

Virus Infection and Breast Cancer



Student: Emily Tsui

Supervisor: Prof Paul Chan

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Department of Microbiology

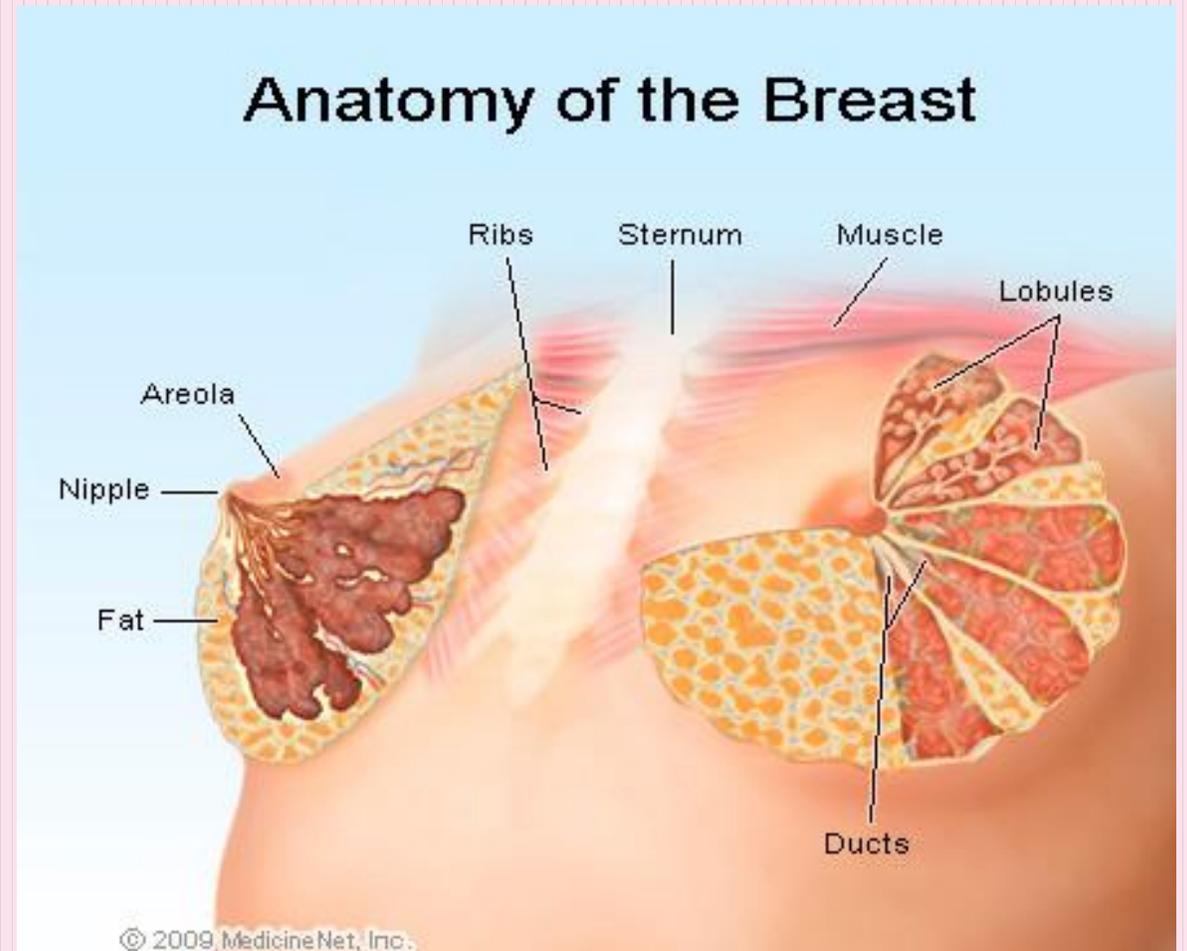
Faculty of Medicine

The Chinese University of Hong Kong

