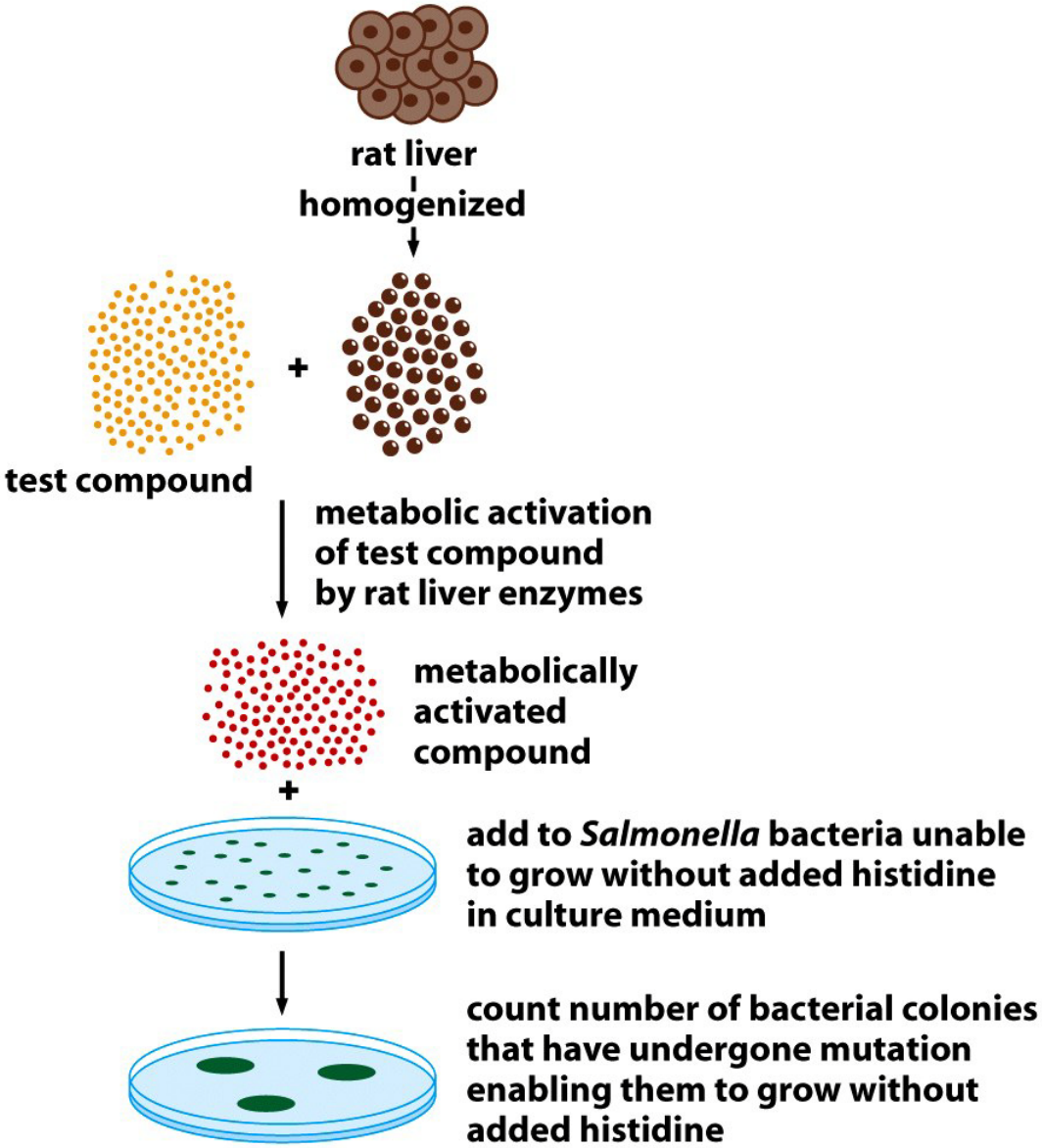
- Epidemiology: do the study of correlation, incidence of cancer and exposure to the compound
- Animal testing: does the same compound give similar cancer?
- Ames test
  - Short-term assay for mutagenicity
  - Test compound for ability to induce reversion in *Salmonella typhimurium* strains
  - $his^- \rightarrow his^+$; base substitution or frameshift
  - Liver microsomal extracts used for activation
  - Senstive, fast, inexpensive

