McGill EPIB-671 Symposium - 2014

Scientific Program, Friday, June 20

Time	Presenter	Title
12:30 - 12:45	Host	Introduction to the Symposium and Instructions
12:45 - 13:00	Maryam Alshareef	Epidemiology and Prevention of HTLV-I and Adult T cell Leukemia
13:00 - 13:15	Alain Ngoma	Hepatocellular carcinoma: Risk factors and Prevention
13:15 - 13:30	Kamran Kafi	PSA testing in Prostate Cancer Screening
13:30 - 13:45	Reem AlBeesh	Lung Cancer Screening
13:45 - 14:00	Mamatha Bhat	Chemopreventive Agents in Hepatocellular Carcinoma
14:00 - 14:15	Kyrie Wang	Environmental Risk Factors for Gastric Cancer
14:15 - 14:30	Duc-Vinh Thai	Epidemiology of Thyroid Cancer
14:30 - 14:45	Josef Braun	Comparative Epidemiology of Esophageal Cancer: Japan vs. the West
14:45 - 15:00	***Coffee/Ice Cream Break***	
15:00 - 15:15	Angel Rodriguez	Multiple Primary Malignancies
15:15 - 15:30	Samaher Ashram	Epidemiology of Laryngeal Cancer
15:30 - 15:45	Robyn Lee	Electromagnetic Fields and Brain Tumours
15:45 - 16:00	Sreenath Madathil	Paan Chewing and Oral Cancer Risk
16:00 - 16:15	Akanksha Srivastava	Mouthing the Oral Cancer Screening Debate
16:15 - 16:30	Yousef Katib	Epidemiology and Prevention of Ovarian Cancer
16:30 - 17:00	Barbara Gauthier	Intratypic variation of HPV and Cervical Cancer Risk
17:00 - 17:20	Final remarks, exam, and end of course: Have a Happy Summer!	

Duration of presentations: 10 minutes; Q&A: 5 minutes

Epidemiology and Prevention of HTLV-I and Adult T cell Leukemia

Maryam Alshareef

Cancer Epidemiology and Prevention Course

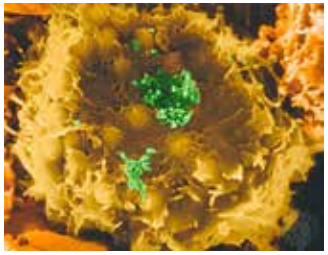
EPIB 671

Outline

- HTLV-1 and ATL Background
- The Etiological Association: HTLV-1 with ATL.
- Epidemiology of HTLV-1and ATL.
- Route of HTLV-1 Transmission and Prevention
- Concluding remarks

HTLV-1 and ATL Background

- In 1977, Adult T-cell leukemia was first described as a distinct clinical entity in Japan. (Takatsuki et al., 1977)
- In 1980 in USA, Dr. Robert Gallo identified the first human pathogenic retrovirus HTLV-1 which was isolated from several cell lines that were obtained from a patient diagnosed with cutaneous T-cell lymphoma (ATL).
- In 1982 in Japan, Hinuma described a cell line that harbored HTLV-1 form patient with ATL (Takatsuki et al., 2005), (Fujino et al., 2000).



Evidence of The Etiological Association: HTLV-1 with ATL

1. All ATL patients are seropositive for HTLV-1.
2. HTLV-1primarily infects CD4+ T cells and immortalizes them in vitro
3. The regions of high incidence of patients with ATL correspond very well with regions of high incidence of HTLV-1 carriers.
4. HTLV-1 is able to integrate its proviral DNA into the genomes of leukemic cells in *vitro* (2,5,8)

HTLV-1 is considered the causal agent of ATL

(Miyoshi et al., 1981), (Takatsuki et al., 2005), (Iwanaga et al., 2012),

Epidemiology of HTLV-1and ATL

- Incidence:

- Around 20 million people around the world are infected with HTLV-1.

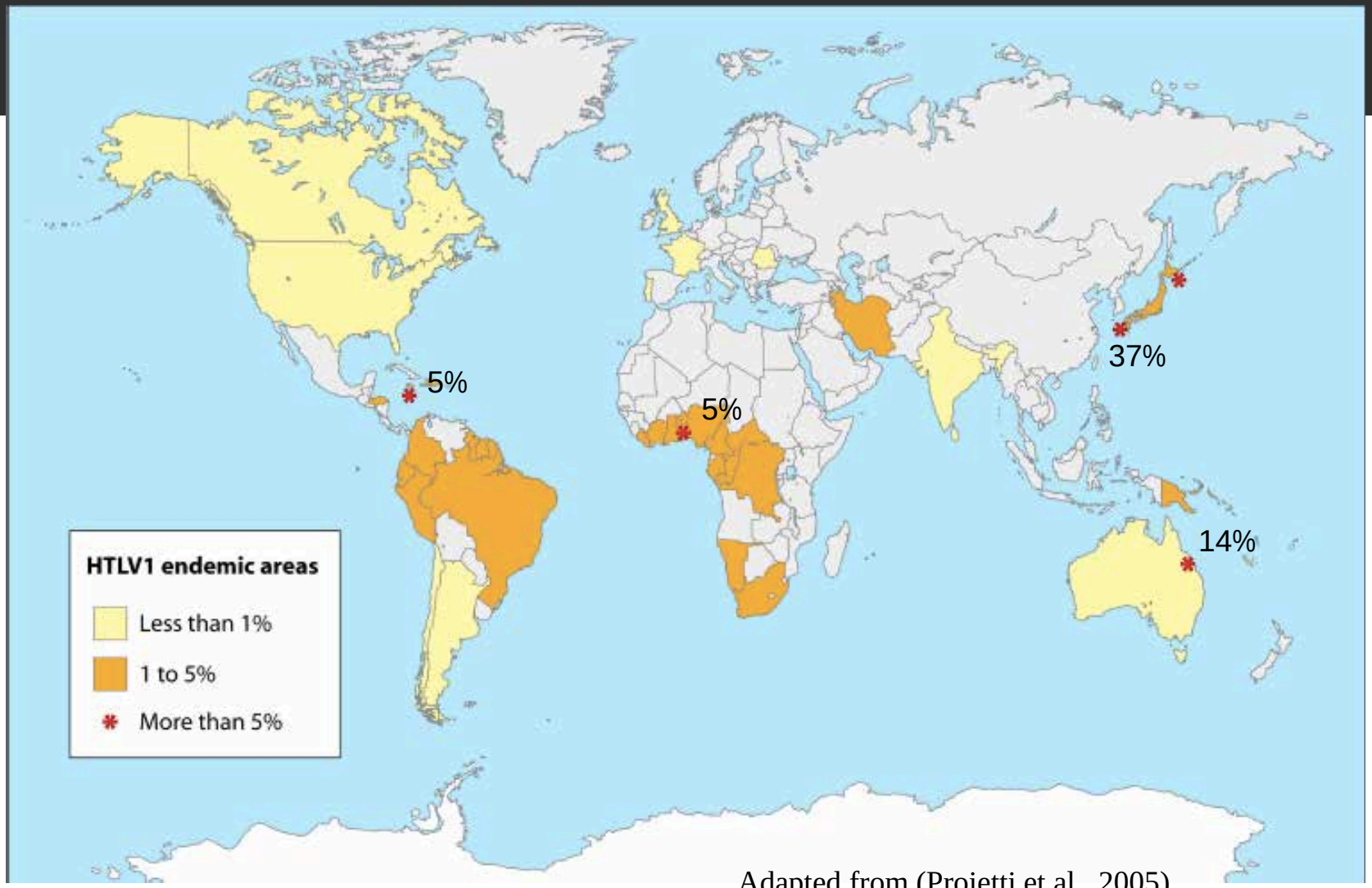
- The majority (90%) of infected individuals with HTLV-1 will remain asymptomatic during their lives (Gonçalves et al., 2010).

- Only 2-5% of infected people will develop ATL in their lifetime, in about 20 to 30 years after infection (Shimoyama et al., 1991).

- These infections concentrated in certain regions of the world.

Epidemiology of HTLV-1and ATL

- The geographic distribution of HTLV-1 has been studied in almost 25 years since its first discovery.
- The diagnostic strategies: the serological screening of healthy blood donors for antibodies against HTLV-1 utilizing an enzyme-linked immunoassay (EIA).



Adapted from (Proietti et al., 2005)

Epidemiology of HTLV-1and ATL

HTLV-1 infection is not sufficient to cause ATL

- Risk factors:
  - Age of infection:
    - ATL presents in people infected in childhood/ rarely presents in people infected in adulthood.
  - Age at onset:
    - Central and south America (around 40 years old)
    - Japan (around 60 years old)
  - Gender (Japan):
    - Male carriers 6-7% , Female carriers 2-3% (male carriers 3 to 5 times higher risk of developing ATL than female carriers) (Iwanaga et al., 2012).

Epidemiology of HTLV-1and ATL

- Risk factors:
  - Family history of lymphoma.
  - Abnormal immune system.
  - Immunosuppressive drugs.
  - High proviral load level (Iwanaga et al., 2012).

Prevention

- There is no preventive vaccine.
- ATL is aggressive, rapidly progressed disease with short survival time.
- ATL patients face a poor prognosis.
- High financial cost for the patient and health system.
- Counseling and education.

(Proietti et al., 2005)

Route of HTLV-1 Transmission and Prevention

- From infected mother-to-child through breastfeeding
- Occurs in 20% of children from a carrier mother.
- Prevention:
- Screening for anti-HTLV-1 antibodies in pregnant women (Japan).
- Seropositive mother:

refraining form breastfeeding (Proietti et al., 2005 , Fujino et al., 2000).

Shorten the period of breast-feeding.

Freeze and thaw the breast milk from infected mothers (lost of the infectivity of HTLV-I) (Fujino et al., 2000).

Result: significant decrease of HTLV-1 infection rate among formula fed children and short time breast-fed children

CONTRY		Incidence of HTLV-1 seropositive	RR	Reference
Japan	Breast-fed > 12 months	15.7 % (37:235)		Hino et al. (1996)
	Formula-fed	3.6 % (41:1141)		
Japan	Breast-fed >=7 months	14.4% (20/139)	3.68	Takahashi et al. (1991)
	Breast-fed <= 6 months	4.4% (4/90)	0.770	
	Formula-fed	5.7% (9/158)	0.770	
Jamaica	breast-fed >= 12 months	32% (19/50)		Wiktor et al. (1997)
	breast-fed<12 months	9% (8/86)		

Adapted and modified from (Fujino et al., 2000)

Route of HTLV-1 Transmission and Prevention

- Blood transfusion:
- Blood transfusion is strongly efficient route of HTLV-1 transmission.
- Seroconversion presented in 44% (24/54) of recipients of HTLV-1 positive peripheral blood (Jamaica) (Manns et al., 1992).
- Prevention:
- Blood donor screening for anti-HTLV-1 antibodies → effective strategy (Manns et al., 1992, Proietti et al., 2005).

Concluding Remarks

- HTLV-I is the first human retrovirus discovered in 1980, and the first one to be directly associated with human cancer.
- HTLV-1 is considered the causal agent of ATL.
- Thankfully, the majority of infected individuals remain asymptomatic.
- HTLV-1 infections are concentrated in certain regions of the world, such as Japan, Africa, the Caribbean island, and central and South America.
- Age of infection and male sex well known risk factors for developing ATL.
- The gold stander of prevention is screening for anti-HTLV-1 antibodies which is the most effective strategy to prevent HTLV-1 transmission through breastfeeding and blood transfusion.

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Takatsuki, Kiyoshi. "Discovery of adult T-cell leukemia." Retrovirology 2.1 (2005): 16.

Gonçalves, Denise Utsch, et al. "Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases." Clinical microbiology reviews 23.3 (2010): 577-589.

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Miyoshi, I., et al. Type C virus particles in a cord T-cell line derived by co-cultivating normal human cord leukocytes and human leukaemic T cells. Nature 294, 770-771 (1981).

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HEPATOCELLULAR CARCINOMA: RISK FACTORS AND PREVENTION

EPIB 671 Cancer Epidemiology and Prevention

Student Symposium 2014

Alain Ngoma

OVERVIEW

I. BACKGROUND

II. RISK FACTORS

III. PREVENTION

BACKGROUND

1. Hepatocellular carcinoma (HCC) : malignant tumor of liver parenchymal cells.

2. HCC is most common primary liver cancer.

3. HCC is the 2nd most common cause of cancer mortality worldwide and 5-year survival rate is less than 10%.

4. HCC is the 6th most common cancer in the world (5.6%).

5. 81% of cases occurring in the developing world and 54% of these occurring in China .

6. The incidence of HCC varies in different countries.

HCC INCIDENCE

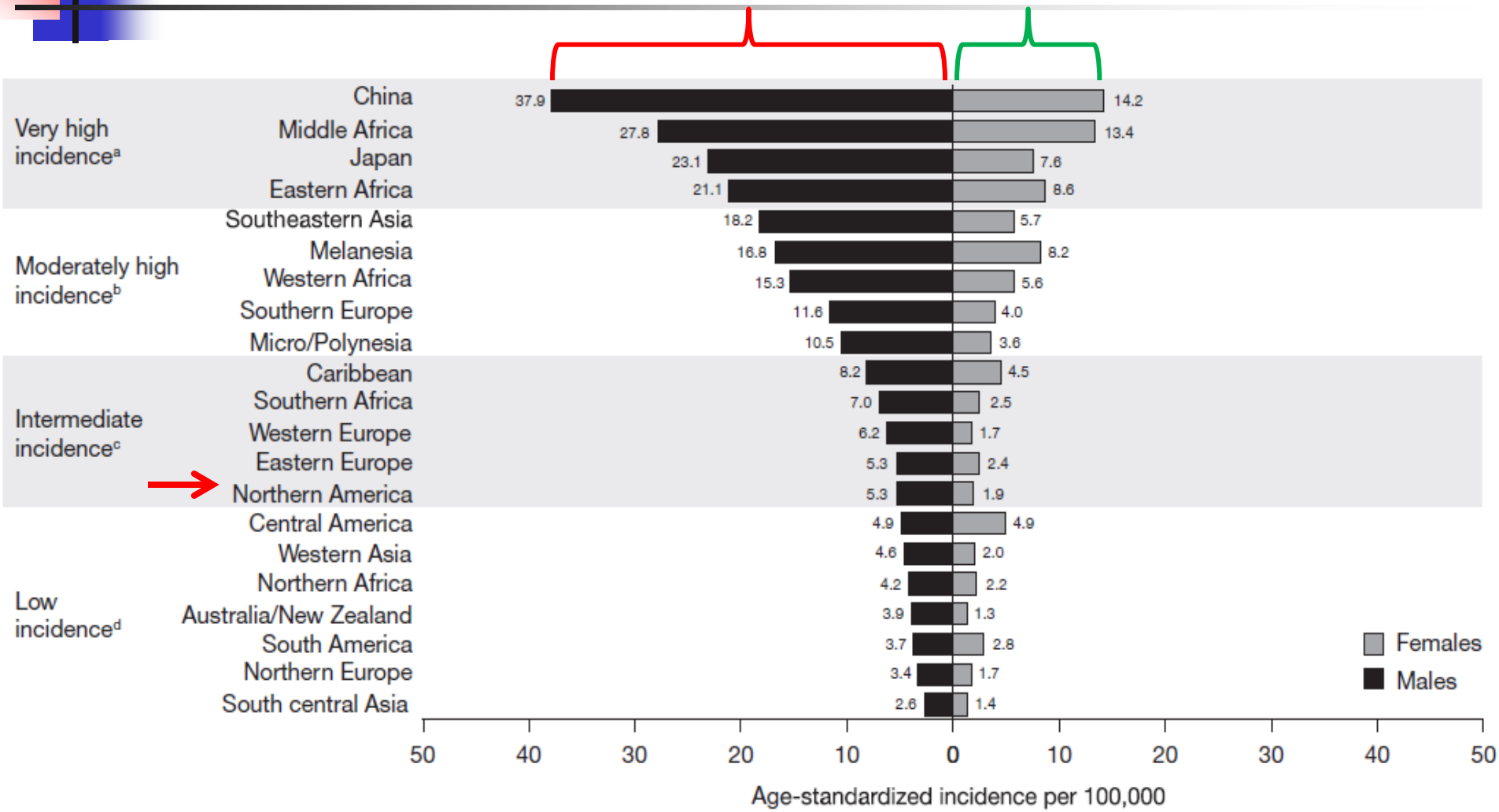
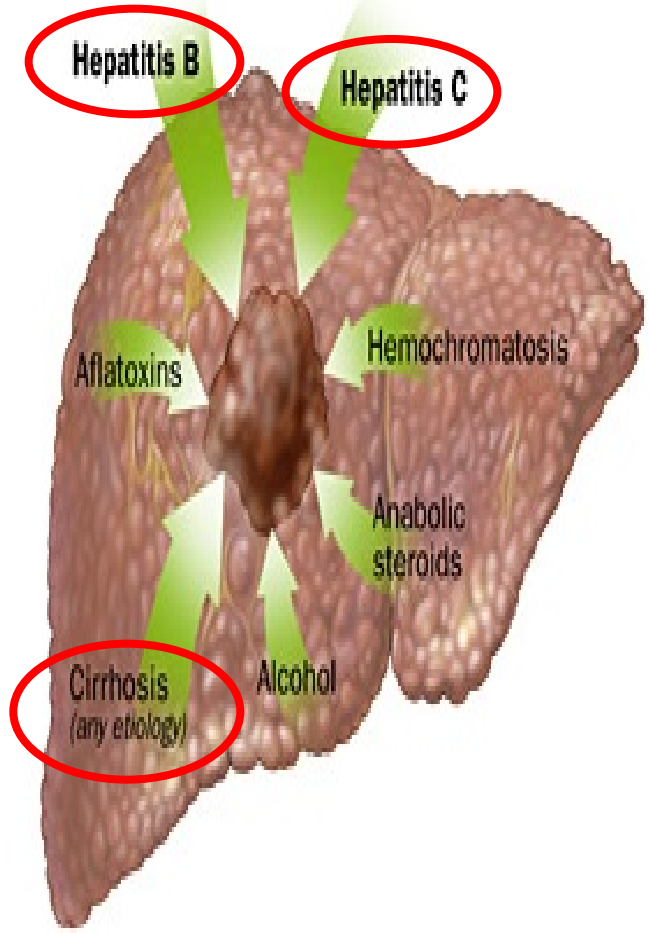


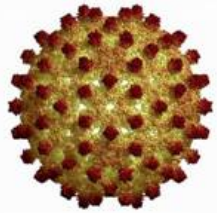
Figure 1. Global variation in liver cancer incidence rates [5]. From Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108, with permission from John Wiley & Sons.

RISK FACTORS AND CAUSES



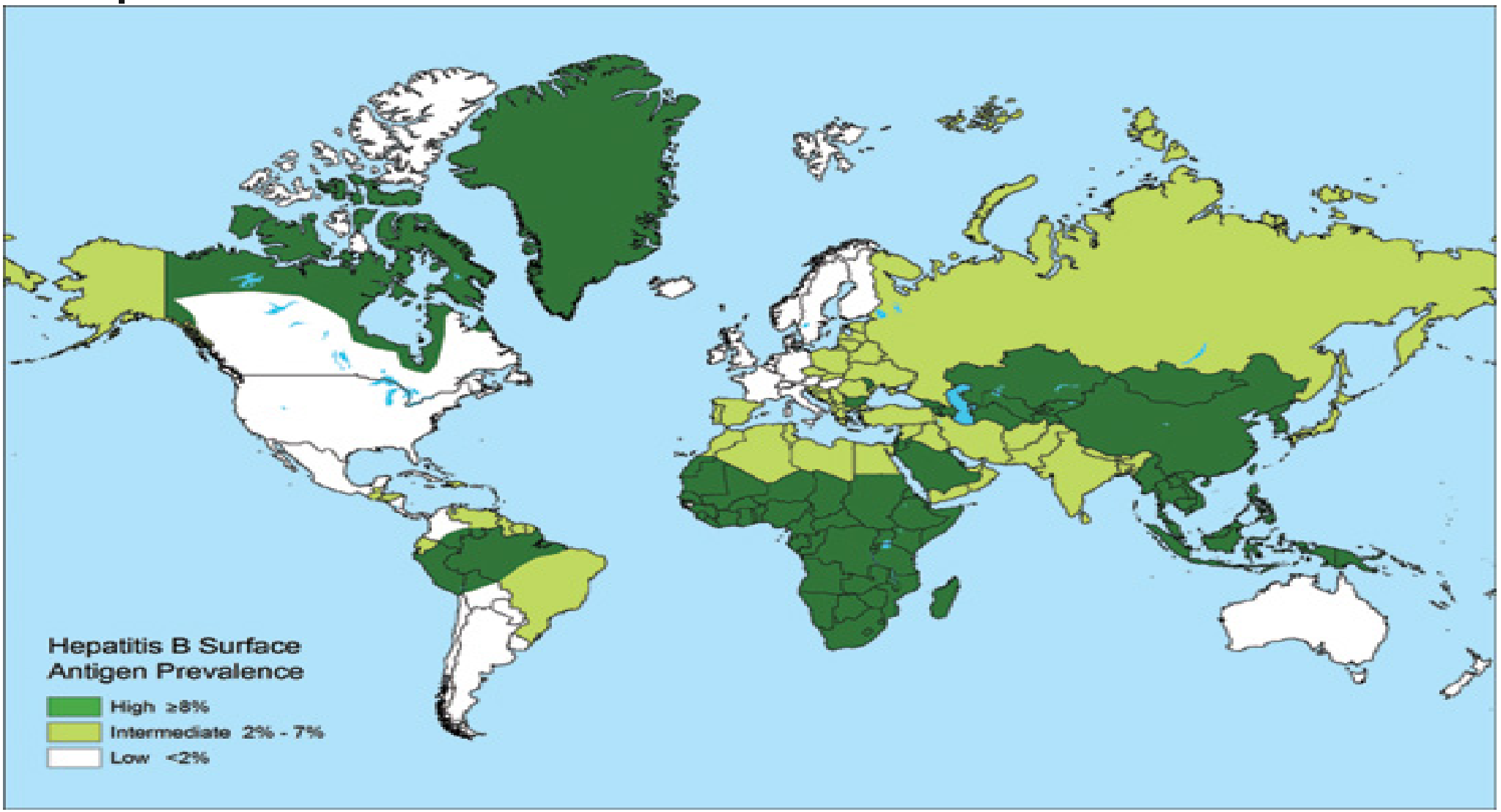
Risk factors for hepatocellular carcinoma development. HCC: Hepatocellular carcinoma; NASH: Nonalcoholic steatohepatitis.

HEPATITIS B VIRUS (HBV)



- HBV is a DNA Virus of the hepadnaviridae family of viruses.
- HBV is differentiated into many genotypes (A-H).
- The incubation of the HBV (hepatitis B) is 90 days (range, 60- 150 days)
- Transmitted through contact with the blood or other body fluids.
- More than 240 million people have chronic (long-term) liver infections.
- About 600 000 people die every year due to the consequences of hepatitis B.
- Hepatitis B prevalence is highest in sub-Saharan Africa and East Asia

HBV PREVALENCE



ASSOCIATION HBV - HCC

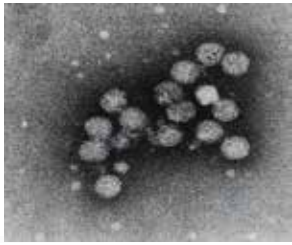
Ø Areas of the world with high mortality rates for HCC also have high HBV infection rates.

Ø Over 80% of HCC are positive for (HBs Ag).

Ø From prospective and case-control studies, HBV carriers showed higher RR for HCC (100-200).

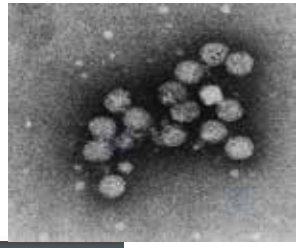
Ø Prevention of HBV reduces risk of subsequent HCC.

HEPATITIS C VIRUS (HCV)

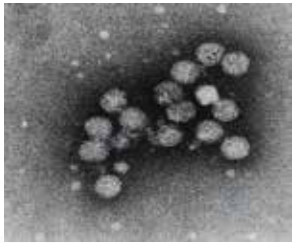


- HCV is a single-stranded RNA virus in the Flaviviridae family .
- There are six basic genotypes of HCV, with 15 recorded subtypes.
- Transmitted essentially through contact with the blood .
- 130- 150 million (3%) people globally have chronic hepatitis C infection.
- 350 000 to 500 000 people die each year from hepatitis C-related liver diseases.
- The most affected regions are Central and East Asia and North Africa.
- Major viral cause of liver cancer in areas with low HBV prevalence.

HCV PREVALENCE



ASSOCIATION HCV - HCC



- Detection of HCV RNA in tumor and nontumor cirrhotic liver tissue of patients with HCC

- Studies suggest that HCC is between 20 and 200 times more common in hepatitis C cirrhosis than in the non-infected.

- In chronic hepatitis C, cirrhosis is almost a necessary precondition for the development of HCC.

PREVENTION OF HCC

- **Prevent HBV infection: vaccination.**
- **Reduce transmission of hepatitis: blood product screening, counseling about risks.**
- **Improve access to diagnosis and treatment .**
- **Screening of Patients with HBV and HCV.**
  - **Serum alpha-fetoprotein (AFP)**
  - **Ultrasonography of the liver**
- **Moderate alcohol consumption.**
- **Exercise and healthy diet.**

SUMMARY

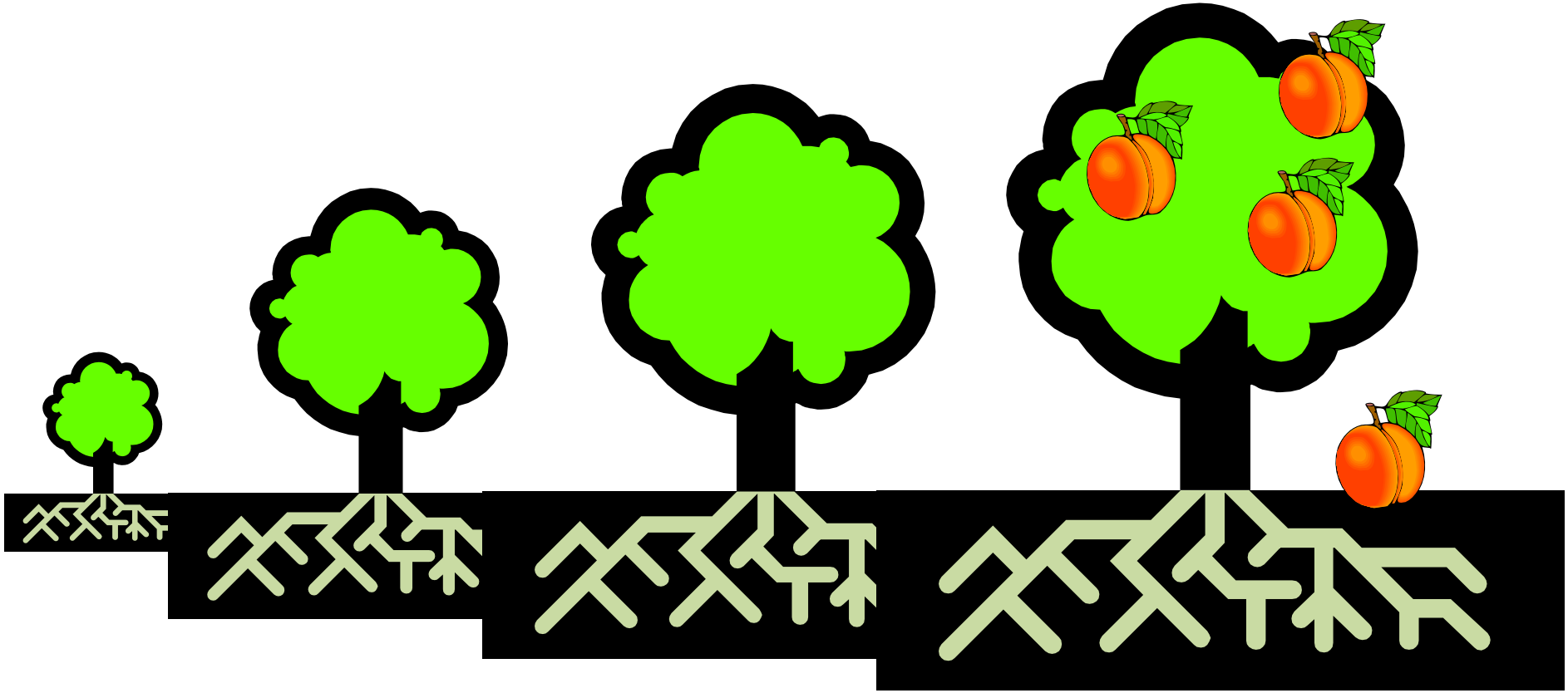
- 80-95% of HCCs are associated with chronic infection with Hepatitis B or C.

- HBV infection is preventable by immunization and HCV is preventable through public health measures.

- Universal vaccination at birth in East Asian countries is leading to a decline in HCC incidence and mortality.