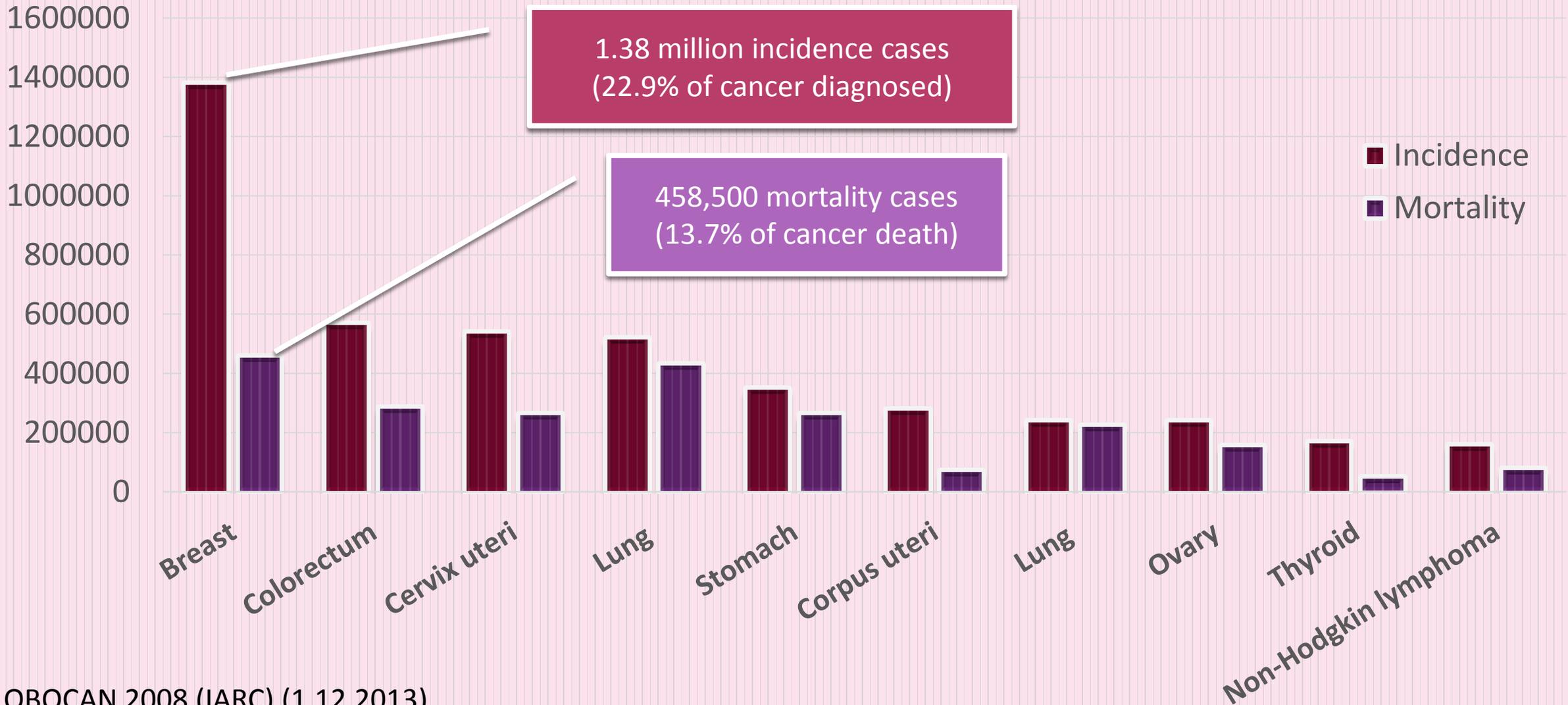
Introduction



- Breast cells divide and grow without normal control
- Tumors large enough to feel >10 years
- Common form of breast cancer
 - Ductal cancer (50-70%)
 - Lobular cancer (10-15%)