The Standard Ames Assay



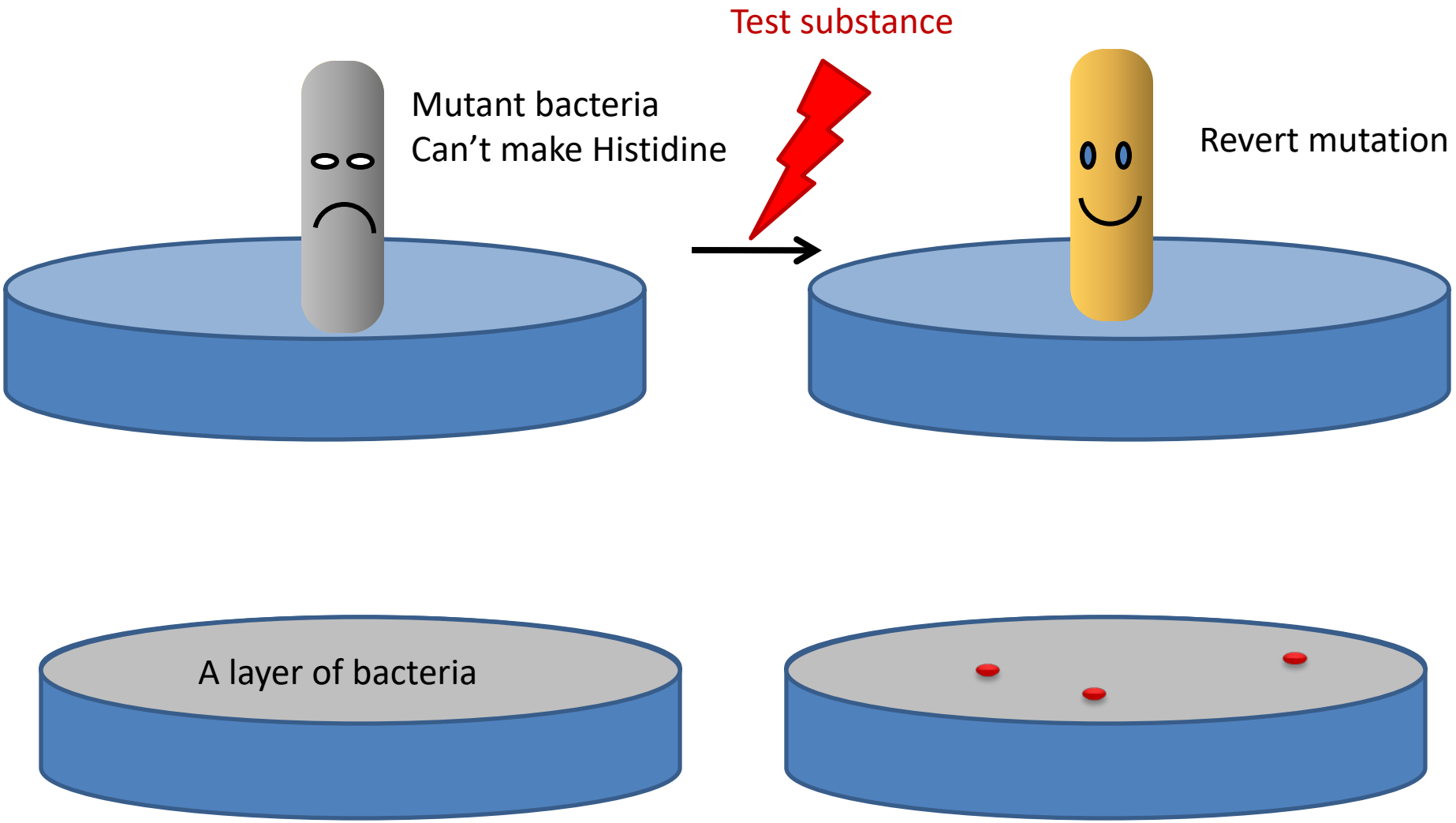
Prof. Dr. Bruce Ames
DoB 16th Dec, 1928
Biochem Mol Biol
UC Berkeley, USA