CONCLUSION

Ø **Future research: HCV vaccine, new treatments for established HCC**



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PSA in Prostate Cancer Screening

Kamran Kafi, M.D, C.M, M.sc

Prostate Cancer

Subject Line

- 2nd most prevalent cancer in men world wide
  - Est 1.1 millsion men diagnosed in 2012
  - 15% of all cancers in med
- Risk Factors

  Age (median age 71 y/o; <15% younger than 65)

  Family History

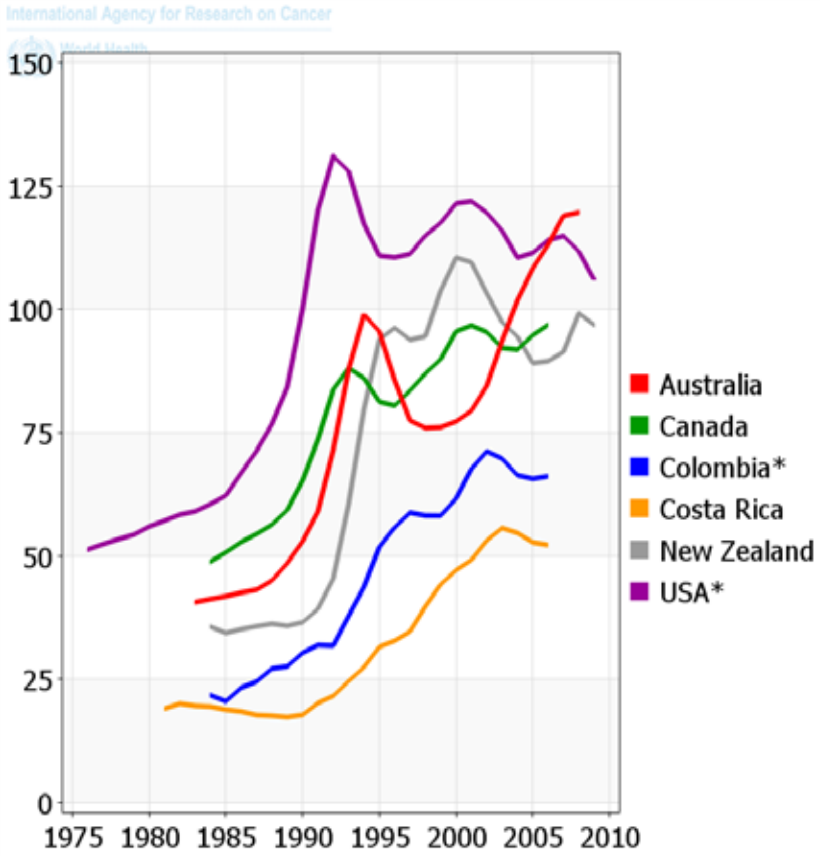
  Geographic location

  Race

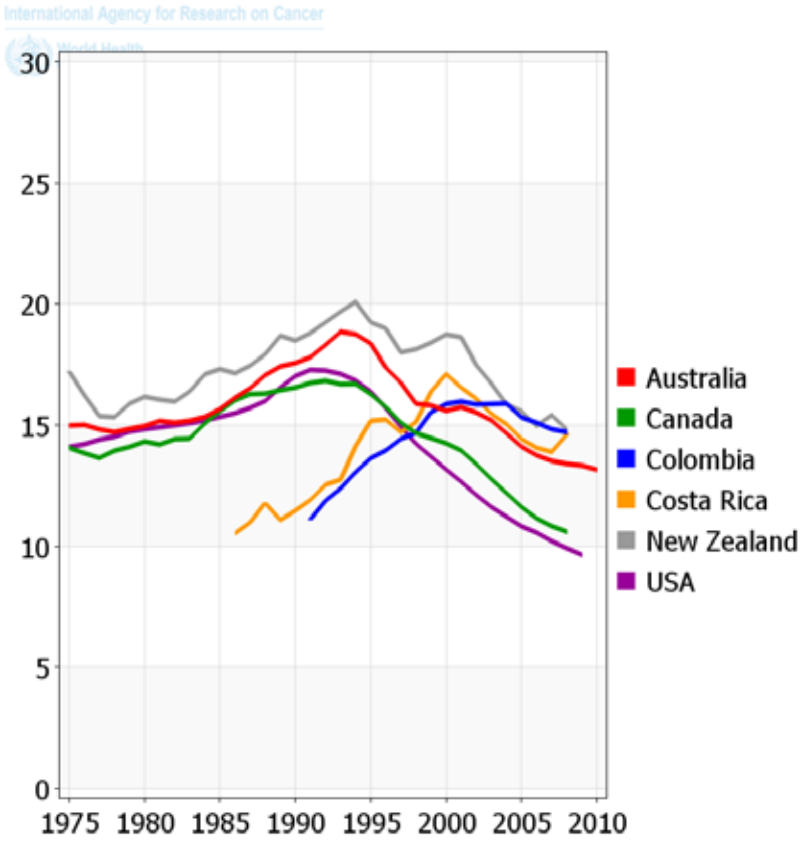
GLOBOCAN 2012

Trends in Prostate Cancer

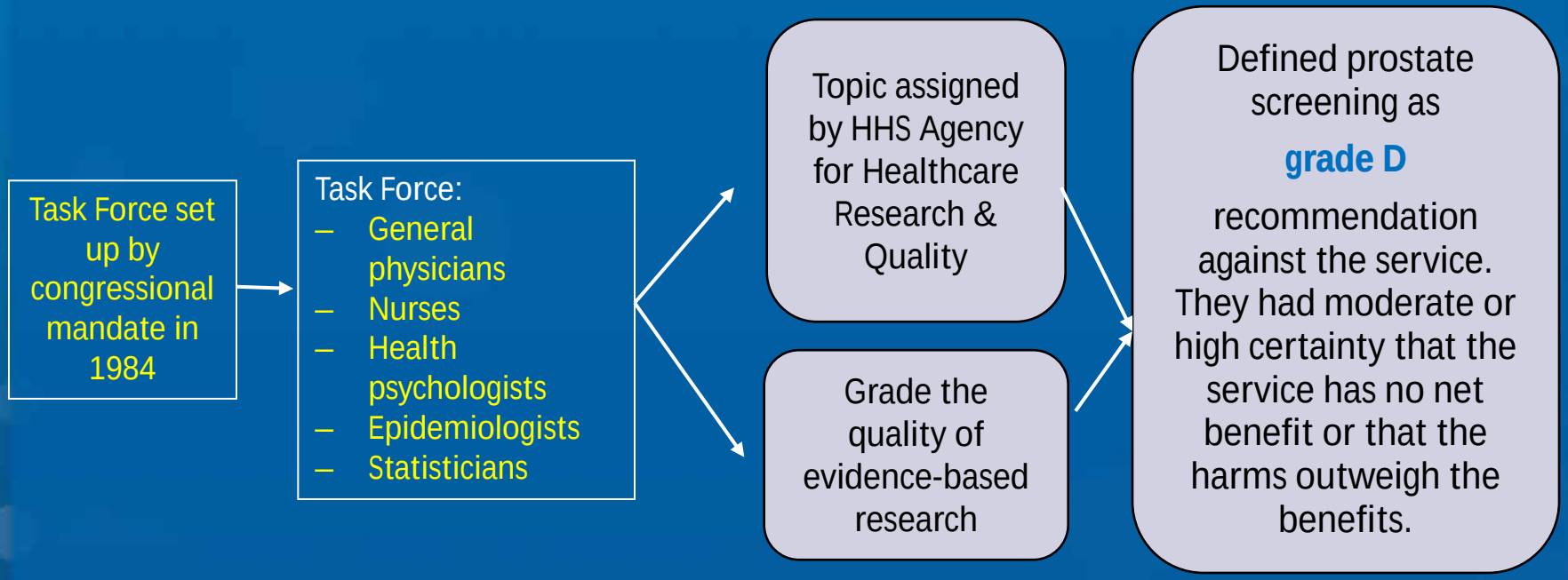
Incidence



Mortality



US Preventive Services Task Force
(USPSTF) Screening Recommendations



- Per the 2012 USPSTF, no healthy man should undergo PSA screening unless symptoms of prostate cancer present
- Full implications have yet to be realized

HHS=US Health & Human Services Department;.

Moyer VA, Ann Intern Med. 2012;157:120-34.

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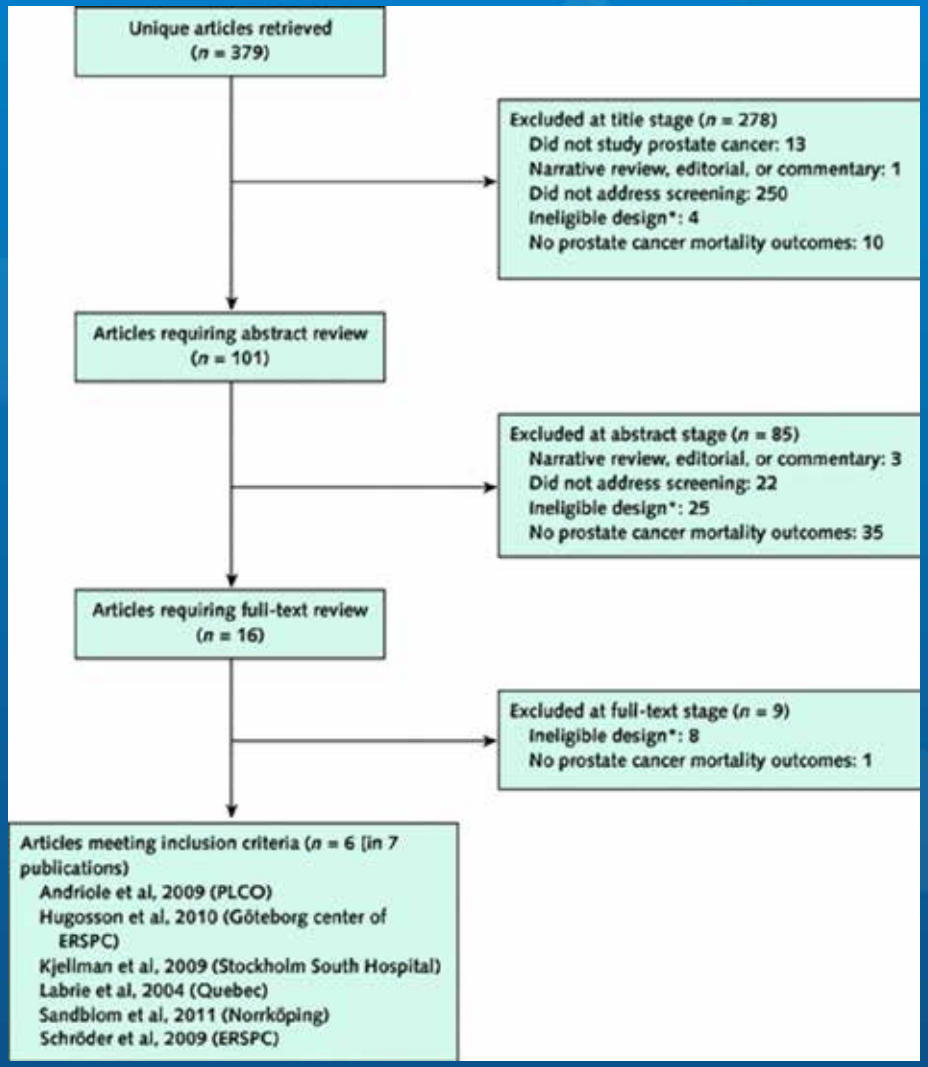
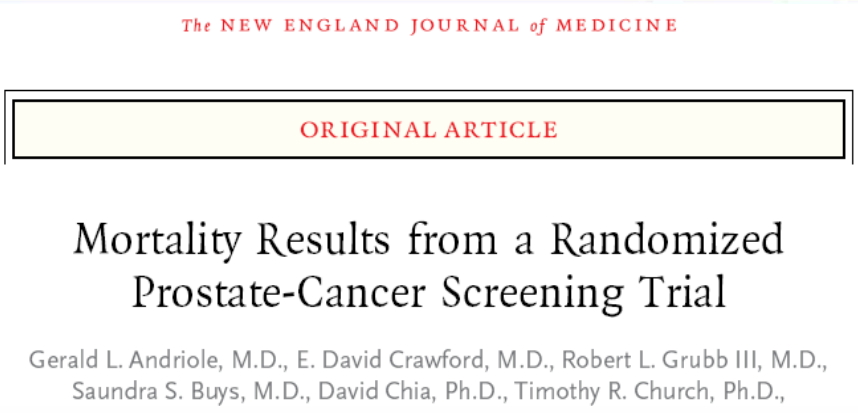


Figure Legend:

Summary of literature search and selection: effectiveness and harms of screening.BMJ = British Medical Journal; ERSPC = European Randomized Study of Screening for Prostate Cancer; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

* Not a randomized, controlled trial; systematic review; or meta-analysis; or was a nonrandomized analysis of a randomized,

PLCO



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D.,

Advance Access publication on January 6, 2012.

ARTICLE

Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up

Gerald L. Andriole, E. David Crawford, Robert L. Grubb III, Saundra S. Buys, David Chia, Timothy R. Church, Mona N. Fouad, Claudine Isaacs, Paul A. Kvale, Douglas J. Reding, Joel L. Weissfeld, Lance A. Yokochi, Barbara O'Brien, Lawrence R. Ragard, Jonathan D. Clapp, Joshua M. Rathmell, Thomas L. Riley, Ann W. Hsing, Grant Izmirlian, Paul F. Pinsky, Barnett S. Kramer, Anthony B. Miller, John K. Gohagan, Philip C. Prorok; for the PLCO Project Team

Manuscript received March 17, 2011; revised November 8, 2011; accepted November 9, 2011.

Correspondence to: Philip C. Prorok, PhD, Biometry Research Group, Division of Cancer Prevention, National Cancer Institute, 6130 Executive Blvd, Ste 3132, Bethesda, MD 20892-7354 (e-mail: prorokp@mail.nih.gov).

- 76 685 Men 55-74 years enrolled from 1993 – 2001 from 10 institutions

- Exclusion criteria: history of a PLCO cancer, current cancer treatment, and having >1 PSA test in past 3yrs

Intervention:

- Annual PSA testing x 6yrs then annual DRE x 4yrs

- PSA > 4.0 ng/mL was considered positive

- Advised to seek diagnostic evaluation with regional MD

Andriole 2009, 2012

PLCO

PLCO 13-year follow up (Andriole GL. JNCI 2012;104:1)

No PCa survival benefit for screening

- Not even for healthier men

12% higher incidence with screening

PLCO criticisms

High proportion of pre-screening with PSA (Nearly 2/3rds)

- Cancers in control group were stage I and II

High proportion of contamination (52% in control group)

- Patient in control group cont. to be screened as per gen. public

Low biopsy rate (68 per 10,000)

ERSPC

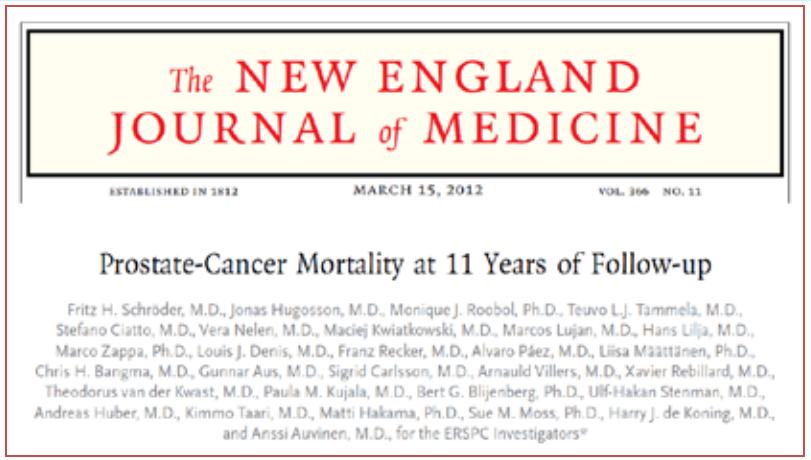
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D.,

- 182 000 men aged 50-74 years were enrolled between
- 1993 – 2003 from 7 European countries
- In 3 countries, randomized prior to informed consent, other 4 underwent randomization after informed consent
- 162 243 in core age group 55-69 years included in analysis



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 15, 2012 VOL. 366 NO. 11

Prostate-Cancer Mortality at 11 Years of Follow-up

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Alvaro Páez, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Sigrid Carlsson, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Paula M. Kujala, M.D., Bert G. Blijenberg, Ph.D., Ulf-Hakan Stenman, M.D., Andreas Huber, M.D., Kimmo Taari, M.D., Matti Hakama, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

Exclusion criteria: prostate cancer

Intervention: PSA q4 years (Sweden: q2 years)

PSA > 3.0 ng/mL was considered positive

Biopsy recommended and provided by screening centre

Schroder et al, NEJM 2009, 2012

ESRCP

§ European Randomized Study of Screening for Prostate Cancer (ERSPC) 11-year follow up
(Schroder FH. NEJM 2012;366:981)

- Screening reduced PCa mortality by 21%

  Absolute benefit low: 1.07 fewer deaths per 1,000

  (r[RR]: 0.80; 95% CI, 0.65–0.98; p = 0.04 ; NNS 1055, NNT 37

- Screening increased incidence by 63%

ERSPC

- ERSPC criticisms

  Variable randomization strategies, testing intervals, biopsy criteria

- Differential treatment
  - Screening-group cancers more likely to be treated in a university setting

ERSPC VS PLCO

Table. Comparing PLCO with ERSPC

	PLCO	ERSPC
Origin	United States	Europe
Patients	76,693	182,000
Age range	55-74 years	55-69 years
Randomization	Annual PSA and DRE vs. "usual care"	PSA and DRE every 4 years vs. no screening
% screened before entering study	Nearly 70%	Unknown, but likely very small
Contamination (controls screened)	52%	15%
Median follow-up	7 years	9 years
Increased chance of diagnosing prostate cancer with screening	17%	39%
Outcome	No significant difference in prostate cancer death	20% reduction in prostate cancer death (increasing with time)

MAYO CLINIC

USPSTF 2012 Recommendations

- "D" rating (Moyer VA. Ann Intern Med 2012;157:120)
  - Recommends against PSA screening for any man, regardless of age or risk factors
- Evidence synthesis (Chou R. Ann Intern Med 2011;155:762)
  - Systematic review of benefits and harms from screening, treatment
    - Heavily weighted PLCO and ERSPC trials

USPSTF 2012 Recommendations

Benefits (screening every 1 to 4 y for 10 y)	Men, n
10-year PCa death no screening	5 in 1000
10-year PCa death with screening	4-5 in 1000
Net benefit	0-1 in 1000

Harms (screening every 1 to 4 y for 10 y)	Men, n
False positive test	100-120 in 1000
Prostate cancer diagnosis	110 in 1000
Death (treatment)	< 1 in 1000
Urinary incontinence (treatment)	18 in 1000
Erectile dysfunction (treatment)	29 in 1000

Moyer VA. Ann Intern Med 2012;157:120

Responses to USPSTF

- Inappropriate to combine PLCO, ERSPC
- NNI similar to mammography for women in 40s, “C” rating
- Men should be supported in shared decision making
- Long-term benefits could be greater

Volk RJ. JAMA 2011;306:2715. Miller DC. JAMA 2011;306:2719.
Kim J. JAMA 2011;306:2717. McNaughton-Collins MF. NEJM 2011;365:1951.
Brett AS. NEJM 2011;365:1949.

American Urological Association

- GUIDELINE STATEMENTS
- 1: The Panel recommends against PSA screening in men under age 40 years. (Recommendation; Evidence Strength Grade C)
- 2: The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (Recommendation; Evidence Strength Grade C)
- 3: For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves **weighing the benefits of preventing prostate cancer against the known potential harms associated with screening and treatment**. For this reason, the Panel strongly **recommends shared decision-making for men age 55 to 69 years that are considering PSA screening**, and proceeding based on a man's values and preferences. (Standard; Evidence Strength Grade B)
- 4: To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening.
- 5: The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy. (Recommendation; Evidence Strength Grade C)

Other Considerations

- Benefits of PSA screening diminished by loss of quality-adjusted life years (QALY) (Heijnsdkijk EAM. NEJM 2012;367:595)
- If screened and positive
  - Prostate cancer intervention versus observation trial (PIVOT)
  - Active Surveillance strategy that delays curative treatment until it is warranted on the basis of defined indicators of disease progression" (Ganz PA. Ann Intern Med 2012:156:591)

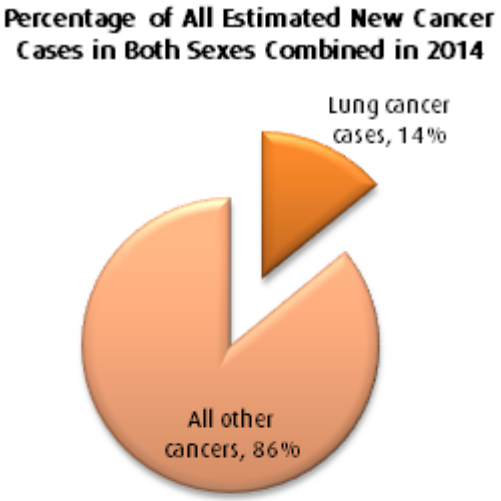
Lung Cancer Screening

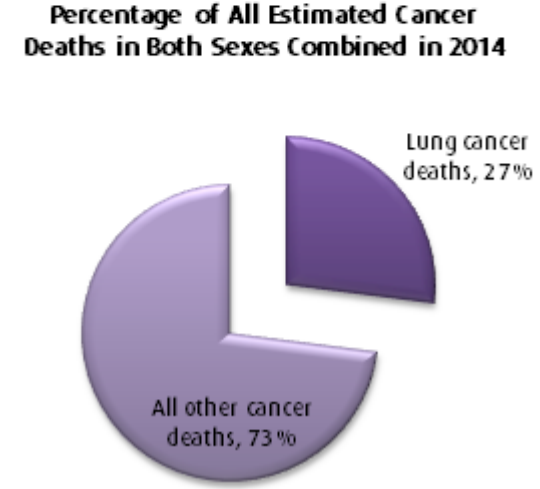
By: Reem AlBeesh
Radiation Oncology PGY-1

- Lung Ca is the leading cause of cancer death in both sexes.

Canadian cancer society estimated that in 2014:

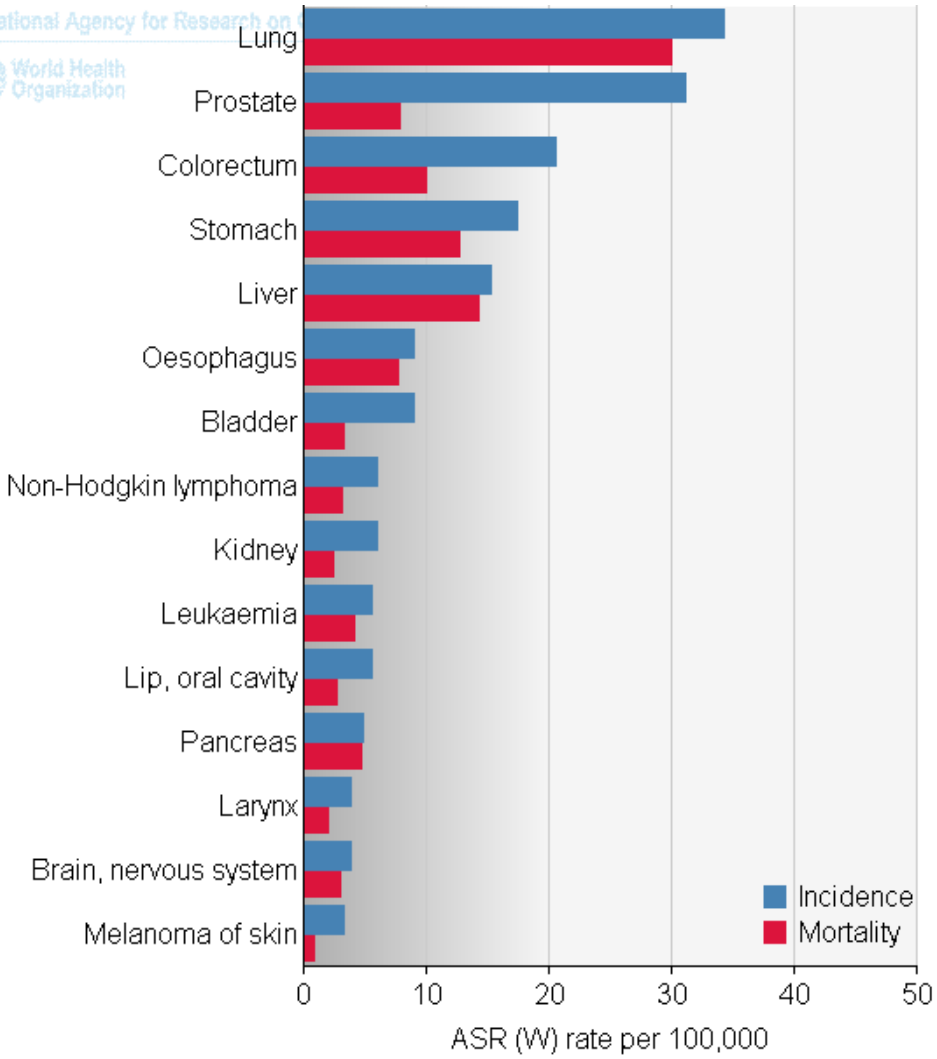
- 26,100 Canadians will be diagnosed with lung cancer.
- 20,500 Canadians will die from lung cancer.

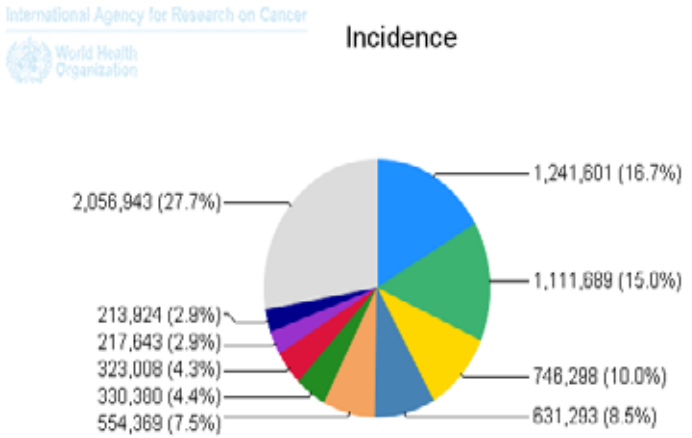


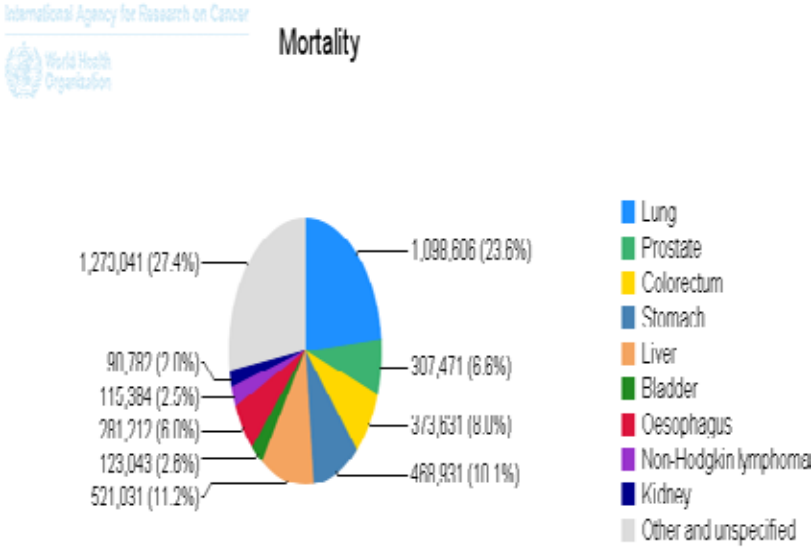


Canadian cancer

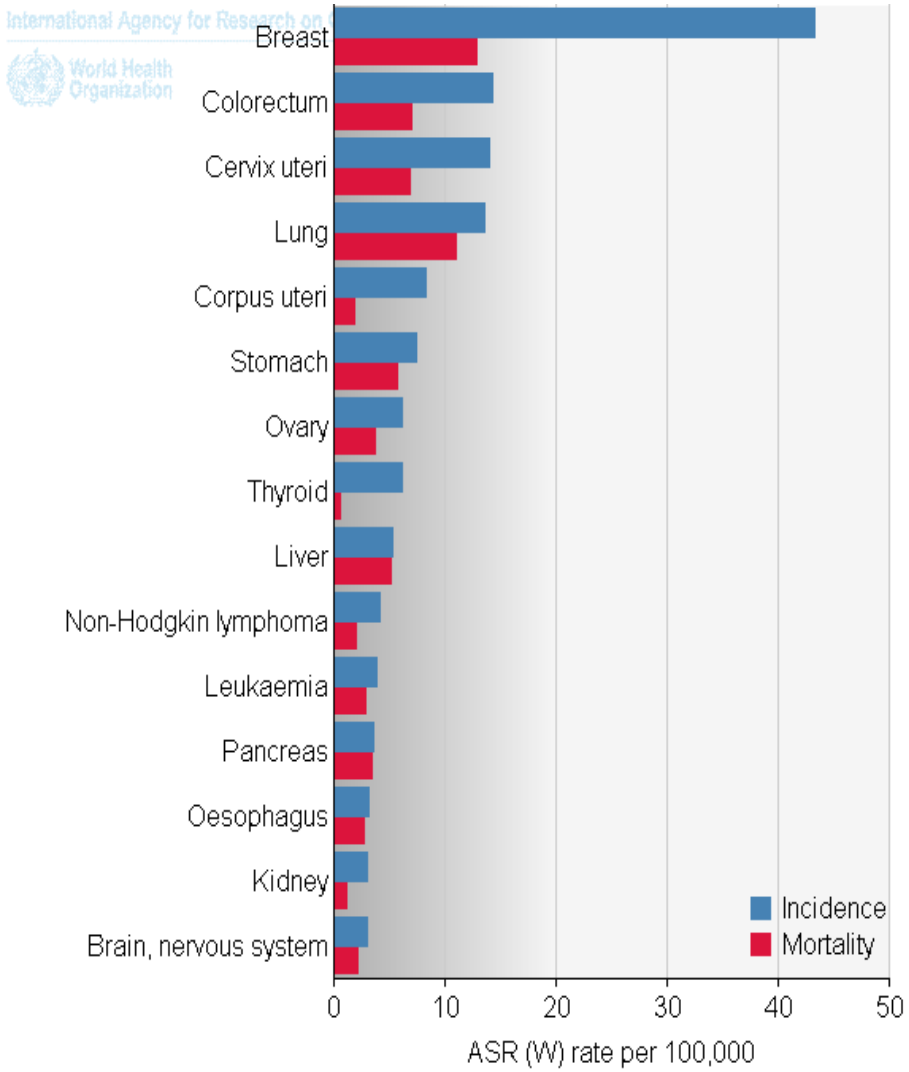
Estimated age-standardised incidence and mortality rates: men

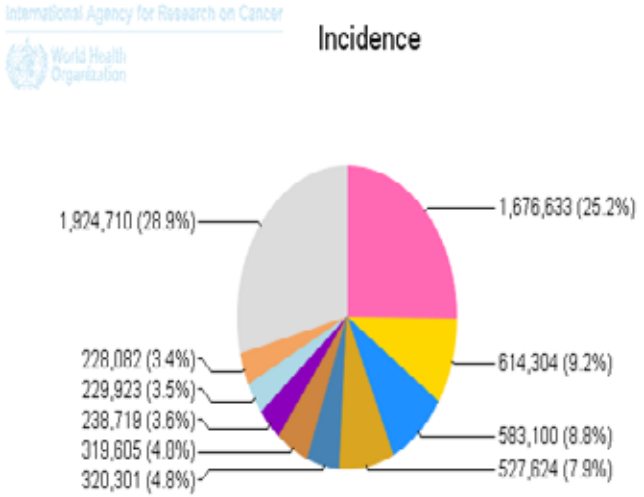


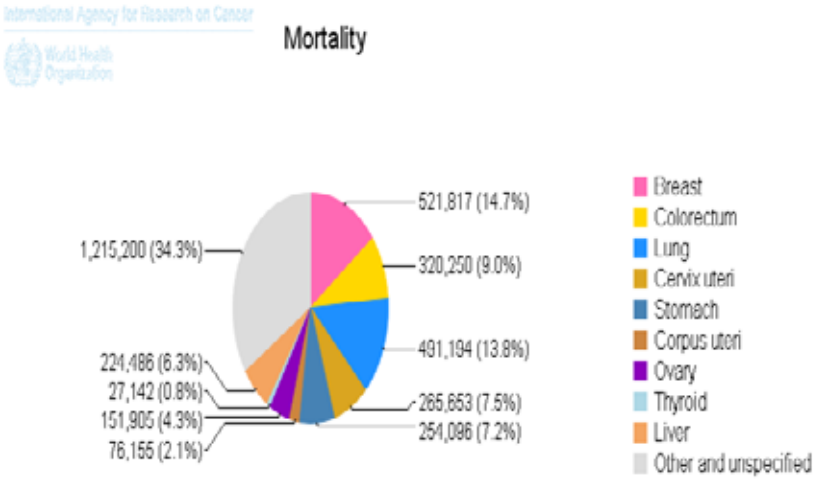




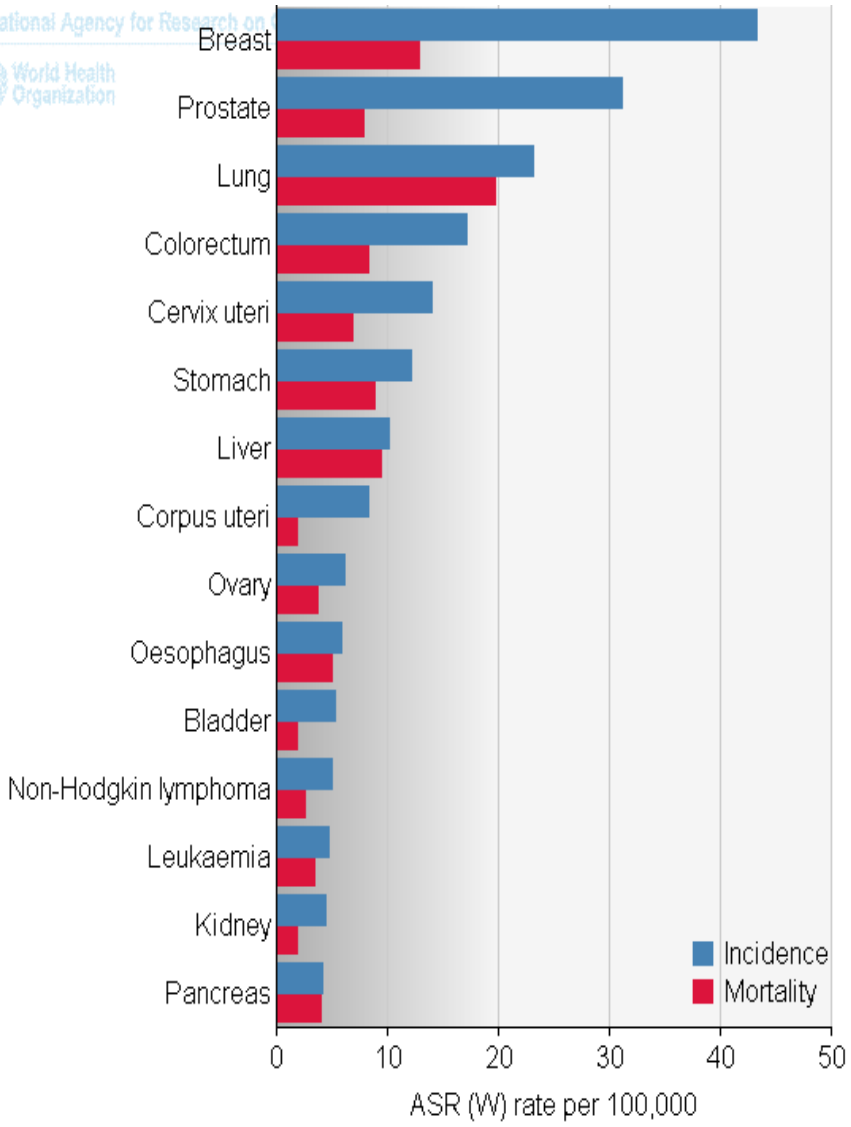
Estimated age-standardised incidence and mortality rates: women

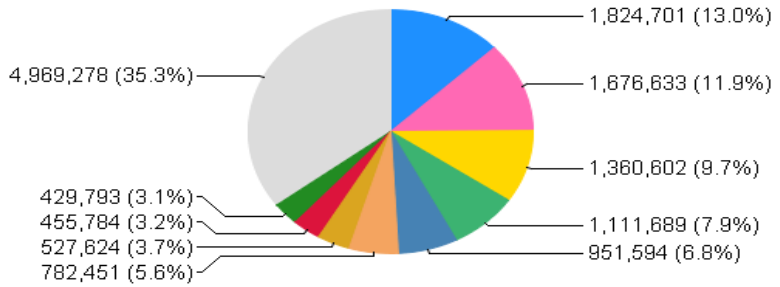


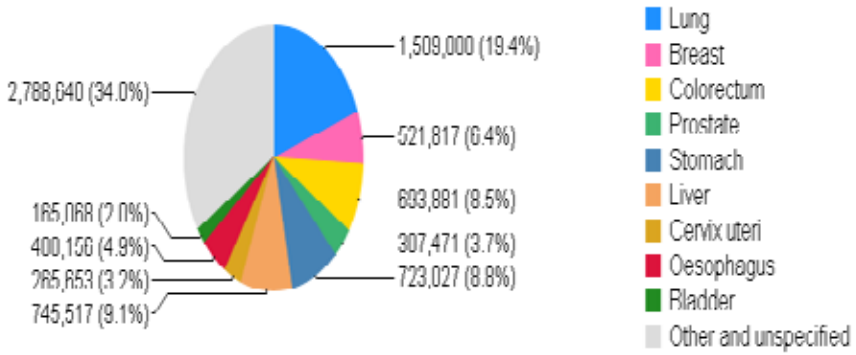




Estimated age-standardised incidence and mortality rates: both sexes







Risk factors

Risk factors	Possible risk factors
Smoking tobacco Second-hand smoke Radon Asbestos Outdoor air pollution Occupational exposure to chemical carcinogens Personal or family history of lung cancer Arsenic Previous lung disease Exposure to radiation Indoor burning of coal Weakened immune system Lupus	Smoking marijuana Indoor burning of wood High-temperature frying Diet Physical inactivity Occupational exposure to certain chemicals Removal of both ovaries

Clinically

- Types: NSCLC and SCLC
- Lung cancer has a poor prognosis
- In Canada: 5-year survival rate was 17% in 2013
- 5-year survival rates approach 70% with surgical resection of stage IA disease
- However, more than 75% of individuals have incurable locally advanced or metastatic disease, the latter having a 5-year survival of less than 5%

Canadian task force
Radiological Society of North America

Previous Research

Experience from Early Chest Radiographic Screening RCTs

Study	Intervention	No. of Participants	No. of Lung Cancers Detected at First Screening (Prevalence)	No. of Lung Cancers Detected After First Screening	No. of Stage III and IV Cancers*	Lung Cancer Mortality†‡	5-year Survival (%)†
Memorial Sloan-Kettering					173	N/A	35
Experimental arm	Annual chest radiography, sputum cytology every 4 mo	4968	30	146	…	…	…
Control arm	Annual chest radiography	5072	23	155	…	…	…
Johns Hopkins					N/A		N/A
Experimental arm	Annual chest radiography, sputum cytology every 4 mo	5226	39	194	…	3.4/1000 PY	…
Control arm	Annual chest radiography	5161	40	202	…	3.8/1000 PY	…
Mayo Lung Project				91 in all			
Experimental arm	Chest radiography, sputum cytology every 4 mo	4618	…	206	123§	4.4/1000 PY	35
Control arm	Recommended annual chest radiography, sputum cytology	4593	…	160	119§	3.9/1000 PY	19
Czechoslovakia				91 in all			
Experimental arm	Chest radiography and sputum cytology every 6 mo × 3 years, annually after year 3	3171	…	108	53	7.8%	…
Control arm	Chest radiography and sputum cytology annually after year 3	3174	…	82	46	6.8%	…

Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial

OBJECTIVE:

- To evaluate the effect on mortality of screening for lung cancer using radiographs

DESIGN, SETTING, AND PARTICIPANTS:

- RCT involved 154,901 participants aged 55-74 years
- November 1993-July 2001.
- The data from a subset of eligible participants for the National Lung Screening Trial (NLST), which compared chest radiograph with spiral computed tomographic (CT) screening, were analyzed.

