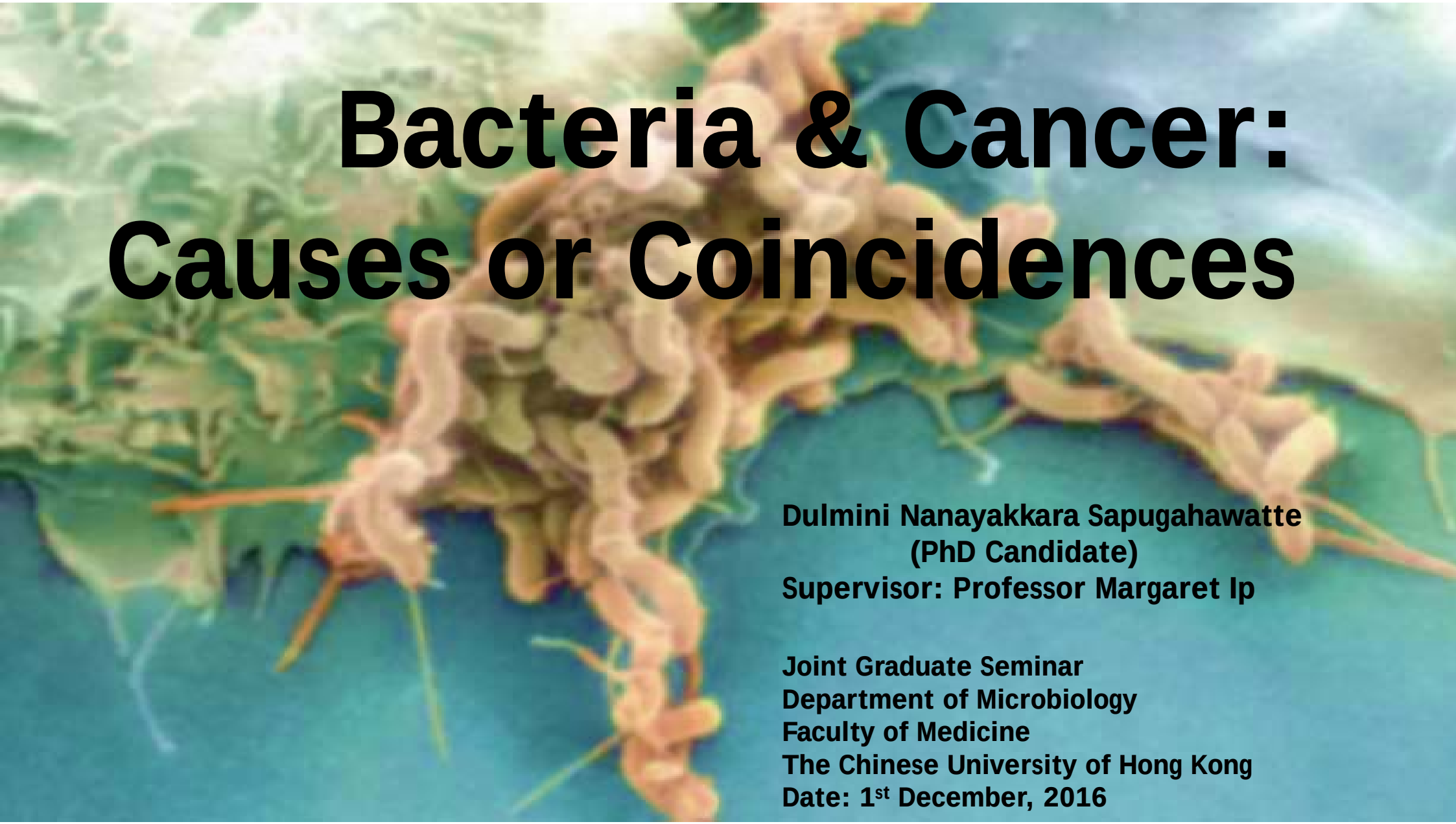

Bacteria & Cancer: Causes or Coincidences

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Definitions

- Cancer – A term for diseases in which abnormal cells divide without control and can invade nearby tissues
- Carcinogen – Any substance that causes cancer
- Cancer bacteria – Organisms known or suspected to cause cancer
- Cancer associated bacteria – Opportunistic bacteria that infect healthy tissues when cancer has been established

(NCI Dictionary)