Ames test: Metabolic activation



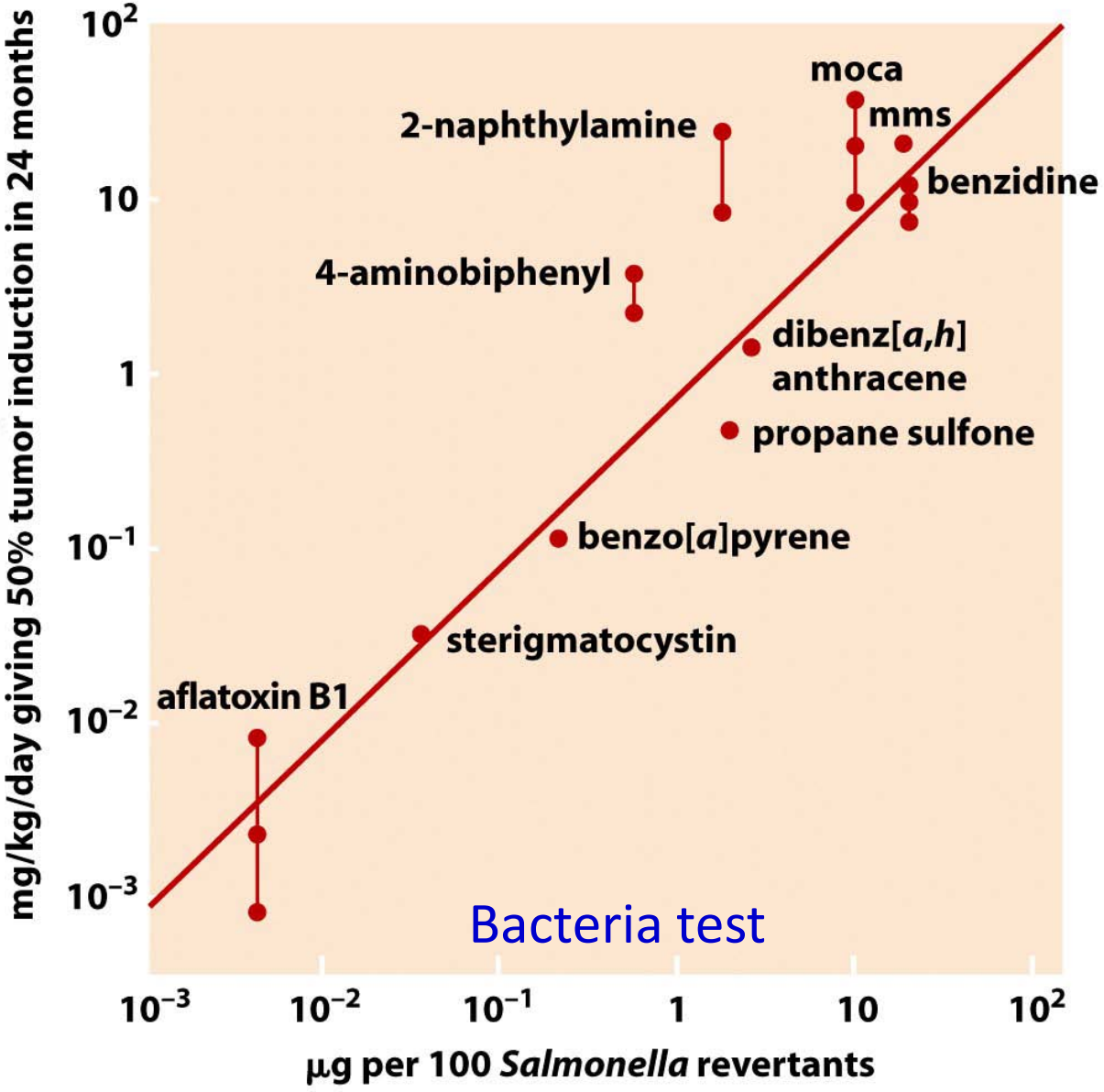
Ames Test

(1970s by Bruce Ames)

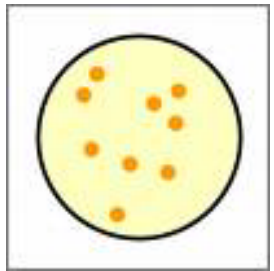


Mutagen ~ Carcinogen

黄曲霉毒素



Bacteria test



Limitation of tests

	In vitro Ames test	*In vivo* Animal model	**Epidemiology study**
Tobacco smoke			
Asbestos 石棉			
Saccharin 糖精			
Phenobarbital 催眠药			
Isoniazid 抗结核药			

Chemical Carcinogen Models

- **1775- Sir Percival Pott,** a London surgeon, noticed that chimney sweepers frequently developed a peculiar form of scrotal cancer. He ascribed it to frequent, direct contact with coal tar. This launched 125 years of research in to the chemical basis of cancer.
- **Treatment of mice with carcinogens** is the basis of numerous mouse models of cancer.

Skin –	7,12-dimethylbenz[α]anthracene (DMBA) + 2-O-tetradecanoylphorbol-13-acetate (TPA)
Lung –	Nitrosamines
Liver –	vinyl chloride
Breast –	N-Nitroso-N-methylurea (NMU)
Colon –	dimethylhydrazine (DMH) Nitrosamines
Bladder –	Aromatic Amines