INTERVENTION:

- Intervention group: annual P-A view chest radiograph for 4 years.
- Usual care group: usual medical care.
- All diagnosed cancers, deaths, and causes of death were ascertained through the earlier of 13 years of follow-up or until December 31, 2009.

MAIN OUTCOME MEASURES:

- Mortality from lung cancer.
- Secondary outcomes included lung cancer incidence, complications associated with diagnostic procedures, and all-cause mortality.

RESULTS

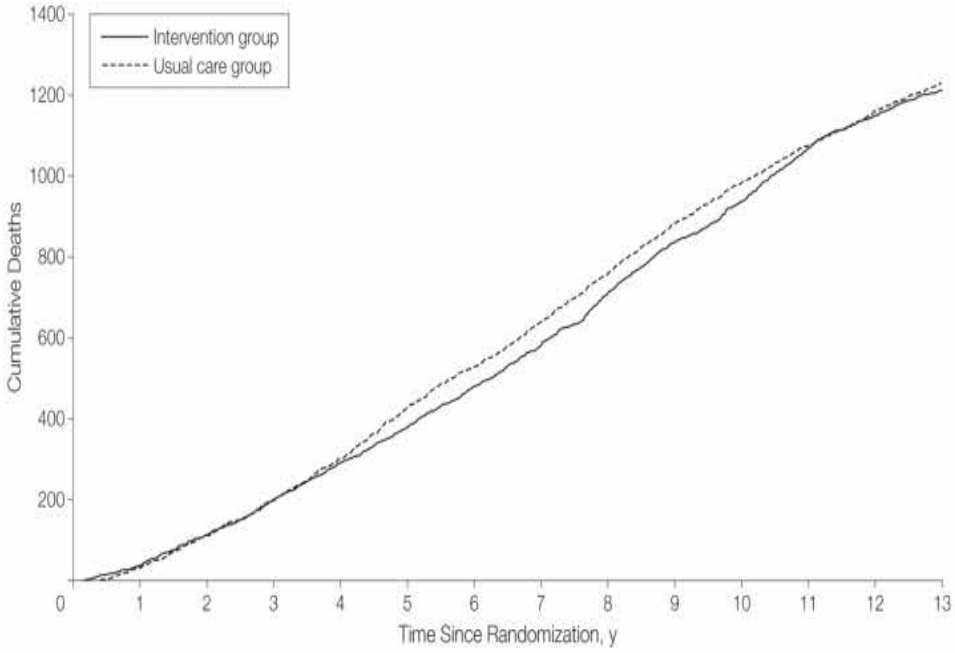
- A total of 1213 lung cancer deaths were observed in the intervention group compared with 1230 in usual care group through 13 years (mortality RR, 0.99; 95% CI, 0.87-1.22).
- The RR of mortality for the subset of participants eligible for the NLST, over the same 6-year follow-up period, was 0.94 (95% CI, 0.81-1.10).

CONCLUSION:

- Annual screening with chest radiograph did not reduce lung cancer mortality compared with usual care.

From: **Screening by Chest Radiograph and Lung Cancer Mortality: The Prostate, Lung, Colorectal, and Ovarian (PLCO) Randomized Trial**

JAMA. 2011;306(17):1865-1873. doi:10.1001/jama.2011.1591



Intervention group													
Cumulative deaths	36	113	196	292	378	480	582	711	838	937	1070	1150	1213
Cumulative person-years	77 268	154 053	230 270	305 833	380 691	454 773	527 937	600 004	670 274	735 098	789 540	832 441	864 227
Usual care group													
Cumulative deaths	30	111	198	301	426	527	639	761	884	987	1076	1162	1230
Cumulative person-years	77 286	154 116	230 348	305 902	380 725	454 719	527 804	599 790	669 955	734 523	788 854	831 678	863 330

Figure Legend:

From: **Screening by Chest Radiograph and Lung Cancer Mortality: The Prostate, Lung, Colorectal, and Ovarian (PLCO) Randomized Trial**

JAMA. 2011;306(17):1865-1873. doi:10.1001/jama.2011.1591

Table 5. Results for National Lung Screening Trial Subset

	Intervention Group (n = 15 183)	Usual Care Group (n = 15 138)	Rate Ratio (95% CI)
Men, No. (%)	9252 (60.9)	9110 (60.2)	
Current smoker, No. (%)	6146 (40.5)	6069 (40.3)	
Median pack-years	52.0	52.5	
Adherence with baseline screen, No. (%)[a]	13 035 (85.9)		
Overall adherence, No. (%)[a]	48 330 (81.4)		
Results through 6 y of follow-up			
Diagnosed cases, No.	518	520	1.00 (0.89-1.13)
Person-years for incidence	85 428	85 474	
Lung cancer deaths, No.	316	334	0.94 (0.81-1.10)
Person-years for death	87 473	87 198	

[a] Percentage of expected screens.

Figure Legend:

The RR of mortality for the subset of participants eligible for the NLST, over the same 6-year follow-up period, was 0.94 (95% CI, 0.81-1.10).

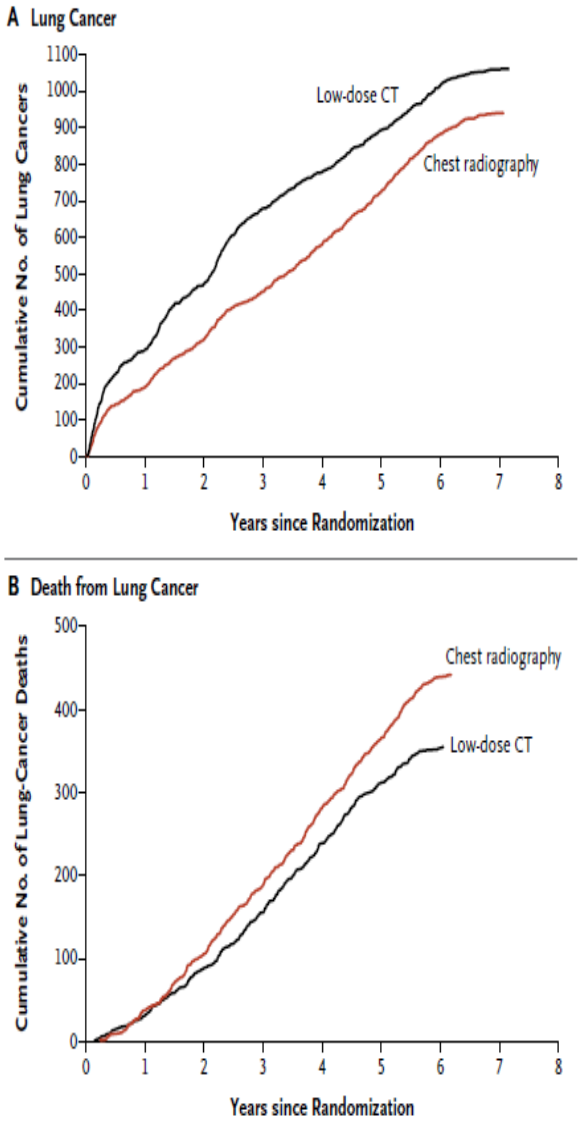
The National Lung Screening Trial

- The largest RCT
- Compared LDCT Vs chest radiography in the screening of participants aged 55-74 yrs with hx of cig. Smoking of at least 30 pack-yr and if former smoker who had quit within 15 yrs.
- Enrolled 53,454 participants between Aug. 2002 - April 2004
- F/U until December 31, 2009
- Participants were randomized to undergo 3 annual screenings with either low-dose CT or single-view P-A chest radiography
- Primary endpoint: Lung cancer mortality

Results

- Reduction in mortality from lung cancer of 20.0% (95% CI, 6.8-26.7; P=0.004).

- The rate of death from any cause was reduced in the LDCT group compared with the radiography group, by 6.7% (95% CI, 1.2-13.6; P=0.02).



- **The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years.**

- **Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.**
  Grade: B recommendation.

http://www.uspreventiveservicestaskforce.org/uspstf/uspslung.htm

unresolved questions about

- Optimal frequency and duration of screening
- Likelihood of harms
- Cost-effectiveness
- Generalizability of the NLST for patients who receive less comprehensive F/U or have limited access to the health-care system.

Other issues:

- Overdiagnosis
- Death from follow-up testing, Hospitalization or medical intervention
- False positives and consequences (e.g. overtreatment)
- Negative consequences of incidental findings (e.g Dx of COPD)
- Anxiety
- Quality of life
- Infection or bleeding from follow-up testing

References

- www.globocan.iarc.fr
- Canadian cancer society
- www.canadiantaskforce.ca/perch/resources/lung-cancer-protocol-v2-0-final.pdf
- U.S. Preventive Services Task Force
- The JAMA network
- Screening by Chest Radiograph and Lung Cancer MortalityThe Prostate, Lung, Colorectal, and Ovarian (PLCO) Randomized Trial *JAMA.* 2011;306(17):1865-1873. doi:10.1001/jama.2011.1591
- Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening, NEJM. 2011 VOL.365 NO.5
- Radiological Society of North America http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3009383/#!po=11.9048

Chemopreventive Agents in Hepatocellular carcinoma

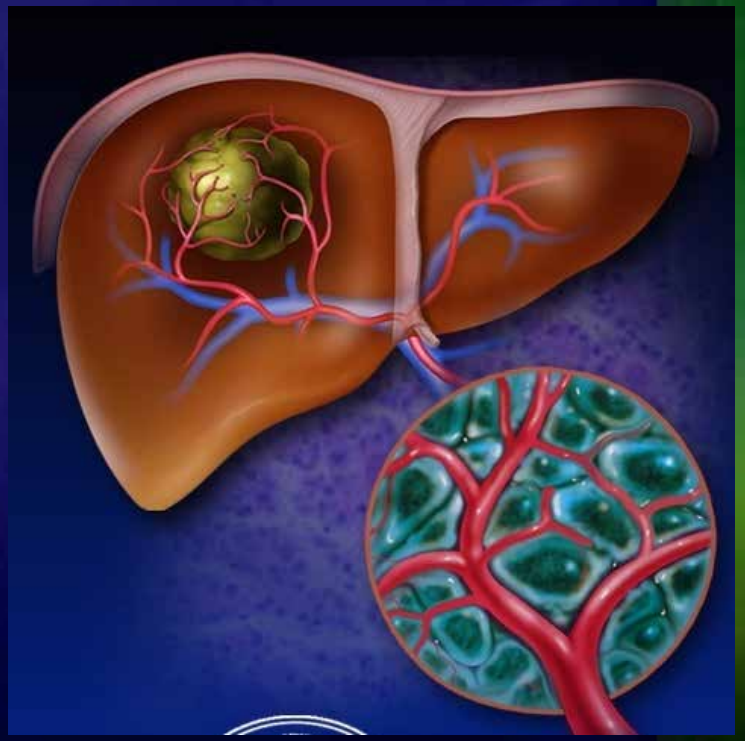
Mamatha Bhat, MD

EPIB-671 Cancer Epidemiology & Prevention
Course presentation

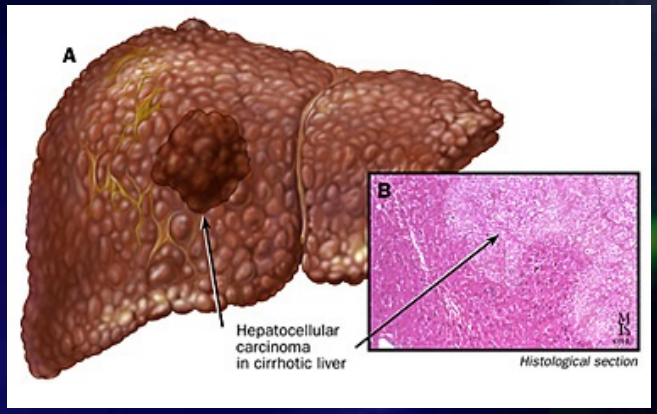
June 20th, 2014

Outline

- Epidemiology of HCC
- Chemoprevention through Antivirals
- Chemoprevention through medications that affect Metabolism/Inflammation:
- i) Metformin
- ii) Statins
- Iii) Aspirin
- Chemoprevention through diet:
- i) Coffee
- ii)Vitamin E
- iii) Fish
- Iv) Curcumin, Reservatrol



Epidemiology



- 5th most common tumor worldwide
- Rising incidence in US & Europe
- Rising incidence of cirrhosis, especially with obesity epidemic
    - HCV, NAFLD, HBV
- Only 13% of HCCs diagnosed in U.S. detected early enough to for curative therapy (surgical resection or liver transplant) Howlader N. *et al. SEER Cancer Statistics Review 1975–2010. National Cancer Institute [online]*
- 5-year survival rate in U.S. is 15%
- Chemoprevention attractive to prevent HCC in patients at known risk, particularly if limited risk of side effects

Chemoprevention through antivirals: HBV

- Decreased viral replication, inflammation => less HCC
- **Lamivudine**: Prospective, randomized, placebo-controlled trial in 651 patients with HBV and advanced fibrosis or cirrhosis
- 3.9% on LAM developed HCC, compared with 7.4% on placebo (P = 0.047) at 2.8 years follow-up (Liaw et al., NEJM, 2004)
- **Level 1 evidence**
- Meta-analysis of 5 studies (2 RCTs, 3 cohort):
- 2,289 patients, risk of HCC 78% lower in LAM (2.5%) vs untreated (11.7%); P = 0.01 (Sung et al. APT 2005)
- **Level 1 evidence**
- **Entecavir**: Prospective cohort study 1,615 patients, 5-year cumulative incidence of HCC in entecavir-treated patients was 3.7%, compared with 13.7% in non-treated (p<0.01)

  (Hosaka et al., Hepatology 2013)
- **Level 3 evidence**

Chemoprevention through antivirals: HCV

- **IFN**: Meta-analysis of 9 RCTs in 1,614 patients with HCV, treatment with IFN => SVR had decreased HCC, compared with patients who did not receive treatment (RR 0.39; 95% CI 0.26–0.59) (Zhang et al., Int J Cancer 2011)
- **Level 1 evidence**
- Hepatitis C Antiviral Long Term Treatment against Cirrhosis trial (180 patients): adjusted cumulative incidence of HCC 7.5 years after enrolment was 1.1% (SVR), 5.5% (relapse after initial response) and 8.8% (non-responders)

(Morgan et al, Hepatology 2010)

Level 3 evidence

Chemoprevention: Statins

- Inhibit cholesterol biosynthesis, antiproliferative, proapoptotic, antiangiogenic, immunomodulatory effects
- Taiwanese National Health Insurance Research Database (TNHIRD)
- 33,413 HBV-infected followed from 1997 to 2008 (8.3% on statin)
- HCC Incidence rate (per 100,000 person years): 210.9 in patients receiving statins, 319.5 in non-users (P <0.01)
- Adjusting for age, sex, cirrhosis, diabetes and medications, statin users had 53% lower risk of HCC than non-users

(Tsan et al, J Clin Onc 2012) **Level 3 evidence**

- Meta-analysis of 10 studies (7 observational, 3 RCTs): 4,298 cases of HCC in ~1.5 million patients, statin users 37% less likely to develop HCC (adjusted OR 0.63; 95% CI 0.52–0.76)

(Singh et al, Gastroenterology 2013) **Level 1 evidence**

- Caveats: Most studies did not adjust for concomitant use of antidiabetic meds, statins avoided in patients with cirrhosis

Chemoprevention: Metformin

- **Metformin** decreased HCC in dose-dependent manner in TNHIRD nationwide case-control study
- 97,430 HCC patients and 19,860 age-, gender- and physician visit date-matched controls
- Each incremental year increase in metformin use resulted in 7% reduction in risk of HCC in diabetic patients (adjusted OR 0.93, 95% CI 0.91 to 0.94, p<0.0001) (Chen et al, Gut 2012) **Level 3 evidence**
- TNHIRD: 19,349 newly diagnosed DM patients 20 years and older and 77,396 comparison subjects without DM identified from claims from 2000 to 2005
- Incidences of HCC at end of 2008 => 51% RR of HCC on metformin (Lai, Am J Gastro 2012) **Level 3 evidence**
- **Insulin**: Meta-analysis of 7 observational studies 22,650 cases of HCC in 334,307 patients with type 2 DM : insulin associated with 2.6-fold increased HCC (95% CI 1.46–4.65)

(Singh S et al, Gastro 2013) **Level 3 evidence**

Chemoprevention: Aspirin

- **Aspirin:** Anti-inflammatory, antineoplastic effects against inflammation-mediated cancers
- National Institutes of Health-AARP Diet and Health Study cohort: prospective data on 300,504 men and women aged 50 -71 in NIH–AARP Diet and Health Study
- Cox proportional hazard regression models with adjustment for age, sex, race/ethnicity, cigarette smoking, alcohol consumption, diabetes, and BMI
- Aspirin use associated with 41% lower risk of HCC
- Sensitivity analysis excluding patients who developed HCC or died within 5 years of reported aspirin use showed persistent protective association
  (Sahasrabudhe et al, J Natl Cancer Inst. 2012)
- **Level 3 evidence**

Chemoprevention: Phytochemicals

- **Coffee**: antioxidants, diterpenes, which modulate enzymes in carcinogen detoxification
- Meta-analysis of 14 studies (8 cohort, 6 case–control; 2,733 cases of HCC)
- => 43% decline in HCC in those who consumed coffee (OR 0.57; 95% CI 0.49–0.67)
- For each cup per day, risk decreased by 23%
- (Bravi et al., Hepatology 2009)
- **Level 3 evidence**
- **Reservatrol, Curcumin** *in vitro* and *in vivo* evidence only

Chemoprevention: Phytochemicals

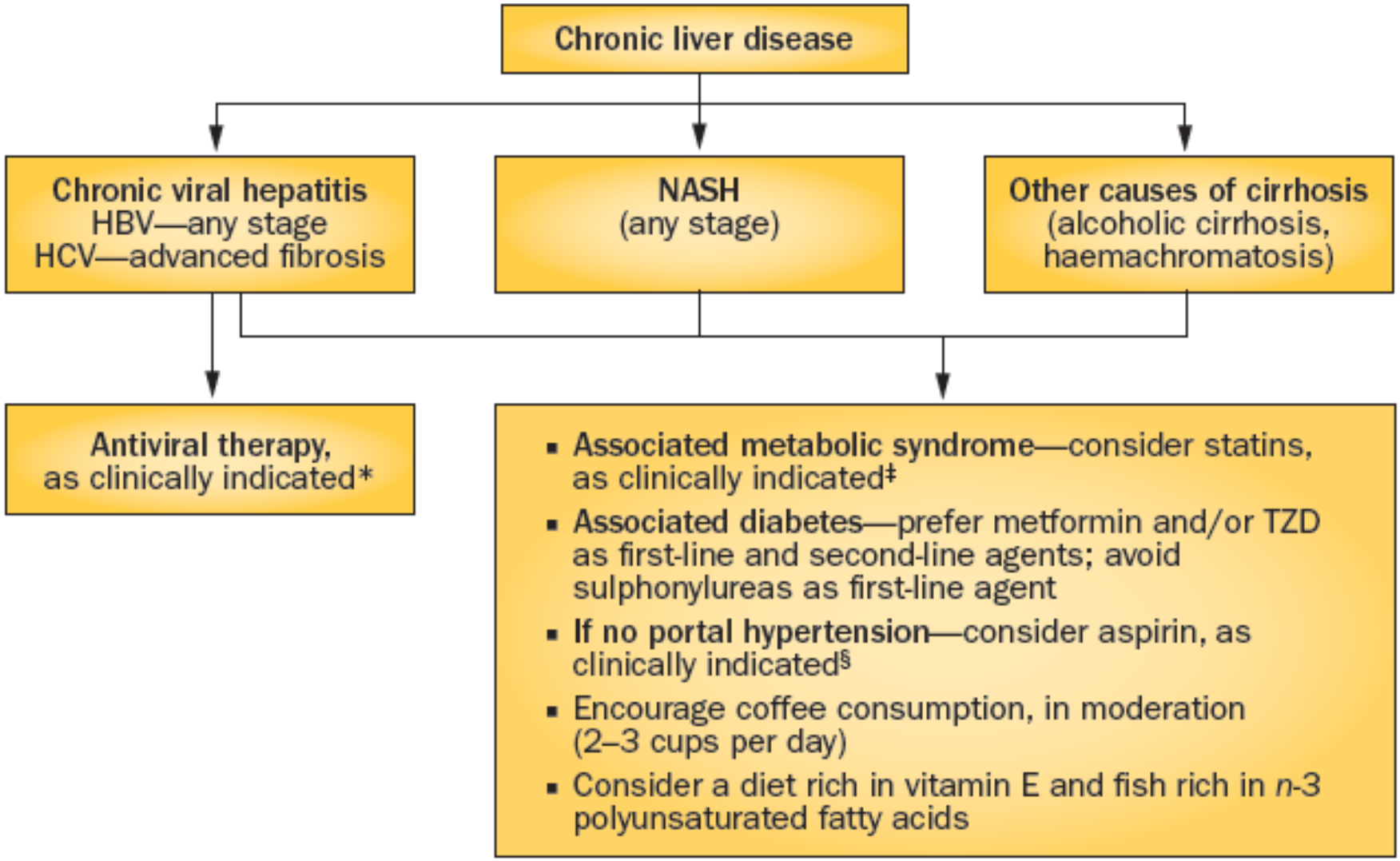
- **Vitamin E:** potent antioxidant effect, prevents DNA damage, enhances DNA repair and inactivation of carcinogens
- Shanghai Women's and Men's Health Study (prospective population-based cohorts with total of 132,837 individuals)
- Lower risk in highest quartile of dietary vitamin E intake than in lowest (RR 0.60; 95% CI 0.40–0.89)
- (Zhang et al, J Natl Cancer Inst 2012) **Level 3 evidence**
- **Fish**: In Japan Public Health Center population-based cohort study (90,296 subjects), dietary consumption of fish rich in n-3 polyunsaturated fatty acids
- => 36% reduced risk of HCC (RR 0.64; 95% CI 0.42–0.96, compared with the lowest quintile of consumption) in dose-dependent manner
- (Sawada et al. Gastroenterology 2012) **Level 3 evidence**

Summary: Chemoprevention in HCC

- Antiviral therapies: effective in 1^0 prevention **(Level 1)**
- Statin use leads to decreased risk of HCC, by inhibiting Myc activation and mevalonate pathway

  (Level 1, although did not adjust for use of antidiabetic meds)
- Metformin reduces HCC risk through mTOR inhibition **(Level 3, did not adjust for use of statins)**
- Insulin/ insulin-secreting agents might increase risk **(Level 3)**
- Aspirin: early epidemiological studies show decreased HCC incidence **(Level 3)**
- Coffee, vitamin E, fish rich in *n*-3 polyunsaturated fatty acids might have antineoplastic effects **(All Level 3)**

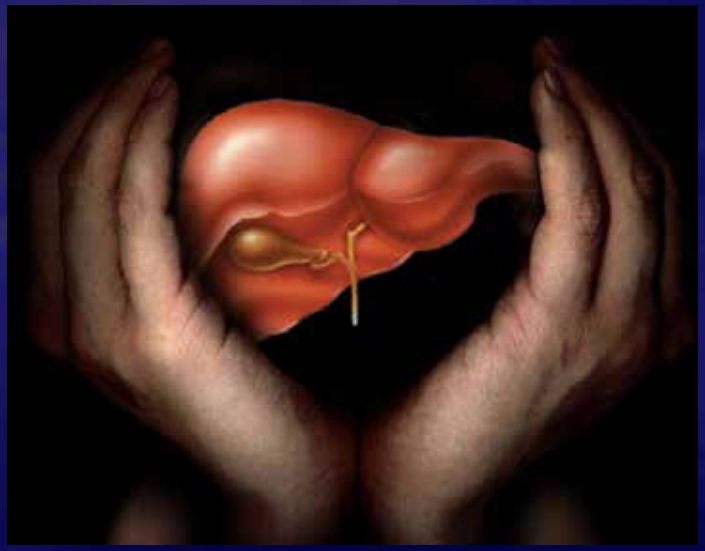
Algorithm for chemoprevention



Singh S *et al. Nat. Rev. Gastroenterol. Hepatol. 2014* 11,45–54

Summary: Chemoprevention in HCC

- RCTs logistically challenging in patients with chronic liver disease, concerns for use of certain medications in cirrhosis
- Prospective cohort studies adjusting for relevant confounders likely best to evaluate these agents



Gastric Cancer

Environmental Risk Factors

Gastric Cancer

- In the world, 3rd leading cause of cancer death in men and the 5th leading cause in women (American Cancer Society , 2008)

- Highest incidence rates in Asia (particularly Korea, Japan, and China) and many parts of South America

Global Cancer Facts & Figures 2nd eds. American Cancer Society.
http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-027766.pdf

Gastric Cancer
Histological Variations

- Adenocarcinoma (90-95%)
- Lymphomas (1-5%)
- Gastrointestinal stromal tumors (GIST) (2%)
- Others (carcinoids, adenoacanthomas, squamous cell carcinomas) (3%)

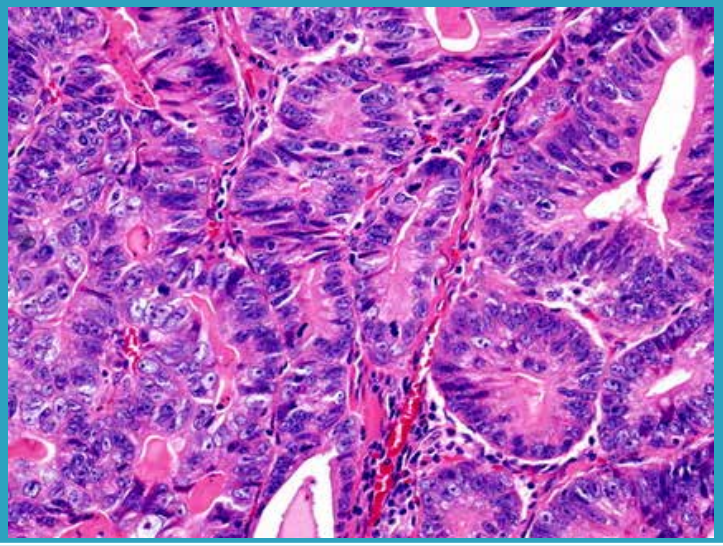
Two types of Gastric Adenocarcinoma

Intestinal:

Grossly, can be polypoid or ulcerated.

Histologically, forms glands.

Resembles colon cancer



Diffuse:

Extends widely with no distinct margins. One variant is Linitis Plastica (leather bottle)

Histologically, rarely forms glands. Often see "signet ring cells"

Worse prognosis.

Environmental Risk factors

- Salt and salt-preserved foods
- Nitroso compounds
- Diets low in fruits and vegetables
- Helicobacter pylori
- Tobacco
- Alcohol

- Bonus: Blood group A

Salt and salt-preserved foods

— Substantial evidence from ecological, case-control, and cohort studies

- Salted fish, cured meat, salted vegetables. And plain salt.

Salt is thought to damage stomach mucosa à induced proliferation à increases susceptibility to food-derived carcinogenesis (and possibly H. pylori)

Decline in gastric cancer worldwide in last 50 years may be attributed to refrigeration.

Int J Cancer. 2006;119(1):196
Br J Cancer. 2011;104(1):198

Salt intake and gastric cancer risk according to Helicobacter pylori infection, smoking, tumour site and histological type. Br J Cancer. 2011;104(1):198.

Nitroso Compounds

- Compounds containing an -NO group (ex: nitrosamines)

- Exposure from diet, tobacco smoke, and other environmental sources
  - 40-75% of total exposure is from endogenous synthesis!

Nitrates from food à Nitrites à NO compounds

(due to oral bacteria, acidic pH of stomach)

Nitroso Compounds

- Nitrites are added to cured and processed meats to enhance color and to extend shelf life.
- Meta-analysis of 15 studies:

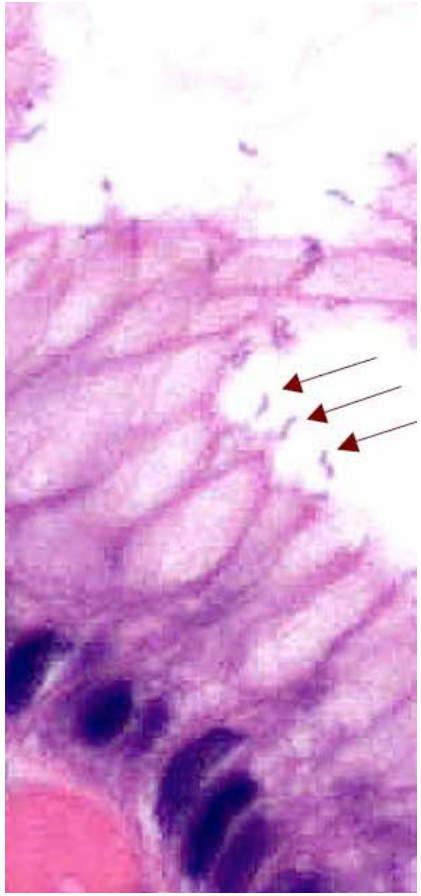
  RR of gastric cancer associated with consumption of >30 g/day of processed meat was 1.15 (95% CI 1.04-1.27)

Larsson SC, Orsini N, Wolk A. Processed meat consumption and stomach cancer risk: a meta-analysis. J Natl Cancer Inst 2006; [illegible]1078.