History

- 1890 – W. Russel – Possibility of bacteria inducing carcinogenesis
- 1926 – T. Glover – Isolation of specific bacteria from neoplastic tissues
- 1931 – E. Esperance – Hodgkin's disease is associated with AFB
- 1941 – G. Mazet – Leukemia and Hodgkin's disease are associated with bacteria
- 1936-55 – M.W. Crofton, V.W. Livingston & E.J. Villesquez – Microbes in cancer tissues
- 1963 – NIC, USA – Rejection of hypothesis association with carcinogenic bacteria
- 1965- M.F. Barile – Latent infection of Mycoplasma in leukemia cases
- 1969 – NIC,USA- Positive association between bacteria and cancer
- 1992 – S.C. Lo – Multistage malignant transformations due to Mycoplasma infection that can reverse by antibiotic therapy

Salmonella typhi & Gallbladder Cancer

- Gallbladder cancer (GC) is the 5th commonest GI tract cancer
- Strong association between chronic *S. typhi* infection and GC

  (Lazcano-Ponce *et al*, 2001 ; Caygill *et al*, 1994; Axelrod *et al*, 1979 ; Welton *et al*, 1971)
- Chronic irritation to gallbladder epithelium (Catterina Ferreccio, 2012)
- Carriers of *S. typhi* have 8.47 times increased risk of developing GC (Lazcano-Ponce et al, 2001)
- 1922 & 1964- Typhoid outbreak in NY & Aberdeen – Carriers have 6 times increased risk of death due to hepatobiliary carcinoma
  (Caygill *et al*, 1994; Welton *et al*, 1971)

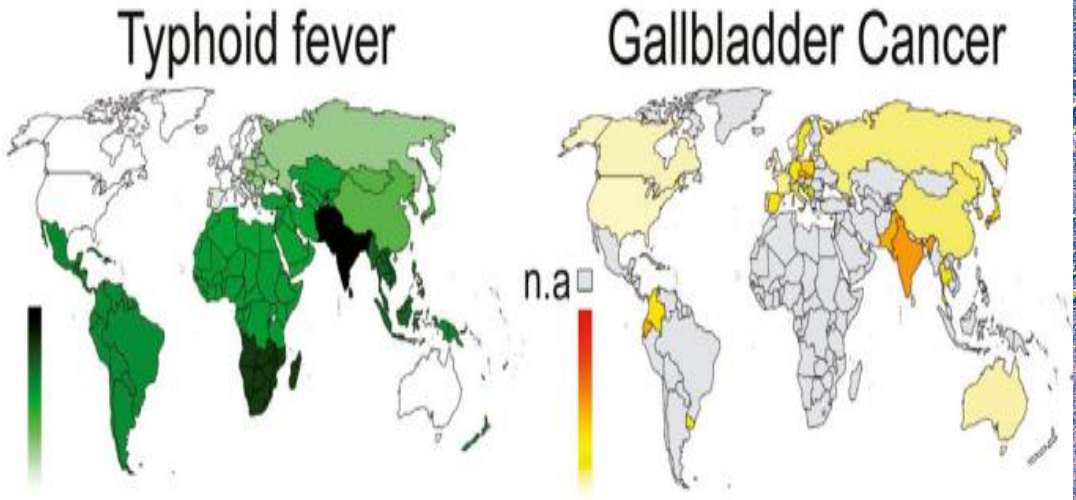
Salmonella typhi & Gallbladder Cancer Cont....

- AvrA protein found in *Salmonella* spp reduces the body's inflammatory response
- Thus, bacteria can avoid the immune system and can grow vividly
- AvrA affects beta-catenin expression, which can promote colonic cancer in human
- Mice infected with *S. typhi* resulted in alterations in body weight, intestinal pathology and bacterial translocation in spleen, liver and gallbladder
- The more AvrA in the intestinal lining, the higher the possibility of developing cancer (Lin *et al*, 2010; Lu *et al*, 2010)