DMBA/TPA

Br J Dermatol 149(5):960-967, 2003

Cancer News

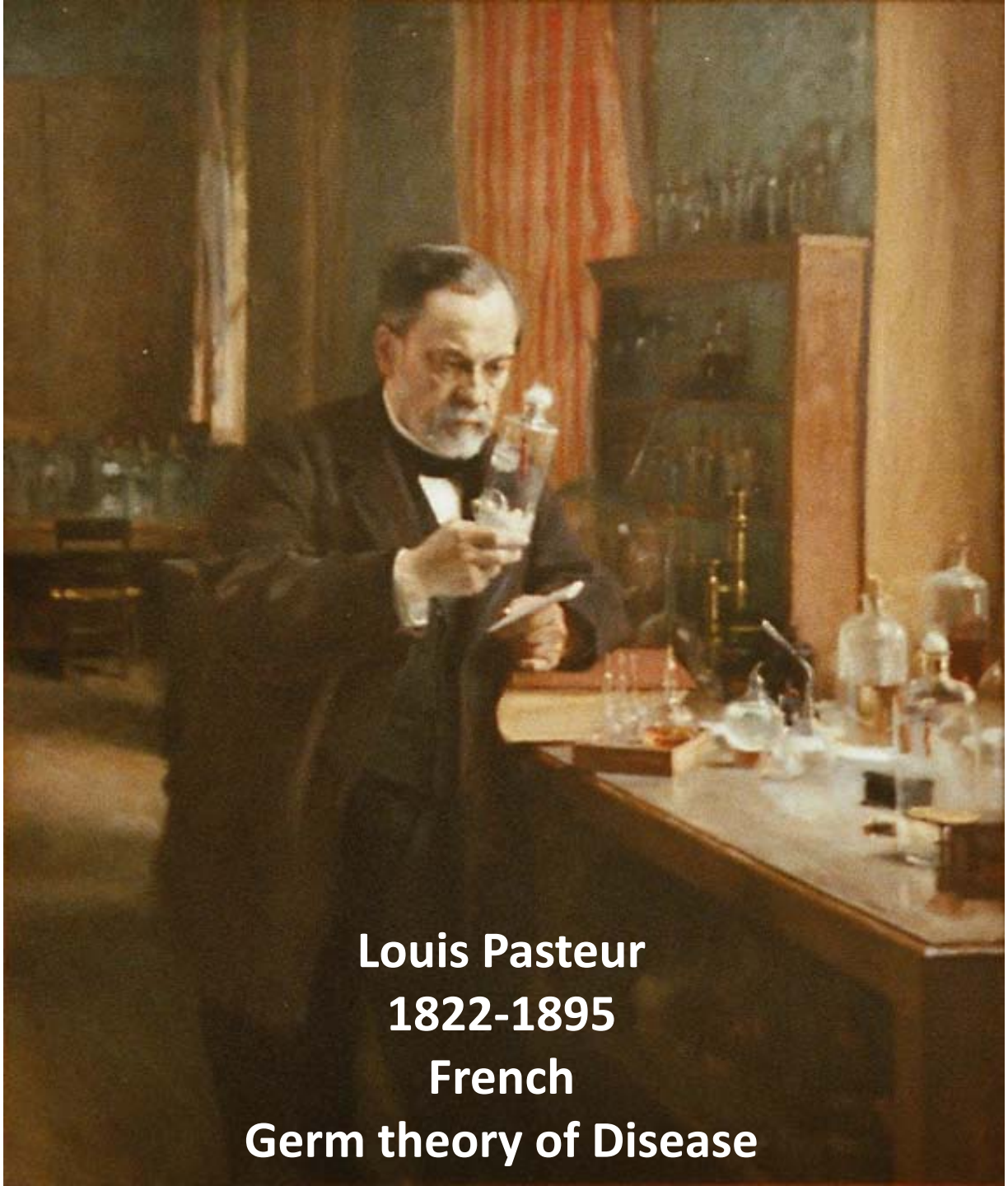
Why the discrepancy?

- Model system (Bacteria, rabbit) ≠ Human
- Dose
- Indirect Mechanism:

    Asbestos → Lung damage → Inflammation

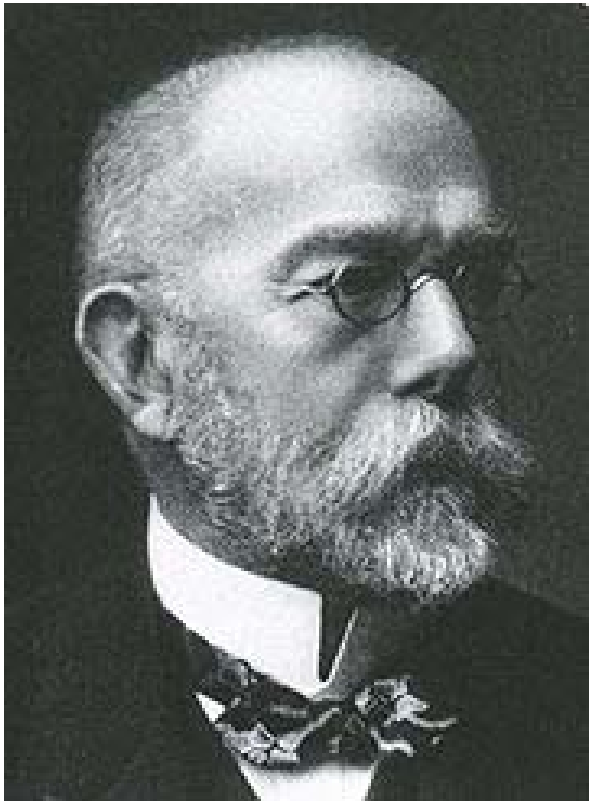
Introduction

- What is cancer?
  - Normal cells go bad.
- What causes cancer?
  - Carcinogens
  - **Infection?**
- How do we deal with cancer?