Diets Poor in Fruits and Vegetables

- Case-control studies[1]: Decreased gastric cancer risk between highest intake group and lowest intake group:
  - Fruits: ~40% decrease (≥2.6 vs ≤1.5 servings/day)
  - Vegetables: ~30% decrease (≥2.4 vs ≤1.3 servings/day)
- Cohort studies[2]: less consistent. In particular, vegetables not as protective. (RR 0.96, 95% CI 0.88-1.06)
- Vitamin C content may be the reason
  - Vit C likely reduces the formation of carcinogenic N-nitroso compounds inside the stomach.

Helicobacter pylori



- Classified by International Agency for Research on Cancer (IARC) as a Group 1 (definite carcinogen).
- The most common cause of gastritis is H. pylori.
- H. pylori gastritis has a role in cancer development:

Chronic gastritis à chronic atrophic gastritis à intestinal metaplasia à dysplasia à Adenocarcinoma

- H. pylori infection: 6-fold increase in gastric adenocarcinomas, including **both** the intestinal and diffuse types.

Effect of diet and Helicobacter pylori infection to the risk of early gastric cancer. J Epidemiol. 2003;13(3):162.

Tobacco

- Risk increased by approximately 1.53-fold (higher in men).
- This risk diminished after 10 years of smoking cessation.
- Approximately 18% of gastric cancer cases were attributed to smoking.

Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control. 2008 Sep;19(7):689-701. Epub 2008 Feb 22.

Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). Int J Cancer. 2003;107(4):629.

Alcohol

- Meta-analysis results from 44 case-control and 15 cohort studies: 34 557 gastric cancer cases:
  - ≥4 drinks/day associated with pooled RR 1.20 (95% CI 1.01-1.44).[1]

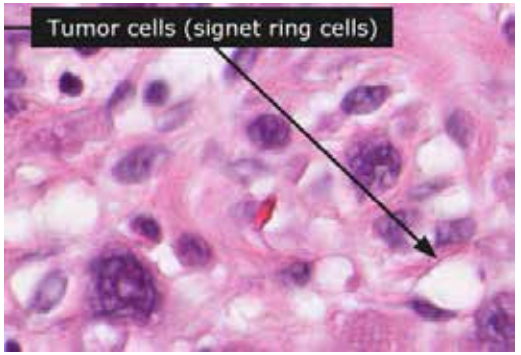
- Not all alcohol created equal
  - Intake of wine may be protective. [2]

1. A meta-analysis on alcohol drinking and gastric cancer risk. Ann Oncol. 2012 Jan;23(1):28-36. Epub 2011 May 2.

2. Intake of wine, beer and spirits and risk of gastric cancer. Grønbaek M. Eur J Cancer Prev. 2005;14(3):239.

Bonus: Blood Group A

- Blood Group A associated with especially with diffuse type of gastric cancer.
- Cohort Study: Swedish and Danish blood donors with known blood type followed for the occurrence of gastric cancer:
  - 1,089,022 donors, followed for up to 35 years. 688 gastric cancer cases
- Confirmed an increased risk of gastric cancer among individuals with blood group A (incidence rate ratio = 1.20, 95% confidence interval: 1.02- 1.42)



WHY?
Maybe because of different susceptibilities and immunologic responses to *H. pylori* infection

Risk of gastric cancer and peptic ulcers in relation to ABO blood type: a cohort study. Edgren G, Hjalgrim H, Rostgaard K, Norda R, Wikman A, Melbye M, Nyrén O Am J Epidemiol. 2010;172(11):1280.

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- Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). González CA, Pera G, Agudo A, Palli D, Krogh V, Vineis P, Tumino R, Panico S, Berglund G, Simán H, Nyrén O, Agren A, Martinez C, Dorronsoro M, Barricarte A, Tormo MJ, Quiros JR, Allen N, Bingham S, Day N, Miller A, Nagel G, Boeing H, Overvad K, Tjonneland A, Bueno-De-Mesquita HB, Boshuizen HC, Peeters P, Numans M, Clavel-Chapelon F, Helen I, Agapitos E, Lund E, Fahey M, Saracci R, Kaaks R, Riboli E. Int J Cancer. 2003;107(4):629.

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- Fruit and vegetable consumption and gastric cancer by location and histological type: case-control and meta-analysis. Lunet N, Valbuena C, Vieira AL, Lopes C, Lopes C, David L, Carneiro F, Barros H. Eur J Cancer Prev. 2007;16(4):312.
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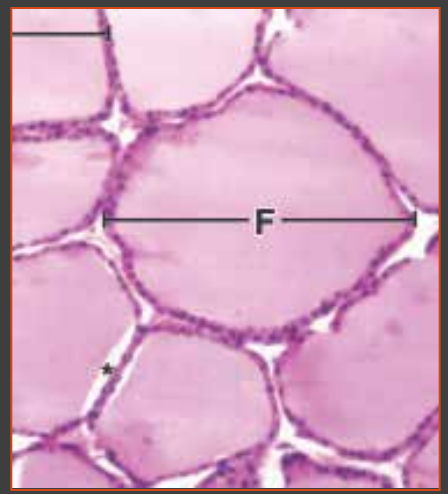
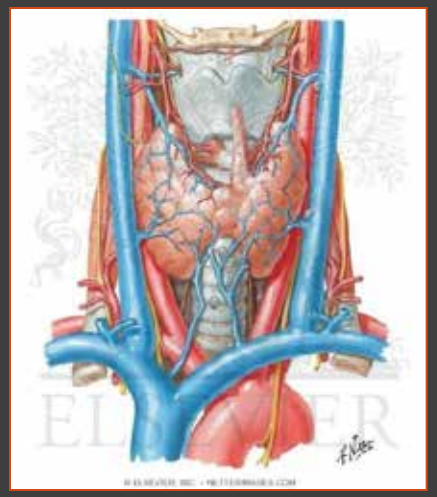




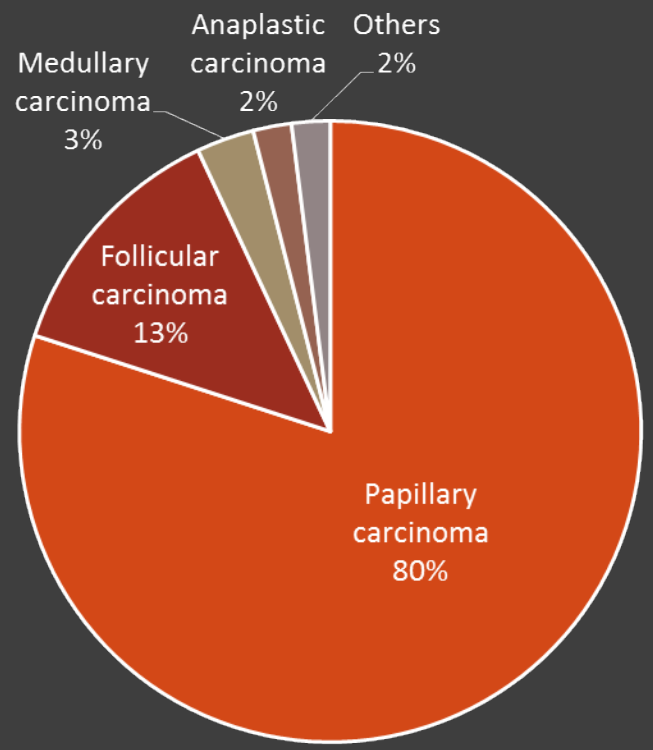
Epidemiology of Thyroid Cancer

DUC-VINH THAI

PGY-1 ANATOMICAL PATHOLOGY

EPIB-671 SYMPOSIUM 2014

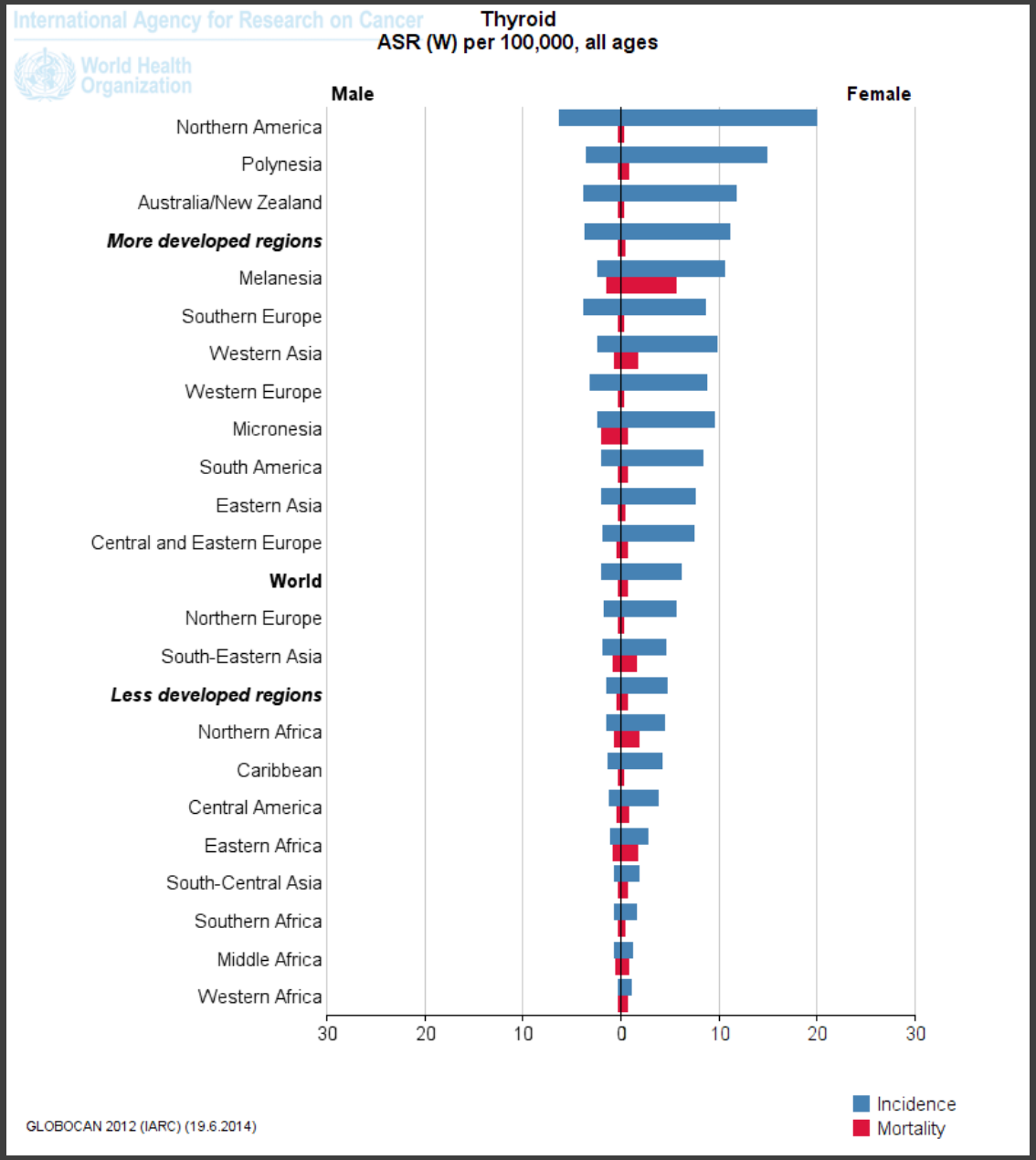
Distribution of Histological Types



Distribution of incidence of thyroid cancers by histological type (SEER-9, ASIR from 1980-2005, 2000 US standard population)

- Follicular cell origin
  - Papillary
  - Follicular
  - Anaplastic
- Parafollicular cell origin
  - Medullary
- Other origin
  - Lymphoma
  - Sarcoma

Source: Sharma PR et al. Thyroid Cancer. Medscape, 2014. URL: http://emedicine.medscape.com/article/851968-overview.
Source: Enewold L et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer Epidemiol Biomarkers Prev 2009.



Source: Age-standardized incidence and mortality rates (per 100,000) of thyroid cancer (IARC, Globocan 2012)

FIGURE 1.2 Percent distribution of estimated new cancer cases, by sex, Canada, 2014

Males
97,700
New cases

Prostate	24.1%
Colorectal	13.9%
Lung	13.7%
Bladder	6.1%
Non-Hodgkin lymphoma	4.5%
Kidney	3.9%
Melanoma	3.6%
Leukemia	3.4%
Oral	2.9%
Pancreas	2.4%
Stomach	2.1%
Brain/CNS	1.7%
Liver	1.6%
Esophagus	1.6%
Multiple myeloma	1.5%
Thyroid	1.4%
Testis	1.0%
Larynx	0.9%
Hodgkin lymphoma	0.6%
Breast	0.2%
All other cancers	8.8%

Females
93,600
New cases

Breast	26.1%
Lung	13.3%
Colorectal	11.6%
Body of uterus	6.4%
Thyroid	4.9%
Non-Hodgkin lymphoma	3.9%
Melanoma	3.2%
Ovary	2.9%
Leukemia	2.7%
Pancreas	2.5%
Kidney	2.4%
Bladder	2.1%
Cervix	1.6%
Oral	1.5%
Brain/CNS	1.3%
Stomach	1.3%
Multiple myeloma	1.2%
Liver	0.6%
Esophagus	0.5%
Hodgkin lymphoma	0.5%
Larynx	0.2%
All other cancers	9.1%

CNS=central nervous system

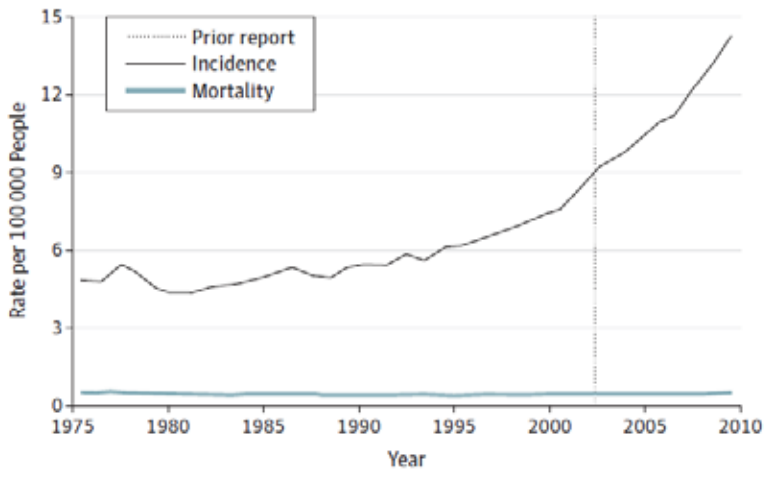
Analysis by: Chronic Disease Surveillance and Monitoring Division, CCDP, Public Health Agency of Canada

Data sources: Canadian Cancer Registry database at Statistics Canada and Quebec Cancer Registry (2008–2010)

Source: Canadian Cancer Statistics. Canadian Cancer Society, 2014.

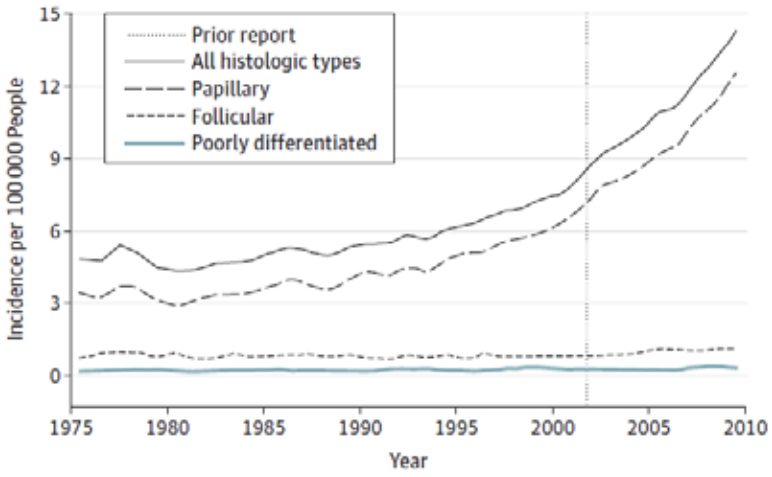
Rising incidence rate of thyroid cancer (SEER-9, 1975-2009)

Figure 1. Thyroid Cancer Incidence and Mortality, 1975 to 2009



Trends are shown for thyroid cancer of all histologic types. Incidence data are from Surveillance, Epidemiology, and End Results (SEER) 9, 1975 to 2009, maintained by the National Cancer Institute, National Institutes of Health, released April 2012, based on the November 2011 submission. Mortality data are from the National Center for Vital Statistics.

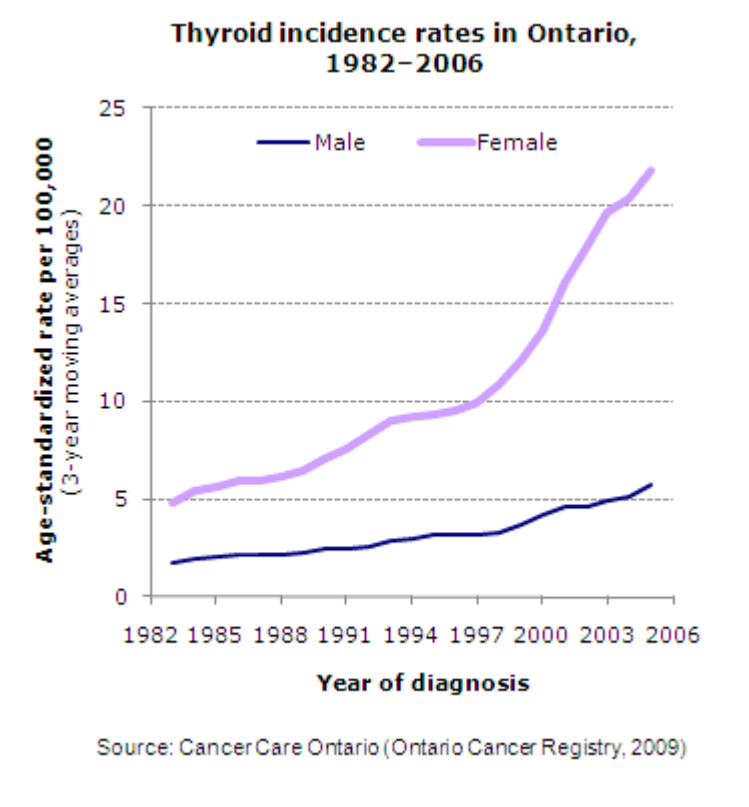
Figure 2. Thyroid Cancer Incidence by Histologic Type, 1975 to 2009



Trends are shown for thyroid cancer of all histologic types and for the 3 major histologic groups: papillary, follicular, and poorly differentiated cancers (anaplastic and medullary). Data are from Surveillance, Epidemiology, and End Results (SEER) 9, 1975 to 2009, maintained by the National Cancer Institute, National Institutes of Health, released April 2012, based on the November 2011 submission.

Source: Davies L. et Welch GH. Current Thyroid Cancer Trends in the United States. JAMA Otolaryngol Head Neck Surg 2014.

Rising incidence rate of thyroid cancer, world



- Canada
- France
  - Colonna M, Guizard AV, Schvartz C, et al. A time trend analysis of papillary and follicular cancers as a function of tumour size: a study of data from six cancer registries in France (1983–2000). Eur J Cancer 2007;43:891–900.
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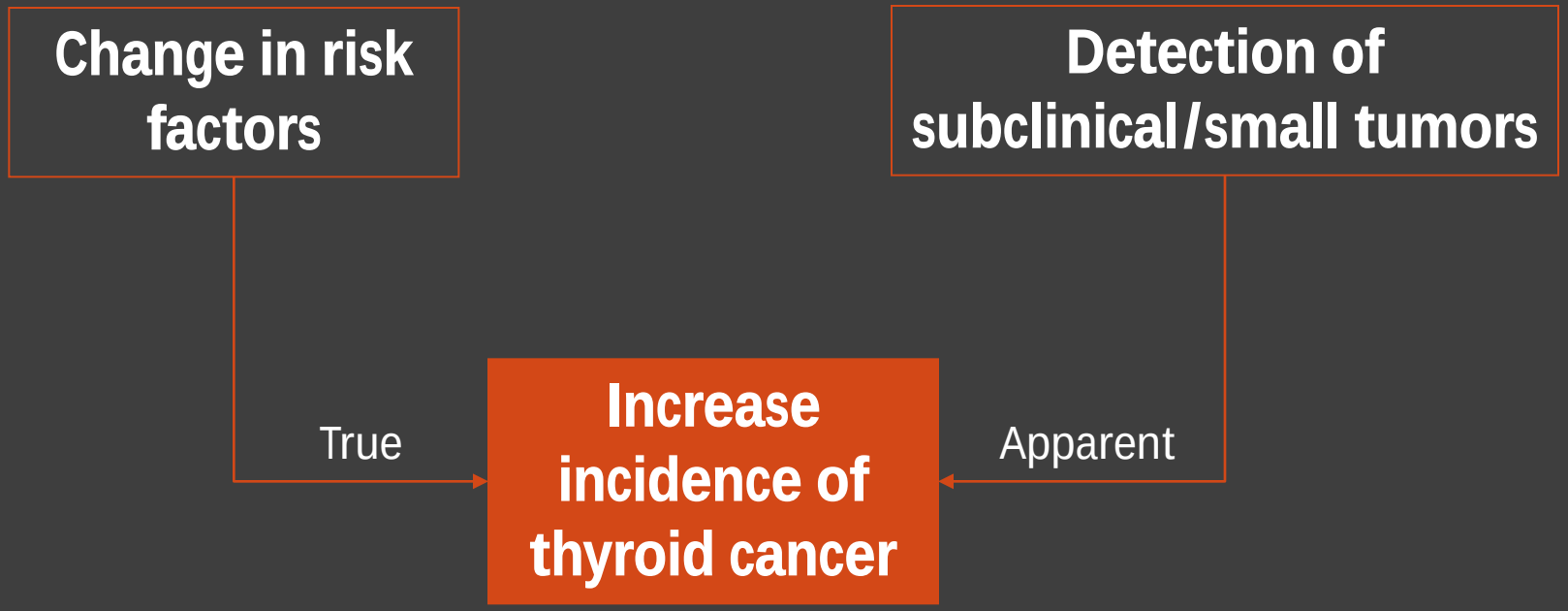
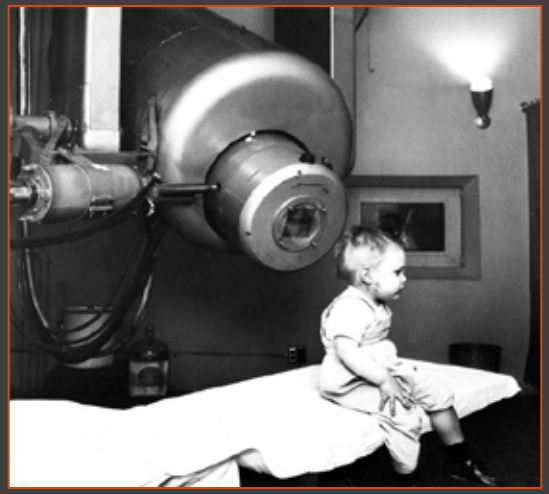
  - Lubina A, Cohen O, Barchana M, et al. Time trends of incidence rates of thyroid cancer in Israel: what might explain the sharp increase. Thyroid 2006;16:1033–40.
- Scotland
  - Reynolds RM, Weir J, Stockton DL, Brewster DH, Sandeep TC, Strachan MW. Changing trends inincidence and mortality of thyroid cancer in Scotland. Clin Endocrinol (Oxf) 2005;62:156–62.

Source: Cancer Care Ontario. Ontario Cancer Registry, 2009. URL: https://www.cancercare.on.ca/cms/one.aspx?portalId=1377&pageId=63896

Rising incidence rate of thyroid cancer, how to explain it?



Risk Factors: Radiation



Radiotherapy for benign (1920-1960) and malignant pediatric conditions
Source: Stanford University. Department of Radiation Oncology. URL: http://news.stanford.edu/news/2007/april18/med-accelerator-041807.html.

Nuclear radiation: Chernobyl (1986), Nevada (1950-1960), Japan (1945)
Source: Wikipedia. Baker nuclear test at Bikini Atoll in July 1946. URL: http://en.wikipedia.org/wiki/Underwater_explosion.

Diagnostic radiation
Source: Lachine Hospital, MUHC. A patient is getting a CT scan by a medical imaging technician 2012. URL: http://muhc.ca/new-muhc/gallery/Lachine.

Risk Factors: Increasing diagnostic radiology usage

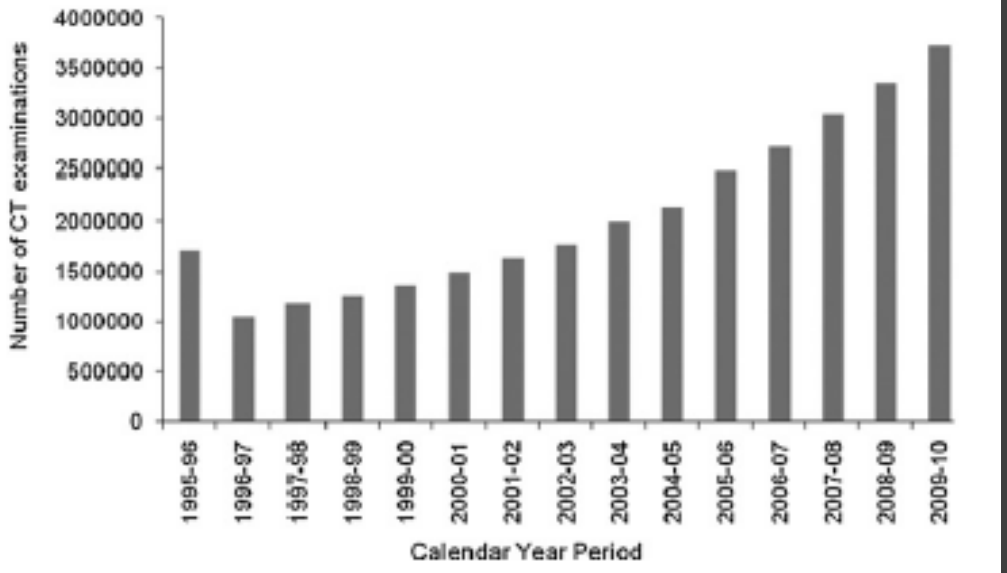


Fig. 2. Total number of computed tomography examinations in England by calendar time. Data adapted from Ref. [25].

Images: Schonfeld SJ et al. Medical Exposure to Radiation and Thyroid Cancer. Clin Oncol (R Coll Radiol) 2011.

Risk Factors: Diagnostic radiation and thyroid cancer risk

Table 2
Mean excess lifetime cancer risk* per 10 000 computed tomography scans by scan type, age at scan and gender

Age at exposure (years)	Type of scan					
	Head		Chest		Cervical spine	
	Mean	(95% uncertainty limits)	Mean	(95% uncertainty limits)	Mean	(95% uncertainty limits)
Females						
0	3	(1, 9)	35	(7, 111)	33	(7, 102)
1	1	(0, 2)	26	(6, 79)	17	(4, 50)
5	0	(0, 1)	14	(3, 41)	8	(2, 24)
10	0	(0, 1)	11	(2, 33)	6	(1, 17)
Males						
0	1	(0, 2)	6	(1, 20)	6	(1, 19)
1	0	(0, 0)	5	(1, 14)	3	(1, 9)
5	0	(0, 0)	3	(1, 7)	1	(0, 4)
10	0	(0, 0)	2	(0, 6)	1	(0, 3)

* Rounded to one significant figure.

Images: Schonfeld SJ et al. Medical Exposure to Radiation and Thyroid Cancer. Clin Oncol (R Coll Radiol) 2011.

Other Risk Factors: Largely unchanged

- Benign thyroid conditions
- Familial & Genetic conditions
- Iodine consumption
- Women's reproductive and hormonal factors
  - Navarro Silvera SA et al. Risk factors for thyroid cancer: A prospective cohort study. Int J Cancer 2005.
- Not associated:
  - Alcohol
  - Smoking

Source: Canadian Cancer Society. Risk factors for thyroid cancer. URL: http://www.cancer.ca/en/cancer-information/cancer-type/thyroid/risks/

Rise of incidence rate: Detection of small tumors

Table 2: Differences in tumour detection from Jan. 1, 1990, to Dec. 31, 2001, for 605 patients with differentiated thyroid carcinoma, by tumour size, sex and age (expressed as slope of the plot of no. of cases v. time)

Group; tumour size, cm	Slope (95% CI)	*p* value
All patients		
≤ 2	9.57 (5.40 to 13.74)	0.001
2-4	3.85 (-1.71 to 5.98)	0.054
> 4	1.08 (0.29 to 1.88)	0.023
Male sex		
≤ 2	1.35 (-0.04 to 2.73)	0.08
2-4	0.49 (-0.60 to 1.59)	0.40
> 4	0.44 (-0.11 to 0.99)	0.15
Female sex		
≤ 2	8.18 (4.95 to 11.42)	0.001
2-4	3.06 (0.95 to 5.18)	0.017
> 4	0.74 (-0.17 to 1.66)	0.14
Age ≤ 45 yr		
≤ 2	2.63 (-0.38 to 5.65)	0.12
2-4	1.64 (-0.02 to 3.30)	0.08
> 4	1.16 (0.83 to 1.49)	0.001
Age > 45 yr		
≤ 2	6.83 (4.87 to 8.80)	0.001
2-4	2.03 (1.12 to 2.94)	0.001
> 4	0.13 (-0.68 to 0.93)	0.76

Note: CI = confidence interval.

Table 2. Thyroid Cancer Size Distribution, 1988-1989 vs 2008-2009[a]

Tumor Characteristic	1988-1989	2008-2009
Observations, No.		
Total	2383	8159
Missing size data	516	376
Implausible size	1	83
No tumor found	6	16
Evaluable	1860	7684
Central tendency, mm		
Mean	22.8	19.0[b]
Median	20	15[c]
Size distribution, mm, %		
1-5	14	21
6-10	11	18
11-15	15	17
16-20	19	12
21-30	21	15
31-40	10	8
41-50	6	5
≥51	5	5

[a] Percentages do not add to 100% because of rounding. Data are from Surveillance, Epidemiology, and End Results (SEER) 9, 1975-2009, maintained by the National Cancer Institute, National Institutes of Health, released April 2012, based on the November 2011 submission.

[b] $P < .001$ by 2 sample *t* tests.

[c] $P < .001$ by Wilcoxon Mann-Whitney test.

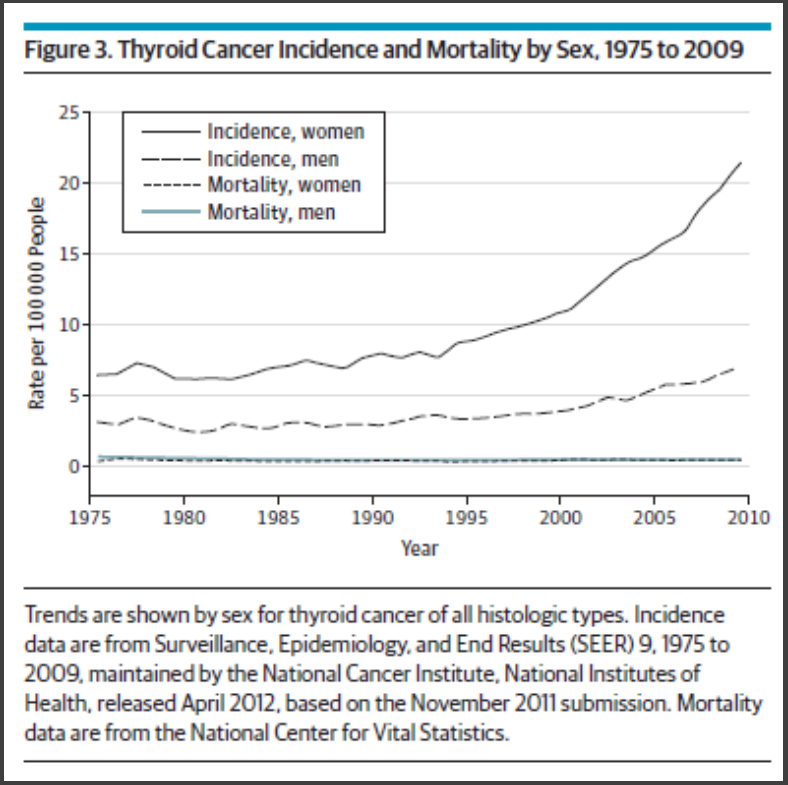
Source: Kent et al. Increased incidence of differentiated thyroid carcinoma in Ontario. CMAJ 2007.
Source: Davies L. et Welch GH. Current Thyroid Cancer Trends in the United States. JAMA Otolaryngol Head Neck Surg 2014.