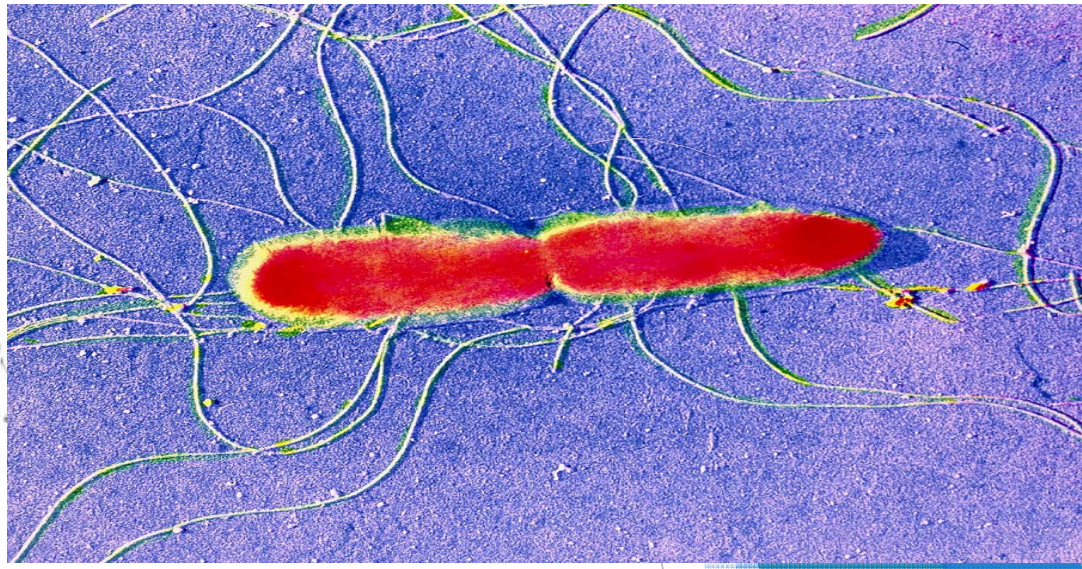
Coincident?

- The ability of AvrA to escape from immune system results in translocation of the pathogen
- Chronic *S. typhi* carriers have an alarming risk for gallbladder cancers
- Interplay of genetic susceptibility to gallbladder cancer and typhoidal fever
  - Populations of Andean area, North American Indians, Mexican Americans
- Proper treatment to *S. typhi* infections reduces the risk of gallbladder cancer

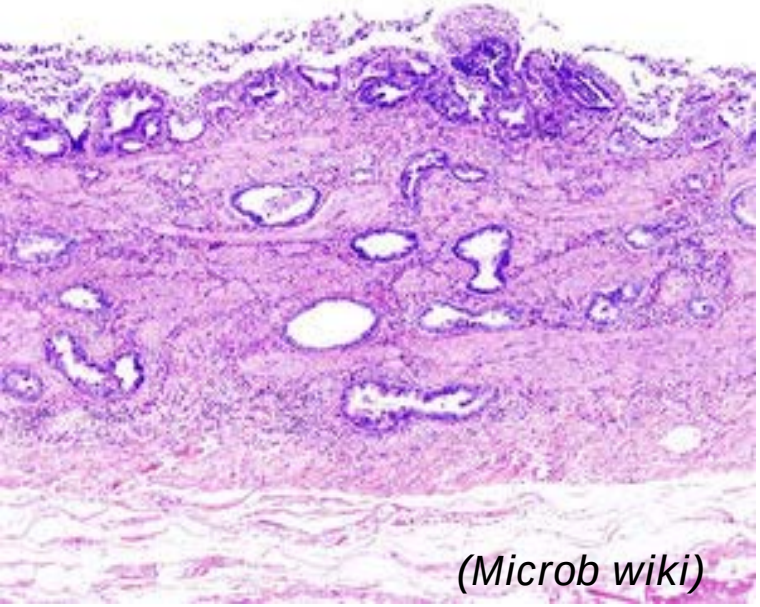
(Lazcano-Ponce *et al*, 2001)



(Scanu *et al*, 2015)