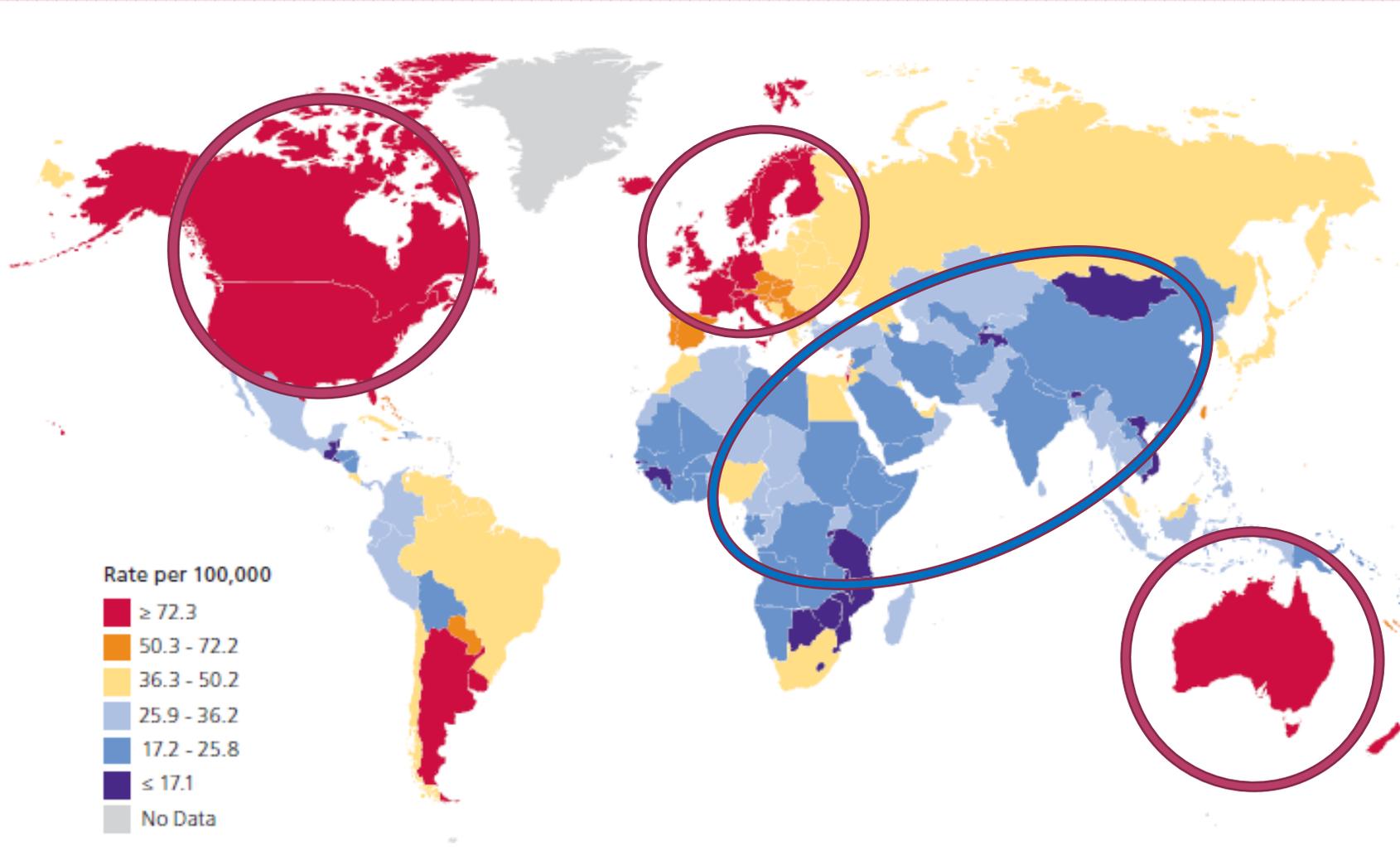
Global burden of Breast Cancer in Women



Breast Cancer Incidence Worldwide

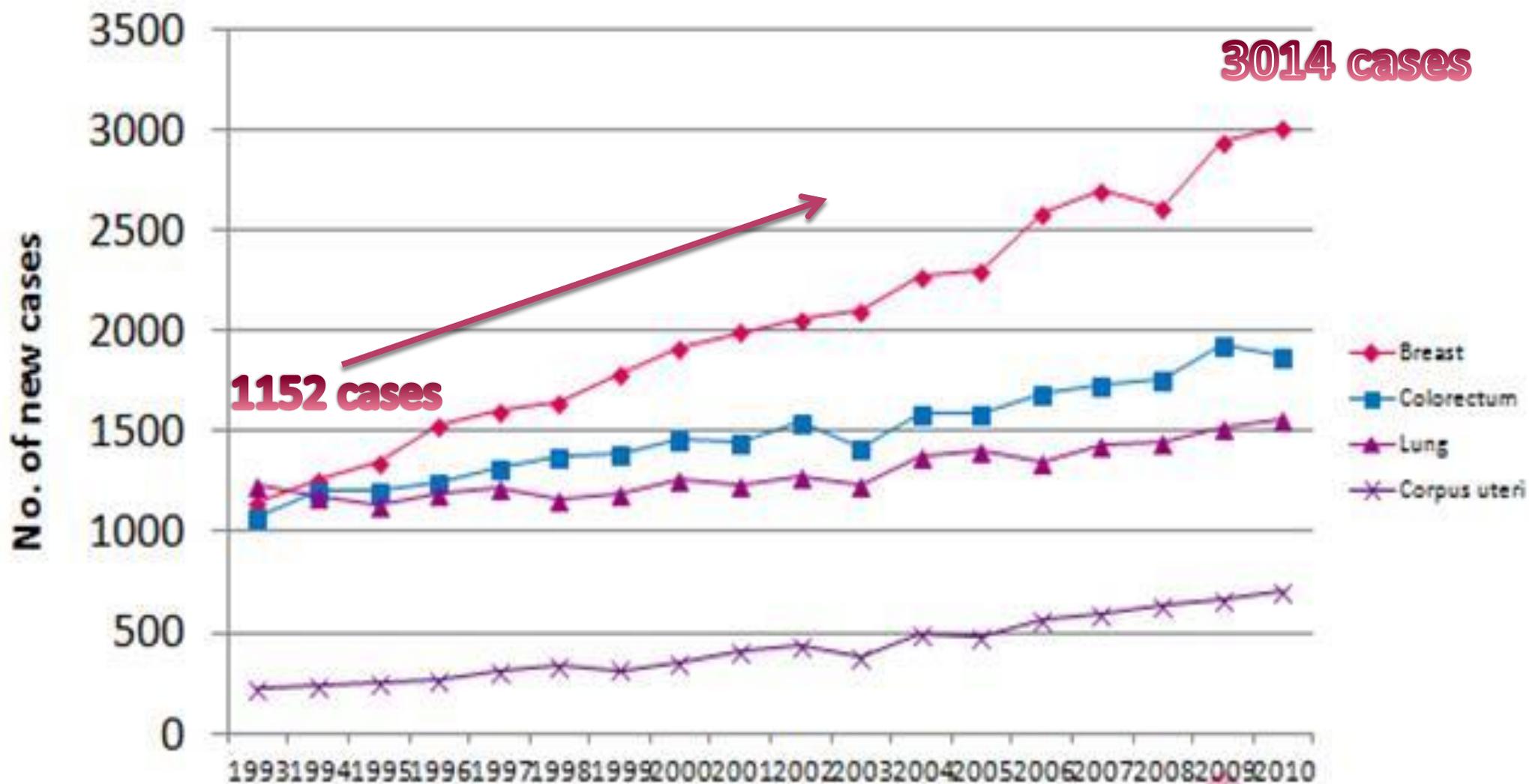


***Worldwide Incidence:
39 per 100,000 women**



Country	Incidence *
Belgium	109.2
Denmark	101.1