Increased detection of small thyroid cancers?

- The case of subclinical thyroid tumors
  - Autopsy studies:
    - Subclinical papillary thyroid carcinoma found in 2.7-36% of patients
- Investigation tools for thyroid nodules
  - Leenhardt L et al. Increased Incidence of Thyroid Carcinoma in France: A True Epidemic or Thyroid Nodule Management Effects? Report from the French Thyroid Cancer Committee. Thyroid 2004.
    - Rise of ultrasound use from 1980 to 2000 (3 to 84.8%)
    - Rise in fine-needle aspiration from 1980 to 2000 (8 to 36%)

Source: Davies L. et Welch GH. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006.

Rise of incidence rate
Stability of mortality rate



- Lead-time bias?
- Treatment improved mortality?

Source: Davies L. et Welch GH. Current Thyroid Cancer Trends in the United States. JAMA Otolaryngol Head Neck Surg 2014.

Conclusion: Thyroid cancer

- Common endocrine cancer
- Several risk factors identified, notably radiation exposure
- Ongoing increase in incidence
  - Increased diagnosis of subclinical tumors?
  - Change in prevalence of risk factors?
    - Radiation exposure, iodine consumption, goiter?
    - Unknown?
- Ongoing debate: best management of thyroid cancers?

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ESOPHAGEAL CANCER EPIDEMIOLOGY 14.6.20

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Dept of Surgical Oncology

Mcgill University

Overview Esophageal CA

- Eighth most common cancer world wide[1]
  - Adenocarcinoma
    - Increased incidence from 1970's à 1990's
      - 0.5-0.9/100,000 à 3.2-4.0/100,000
    - Esophageal Adenocarcinoma has increased steadily over past 50 years in Western Countries[1]
  - Squamous Cell Carcinoma
    - Increased rate in Eastern Asia
    - Rate Unchanged across the globe over past 20-50 years

Table 2 Esophageal carcinomas in men according to residential area

Geographic area		Cumulative rates, age (0–74 years) for esophageal carcinomas[20]		Yearly incidence of esophageal carcinoma per 100 000 population[8]	
		ESCC	EAC	ESCC	EAC
America	North America (white)	0.27–0.28	0.28–1.19	2.2 (1992–1994)[9]	3.2 (1992–1994)[9]
	South America	0.15–1.84	0.01–0.30	10[29]	
Europe	UK/Ireland	0.27–0.53	0.29–0.60		4.2–7.0 (1992–1997)
	South Europe	0.47–1.40	0.08–0.14		0.7–3.9 (1992–1996)
	North Europe	0.28–0.32	0.08–0.24		0.8–2.0 (1992–1996)
	West Europe	0.33–1.40	0.06–0.14		0.4–3.2 (1989–1996)
	East Europe	0.32–0.74	0.07–0.12	8[29]	0.5–0.7 (1992–1987)
	Australia	0.32	0.23		4.8 (1993)[14]
Asia	East Asia	1.18–1.53 (0.92)	0–0.15 (0.06)	8.2–21 (2001)[24,29]	0.4 (2001)[24]
	Southeast Asia	0.22–0.94 (0.03)	0–0.07 (0.02)	3.5 (1968–2002)[28]	0.02–0.06
	South Asia	1.07 (0.60)	0.08 (0.02)		

North America: USA, Canada, South America: Brazil, Uruguay, Argentine, Peru, Ecuador, Columbia. South Europe: Spain, France, Italy, North Europe: Denmark, Norway, Sweden, Finland. West Europe: Germany, the Netherlands, Switzerland, East Europe: Czech, Slovakia, Poland. East Asia: Japan, Korea, Hong Kong, Southeast Asia: Philippines, Thai, French Polynesia. South Asia: India. Numbers in brackets: in East Asia; Chinese in Singapore, in Southeast Asia; Malays in Singapore, in South Asia; Indians in Singapore. EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

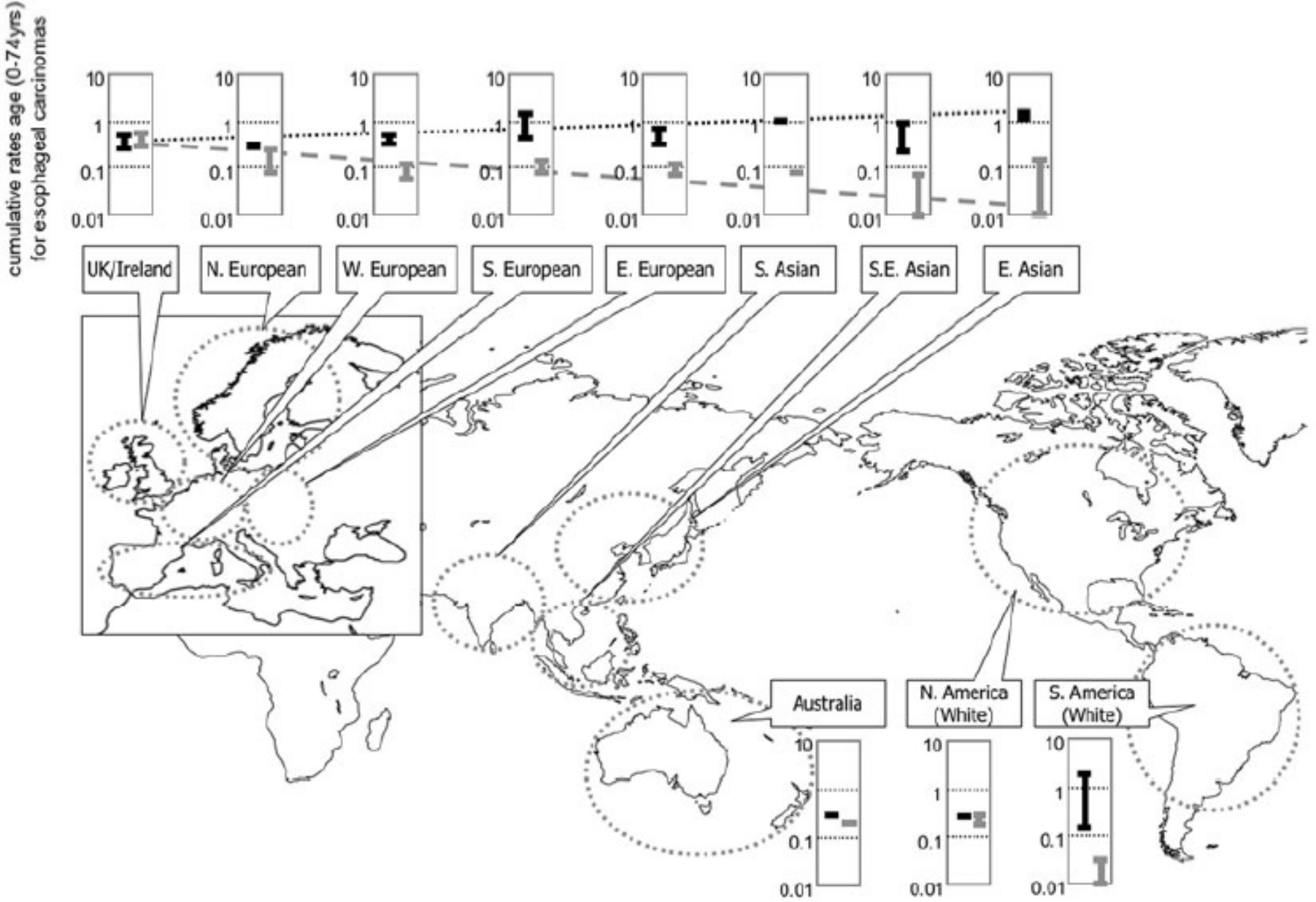

Figure 1 Geographical distribution of cumulative rates, age (0–74 years), for esophageal carcinomas. Rate for esophageal adenocarcinoma (EAC) (gray bars) is high in Western and low in Asian countries. Rate for esophageal squamous cell carcinoma (ESCC) (black bars) is high in the Asian and low in Western countries. EAC is high in the USA and Australia, where British/Irish descendents are dominant. Data shown are the highest and the lowest rates among the countries in the area.[20]

Table 1 Risk factors affecting the development of esophageal malignancies[2])

Risk factors	ESCC	EAC
Tobacco smoking	+++	++
Excess alcohol consumption	++	++
Barrett's esophagus	NS	+++
Reflux (GERD) symptoms	NS	+++
Obesity	NS	++
Excess energy consumption	NS	+
Excess fat consumption	NS	++
Poverty	++	NS
Low education level	+	NS
Excess intake of hot beverage (thermal injury)	+	NS
H. pylori infection*	Protective[3]	Protective[4]

+++, Very strong effect; ++ moderate effect; +, some effect. EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GERD, gastroesophageal reflux disease; NS, not significant. *Role of *Helicobacter pylori* infection as a risk factor affecting esophageal carcinoma was cited from sources other than [2].

Epidemiology

- Correlation with socioeconomic status
- Higher socioeconomic status correlates with
  - Decreased H. pylori infection
  - Increased Obesity
  - Increased GERD
  - Barrett's Esophagus
- Countries where EAC is high (UK, USA, Australia)
  - Obesity is high
  - Energy consumption/person/day is low
- Socioeconomic factors (GDP per capita, education, nutrition, alcohol intake, cigarette smoking)
  - NOT reflective of epidemiological gradient
    - LOWEST indices in S. Asian (India/Pakistan) Where EAC and ESCC are intermediate.

Socioeconomic factors by region relative to Esophageal Cancer Risk

Table 3 Socioeconomic status of geographic areas

	Economy		Education		Nutrition						Alcohol		Tobacco	
	Per capita GDP in $US		Mean years of education		Dietary energy consumption per person per day		Dietary fat consumption per person per day		% Obesity, BMI ≥ 30 kg/m^2 in men		Alcohol consumption per capita, in litters of pure alcohol		Smoking rate in men	
Japan	34 225	USD	9.8	yrs	2750	kcal/day	85.0	g/day	1.8	%	7.38	L	41.0	%
East Asia	11 223 (17 043 include $HK)		6.3		3010		86.5		2.8		6.08		53.7	
Southeast Asia	3 331 (9 938 incl. Singaporean dollar)		5.4		2618		60.5		1.3		4.00		31.9	
South Asia	986		1.6		2350		61.0		1.0		0.42		22.2	
East Europe	13.842		10.8		3248		121.8		14.5		12.30		35.3	
South Europe	29 675		5.8		3530		148.3		14.1		11.29		32.9	
North Europe	59 570		9.9		3250		131.0		14.0		7.70		21.6	
West Europe	42 307		8.6		3337		144.3		13.0		12.05		31.1	
UK	45 549		N.A. (11.0)		3440		137.0		21.6		10.39		28.8	
North America	44 208		12.2		3695		164.0		30.1		8.38		19.8	
Australia NZ	43 180		10.1		3105		123.0		23.4		9.47		22.8	
Source (reference)	World Bank	a	UN	b	FAO	c	FAO	c	WHO	d	FAO	e	WHO	d

N.A., not available from the primary source. Data in the following area are the mean of the available data from the source. East Asia: China, Korea, (Hong Kong). Southeast Asia: Malaysia, Thai, Vietnam, Philippines (Singapore). South Asia: India, Pakistan. East Europe: Hungary, Poland, Czechoslovakia, Slovakia. South Europe: Spain, Italy, Portugal. North Europe: Norway, Sweden, Finland. West Europe: Germany, the Netherlands, France. North America: USA, Canada. Australia NZ: Australia, New Zealand. Data source: (a) Estimates of Per Capita GDP in US Dollars (http://unstats.un.org/unsd/snaama/selectionbasicFast.asp). (b) Psacharopoulos G, Arriagada AM. The Educational Attainment of the Labor Force: The International Comparison 1986 (www-wds.worldbank.org/external/default/WDSContentServer/WDSP/IB/2005/09/01/000112742_20050901145133/Rendered/PDF/edt38.pdf). (c) FAOSTAT Food security. (www.fao.org/faostat/foodsecurity/index_en.htm). (d) WHO Global InfoBase. (www.who.int/infobase/report.aspx). (e) FAO (Food and Agriculture Organization of the United Nations), World Drink Trends 2003 (www.who.int/substance_abuse/publications/global_status_report_2004_overview.pdf)

Comparing Different Ethnic Groups Within Particular Regions:

Table 4 Prevalence of Barrett's esophagus in endoscopy (columnar-lined esophagus with proven intestinal metaplasia)

Area/surveyed year	White	Hispanic	Native American	Black	South. Asian (Indian)	Southeast Asian (Malay)	East Asian (Chinese)
USA (1993–1996)	5.3 %	3.8%		0%			0%
USA (1992–1994)	9.1%			2.4%	4.8%		0%
Singapore (1997–2000)					2.7%	1.5%	1.4%
USA (2000–2006)	Non-Asian 2.1%					Asian 0.76%	
UK (2000–2005)	2.8%				0.3%		
USA (per 100 000 population) (2006)	39	22		6			
South Africa (1970–1993)	*	>		*			

Table 5 Incidence of EAC and ESCC per 100 000 population in different ethnic groups living in the same geographic areas

Area/surveyed year	White		Hispanic		Native American		Black		South. Asian (Indian)		Southeast Asian (Malay)		East Asian (Chinese)	
	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC	ESCC
USA (1992–1998)	1.8	4.2	1.8	2.08	1.8	0.5	8.8	0.8					3.9	0.7
Singapore (1988–1992)									0.60	0.02	0.03	0.02	0.92	0.06
USA (1988–1992)	0.28	0.27					1.61	0.06						
USA (1997–1998)	1.8	4.0					8.8	0.8						
USA (1992–1994)	2.2	3.2					13	0.6						
USA (1980–1995)	12 cases	7 cases					127 cases	4 cases						

EAC, Esophageal adenocarcinoma; ESCC, Esophageal squamous cell carcinoma.

Relative risk of populations within specific geographic regions

- In South Africa black subjects have lower prevalence of Barrett's Esophagus than White Counterparts
- Barrett's Esophagus is higher in white Americans than black Americans and intermediate in Hispanics and Native Americans

Table 3. Independent Predictors of Barrett's Esophagus

	Odds Ratio (95% Confidence Interval)	
Characteristic	Univariate	Multivariate
Age	1.00 (0.98–1.02)	1.01 (0.99–1.04)
Male	3.12 (1.70–5.74)	2.68 (1.32–5.45)
Non-Asian ethnicity	3.39 (1.88–6.12)	3.55 (1.85–6.85)
Smoking	3.16 (1.70–5.88)	1.71 (0.78–3.76)
Alcohol	2.57 (1.39–4.75)	1.29 (0.58–2.86)

Dysplasia Model Leading to Adenocarcinoma

Obesity

- à GERD
- à Barrett's Esophagus
- à Dysplasia
- à High Grade Dysplasia
- à Esophageal Adenocarcinoma

Summary of Risk Factors

Table 1
Risk factors for squamous cell carcinoma and adenocarcinoma of the esophagus

Risk Factor	Squamous Cell Carcinoma	Adenocarcinoma
Geography	Southeastern Africa, Iran, Asia	Western Europe, North America
Race	B > W	W > B
Gender	M > F	M > F
Alcohol	↑↑↑↑	–
Tobacco	↑↑↑↑	↑↑
Obesity	–	↑↑↑
GERD	–	↑↑↑↑
Diet		
Low fruits and vegetables	↑↑	↑↑
Pickled vegetables	↑↑	–
Hot beverages	↑↑	–
Socioeconomic conditions	Low, nonurban	High, urban, industrialized

Abbreviations: B, black; F, female; GERD, gastroesophageal reflux disease; M, male; W, white; ↑, associated risk; –, no risk associated.

McGill EPIB-671 Symposium

Angel M Rodriguez, MD, FACS
Surgical Oncology Fellow
June 20, 2014

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Case

- 68yoF LABC...
  - Anemia > C-scope > CRC

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Multiple primary cancers

- Defined as two or more primary cancers occurring in an individual that originate in a primary site or tissue and that are neither an extension, nor a recurrence, nor metastasis
  - Synchronous
  - Metachronous

Synchronous cancers

(1) Two or more histologically distinct simultaneously detected malignancies

(2) Two or more histologically distinct malignancies diagnosed during the same hospital admission

(3) **Two or more histologically distinct malignancies arising in the same site, following each other in sequence by less than 2 months**

(3) Surveillance, Epidemiology, and End Results Program

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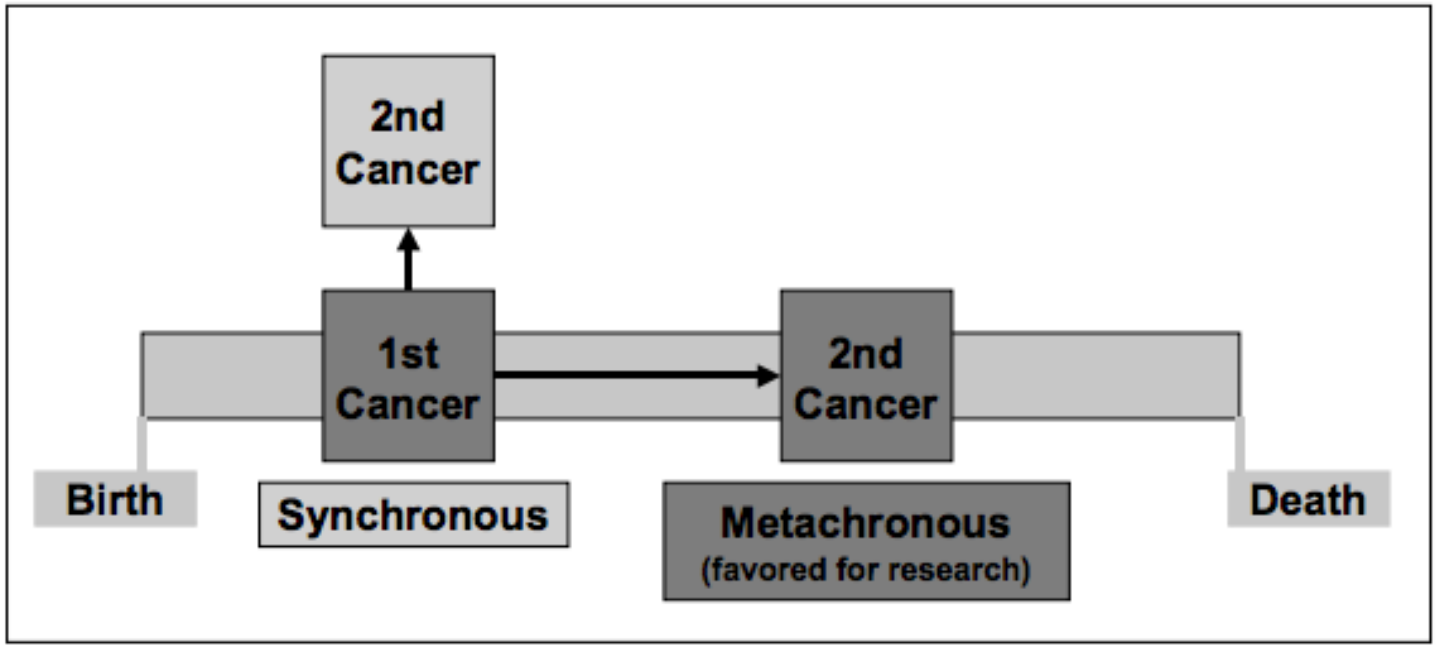
Multiple primary cancers



Mukesh Verma (ed.), Methods in Molecular Biology, Cancer Epidemiology, vol. 471 (2009)

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Multiple primary cancers

- Cancer patients have a 20% (RR 1.2) higher risk of new primary cancer compared with the general population
- Approximately one third of cancer survivors aged >60 years are diagnosed more than once with another cancer.

Fraumeni, J. F. J. (2006) Introduction. Bethesda, MD: National Cancer Institute. pp. 1–7.

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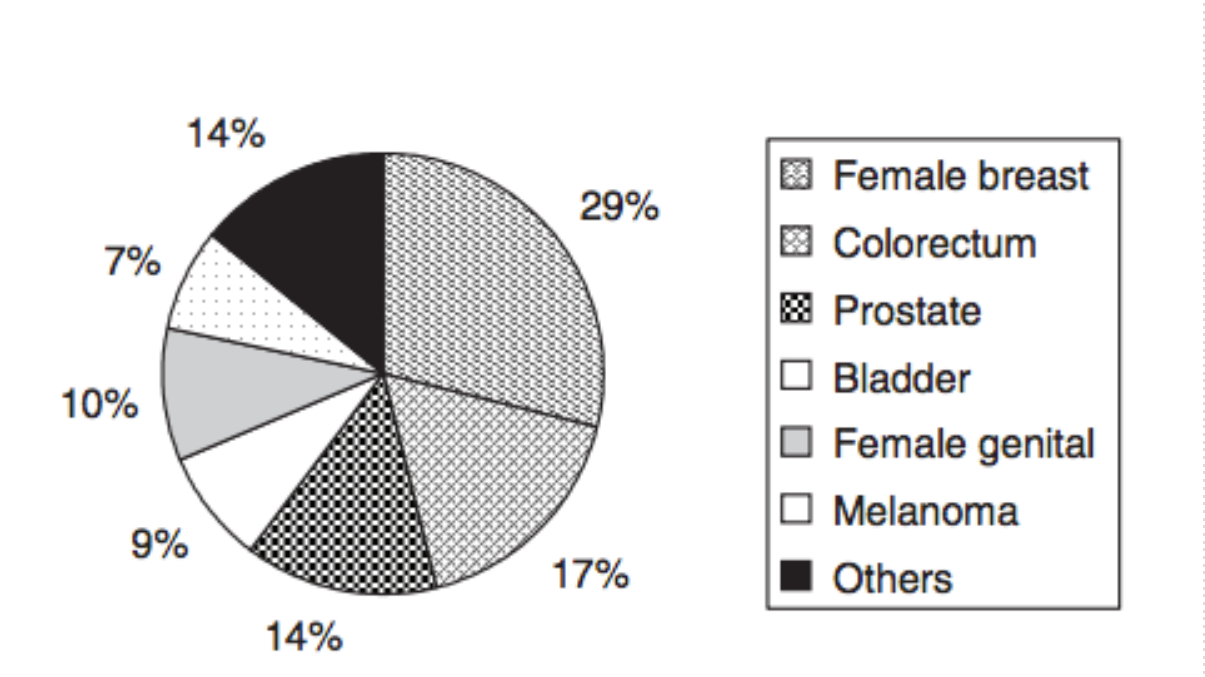
First primary



Surveillance, Epidemiology, and End Results program (1975-2001)

Mariotto (2007) Multiple cancer prevalence: a growing challenge in long-term survivorship. Cancer Epidemiol Biomark Prev 16, 566–71.

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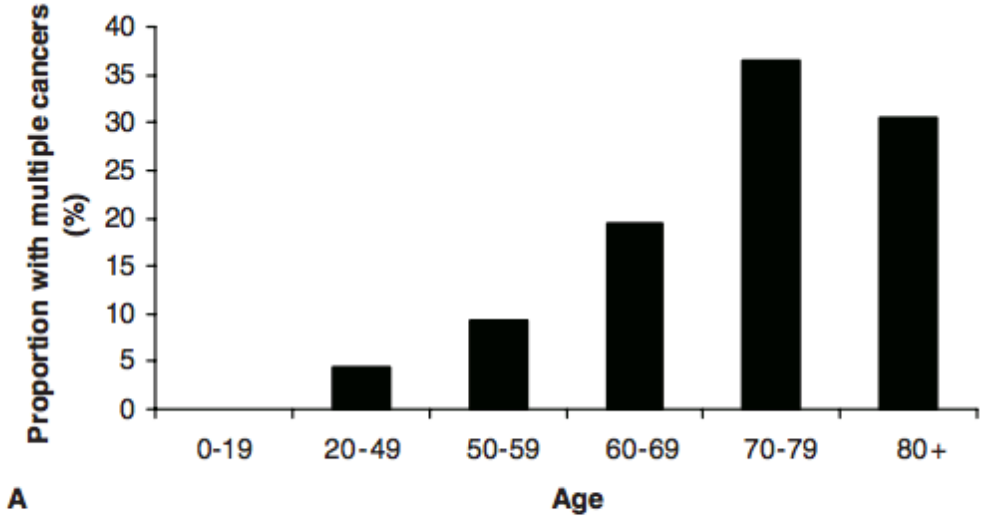

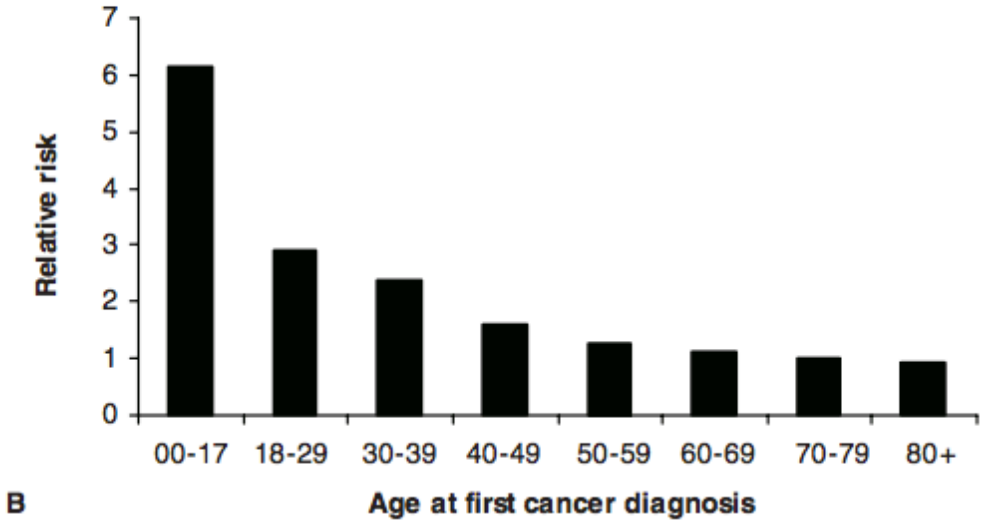

Surveillance, Epidemiology, and End Results program (1975-2001)

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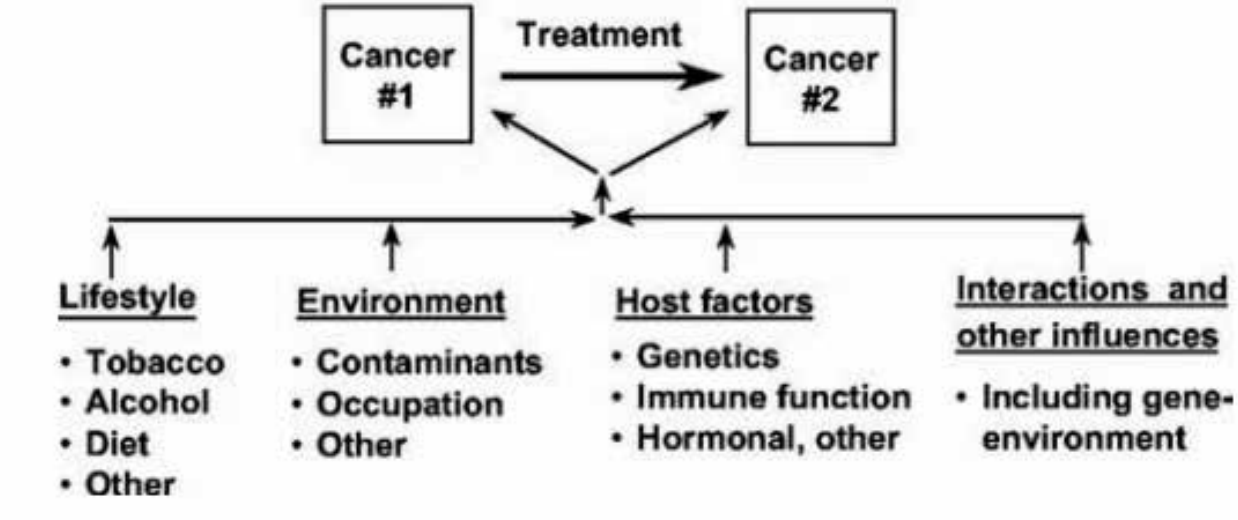
Mariotto (2007) Multiple cancer prevalence: a growing challenge in long-term survivorship. Cancer Epidemiol Biomark Prev 16, 566–71.

Second cancers: Etiology



Travis, L. B. (2002) Therapy-associated solid tumors. Acta Oncol.

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Selected inherited cancer syndromes, reported in various multiple cancer cases

Syndrome	Affected sites	Penetrance (%)	Gene(s)
Familial breast cancer	**Breast**, ovary, male breast, pancreas, prostate, melanoma	Up to 85	BRCA1, BRCA2
HNPCC or Lynch syndrome	**Colorectum**, corpus uteri, ovary, hepatobiliary and unrinary tract, brain. Also Muir-Torre and Turcot variant-related tumors.	90	MLH1, MSH1, MSH2, PMS1, PMS2
Hereditary retinoblastoma	**Eyes**, bone and soft tissue sarcoma	90	RB
Li-Fraumeni syndrome	**Sarcoma, breast**, brain, leukaemia and adrenocortical cancer	90–95	TP53
Cowden syndrome	**Breast**, thyroid corpus uteri	~50	PTEN (MMAC1)
Familial melanoma	**Melanoma**, pancreas	~90	CDKN2A (p16)
Multiple endocrine neoplasia type 1	**Parathyroid**, entero-pancreas, pituitary	95	MEN1
FAP	**Colorectum**, thyroid, pancreas, liver, central nervous system, and other benign conditions	~100	APC

Fearon, E. R. (1997) Human cancer syndromes: clues to the origin and nature of cancer. Science
Nagy, R. (2004) Highly penetrant hereditary cancer syndromes. Oncogene

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Risk of primary breast, endometrial, and colorectal cancer after breast cancer, according to BMI before or at the diagnosis of first primary breast cancer

Site of second primary/risk factor	Breast[a]		Endometrial[b]			Colorectal[b]	
	HR	95% CI		HR	95% CI	HR	95% CI
BMI (kg/m²)			BMI[c] (kg/m²)				
≤24.9	1		< 22.5	1		1	
25.0–29.9	1.22	0.87–1.71	22.5–25.0	0.98	0.50–1.90	0.91	0.51–1.60
≥30.0	1.58	1.10–2.25	25.1–28.8	1.07	0.55–2.07	1.54	0.92–2.59
			≥ 28.9	2.23	1.23–4.05	1.67	0.99–2 .82

[a] HR adjusted for treatment age, menopausal status, race, tumor size, ER/PR receptor.

[b] HR adjusted for year of dx, stage of breast cancer, family history of breast cancer, years of cigarrete smoking, recent alcohol intake, parity, and postmenopausal therapy.

Dignam, JJ. (2003) Obesity, tamoxifen use, and outcomes in women with estrogen receptor positive early stage breast cancer. J Natl Cancer Inst.
Trentham, A. (2006) Breast cancer risk factors and second primary malignancies among women with breast cancer. Breast Cancer Res Treat

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Breast cancer

- Breast cancer patients with the highest alcohol intake exhibited almost a two-fold higher risk of colorectal cancer compared with nondrinkers
- Cancer patients who had premature menopause, i.e., due to chemotherapy, exhibited a lower risk of second primary breast cancer
- Breast cancer survivors who were younger at menarche and had fewer children showed an increased risk of second primary breast cancer
- A reduced colorectal cancer risk is observed among those who later menarche and earlier menopause

Trentham-Dietz, A, et al. (2006) Breast cancer risk factors and second primary malignancies among women with breast cancer. Breast Cancer Res Treat

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Treatment related cancers

- Tamoxifen has demonstrated a protective effect against the increased risk of a second primary breast cancer.
- However, it has been consistently related to an elevated risk of endometrial cancer

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet 365, 1687-717 (2005)

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Chemotherapy and related multiple cancers

Chemotherapeutic agents	Treatment for primary cancer	Therapy-related cancer
Alkylating agent (mechlorethamine, chlorambucil, cyclophosphamide, melphalan, semustine, lomustine, carmustine prednimustine, busulfan and dihydroxybusulfan	Lymphomas *(108)* Breast *(13,109)*	Leukemia[b,c]
Platinating agents (cisplatin and carpboplatin)	Ovary *(110,111)* Testis *(112,113)*	Leukemia[b]
Topoisomerase II inhibitors (epipodophyllotoxins etoposide and teniposide)	Lung, testis, solid *(114)* and nonsolid childhood cancers *(115)*	Leukemia[b,d]
Intercalating topoisomerase II inhibitors (anthracycline, doxorubicin and 4-epidoxorubicin)	Lymphomas *(108)* Breast *(13,109)*	Leukemia[b,d]
Cyclophosphamide	NHL *(90)* Ovarian *(116)*	Bladder cancer
Alkylating agent MOPP regimen (mechloretamine, vincristine, procarbazine, prednisone) CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone)	HD *(59,62,63)* NHL *(92)*	Lung cancer
Alkylating agent and anthracycline	Childhood cancers *(91,117)*	Bone sarcoma

van Leeuwen, F. E., Travis, L. B. (2005) Second Cancers, 7 ed. Philadelphia. PA: Lippincott Williams and Wilkins. pp. 2575–602

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Radiation related cancers

- Thyroid, breast, and bone marrow are reported as the most radiosensitive tissues

- The effect of radiation is amplified when such tissue received radiation at an early age, i.e. breast cancer after HD is highest for those treated before age 30.