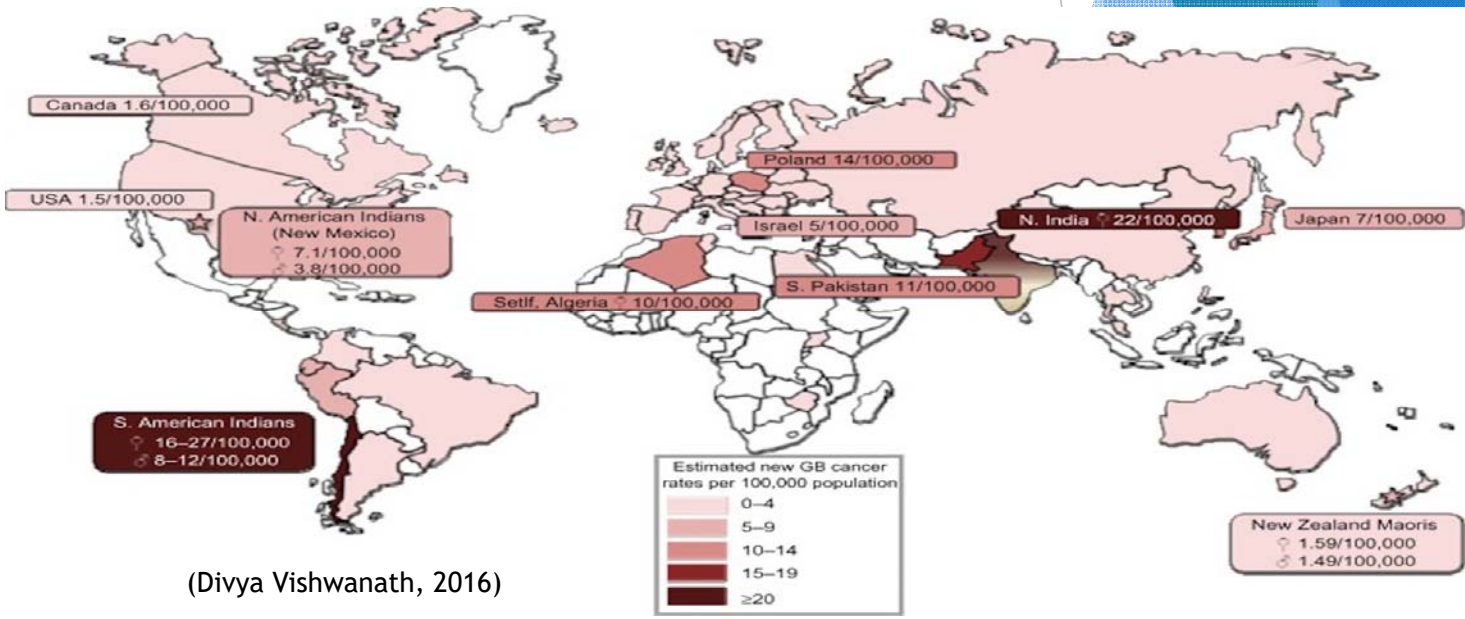


Gallbladder carcinoma



(Microb wiki)

Non-typhoidal *Salmonella* **in gallbladder cancer**



(Divya Vishwanath, 2016)