United Kingdom	89.1
Australia	84.8
Canada	83.2
United States	76.0
Singapore	59.9
Hong Kong**	54.8
Japan	42.7
China	21.6
Taiwan	52.8

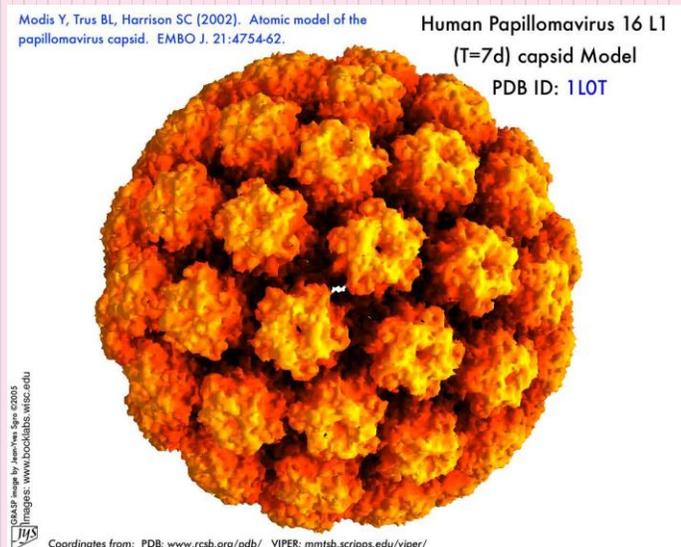
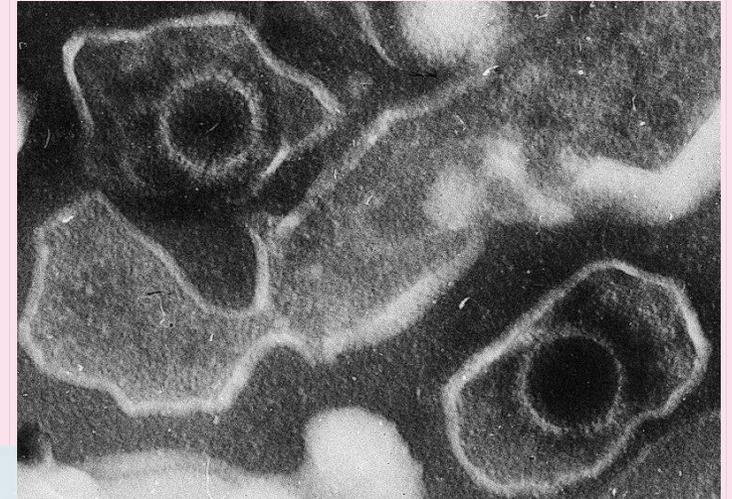
Crude Incidence Rate of Breast Cancer in Hong Kong