Louis Pasteur
1822-1895
French
Germ theory of Disease

Disease and infection



Robert Koch (1843 –1910)
German physician

- Isolated

  anthrax (炭疽菌),
  tuberculosis (结核）, cholera（霍乱）

- Koch Postulates:

  Germs → Diseases

1905

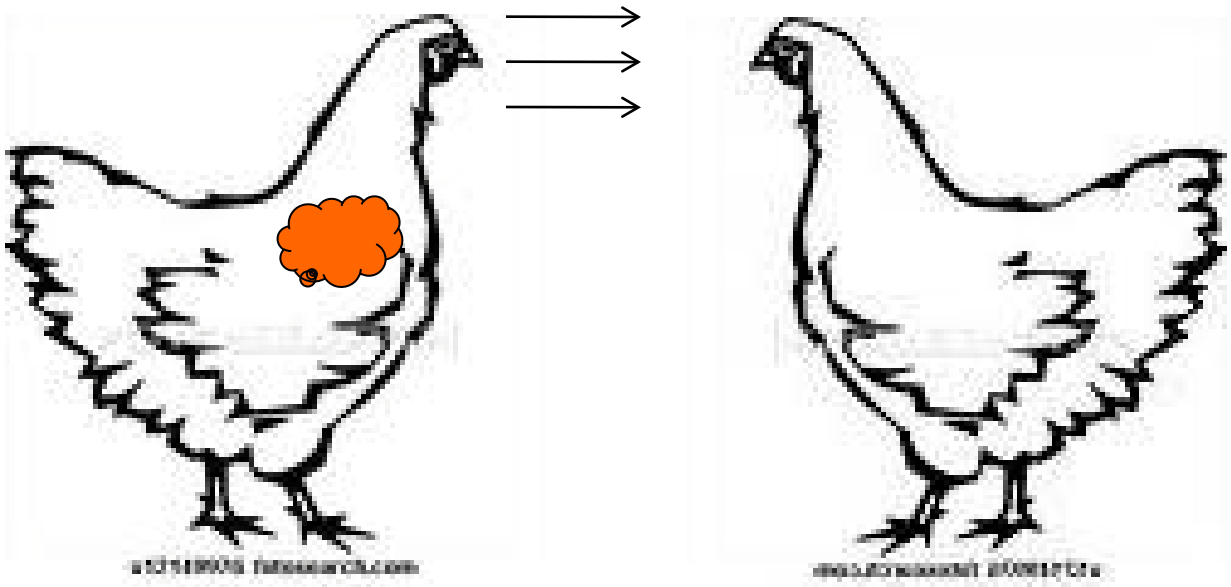
Cancer and infection

Chicken tumor

- 1909 Peyton Rous , Long island, New York
- A farmer with sick chicken

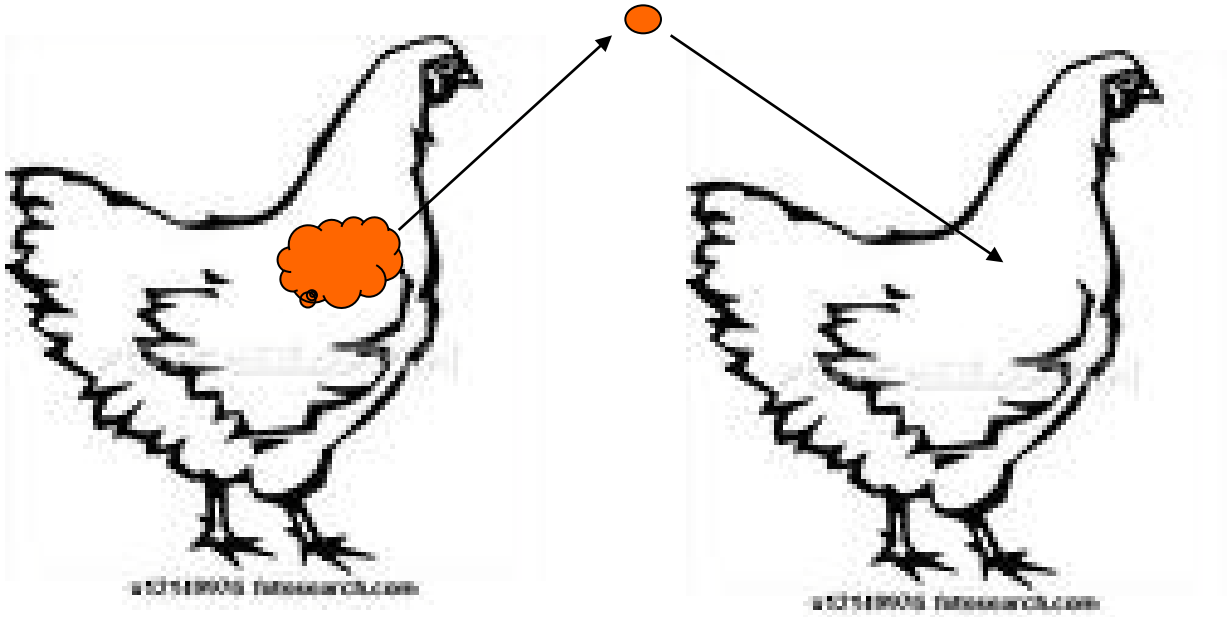
1879-1970

Rous experiment #1



Conclusion ?