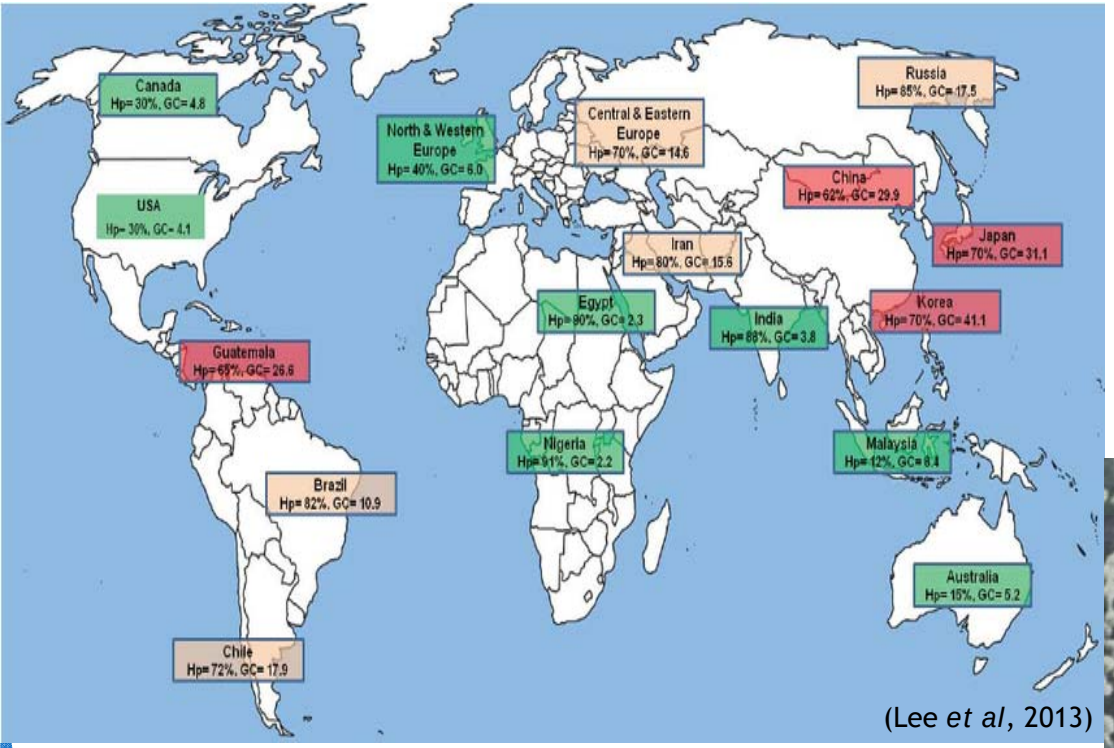
Helicobacter pylori and Stomach Cancer

- *H. pylori* was first discovered in 1982 (Belzer *et al*, 2006)
- Chronic infection causes inflammation, leading to stomach ulcers (Amin Talebi Bezmin Abadi, 2016 ; Wang *et al*, 2016)
- Involves increased epithelial cell proliferation in a background of chronic inflammation
- Gastritis → Gastric atrophy → Intestinal metaplasia → Dysplasia → Cancer
- 3% of infected patients develop cancer
- *H. pylori* genome contains Cytotoxin-associated A (*CagA*) gene
- Injection of *CagA* to gastric epithelial cells → initiation of signaling cascade that mimics unregulated growth factor stimulation
- Hence *CagA* is an oncogenic protein (Luisa *et al*, 2016 ; Nath *et al*, 2010 ; Alicia *et al*,2010)

Coincidence?

- It is a class I carcinogen
- Chronic infection with *H. pylori* has an alarming risk of developing stomach cancers
- Proper treatment to *H. pylori* infection can reduce *H. pylori* associated gastric cancers

Prevalence of *H. pylori* infection & incidence of gastric cancer



(Lee *et al*, 2013)

(Blaser *et al*, 1989)

Streptococcus bovis & Colorectal Cancer

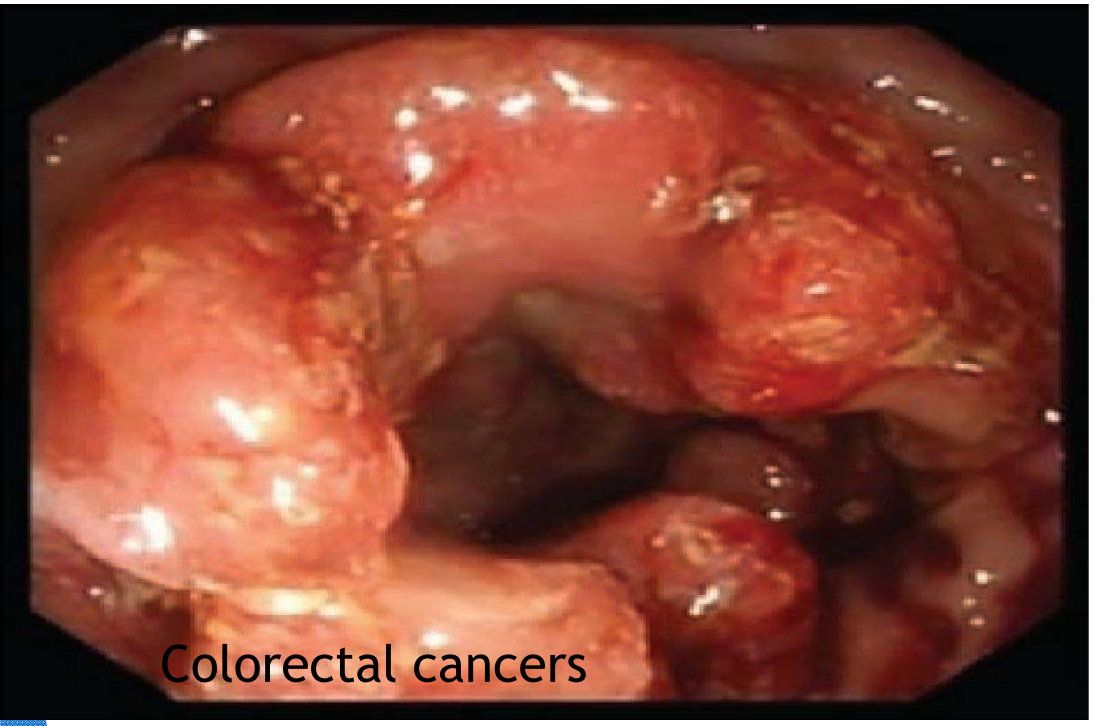
- *S. bovis* is a commensal in human GI tract, causing bacteremia, endocarditis and UTIs
- 1951- Relationship between colonic carcinoma & infectious endocarditis was suggested (McCoy & Mason, 1951 ; Tsai *et al*, 2016)
- 1974 – Association of *S. bovis* & colonic neoplasia was proposed (Roses *et al*, 1974)
- 25-80% of patients with *S. bovis* bacteremia had colorectal cancers (Zarkin *et al*, 1990)