- A combination of chemotherapy with radiation may cause a higher risk of a second cancer than for the individual therapy alone

van Leeuwen. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 18, 487-97 (2000)

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Relative risk of subsequent lung cancer by treatment and smoking habits in patients treated for Hodgkin's disease

Treatment for Hodgkin's disease	Moderate–heavy smokers	
	No. of lung cancers	RR (95% CI)
No	10	6 (1.9–20.4)
Radiation >5 Gy	20	20.2 (6.8–68)
Chemotherapy	33	16.8 (6.2–53)
Radiotherapy and chemotherapy	24	49.1 (15.1 –187)

Reference group was patients without radiation or chemotherapy who were non- or light smokers 5 years before lung cancer diagnosis.

Moderate represents individuals who smoked one to two packs a day, and heavy represents individuals who smoked two or more packs a day

Travis, LB. (2002) Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst.

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Take home points

- Improvements in early detection, diagnosis, and treatment of cancers have increased survival of patients with cancer
- Also increasing the number of individuals with multiple malignancies
- This problem will grow larger in societies with increasing proportion of elderly persons

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The need...

- Development of new technology and biomarkers to assess risk and etiologic pathway of multiple cancers
- Design of new studies; accurate projections of new primary cancer risk among cancers survivors to facilitate the surveillance recommendations
- Development of clinical practice guidelines, including intervention strategies such as behavior modification to prevent occurrence of a new primary cancer; follow-up of cancer survivors

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Epidemiology and risk factors of laryngeal cancer

Samaher Ashram

R1 Radiation Oncology

Epidemiology

- Overall, head and neck cancer accounts for more than 550,000 cases annually worldwide
  - M:F ratio ranging from 2:1 to 4:1
- Worldwide, there are an estimated 130,000 new laryngeal cancer cases and 82,000 deaths annually
- Inn US, laryngeal cancer account for about one-fourth of the 55,000 cases of H&N cancer diagnosed annually.

In Canada

Estimated cases of laryngeal cancer in 2014:

- 1,050 Canadians will be diagnosed with laryngeal cancer (M:890, F:170)
- 380 Canadians will die from laryngeal cancer (M:310, F:75).

FIGURE 1.2 Percent distribution of estimated new cancer cases, by sex, Canada, 2014

Males
97,700
New cases

Prostate	24.1%
Colorectal	13.9%
Lung	13.7%
Bladder	6.1%
Non-Hodgkin lymphoma	4.5%
Kidney	3.9%
Melanoma	3.6%
Leukemia	3.4%
Oral	2.9%
Pancreas	2.4%
Stomach	2.1%
Brain/CNS	1.7%
Liver	1.6%
Esophagus	1.6%
Multiple myeloma	1.5%
Thyroid	1.4%
Testis	1.0%
Larynx	0.9%
Hodgkin lymphoma	0.6%
Breast	0.2%
All other cancers	8.8%

Females
93,600
New cases

Breast	26.1%
Lung	13.3%
Colorectal	11.6%
Body of uterus	6.4%
Thyroid	4.9%
Non-Hodgkin lymphoma	3.9%
Melanoma	3.2%
Ovary	2.9%
Leukemia	2.7%
Pancreas	2.5%
Kidney	2.4%
Bladder	2.1%
Cervix	1.6%
Oral	1.5%
Brain/CNS	1.3%
Stomach	1.3%
Multiple myeloma	1.2%
Liver	0.6%
Esophagus	0.5%
Hodgkin lymphoma	0.5%
Larynx	0.2%
All other cancers	9.1%

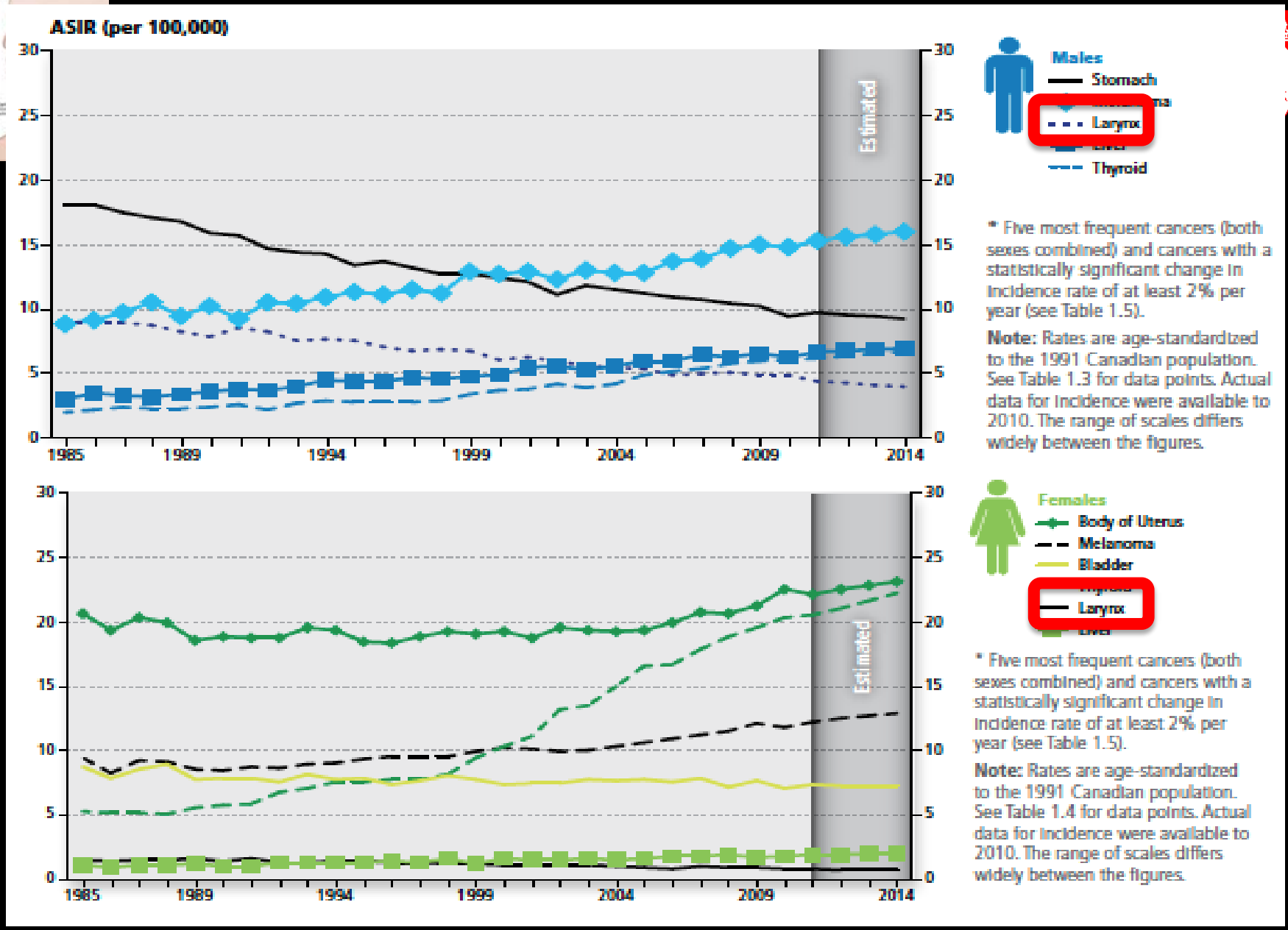
FIGURE 3.2 Percent distribution of estimated cancer deaths, by sex, Canada, 2014

Males
40,000
Deaths

Lung	27.0%
Colorectal	12.8%
Prostate	10.0%
Pancreas	5.5%
Bladder	3.9%
Esophagus	3.9%
Leukemia	3.8%
Non-Hodgkin lymphoma	3.6%
Stomach	3.2%
Brain/CNS	2.9%
Kidney	2.8%
Liver	2.0%
Oral	2.0%
Multiple myeloma	1.9%
Melanoma	1.6%
Larynx	0.8%
Breast	0.2%
All other cancers	12.2%

Females
36,600
Deaths

Lung	26.5%
Breast	13.8%
Colorectal	11.5%
Pancreas	6.0%
Ovary	4.7%
Non-Hodgkin lymphoma	3.3%
Leukemia	3.1%
Body of uterus	2.5%
Brain/CNS	2.2%
Stomach	2.2%
Kidney	1.8%
Bladder	1.8%
Multiple myeloma	1.7%
Esophagus	1.2%
Melanoma	1.1%
Oral	1.0%
Cervix	1.0%
Liver	0.7%
Larynx	0.2%
All other cancers	13.7%



Age-standardized incidence rates (ASIR) for selected* cancers, males and female
Canada, 1985–2014

Risk factors

Age (years)	Larynx		
	Obs.	Exp.	PAF (%)
Males			
0–14	0	0	0
15–34	2	2	0
35–44	35	24	31
45–54	195	58	70
55–64	535	92	83
⩾65	1035	202	81
Total	1802	378	79
Females			
0–14	0	0	0
15–34	2	2	0
35–44	12	9	26
45–54	53	15	71
55–64	105	16	84
⩾65	210	38	82
Total	382	80	79

Cases attributable to smoking in 2010

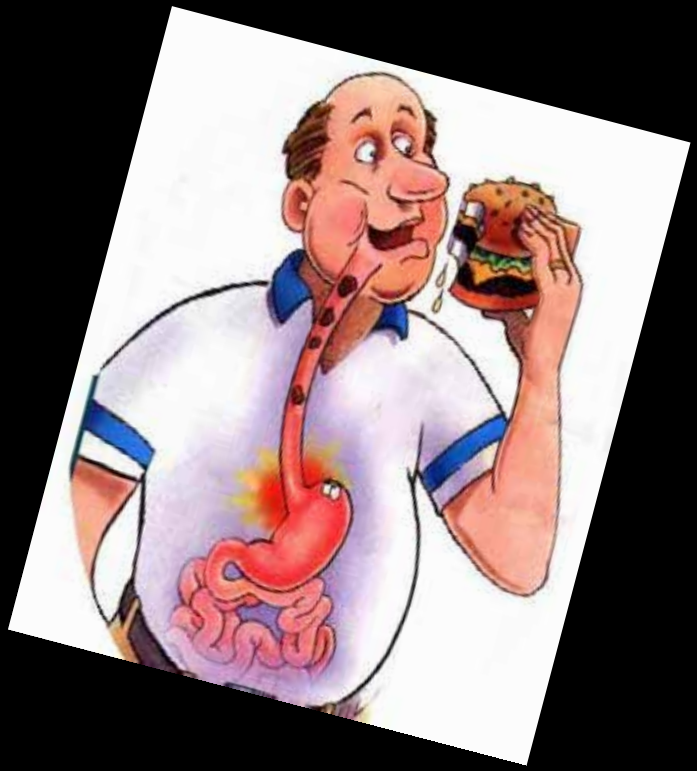
Age (years)		Larynx		
At exposure	At outcome (+10 years)	PAF	Obs.	Excess attrib. cases
Men				
15–24	25–34	0.26	2	0.5
25–34	35–44	0.29	35	10.3
35–49	45–59	0.30	407	121.3
50–64	60–74	0.28	914	253.9
⩾65	⩾75	0.24	444	105.3
Total			1803	491.3
%				27.3
Women				
15–24	25–34	0.17	2	0.3
25–34	35–44	0.13	12	1.5
35–49	45–59	0.13	99	13.1
50–64	60–74	0.12	168	20.9
⩾65	⩾75	0.11	101	11.4
Total			386	47.3
%				12.2
Persons				
15–24	25–34		4	0.9
25–34	35–44		47	11.8
35–49	45–59		506	134.4
50–64	60–74		1082	274.8
⩾65	⩾75		545	116.7
Total			2189	539
%				24.6

Cancer cases diagnosed in 2010 attributable to alcohol consumption in 2000–2001

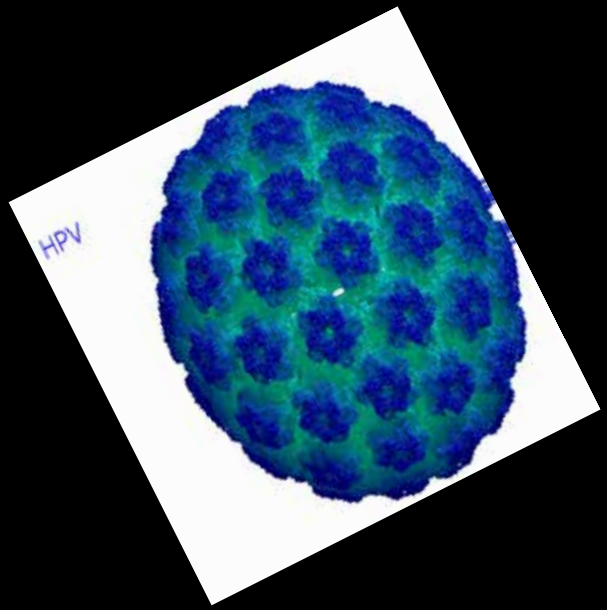
Tobacco	Alcohol	Cases	Controls	OR[1]	95%CI	PAR	95%CI
Never	Never	1.6	14.9	1.00			
1–20 cigs/day	Never	5.9	7.9	6.06	(4.03, 9.11)	4.9	(4.4, 5.2)
>20 cigs/day	Never	3.9	2.2	12.83	(7.95,20.71)	3.6	(3.4, 3.7)
Never	1–2 drinks/day	1.8	16.3	1.20	(0.72, 2.02)	0.3	(−0.7, 0.9)
1–20 cigs/day	1–2 drinks/day	20.8	21.3	8.33	(5.07,13.69)	18.3	(16.7, 19.3)
>20 cigs/day	1–2 drinks/day	12.7	7.3	16.91	(9.66,29.61)	11.9	(11.4, 12.3)
Never	>=3 drinks/day	1.2	6.6	3.16	(1.23, 8.16)	0.8	(0.2, 1.0)
1–20 cigs/day	>=3 drinks/day	28.8	16.5	18.94	(10.64,33.71)	27.3	(26.1, 27.9)
>20 cigs/day	>=3 drinks/day	23.4	7.1	36.87	(16.60,81.90)	22.8	(22.0, 23.2)
Total		**2,901**	**12,935**			**89.9**	**(83.5, 93.5)**

Odds ratios and population attributable fractions for tobacco and alcohol frequency categories, for head and neck cancer and subsites

Other risk factors



- Asbestos
- Sulphuric acid
- Family history of cancer
- Diet



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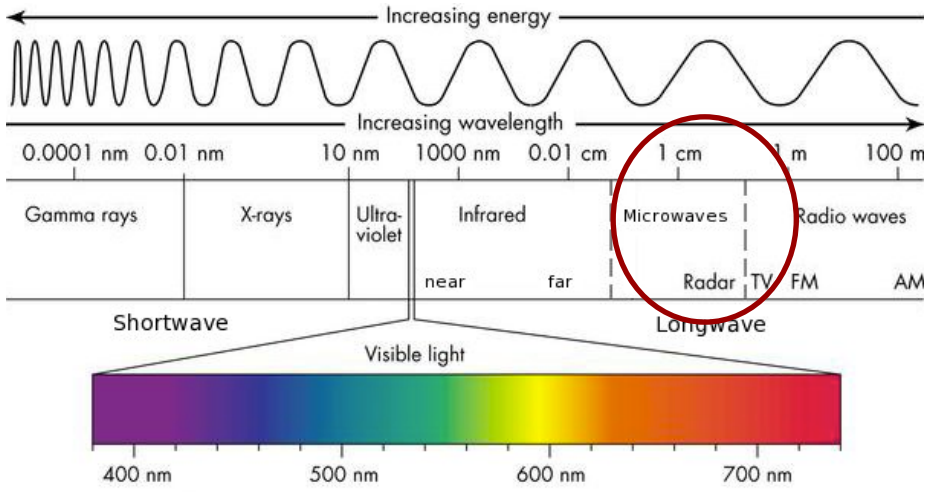
Electromagnetic Fields and Brain Tumours

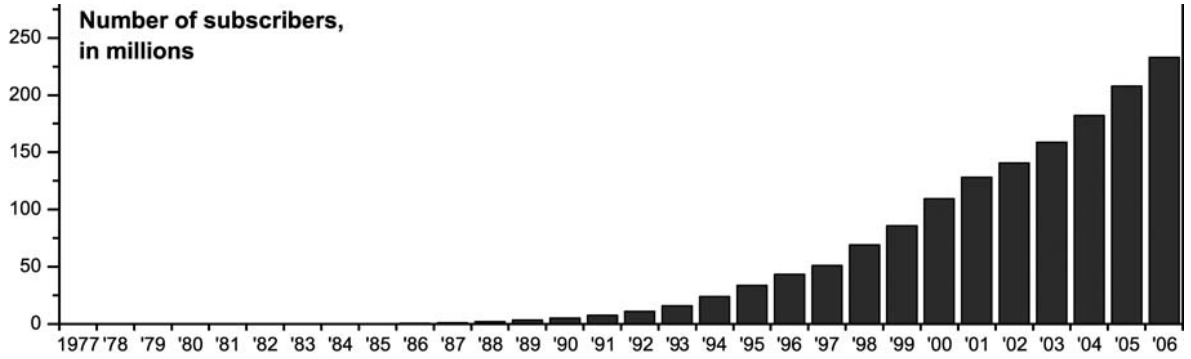
RLee, PhD Epi candidate

Wireless phones and electromagnetic fields

- In 2010, there were more than 5 billion cell phone subscriptions worldwide (Frei et al., 2011)
- Cell phones emit radio-frequency electromagnetic fields (RF-EMF) between 800-2000 MHz
- While ionizing radiation such as x-rays has been shown to cause cancer via DNA damage, there is no current evidence for low frequency, non-ionizing radiation
- Experimental (basic science) research
  - Use associated with transient 0.1°C increased temperature of brain (Van Leeuwen et al. 1999)
  - Increased glucose metabolism on the ipsilateral side with 50 min of use (Volkow, 2011)



Secular trends



United States data (Iskip, Hoover, Devesa, 2010)

- International Agency for Research on Cancer (IARC) coordinated a feasibility study in 1998-1999
  - International study of cell phone use and brain tumour risk both informative and feasible
- Led to the INTERPHONE study

The INTERPHONE Study

- Glioma and meningioma (also looked at acoustic nerve and parotid gland)
- 13 countries with 16 study centres
- Cases - ascertained from ~ all neurological/neurosurgical facilities or via registries, confirmed histologically or via unequivocal imaging
- Controls – population-based sampling, matched 1:1 or 1:2 on age; sex; region of residence within study centre

The INTERPHONE Study Group, 2010

The INTERPHONE Study

- Exposure ascertainment – face-to-face interviews with questionnaires (some via phone)
  - Interviewers not blinded to disease status
  - Proxy interviews if patient deceased
- Exposures (not all inclusive)
  - Ever-use of mobile phones = average of one call per week for >=6 months
  - Cumulative use – excluding hands-free time
  - Only previous year's exposure excluded
- Covariates – age, sex, education (surrogate for SES), study centre

The INTERPHONE Study Group, 2010

The INTERPHONE Study: Results

- Participation
  - 2425 meningioma cases (78%); 2765 glioma cases (64%); 7658 controls (53%)
  - Higher proxy interviews with glioma cases (13%) vs 1% of controls
- Regular use for >=1 year – glioma OR 0.81 (95% 0.70-0.94); meningioma OR 0.79 (0.68-0.91)

Cumulative call time with no hands-free devices (h)[b]	Meningioma			Glioma		
Never regular user	1147	1174	1.00	1042	1078	1.00
<5 h	160	197	0.90 (0.69–1.18)	141	197	0.70 (0.52–0.94)
5–12.9	142	159	0.82 (0.61–1.10)	145	198	0.71 (0.53–0.94)
13–30.9	144	194	0.69 (0.52–0.91)	189	179	1.05 (0.79–1.38)
31–60.9	122	145	0.69 (0.51–0.94)	144	196	0.74 (0.55–0.98)
61–114.9	129	162	0.75 (0.55–1.00)	171	193	0.81 (0.61–1.08)
115–199.9	96	155	0.69 (0.50–0.96)	160	194	0.73 (0.54–0.98)
200–359.9	108	133	0.71 (0.51–0.98)	158	194	0.76 (0.57–1.01)
360–734.9	123	133	0.90 (0.66–1.23)	189	205	0.82 (0.62–1.08)
735–1639.9	108	103	0.76 (0.54–1.08)	159	184	0.71 (0.53–0.96)
⩾1640	130	107	1.15 (0.81–1.62)	210	154	1.40 (1.03–1.89)

The INTERPHONE Study Group, 2010

The INTERPHONE Study: Results

- Potential flaws of INTERPHONE
  - Non-response bias
  - Residual confounding (ex. SES)
  - Exposure categories and method of exposure ascertainment
    - Recall bias, exposure ascertainment bias, timing of control interviews
  - Sufficient lag time?
  - Biological plausibility - lower risk for cell phone users?

The INTERPHONE Study Group, 2010

Swerdlow et al., 2011

Cohort studies (I)

Population-based cohort studies – Denmark (Schuz et al., 2006; Frei et al., 2011)

- 420, 095 persons with 1st cellular phone subscription between 1982-1995, followed through 2002 for cancer incidence – excluding corporate subscriptions
- Record linkage to Central Population Register and Danish Cancer Registry
- Follow-up - began on date of 1st subscription, ended on date of 1st CA Dx, death, emigration, or December 31, 2002
- Generated standardized Incidence Ratios (5 year age strata + calendar periods)

Glioma – SIR 1.01 (95% CI 0.89 -1.14); temporal lobe + parietal lobe glioma – SIR 0.93 (95% CI 0.73-1.17)
Meningioma – SIR 0.86 (95% CI 0.67-1.09)

		Brain and nervous system		
Latency†, y	Person-years	Obs	Exp	SIR (95% CI)
<1	419 535	51	56.9	0.90 (0.67 to 1.18)
1–4	1 656 211	266	256.3	1.03 (0.91 to 1.17)
5–9	1 326 814	235	244.1	0.96 (0.84 to 1.09)
≥10	169 595	28	42.5	0.66 (0.44 to 0.95)
P_{trend}‡				.51

Potential flaws:

- Eligible for event as soon as they subscribe?
- Missing covariate data – confounding?
- Missing data on actual use of cell phone – misclassification of exposure?
- Cell phone-subscribing cohort possibly healthier than general population

Cohort studies (II)

The Million Women's Study (Benson et al., 2013) – Breast CA screening program

- 1.3 million recruited in UK between 1996-2001, 65% participation
- Cell phone use asked at baseline and q3-4 y
- 791, 710 middle-aged women (who had answered 2 cell phone Q's) followed for 7 years
- Exposure measurement:
  - 'About how often do you use a mobile phone?' - 'never', 'less than once a day', 'every day'
  - 'For how long have you used one?' (participants were asked to provide total years of use).
- Outcome measurement: national registry

Ever Vs Never users: all intracranial CNS tumours – RR 1.01 (95% CI 0.90–1.14)

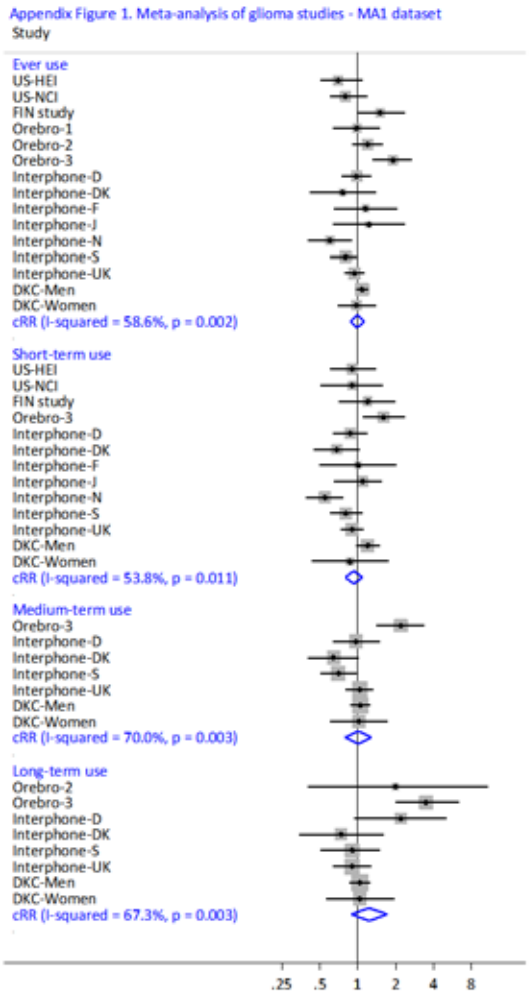
Long- term users (>=10 years) Vs never users – glioma RR 0.78 (95% CI 0.55–1.10), meningioma RR 1.10 (95% CI 0.66–1.84)

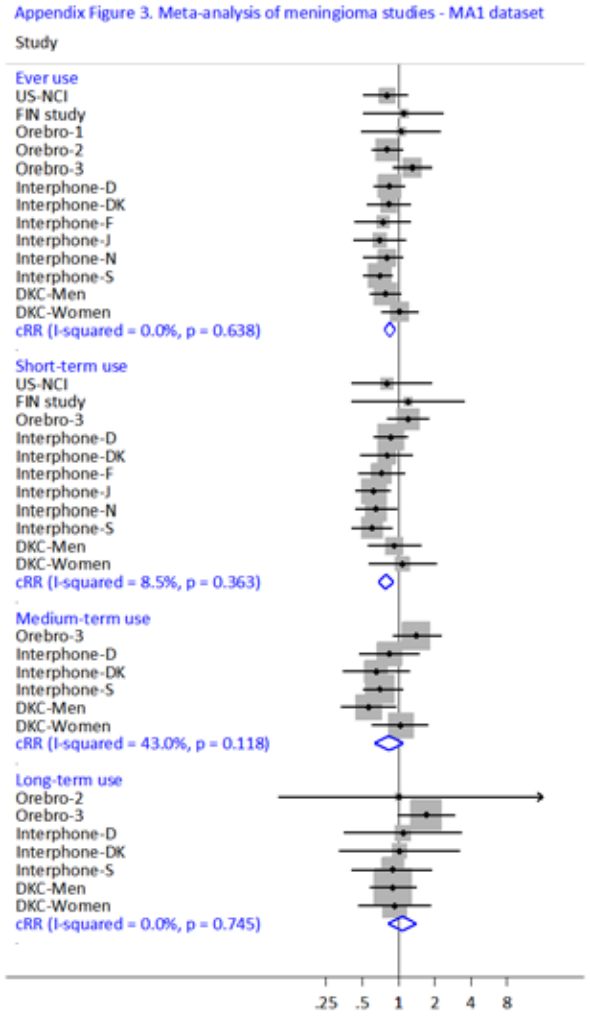
Potential flaws:

- Exclusion of prevalent cases? – excluded those with Dx before study, but no assessment at baseline for CA
- Length of follow-up?
- Selection bias?
- Missing indicator categories

Meta-analyses

- Showing primary studies only
- "Short-term" - 0.5–6.5 years overall, with variable length depending on the study)
- "Medium-term" - 5–9 years in general; 5–10 years for Örebro series
- "Long-term" - usually >=10 years; >10 years for Örebro series





Lagorio & Roosli, 2013

Why the inconsistencies?

- Case-control studies
  - Varying case/exposure definitions
  - Incomplete case ascertainment
  - Selection bias
  - Recall bias and poor recall
  - Secular trends
  - Analytic differences
- Cohort studies
  - Selection bias at start of study*
  - Incomplete case ascertainment*
  - Differential loss to follow-up*
  - Analytic differences

Also: data collection methods, time of follow-up / since exposure initiation

*Likely less in population registry-based cohorts (Denmark) Alhbom et al., 2009

Summary

- FDA states there is “no evidence linking cell phone use to risk of brain tumors” (US FDA, 2010)
- WHO/International Agency for Research on Cancer (IARC) classifies RF-EMF as possibly carcinogenic (group 2B; WHO, 2011)
- “Limited” evidence on carcinogenicity of cell phones (WHO, 2011) à positive association has been seen but could be due to chance, bias or confounding

Discussion

- How would you design a study to assess the effect of EMF on brain cancer?
  - What are key considerations?
  - How to measure the exposure with minimal measurement error?
  - How would you identify all (or a random sample of all) cases?
  - If case-control, what would be your control sampling frame?
  - How would you increase participation?

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100

TOBACCO

One person every 6.5 sec

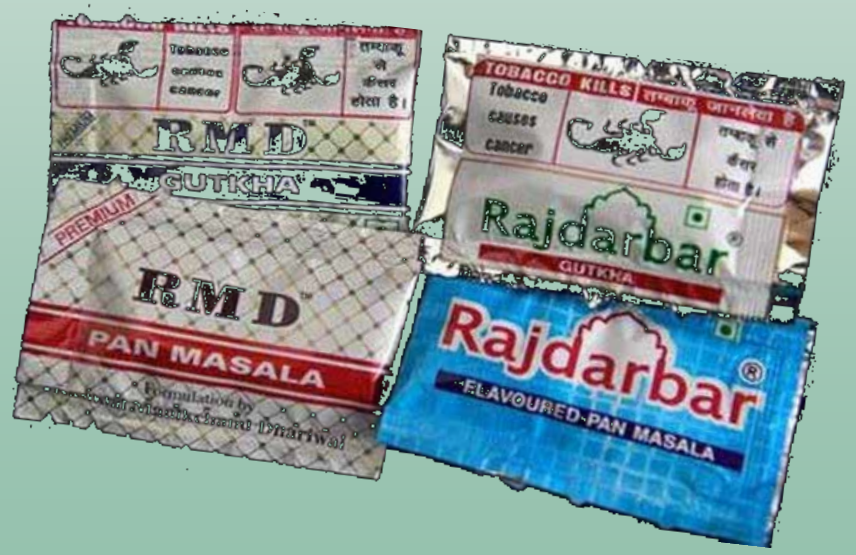
–Dr. Lee jong-wook Director general, WHO 2004

PAAN CHEWING & ORAL CANCER RISK

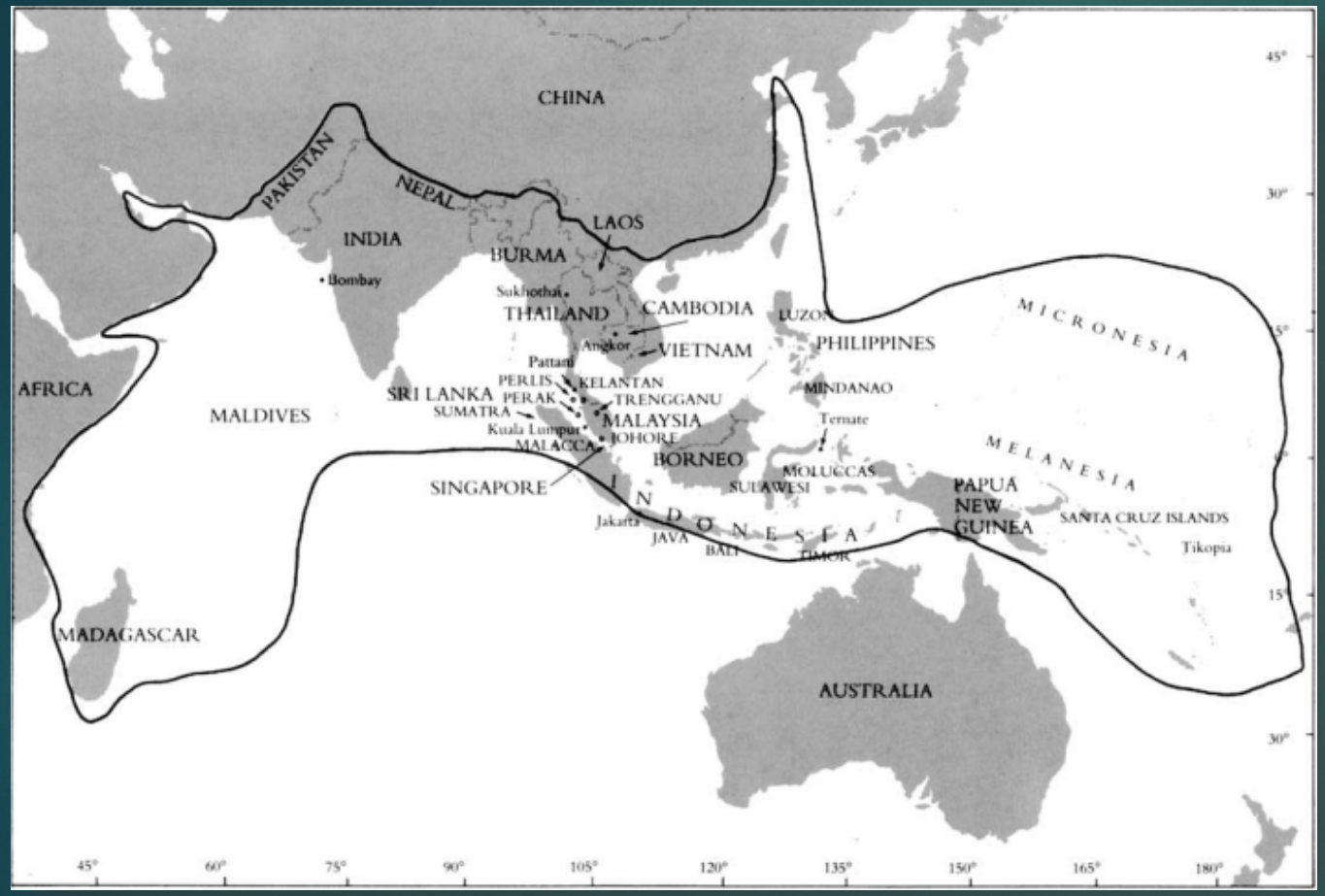
Sreenath Madathil, Faculty of Dentistry, McGill

Varieties..