Viruses and human breast cancer



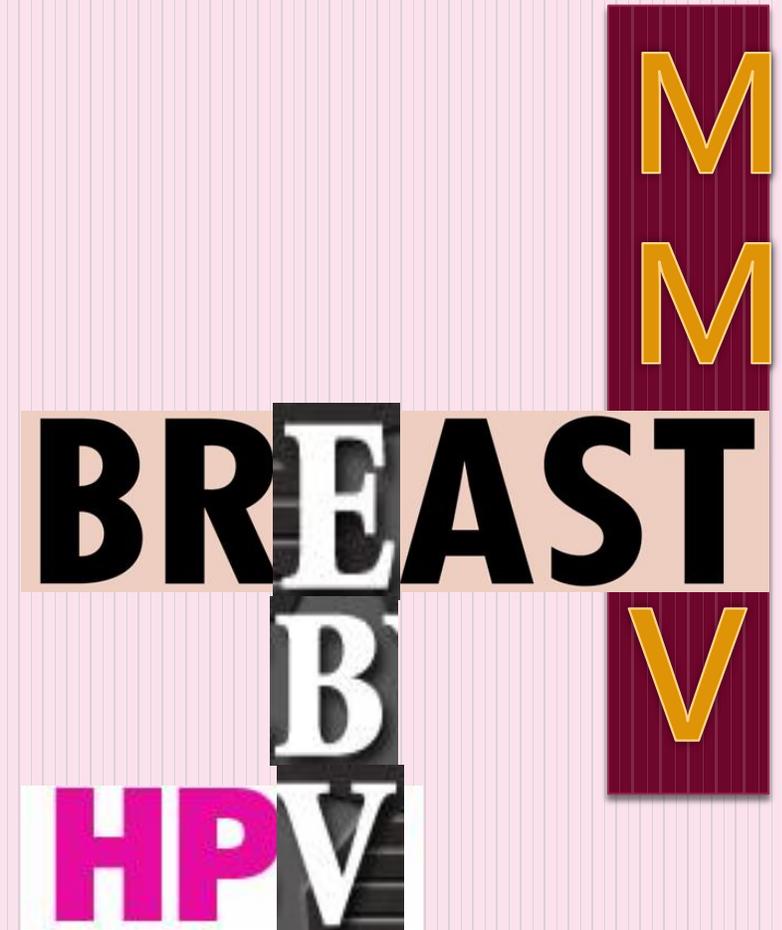
- Epstein-Barr virus (EBV) ~50%
- Mouse mammary tumor virus (MMTV) ~37%
- Human papilloma virus (HPV)



Modified Koch's postulates



- Identify microbes that are associated with a disease
- Pathogen-associated nucleic acid sequences
 - Present in most cases of an infectious disease
 - Found preferentially in diseased organs
 - Fewer, or no in hosts or tissues without disease
 - Decrease with resolution or vice versa
- sequence copy number \propto severity of disease
 - Causal relationship
- Evidence should be reproducible



Viruses and human breast cancer



- **Epstein-Barr virus (EBV)**
- Mouse mammary tumor virus (MMTV)
- Human papilloma virus (HPV)

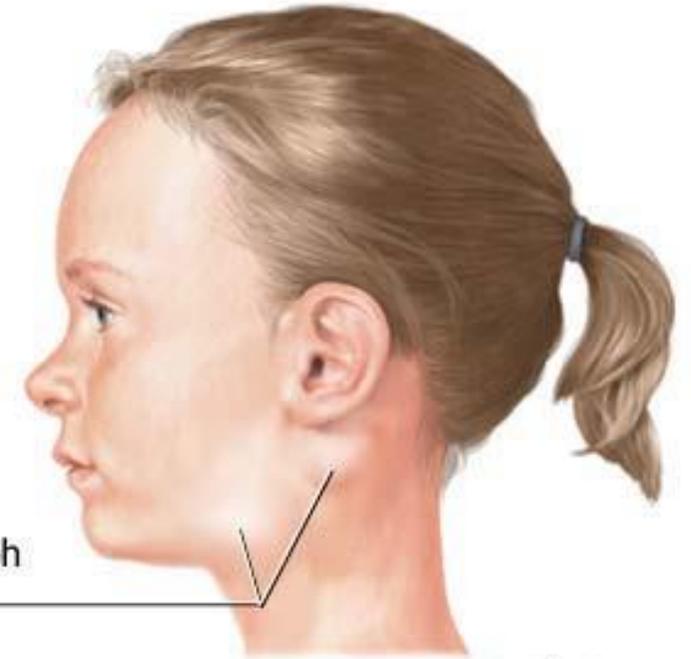
Introduction of EBV



- >90% of adult human population infected by EBV
- Life-long infection
- Asymptomatic / Infectious mononucleosis
- Contagious
 - Oral contact (kissing)
 - Saliva
 - Blood transmission
 - Transplantation