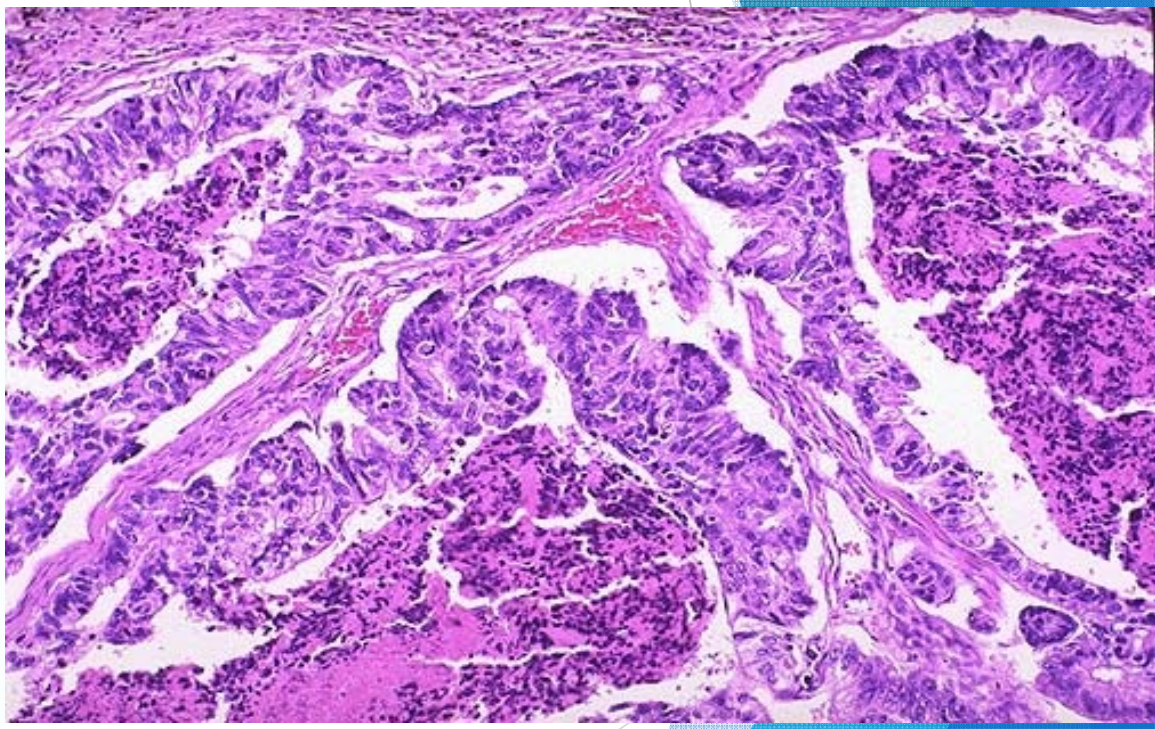
Streptococcus bovis & Colorectal Cancer Cont….

- Administration of *S. bovis* or its cell wall extract antigen to rats were able to promote carcinogenesis
- Promotes
  - progression of pre-neoplastic lesions
  - formation of hyperproliferative aberrant colonic crypts
  - enhance expression of proliferation markers
  - increased production of IL-8 (Gold *et al*, 2004 ; Shanan *et al*, 2011 ; Abdulamir *et al*, 2011 ; Marmoli *et al*, 2016)

Coincidence?