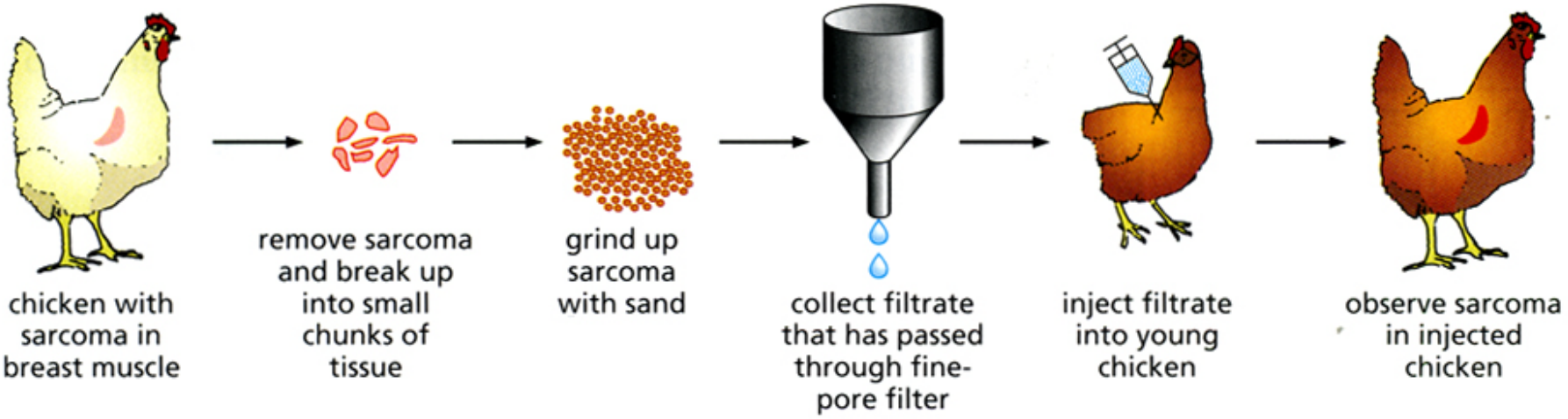
Rous experiment #2



Conclusion ?

NEXT ?

Rous experiment #3



Conclusion:

1. Tumor develops in a few weeks→good model for research

2. It can be passed again and again→ Something alive

3. It is very small→ Virus (Rous Sarcoma Virus: RSV)

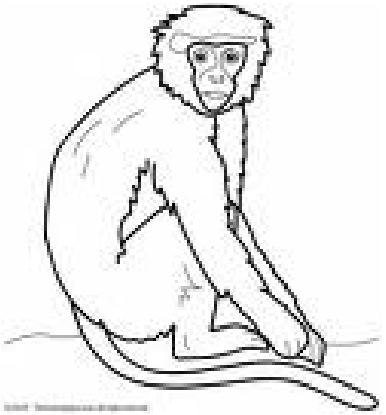
Victory of infectious theory

- 1911 Rabbit virus→ Myxomas 黏液瘤
- Rous and Collaborators: （1930-1970）
  2 more chicken viruses→ papilloma