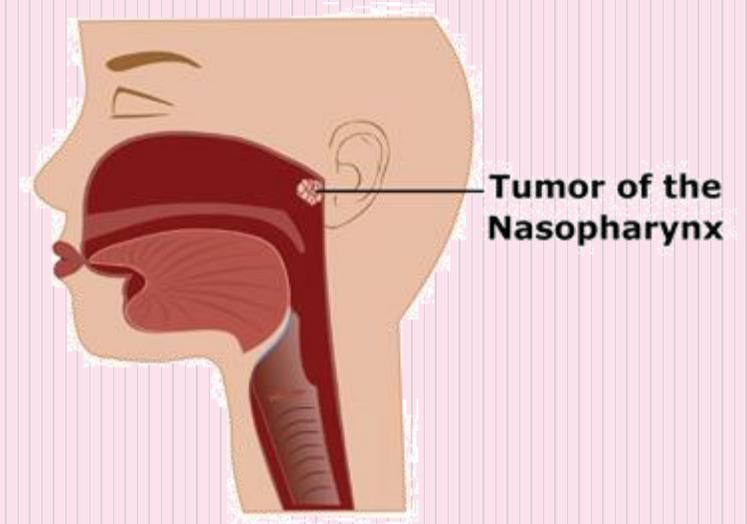
Mononucleosis causes:

- Fever
- Fatigue
- Sore throat
- Swollen lymph glands



Introduction of EBV (cont'd)

- 11% of viral associated human cancers
 - Nasopharyngeal carcinoma
 - Burkitt's lymphoma, Hodgkin's lymphoma
 - Gastric cancer of stomach
- In Western, infectious mononucleosis is common & incidence of breast cancer is high
 - **EBV may also contribute to some breast cancers**



EBV and breast cancer - Findings

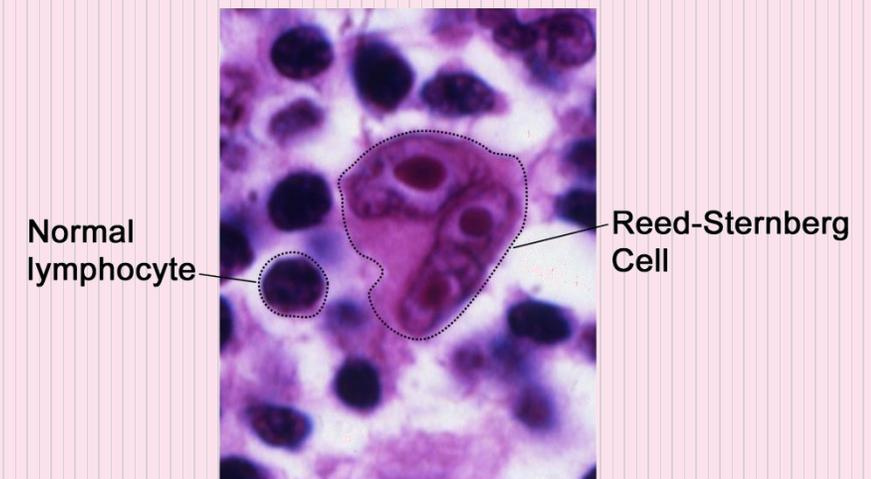


- Identify EBV gene sequences within breast tumours
- 32 published studies concerning EBV in breast cancer
 - 25 studies were positive with EBV sequences
 - 32-51% of breast carcinomas contained EBV DNA
- Correlation between EBV & ductal carcinoma
 - The higher the tumour grade, the more the EBV DNA
- Transfection of EBV DNA stimulates the growth of human milk cells

EBV and breast cancer

	Hodgkin's lymphoma	Breast cancer
Age of most EBV infections	Teenage–young adult Western	Teenage–young adult Western females
Malignant cell type	B lymphocytes	Putative lymphocytes and epithelial cells
EBV histology	Reed/Sternberg cells	

- Evidence is substantial but not conclusive
 - EBV DNA in cancer cells or infiltrating lymphocytes?
 - EBV-associated Hodgkin's lymphoma is common but EBV-associated Breast cancer is rare



Viruses and human breast cancer



- Epstein-Barr virus (EBV)
- **Mouse mammary tumor virus (MMTV)**
- High risk Human papilloma virus (HPV)

Introduction of MMTV



- John Bitterner et al (1936)
 - mouse milk contained an unknown factor (MMTV)
 - caused mammary tumors

	Mouse
Transmission	Milk and germ line
Ingestion	Gut-Peyer's patches
Tropism	Tropic mammary epithelial cells
Latency	Adult mammary tumors