Pan Masala
Betel quid + tobacco
Khaini
Gutka
Lao-hwa quid
Mawa, kharra



Geographical distribution of paan chewing



10 – 20% prevalence

> 600 million users

- Majority in South and South-East Asia and Pacific Islands.
- Also among immigrant population of Africa, Europe & North America including Canada.

History of paan chewing

Areca nut remains in Spirit caves of Thailand dating back to10000BC.

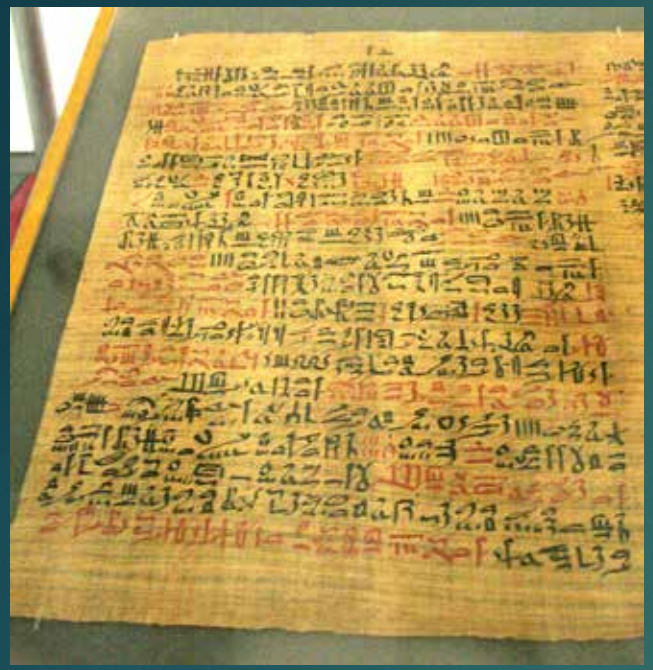
Paan stains in dental remains
Nui Nap, Vietnam – Bronze age.

Introduction of tobacco by
Europeans in 1600's

Oral Cancer

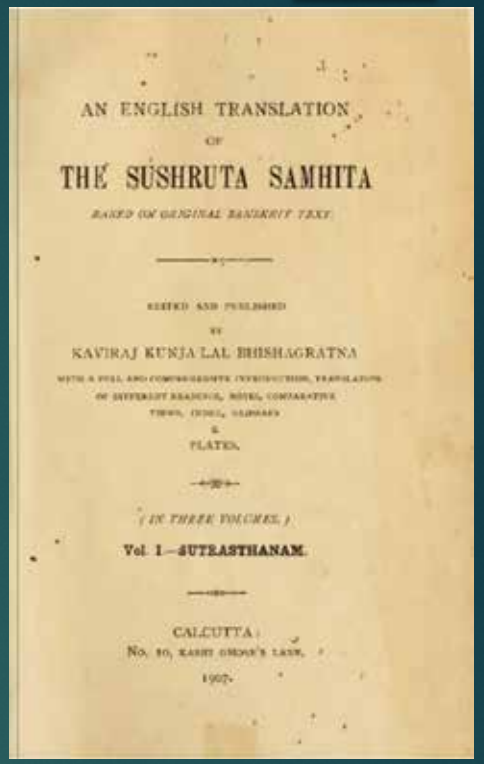
- Malignant neoplasms affecting the lip, tongue, gingiva, floor of mouth, palate, cheek mucosa, retro-molar area and vestibule of mouth.
- International Statistical Classification of Diseases and Related Health Problems (ICD) 10 code - C00 to C06.

Oral cancer - history



Smith and Ebers papyri
1600BC

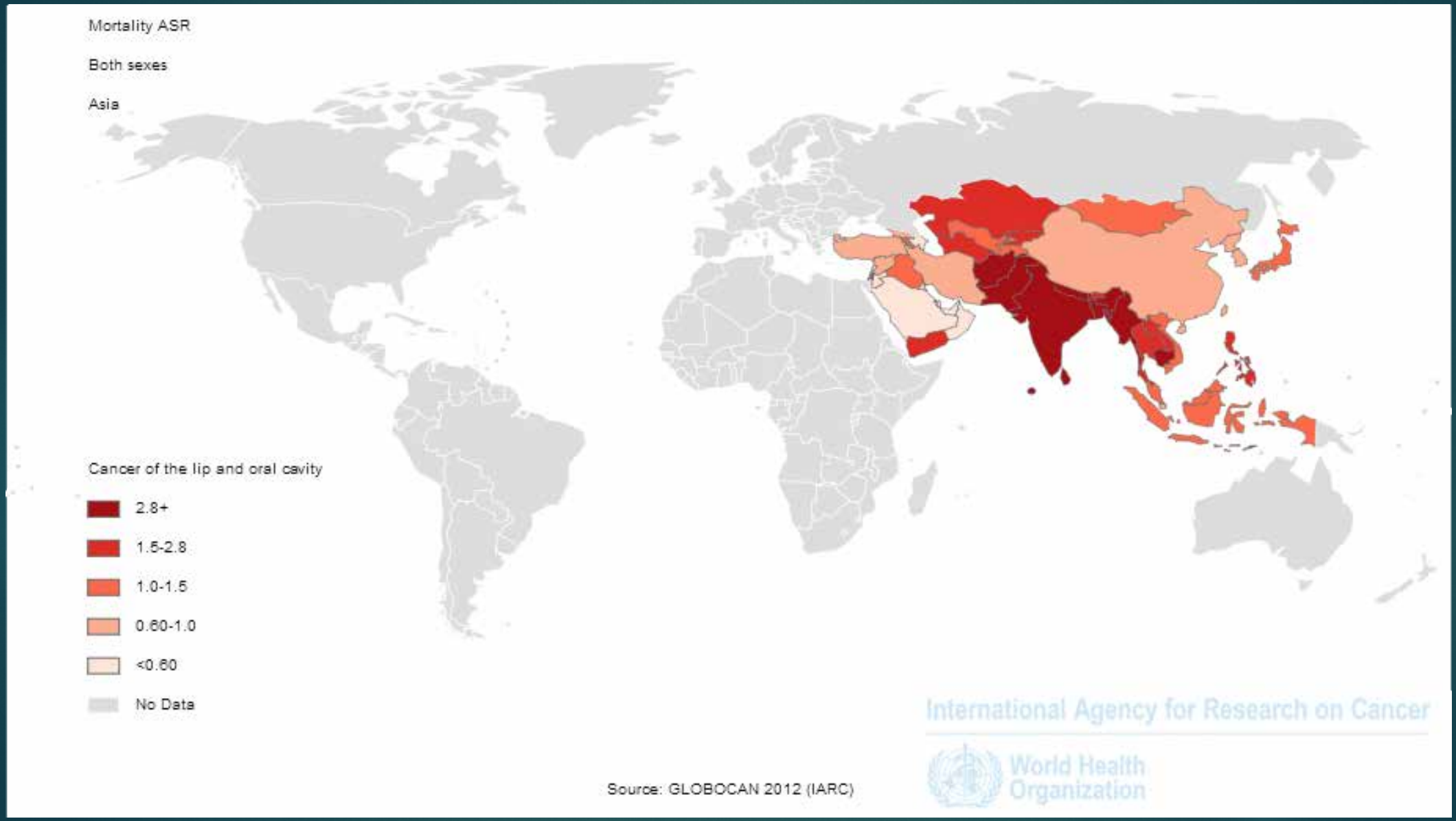
600 BC
Mukharbuda - Granthi (minor neoplasm)
Arbuda (major neoplasm)
? Causes - lifestyle errors, bad habits (tobacco, alcohol), poor hygiene, and unhealthy foods


AN ENGLISH TRANSLATION
OF
THE SUSHRUTA SAMHITA
BASED ON ORIGINAL SANSKRIT TEXT
EDITED AND PUBLISHED
BY
KAVIRAJ KUNJA LAL BHISHAGRATNA
WITH A FULL AND COMPREHENSIVE INTRODUCTION, TRANSLATION
OF DIFFERENT READINGS, NOTES, COMPARATIVE
TERMS, INDEX, GLOSSARY
&
PLATES.
(IN THREE VOLUMES.)
Vol. I—SUTRASTHANAM.
CALCUTTA:
No. 80, KASHI GHOSE'S LANE.
1907.

Epidemiology of Oral Cancer

- 17th most common cancer (Incidence); more than 3 million cases
- 90% - Squamous cell carcinoma
- Highest age standardized incidence rate in Papua New Guinea (25.0) , Maldives (11.0), Sri lanka (10.3), India (7.2),……., Canada(4.2).
- 5 year survival rate around 50% in many countries.

Epidemiology of Oral Cancer



Paan and oral cancer

"The inveterate habit of "betel chewing" from, childhood is suggestive of the cause, either by mechanical irritation or a medium suitable for the growth of a possible cancer germ."

-W.C. Bentall (BMJ 1908)

IARC 1985 – Sufficient evidence for paan with tobacco

Several studies

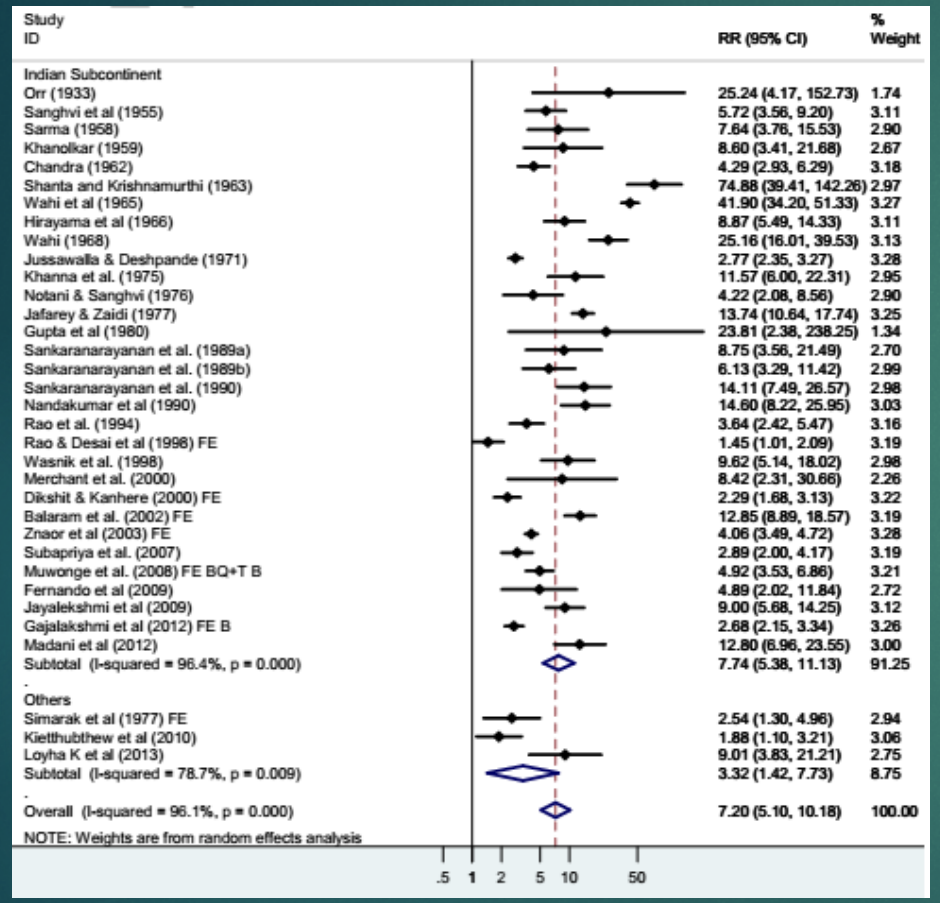
IARC 2004 – Paan without tobacco also Group 1

Several studies

IARC group 2013 – Meta-analysis

Pooled estimates of RR-IARC group 2013

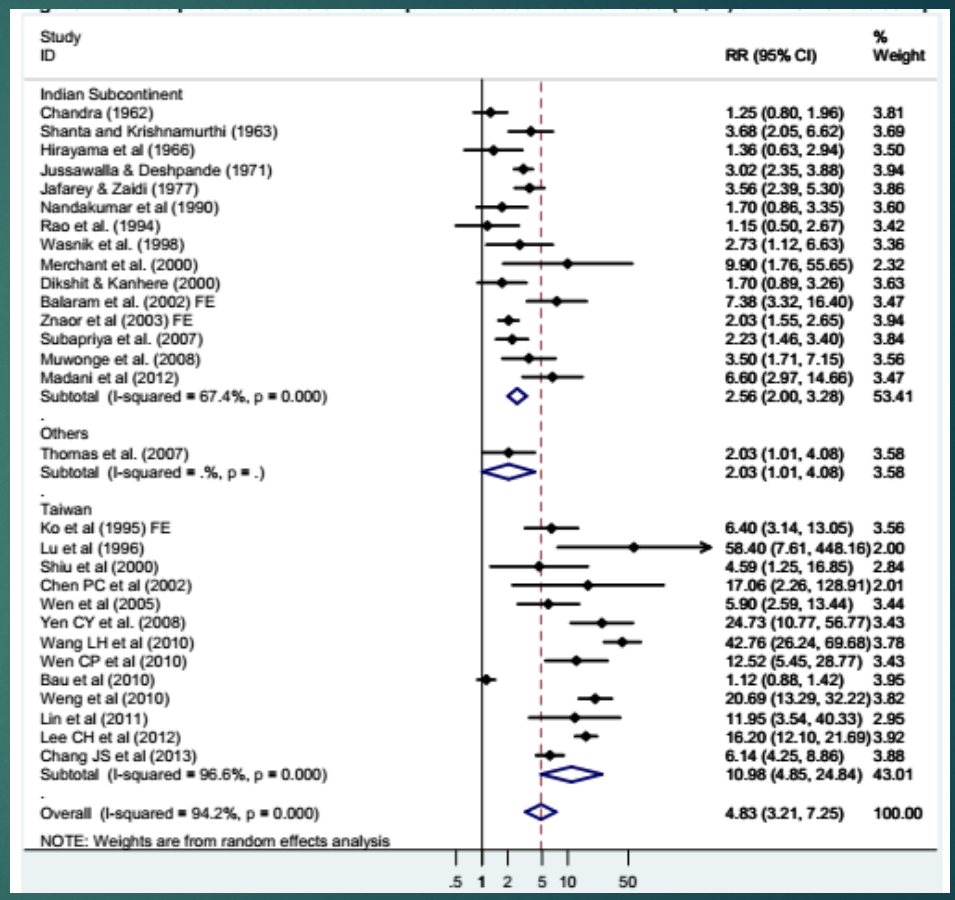
With tobacco



7.72 (5.10 – 11.18)

I^2 = 96.1%

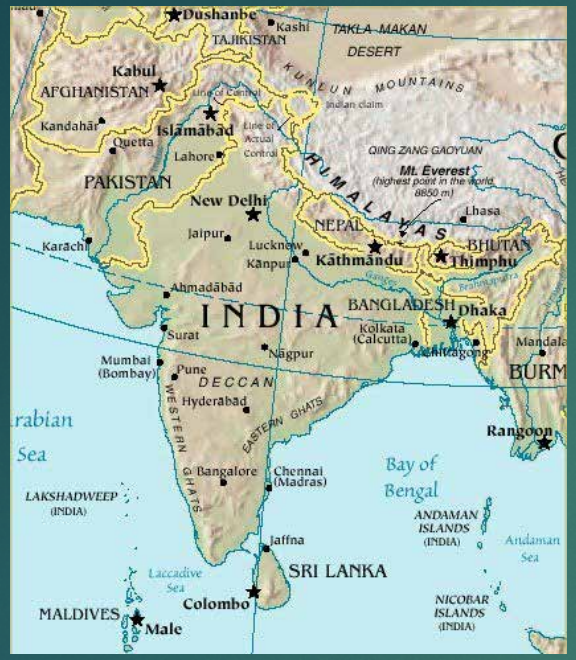
Without tobacco



4.83 (3.21 – 7.25)

I^2 = 94.2%

Population attributable fraction (PAF)



Indian subcontinent

PAF – 49.5%
with tobacco – 34,528 cases
without tobacco- 3,208 cases

Taiwan, China

PAF – 53.7%
without tobacco- 2,610 cases

Carcinogenicity of paan

- Sub-multiplicative interaction with tobacco smoking and supra - multiplicative interaction with alcohol consumption.
- Major carcinogens

  Areca nut– Arecoline, Arecaidine, Guvacine, Guvacoline

  Slaked lime - Calcium hydroxide

  Smokeless tobacco carcinogen.
- Genetic suseptability

  DNA repaire genes – XRCC1 & XPD among Indians

  - XRCC4 among Taiwanese

  Phase-I detoxifying enzyme - CYP2A6 among Sri lankans, Indians

Knowledge → prevention

SHORT TERM

LONG TERM

Targeted Audience

Targeted Audience

Knowledge inquiry

Synthesis

Qualitative &
Mixed method studies to

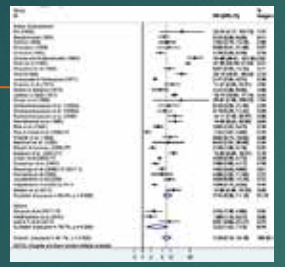
Genetic Studies

Products /tools

Tailoring knowledge

Clinicians

Decision support for Clinicians



Meta- analysis
Combining Qualitative and Quantitative evidence

Researchers

Academic publications

Current users of Paan

Individualized risk assessment tool

Self detection tools for Oral premalignant Conditions
(Brochures & mobile apps)

Ban the use & the product

Health Policy Makers

Alternative models for farmers

Agricultural Policy Makers

Cultural leaders as Knowledge Brokers

Community Participation

Reaching young population though social media

Potential future users of paan

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Gutka - http://www.thehealthsite.com/news/kerala-looks-to-emulate-assam-in-banning-gutka-and-pan-masala/

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http://chadizzy1.blogspot.ca/2011/01/chaini-khaini-saffran-review-19-january.html

Sushrutha - http://livelystories.com/2011/12/22/surgery-in-india/

Maps - http://www.worldatlas.com/webimage/countrys/asia/indiansub.htm

http://en.wikipedia.org/wiki/Cross-Strait_relations

Mouthing the Oral Cancer Screening Debate

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McGill University, Montreal, Canada

Because mortality rates are too cliché…

Every hour of every day 365 days a year someone dies in the United States resulting from oral cancer!!!

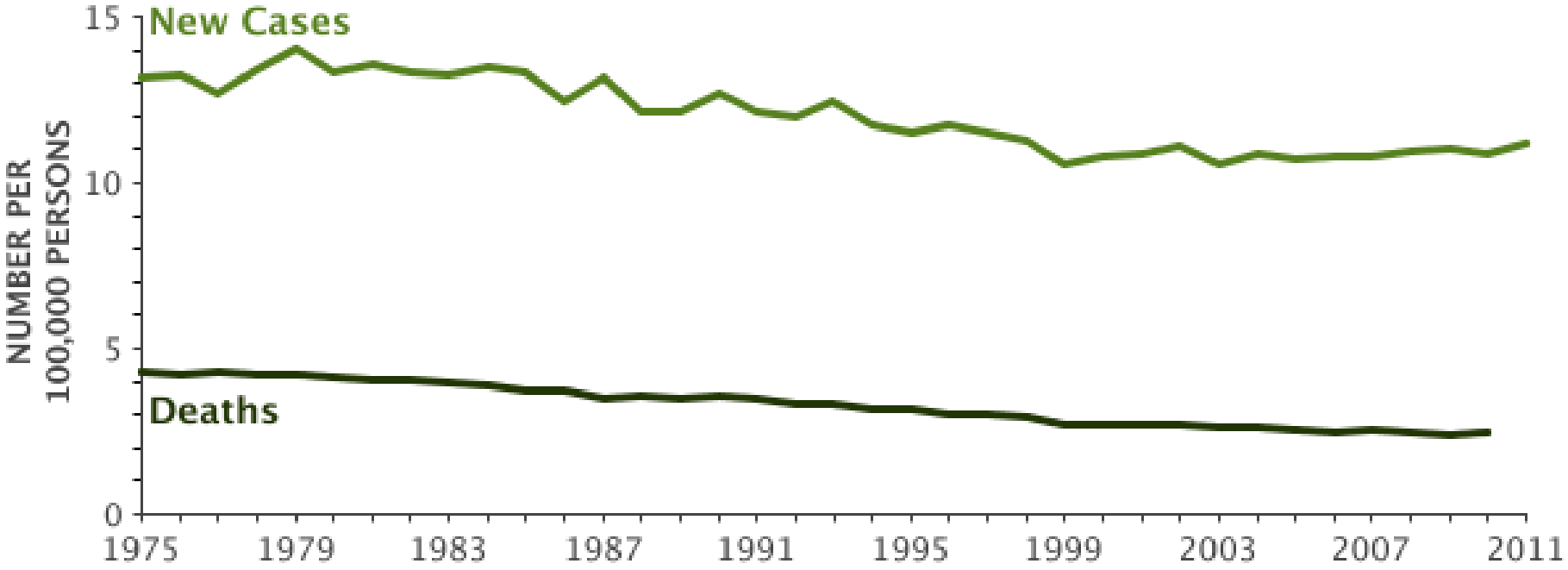
-Jonathan A. Bregman (2008)

Number of hours in a year
= 8,760

SEER estimated oral cancer related deaths in US (2014)
= 8,390

(SEER Cancer Statistics Review 1975-2011)

Jokes apart…



Source: SEER- Incidence 1975-2011 & U.S. Mortality 1975-2010
All Races, Both Sexes. Rates are Age-Adjusted.

Screening methods

- **Visual examination**
- **Toluidine blue dye**
- **Fluorescence visualization**
- **Brush biopsy**

Can we do it? Should we do it?

Wilson and Jungner (1968) Criteria for screening program

The condition should be an important health problem

There should be a recognizable latent or early symptomatic stage

The natural history of the condition, including development from latent to declared disease, should be adequately understood

There should be a suitable test or examination that has a high level of accuracy

There should be an accepted treatment for patients with recognized disease

Can we do it? Should we do it?

The test should be acceptable to the population

There should be an agreed policy on whom to treat

The chance of harm resulting form the screening should be outweighed by the chance of benefit (sensitivity, specificity, positive predictive power etc.)

The cost of screening should be economically balanced in relation to possible expenditure on medical care as a whole, and

Screening should be a continuing process

Walsh T et al. Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review). Cochrane Library 2013, Issue 11

- *Objectives:* To estimate the diagnostic accuracy of conventional oral examination (COE), vital rinsing, light-based detection, biomarkers and mouth self examination (MSE), used singly or in combination, for the early detection of PMD or cancer of the lip and oral cavity inapparently healthy adults.

- *Search strategy:* Multiple sources (till April 2013)

- *Selection criteria:* Studies reporting diagnostic test accuracy

- *Main results:* 13 studies (68,362 participants)
  - 1 RCT evaluated COE and vital rinsing
  - No eligible diagnostic accuracy studies light-based detection or blood or salivary sample analysis
  - Due to heterogeneity, data could not be pooled

Walsh T et al. Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review). Cochrane Library 2013, Issue 11

- *Clinical Oral Examination:* 10 studies (25,568 participants)
  - Prevalence in the diagnostic test accuracy sample ranged from 1- 51%
  - Sensitivity estimates ranged from 0.50 (0.07-0.93) to 0.99 (0.97-1.00) and specificity estimates were around 0.98 (0.97-1.00).

Study	TP	FP	FN	TN	Prevalence %	Sensitivity (95% CI)	Specificity (95% CI)
Julien 1995a	26	12	6	998	3.1	0.81 [0.64, 0.93]	0.99 [0.98, 0.99]
Mehta 1986	16	35	11	1859	1.4	0.59 [0.39, 0.78]	0.98 [0.97, 0.99]
Warnakulasuriya 1990	384	276	21	1191	21.6	0.95 [0.92, 0.97]	0.81 [0.79, 0.83]
Warnakulasuriya 1991	1741	431	52	1298	50.9	0.97 [0.96, 0.98]	0.75 [0.73, 0.77]
Downer 1995	12	2	5	290	5.5	0.71 [0.44, 0.90]	0.99 [0.98, 1.00]
Ikeda 1995	9	9	6	130	9.7	0.60 [0.32, 0.84]	0.94 [0.88, 0.97]
Julien 1995	14	8	8	955	2.2	0.64 [0.41, 0.83]	0.99 [0.98, 1.00]
Mathew 1997	200	31	12	1826	10.3	0.94 [0.90, 0.97]	0.98 [0.98, 0.99]
Chang 2011	282	172	3	13149	2.1	0.99 [0.97, 1.00]	0.99 [0.99, 0.99]
Sweeny 2011	2	2	2	82	4.6	0.50 [0.07, 0.93]	0.98 [0.92, 1.00]

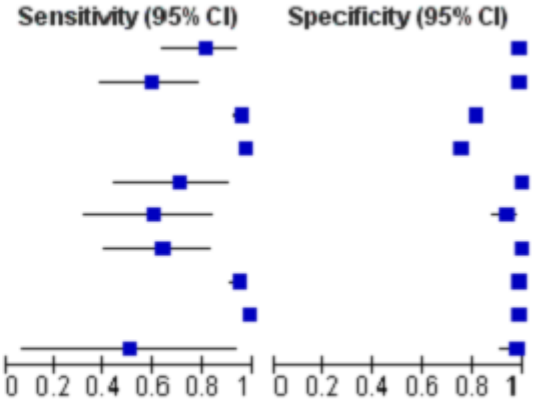


Figure. Forest Plot of Clinical Oral Examination

Walsh T et al. Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review). Cochrane Library 2013, Issue 11

- *Conclusions:*
  - COE estimates of sensitivity over the range of prevalence levels varied widely.
  - Observed estimates of specificity were more homogeneous.
  - Index tests at a prevalence reported in the population (between 1% and 5%) were better at correctly classifying the absence of PMD or oral cavity cancer in disease-free individuals than classifying the presence in diseased individuals.
  - Incorrectly classifying disease-free individuals as having the disease would have clinical and financial implications.
  - General dental practitioners and dental care professionals should remain vigilant for signs of PMD and oral cancer whilst performing routine oral examinations in practice.

Kujan O, Glenny AM, Duxbury AJ, Thakker N, Sloan P. Screening programmes for the early detection and prevention of oral cancer (Review). Cochrane Library 2003 Issue 4

- *Objectives*: To assess the effectiveness of current screening methods in decreasing oral cancer mortality.
- *Search strategy:* Multiple sources
- *Selection criteria:* RCTs for screening of oral cancer or potentially premalignant oral lesions using visual examination, toluidine blue, fluorescence imaging or brush biopsy
- *Main results:* 1 ongoing RCT (n = 13 clusters: 153,708 eligible subjects, 130,799 included subjects).
  - No difference in the age-standardized oral cancer mortality rates for the screened group (21.2/100,000) and the control group (21.3/100,000)
- *Conclusion:* no evidence to support or refute the use of a visual examination as a method of screening for oral cancer using a visual examination in the general population

Brocklehurst P, Kujan O, O'Malley LA, Ogden G, Shepherd S, Glenny AM. Screening programmes for the early detection and prevention of oral cancer (Review). Cochrane Library 2013 Issue 11

- *Objectives*: To assess the effectiveness of current screening methods in decreasing oral cancer mortality.

- *Search strategy:* Multiple sources

- *Selection criteria:* RCTs for screening of oral cancer or potentially premalignant oral lesions using visual examination, toluidine blue, fluorescence imaging or brush biopsy

- *Main results:* 1 RCT- 15yr follow up (n = 13 clusters: 191,873 participants).
  - No statistically significant difference in the oral cancer mortality rates for the screened group (15.4/100,000) and the control group (17.1/100,000)
  - RR: 0.88 (0.69 - 1.12).
  - 24% reduction in mortality for screening group (30/100,000 person-years) and the control group (39.0/100,000) for high-risk individuals who used tobacco or alcohol or both, which was statistically significant
  - RR: 0.76 (0.60 - 0.97).

Brocklehurst P, Kujan O, O'Malley LA, Ogden G, Shepherd S, Glenny AM. Screening programmes for the early detection and prevention of oral cancer (Review). Cochrane Library 2013 Issue 11

- *Conclusion:*
  - no evidence to support or refute the use of a visual examination as a method of screening for oral cancer using a visual examination in the general population
  - studies to elucidate the effectiveness of opportunistic screening in high risk groups are needed.