Rous sarcoma virus, now known to be a retrovirus

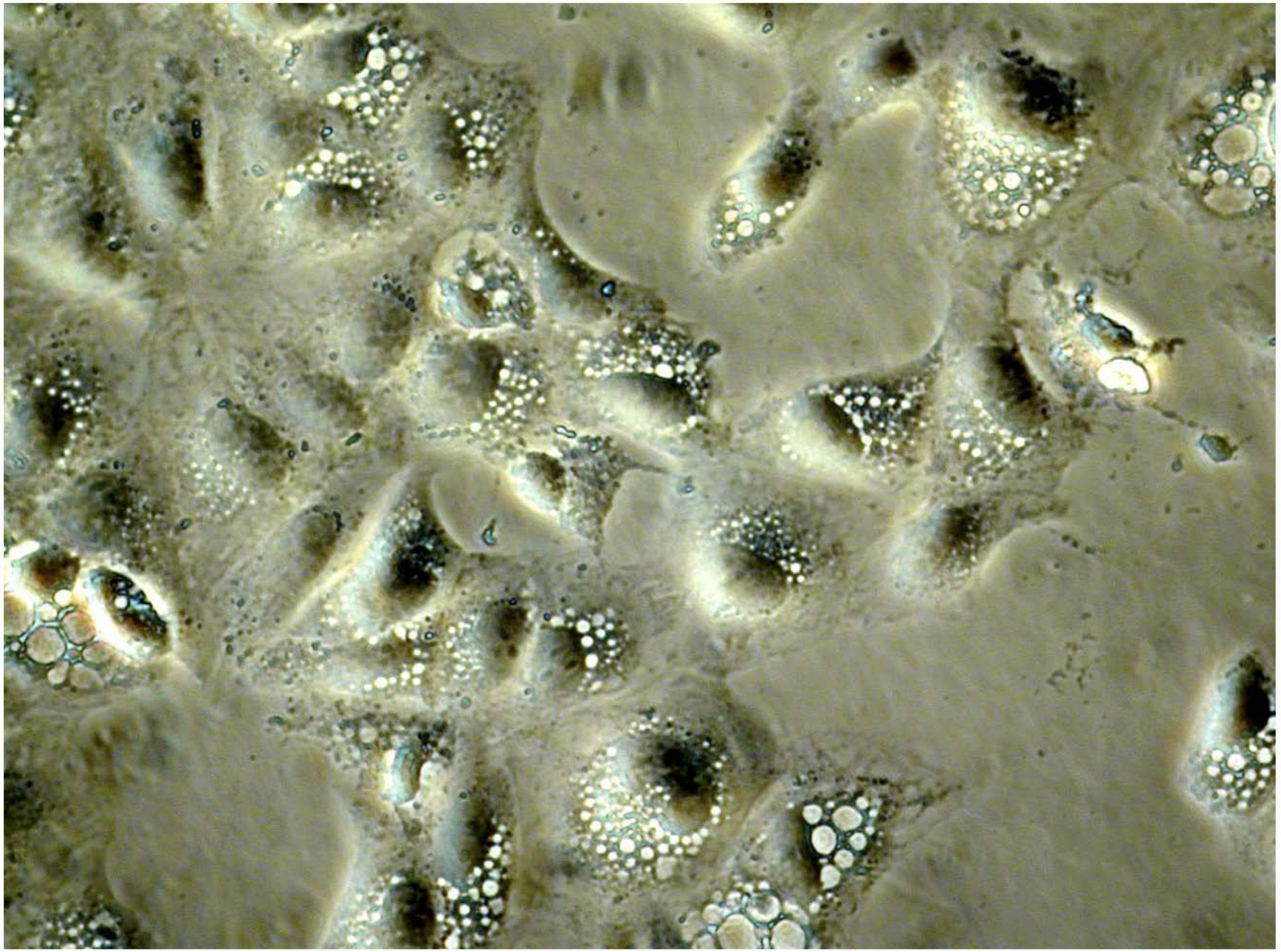
Cancer = Infectious disease

SV40 virus

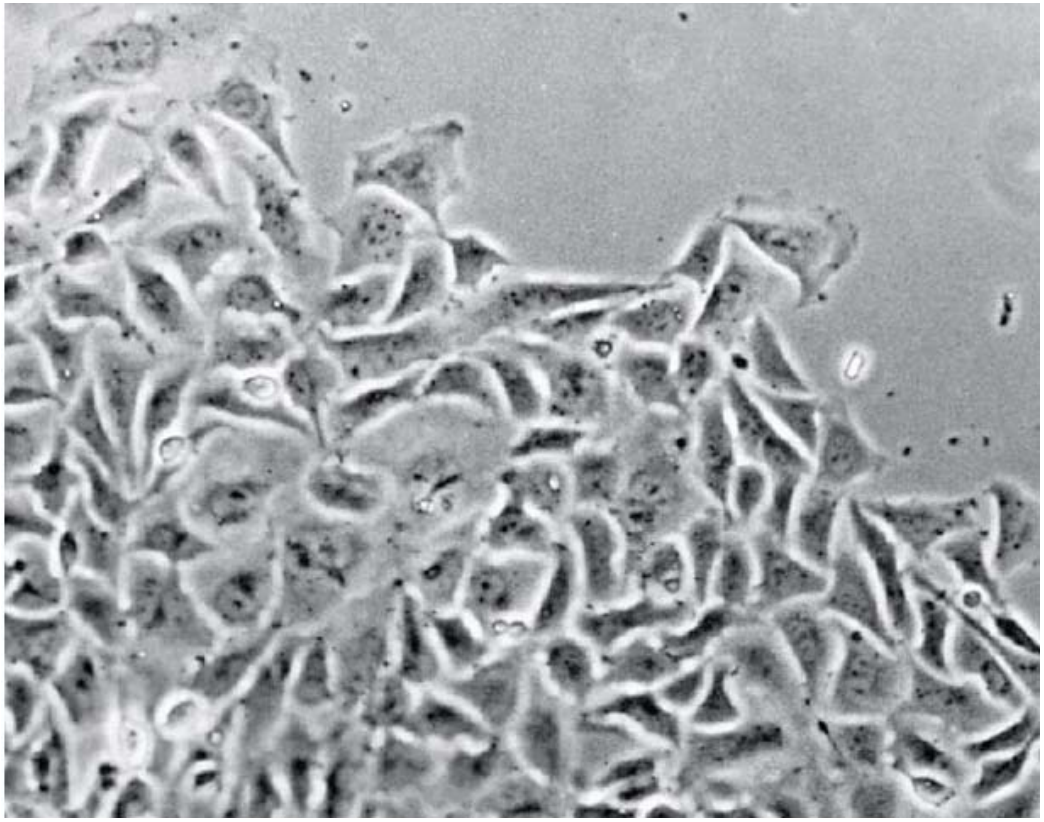


- Monkey cell lines → replicate → Kill cells
- Lytic life cycle

SV40 infected monkey cells



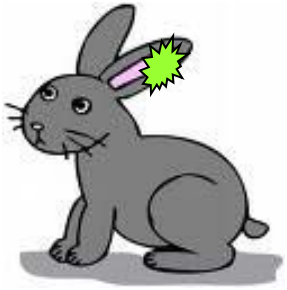
Chicken embryonic fibroblasts



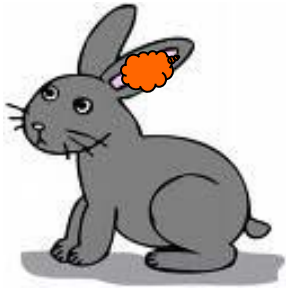
+ RSV

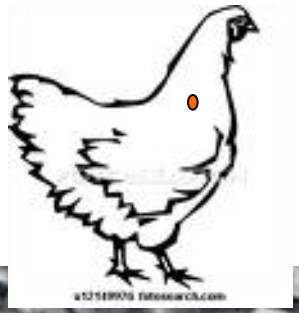
→ **Cells survive !**

A new study system

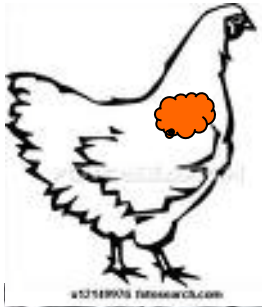


1. Months,years



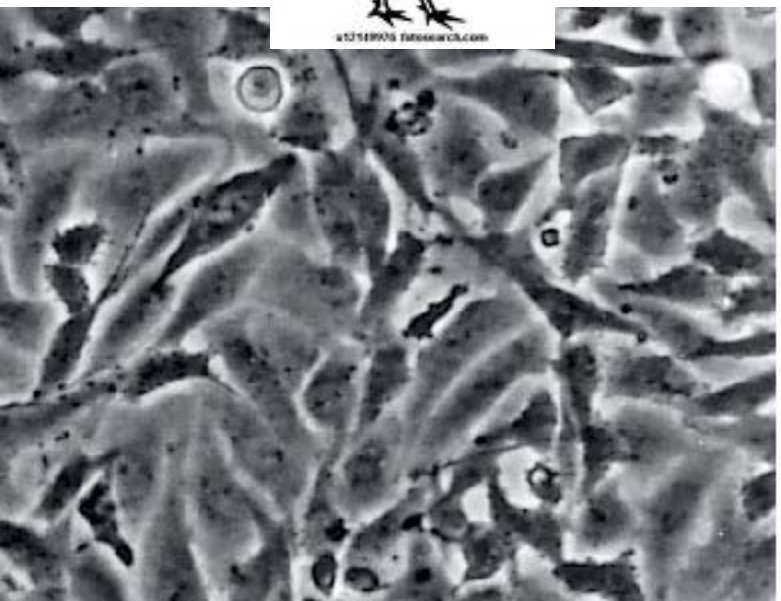