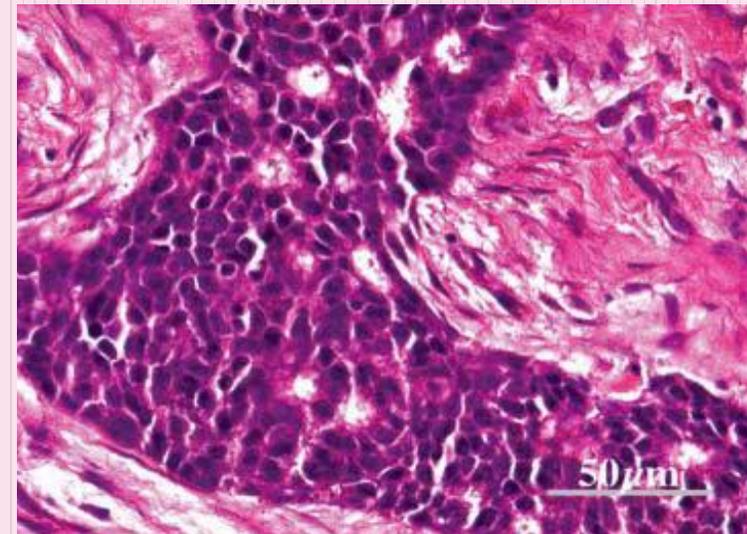
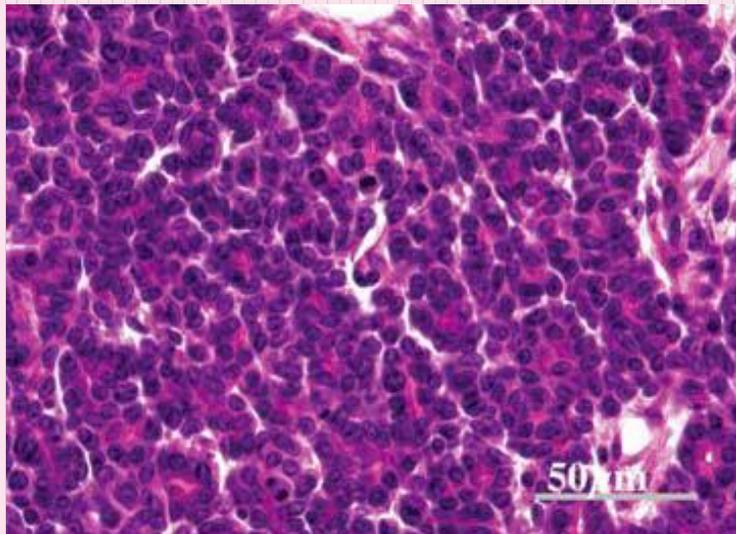


- Well-established etiologic agent of mammary tumours in mice & Common MMTV positive house mice ~ high breast cancer Incidence
 - Would MMTV or MMTV-like virus cause similar impact in human?

MMTV and breast cancer - Findings



- Identify MMTV-like gene sequence in human breast tumors
 - 17 out of 23 studies conducted in 11 countries
 - display 91% to 99% homology to MMTV from mouse mammary tumors
 - located in the breast cancer cell nuclei
- Similar Histological characteristics of
 Mouse mammary tumors & Human IDC breast cancer carcinoma



MMTV and breast cancer - Findings



- Similar oncogenic features of mouse mammary tumors and human breast cancers

	Mouse mammary tumors	Human breast cancer
MMTV infections	0–100%	0–65%
MMTV positive tumors	25%	15%
Tumor histology	Sheets round cancer cells	Sheets round cancer cells
Tumor molecular structure	LTR/gag/pro/pol/env/LTR- 10,000 base pairs	LTR/gag/pro/pol/env/LTR- 10,000 base pairs