- Inhabitant of normal GI tract & opportunistic pathogen
- Changes to the composition on mucus membrane with excess of antibiotics or chemicals allow the commensal organism to develop as opportunistic pathogen
- Bacteremia or endocarditis due to *S. bovis* has an alarming risk of developing colorectal cancers





(Raul Gonzalez, 2015)

Chlamydophila pneumoniae & Lung Cancer

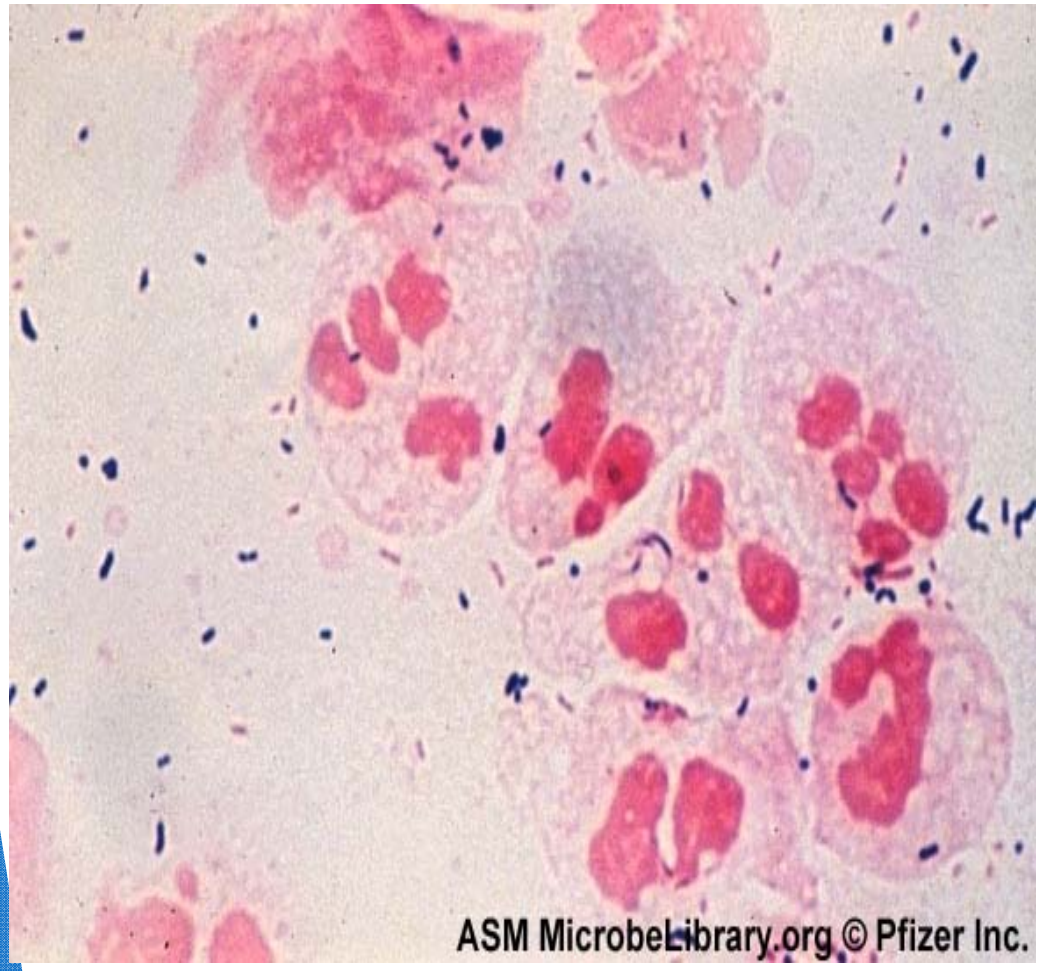
- Transmission through aerosols via respiratory secretions
- Responsible for attacks of asthma, pneumonia, bronchitis, sinusitis, rhinitis and chronic obstructive pulmonary disease
- After acute infections, metabolically inert atypical persistent inclusions can observe in intracellular lifecycle
  - Inclusions contain increased quantity of chlamydial heat shock protein 60
  - Highly immunogenic (khan *et al*, 2016)
  - Implicated in pathogenesis in chronic chlamydial infections and cancer

Chlamydophila pneumoniae & Lung Cancer Cont…

- 2001 – Relationship between chronic *C. pneumonia* infection and lung cancer was suggested
  - 123 lung cancer patents with history of smoking were checked for IgA and IgG for chronic *C. pneumoniae* infections
  - IgG antibody titers of ≥512 & IgA antibody titer of ≥40 were found compared to control group (Kocazeybek *et al*, 2003)
- Individuals with elevated IgA antibody titer to this organism have 50%-100% increased lung cancer risk (Littman *et al*, 2004)

Coincidence?