2. Several weeks

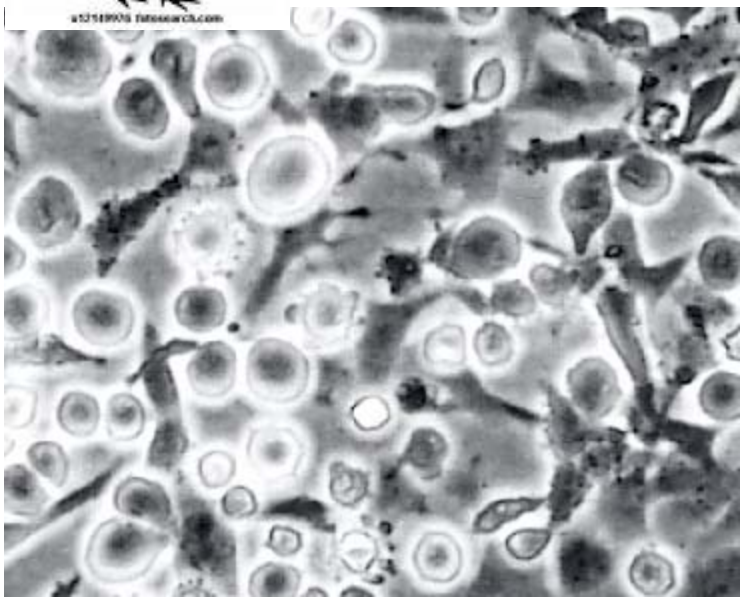


3. Several days

Transformation



+RSV



Transformed cells

- Change in cell shape
- Loss of contact inhibition
- Proliferate indefinitely

- → Your evaluation of the transformed cells:
  - Neoplasia
  - Metastatic tumor

Other viruses can also induce cancer

- Richard Shope: rabbit papillomas (Warts) DNA virus
- SV40 – the 40th simian virus
- MMLV- mouse mammary tumor virus (RNA)

Peyton Rous:
Discovery of tumour-inducing viruses

1909 Chicken sarcoma

1966

(1879 - 1970)