Viruses and human breast cancer

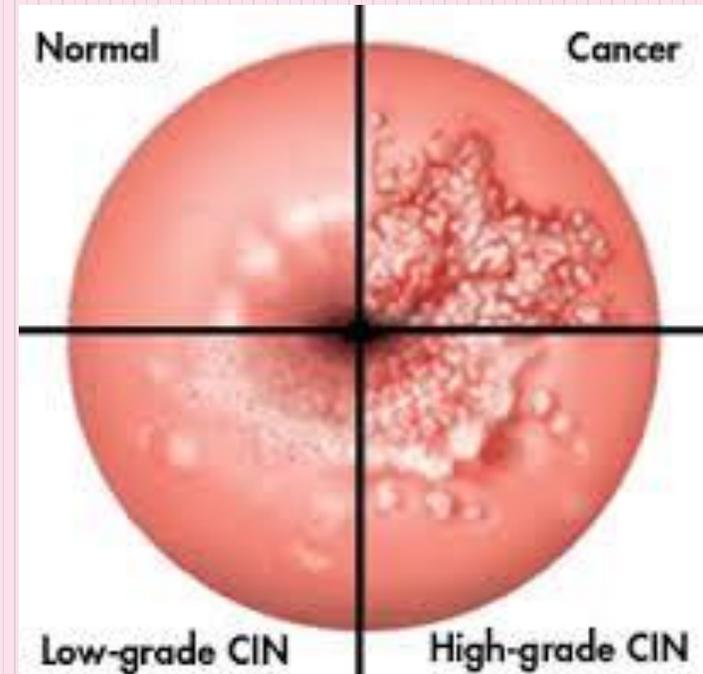


- Epstein-Barr virus (EBV)
- Mouse mammary tumor virus (MMTV)
- **Human papilloma virus (HPV)**

Introduction of HPV



- Infections in keratinocytes of the skin or mucous membranes
- High risk HPV
 - Carcinogenic
 - HPV-16,18,31,35,33 etc....
 - Transmitted through sexual contact
 - Infect anogenital region
 - Persistent infection may progress invasive cancer
- Associated with human cancer
 - Cervical cancer
 - cancers of the anus, vulva, vagina
 - cancers of the oropharynx
 - penile cancer



High risk HPV and breast cancer - Findings

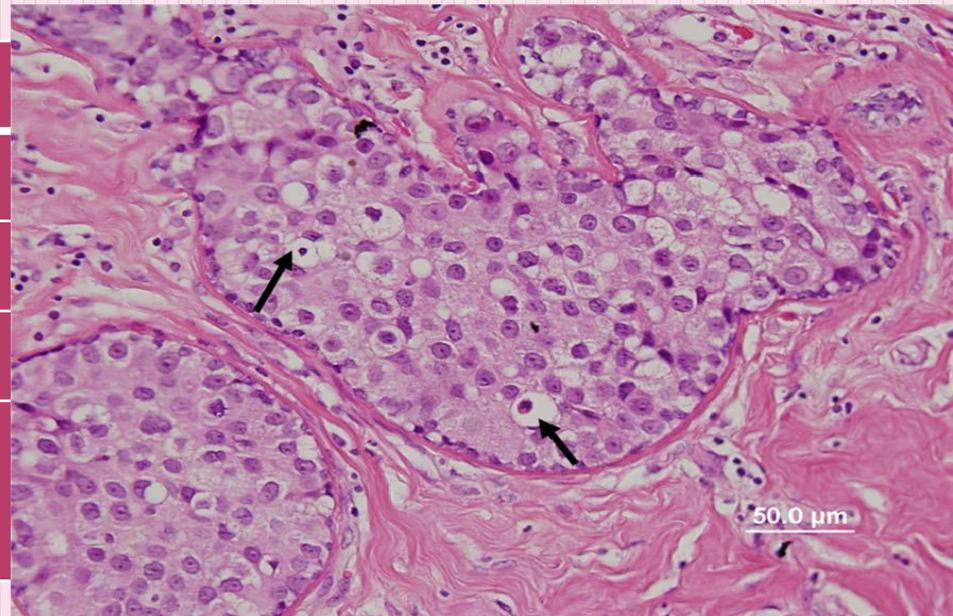
- Identify high risk HPV (HPV-16,18,33) in breast cancers
 - Australia, Italy, Norway, China, Japan, USA, Austria, Brazil, Taiwan, Turkey, etc....
 - Range from 4.4% to 86.2%
 - More prevalent in breast cancer than normal tissues
 - In the nuclei of breast tumor cells

HPV positive

HPV types

Koilocyte positive

Possible oncogenesis



Cancer

6

6/18

0%

n

o53

High risk HPV and breast cancer - Findings

- Causal role for HPV in breast cancers
 - HPV associated precancerous koilocytes
- Not a causal role for HPV in breast cancers
 - Epidemiological evidence
 - Simple parasites in pre-existing cancer tissues
 - 1) Similar concentration of HPV 16 antibodies concentration between breast cancer patients and normal women.
 - 2) Differences between the trend of HPV associated cervical cancer and breast cancer.

Conclusion



- EBV, HPV and MMTV prime candidate viruses for human breast cancer.
- Viral genetic material identified in breast tumors but rarely in normal breast tissue
- Similar histological characteristics
 - HPV-positive human breast tumors ~ HPV-positive human cervical cancer
 - MMTV-positive human breast tumors ~ MMTV-induced mouse mammary tumors
- Transformation of normal breast cell cultures
 - HPV
 - MMTV activates cellular oncogenes
 - EBV immortalizes breast epithelial cells
- Substantial but not conclusive evidence that
“HPV, MMTV and EBV may have a role in the etiology of human breast cancer”

Thank You



Reference



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