- Patients with acute lower respiratory infections with *C. pneumoniae* have an alarming risk of getting lung cancers
- Elevated IgA antibody titers for *C. pneumoniae* can be used as a cancer detection marker before moving to surgical techniques like taking biopsy
- Proper treatments to *C. pneumoniae* infections reduce the risk of lung cancers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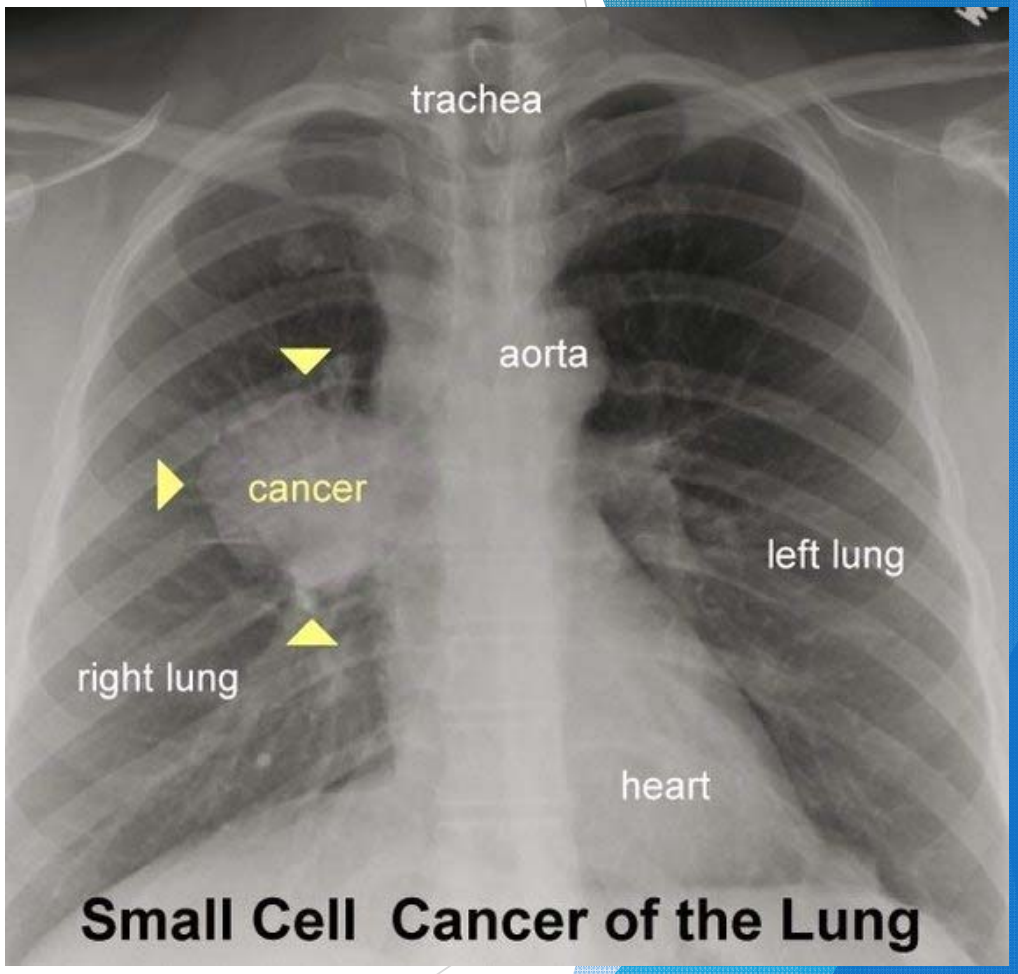
trachea
aorta
cancer
left lung
right lung
heart
Small Cell Cancer of the Lung

Summary

Type of cancer	Cause	Predisposition
Gallbladder cancer	*Salmonella typhi*	Chronic carriers and genetic susceptibility
Stomach cancer	*Helicobacter pylori*	Chronic carriers of *H. pylori* in a risk of gastric cancers
Colorectal cancer	*Streptococcus bovis*	Commensals become opportunistic pathogens when mucus membrane damage due to various factors
Lung cancer	*Chlamydophila pneumoniae*	Elevated IgA level indicates the risk of getting lung cancer

THANK YOU