Recommendations:
US Preventive Services Task Force (November 2013)

- **Evidence is insufficient to recommend for or against routinely screening adults for oral cancer.**
- **Grade: I recommendation**

- **Update to 1996 recommendations:**
  - **The USPSTF found no new good quality evidence that screening for oral cancer leads to improved health outcomes for either high-risk adults or for average-risk adults in the general population.**
  - **It is unlikely that controlled trials of screening for oral cancer will ever be conducted in the general population because of the very low incidence of oral cancer in the United States.**
  - **No new evidence for the harms of screening.**

Recommendations:
Canadian Task Force on Preventive Health Care (1999)

- **There is good evidence to specifically consider smoking cessation counseling in a periodic health examination (grade A recommendation).**
- **For population screening, there is fair evidence to specifically exclude screening for oral cancer (grade D recommendation).**
- **For opportunistic screening during periodic examinations, there is sufficient evidence to recommend inclusion or exclusion of screening for oral cancer (grade C recommendation).**
- **For patients at high risk, annual examination by physician or dentist should be considered. Risk factors include tobacco use and excessive consumption of alcohol.**

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1. Jonathan A. Bregman (2008*). Early Oral Cancer Detection and Screening: The Dental Team is the Front Line.* Dental compare (online publication)
2. SEER Cancer Statistics Review 1975-2011.
3. Wilson JMG and Jungner G (1986). *Principles and practice of screening for disease.* Public Health Papers no. 34. World Health Organization. Geneva
4. Kujan, O., et al. (2006). *Screening programmes for the early detection and prevention of oral cancer*. Cochrane Database Syst Rev(3).
5. Brocklehurst, P., et al. (2013). *Screening programmes for the early detection and prevention of oral cancer*. Cochrane Database Syst Rev(11).
6. Walsh T, Liu JLY, Brocklehurst P, Glenny AM, Lingen M, Kerr AR, Ogden G, Warnakulasuriya S, Scully C. Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. Cochrane Database Syst Rev(11).
7. U.S. Preventive Services Task Force (2013). *Screening for Oral Cancer: Clinical Summary of U.S. Preventive Services Task Force Recommendation.* AHRQ Publication No. 13-05186-EF-3.
8. Canadiantaskforce.ca/ctfphc-guidelines/1999-oral-cancer/

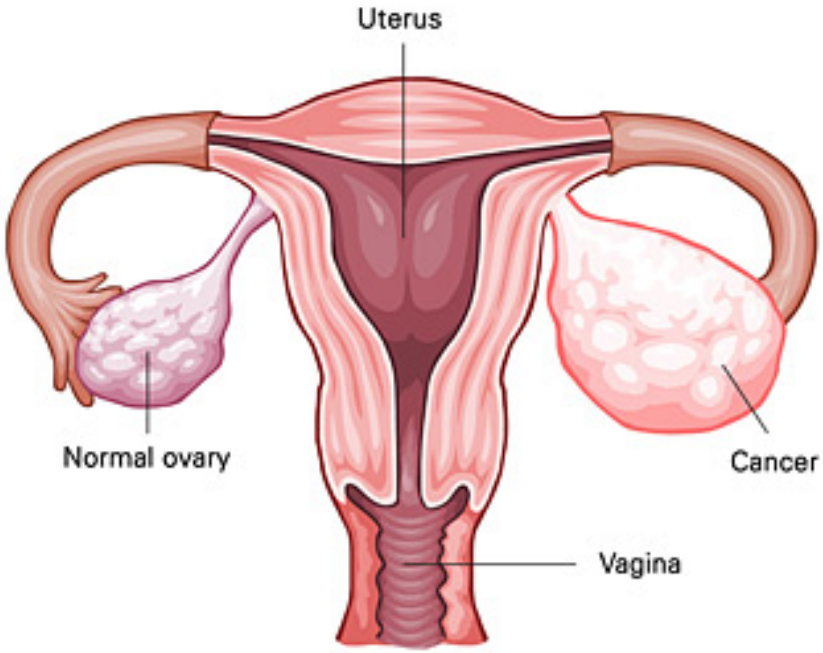
EPIDEMIOLOGY AND PREVENTION OF OVARIAN CANCER

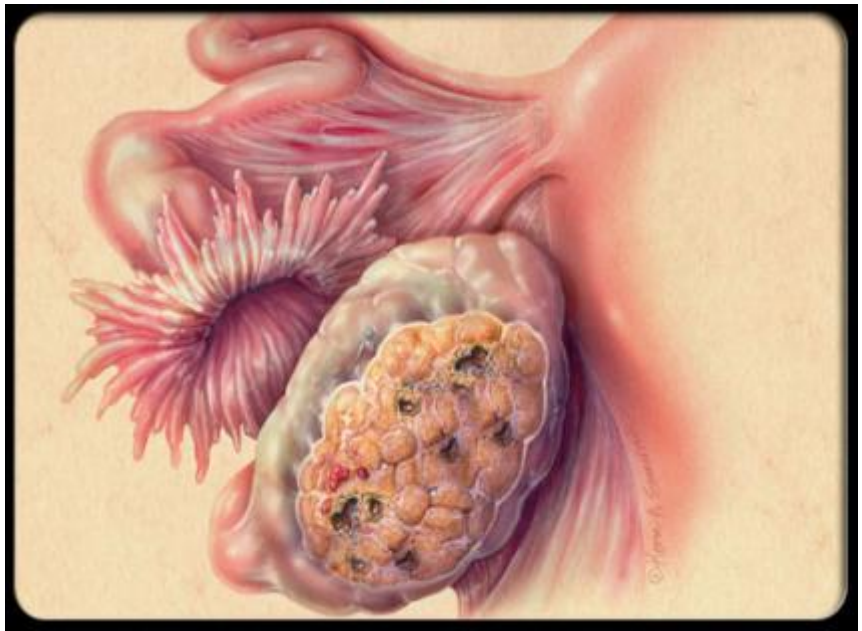
Yousef Katib
PGY1 in Radiation Oncology

Cancer epidemiology symposium
June 20, 2014

Outlines

- Epidemiology
- Risk factors
- Screening
- Prevention
- Summary
- References





Epidemiology

- There are large variations in the incidence of ovarian cancer in different area of the world.
- World wide in 2008:
  . 225,000 women were diagnosed with ovarian cancer.
  . 140,000 died from ovarian cancer.
- The 5th most cancer in women.
- Most common cause of gynecologic mortality

- In developed countries:

.The third most common gynecologic malignancy (cervical cancer is the most common)

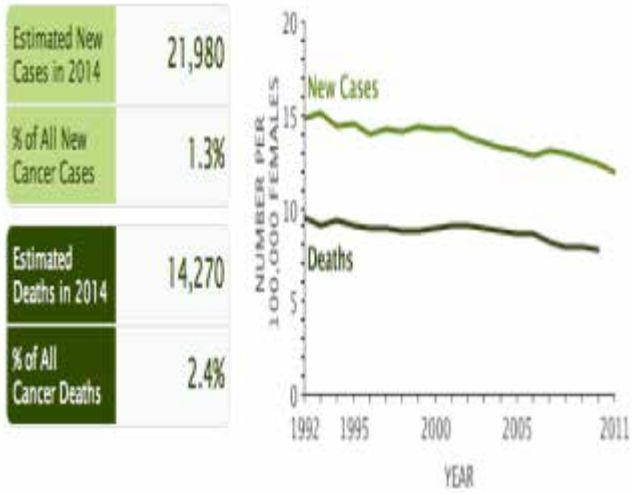
. Incidence of 5.0 per 100.000

. Mortality rate of 3.1 per 100,000

Global cancer statistics. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D, CA Cancer J Clin. 2011;61(2):69.

Epidemiology

- In United State:
  - Second most common gynecologic malignancy
    . Incidence of 9.4 per 100,000 women
    . Mortality rate of 5.1 per 100,000



- Based upon data from the US national cancer database Surveillance, Epidemiology and End Results, the annual incidence of ovarian cancer from 2005 to 2009 was 12.7 per 100,000 women.

- In 2014, it is estimated that there will be 21,980 new cases of ovarian cancer and an estimated 14,270 people will die of this disease (US).

- 1 in 70 women will develop ovarian cancer and the risk of death from ovarian cancer is 1 in 95.

- It is estimated that there will be 2,700 Canadian women will be diagnosed with ovarian cancer and an estimated 1,750 women will die from ovarian cancer in Canada.

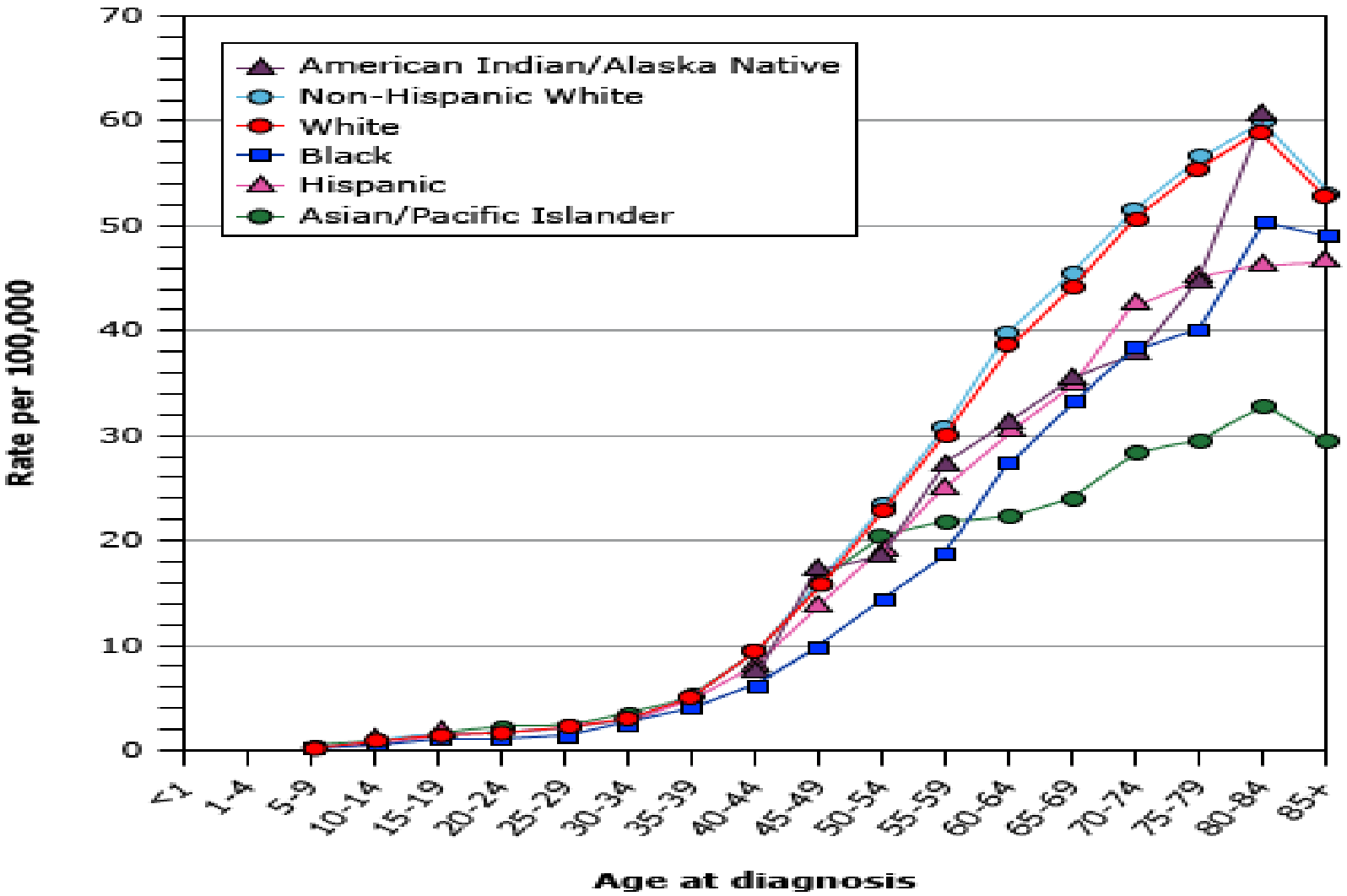
Cancer statistics, 2014. Siegel R, Ma J, Zou Z, Jemal A, CA Cancer J Clin. 2014;64(1):9.

How common is this cancer?

Common Types of Cancer	Estimated New Cases 2014	Estimated Deaths 2014
Prostate Cancer	233,000	29,480
Breast Cancer (Female)	232,670	40,000
Lung and Bronchus Cancer	224,210	159,260
Colon and Rectum Cancer	136,830	50,310
Melanoma of the Skin	76,100	9,710
Bladder Cancer	74,690	15,580
Non-Hodgkin Lymphoma	70,800	18,990
Thyroid Cancer	62,980	1,890
Endometrial Cance	52,630	8,590
Ovary Cancer	21,980	14,270

Ovary cancer represents **1.3%** of all new cancer cases in the U.S.

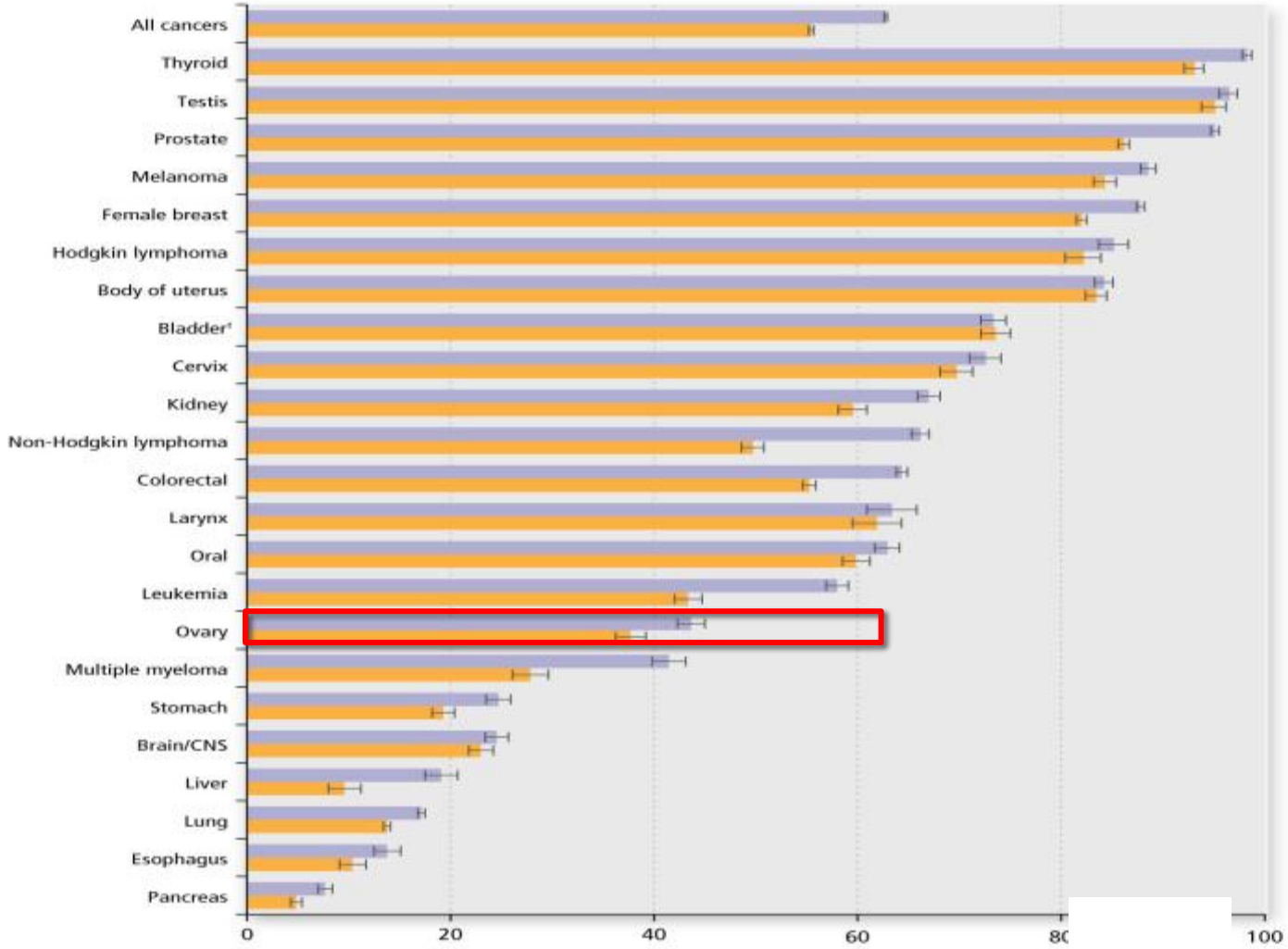
Incidence by age and race / ethnicity



Racial disparities in the treatment of advanced epithelial ovarian cancer.Howell EA, Egorova N, Hayes MP, Wisnivesky J, Franco R, Bickell N,Obstet Gynecol. 2013 Nov;122(5):1025-32.

Canadian Cancer Society / Société canadienne du cancer
Public Health Agency of Canada / Agence de la santé publique du Canada
Statistics Canada / Statistique Canada

FIGURE 5.2 Age-standardized five-year relative survival ratio (RSR) for selected cancers, Canada (excluding Quebec*), 2006–2008 versus 1992–1994



CNS=central nervous system

* Data from Quebec were excluded, in part, because the method for ascertaining the date of cancer diagnosis differs from the method used by other provinces/territories and because of issues in correctly ascertaining the vital status of cases.

† Excludes data from Ontario, which does not currently report *in situ* bladder cancers.

Note: These data are based on people aged 15–99 years at diagnosis. "All cancers" excludes adolescent (15–19 years) bone cancers, which are dissimilar to those diagnosed in older adults, and non-melanoma skin cancers (neoplasms, NOS; epithelial neoplasms, NOS; and basal and squamous). Error bars refer to 95% confidence intervals.

Analysis by: Health Statistics Division, Statistics Canada
Data sources: Canadian Cancer Registry database and life tables at Statistics Canada

Histopathology

- Derived from:

A - Epithelial cells “95% of all ovarian cancers”

. Serous carcinoma 75% “ previously papillary”

. Endometrioid “15%”

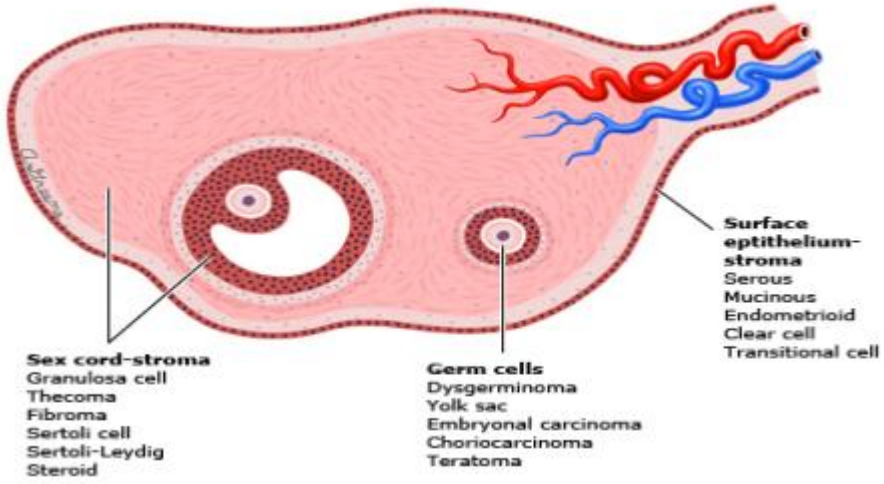
. Mucinous “5%”

. Clear cell “5%”

B – Others “5% of all ovarian cancers”

. Germ cell tumors

. Sex cord- stromal tumors



Lacey JV, Sherman ME. Ovarian neoplasia. In: Robboy's Pathology of the Female Reproductive Tract, 2nd ed., Robboy SL, Mutter GL, Prat J, et al.. (Eds), Churchill Livingstone Elsevier, Oxford 2009. p.601.

Risk Factors

- The pathogenetic mechanism(s) that explains the link between many of the risk factors and development of epithelial ovarian carcinoma (EOC) have not been determined.
- Many hypotheses were proposed:

Hypotheses on physiologic susceptibilities to epithelial ovarian cancer.

Hypothesis	Proposed mechanism	Best evidence
Incessant ovulation	OSE is damaged during ovulation and repair makes cells susceptible to mutations	Risk of EOC decreases with decreased number of cycles, (pregnancy, lactation, and OC use)
Gonadotropin stimulation	Stimulatory effects of FSH and LH promote growth, increased cell divisions and mutations	Increased EOC risk with infertility, PCOS; decreased risk with progesterone-only OCs; FSH upregulates many oncogenes
Hormonal stimulation	High concentrations of androgens in the tumor microenvironment promote carcinogenesis; whereas progestins decrease risk	Conditions of high circulating androgens (within inclusion cysts, PCOS) increase risks; progestin use decreases risk of EOC and induces OSE apoptosis
Inflammation	Damaged OSE with ovulation induces inflammation, which promotes reconstruction and mutation susceptibility	Possible reduced risk with NSAID use; increased risk with talc or asbestos; abundance of inflammatory mediators in tumors

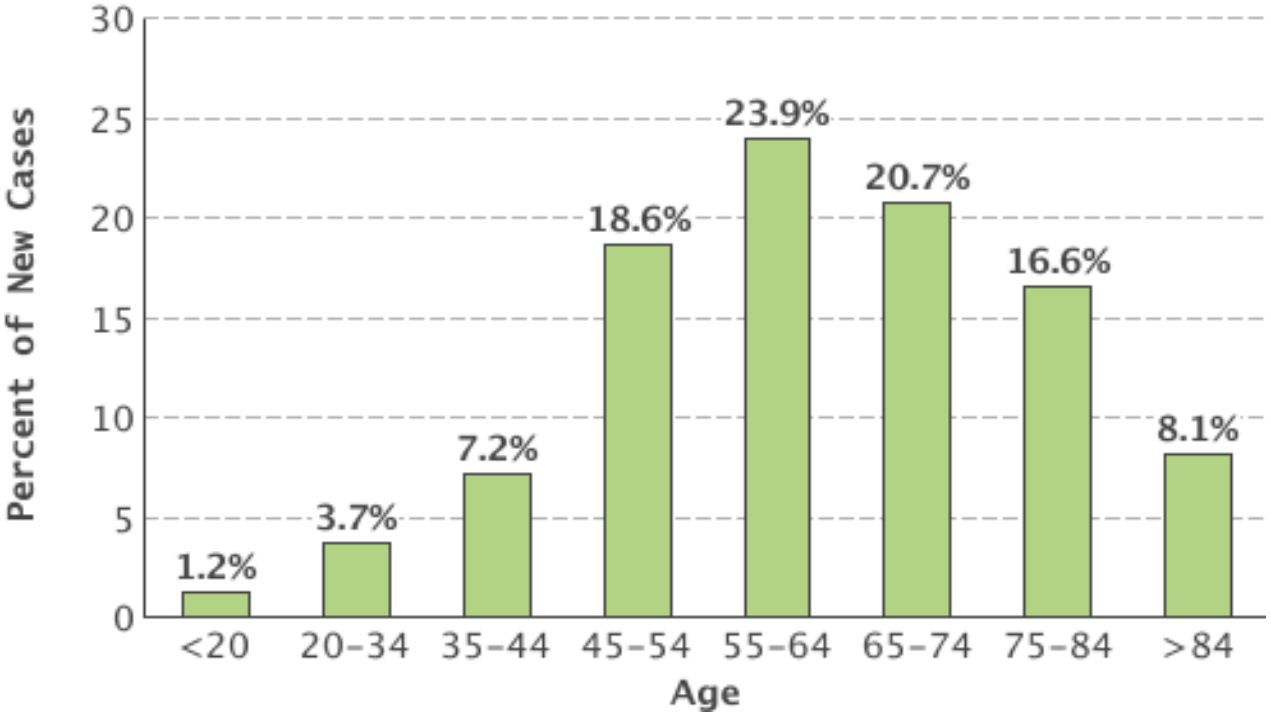
Risk Factors

Known risk factors	Possible risk factors
Age	Obesity
Family history of ovarian cancer	Using talc on the genitals
Never being pregnant (Nulliparity)	Early menarche or late menopause
Family history of certain cancers	Diet (fat)
Personal history of breast cancer	Infertility
Ashkenazi Jewish ancestry	Endometriosis
Hormone replacement therapy	**Environmental factors:**
Genetic factors:	Smoking
BRCA gene mutations	Asbestos
Lynch syndrome	

Risk factors

Age

- The average age at diagnosis is 63 years old .
- Increased approximately 2 percent for each additional year of age in women <50 years old and 11 percent in women ≥50 years old
- The age at diagnosis of ovarian cancer is younger among women with a hereditary ovarian cancer syndrome.



Risk factors for epithelial ovarian cancer by histologic subtype. Gates MA, Rosner BA, Hecht JL, Tworoger SS, Am J Epidemiol. 2010 Jan;171(1):45-53. Epub 2009 Nov 12

Risk factors

- The risk of ovarian cancer reaches 2 to 3 percent in women with a *BRCA1* gene mutation at age 35 and for those with a *BRCA2* mutation at age 50.

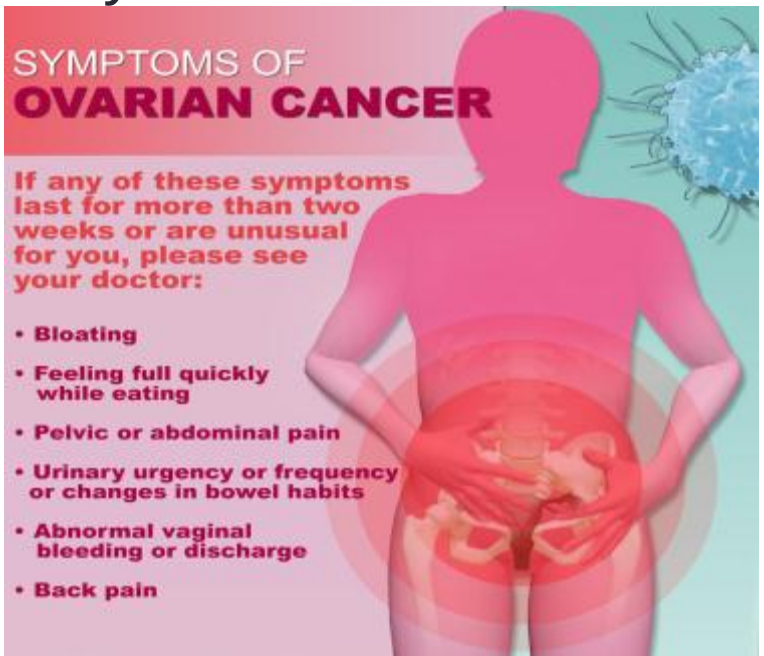
- Screening with ultrasound and CA-125 is recommended for women BRCA +ve mutation.

- More than 70% of women with ovarian cancer are diagnosed in late stage (stage III – IV).

"BRCAness" syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations.Tan DS, Rothermundt C, Thomas K, Bancroft E, Eeles R, Shanley S, Ardern-Jones A, Norman A, Kaye SB, Gore MEJ Clin Oncol. 2008;26(34):5530.

Clinical Approach

- History and symptoms:
  - . Abdominal or pelvic pain
  - . Increased abdominal size / bloating
  - . Urinary urgency or frequency
  - . Difficulty eating or feeling full quickly
- Physical examination
- Laboratory and imaging studies



Screening

- History and physical examination
  . Routine pelvic examination is not effective

- Laboratory tests
  . Tumor marker “CA-125”

- Imaging (Ultrasound)

- Results of trials (PLCO)

CA - 125

- CA -125 is a serum glycoprotein antigen “epithelial marker” derived from coelomic epithelium, produced by a variety of cells.
- Low Specificity 98%:
  - Any process that disrupts the peritoneum could increase it .
  - Common enough in pre/peri menopausal women
  - Pregnancy, Leiomyomata , Ovarian cysts, Endometriosis
  - Appendicitis , diverticulitis
  - Other malignancies as well

- Low sensitivity 68-82% :
  - Elevated in 90% of epithelial ovarian cancer.
- However:
  - CA125 are normal in 50% to 60% of patients with early stage
  - Less likely to detect Mucinous Adenocarcinoma of Ovary

The significance of serum CA 125 elevation in malignant and nonmalignant diseases. Sjövall K, Nilsson B, Einhorn N, Gynecol Oncol. 2002;85(1):175.

Causes of elevated CA125

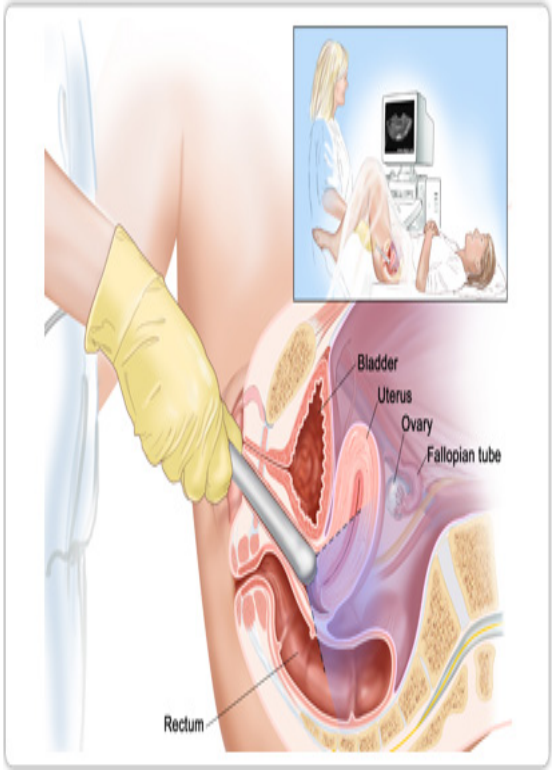
- Malignant conditions
- Gynecologic cancers
  - Epithelial ovarian cancer
  - Some germ cell tumors
  - Some stromal tumors
  - Fallopian tube cancers
  - Endometrial cancer
  - Endocervical cancer
- Non Gynecologic Cancer
  - Pancreatic cancer
  - Lung cancer
  - Breast cancer
  - Colon cancer

- Benign conditions

Gynecologic conditions
- Endometriosis
- Adenomyosis
- Leiomyomata uteri
- Ectopic pregnancy
- Normal pregnancy
- Pelvic inflammatory disease
- Menses

Non gynecologic conditions
- Pancreatitis
- Cholecystitis
- Cirrhosis
- Passive liver congestion
- Peritonitis
- Peritoneal tuberculosis
- Peritoneal sarcoidosis
- Recent laparotomy

Ultrasound



- Transvaginal ultrasonography

- Using morphology and Doppler imaging together:
  - Sensitivity of 86%
  - Specificity of 91%

- Better than CA-125 but definitely:
  - Not very effective in diagnosis early stage ovarian cancer
  - Not sufficient as a modality on its own

- A combination of ultrasound and CA125 better sensitivity and worse false positive rate

The prostate, lung, colorectal and ovarian (PLCO) cancer trial

- To evaluate the effect of screening for ovarian cancer on mortality
- Randomized control trial of 78,216
- women aged 54-74 years
- Enrolment from November 1993 to July 2001

- Intervention group was offered (Annual CA-125 x 6 years and TVUS x 4 years)
  vs.
  Usual care group (received usual medical care)

- Participants were follow up for maximum 13 years

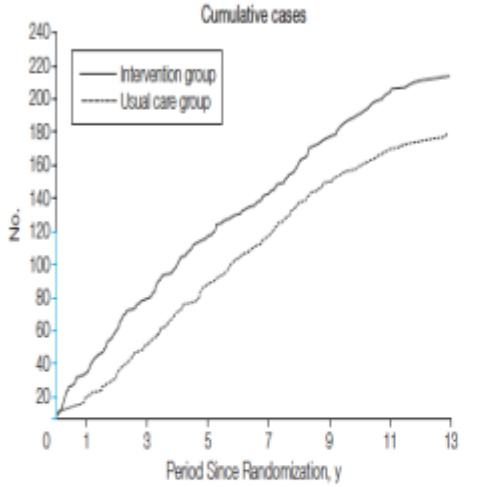
- Positive results defined as:
  - CA-125 >35
  - TVUS with any of the worrisome morphologic features
- Main outcomes:
  - Primary outcome: Mortality from Ovarian Cancer (powered to detect a 35% decrease)
  - Secondary outcomes: Incidence and complications associated with screening examinations and diagnostic procedures.

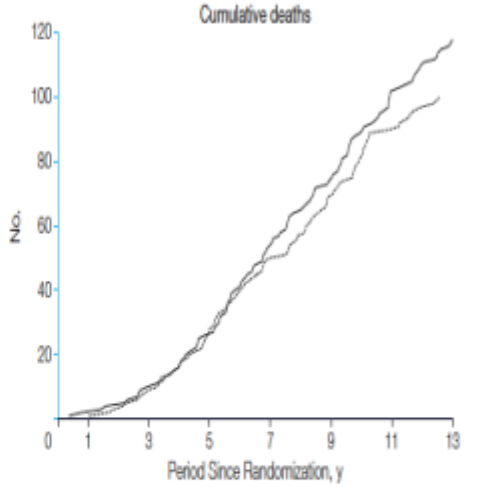
PLCO (results)

- Screening for ovarian cancer with cancer antigen 125 (CA-125) and transvaginal ultrasound has an unknown effect on mortality.

- Simultaneous screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false-positive screening test result was associated with complications.

Figure 2. Ovarian Cancer Cumulative Cases and Deaths

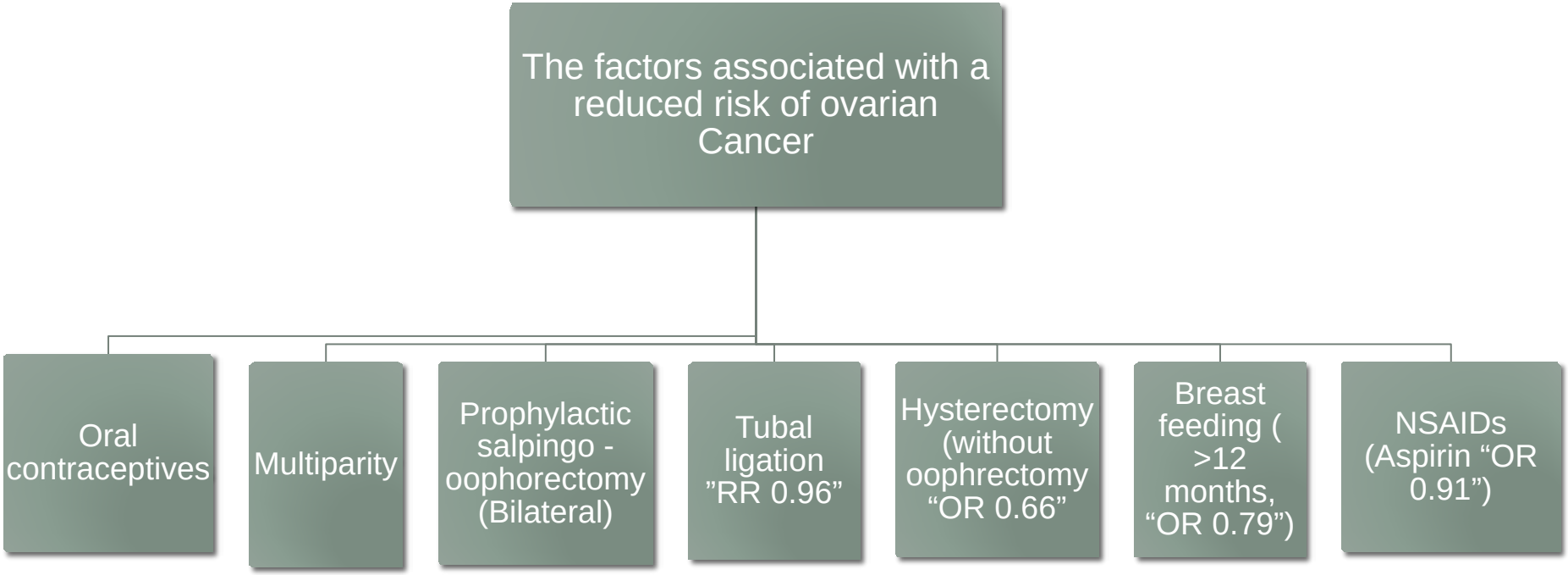




Intervention group														
Cumulative cancers	28	74	113	139	174	202	212	2	10	26	54	74	102	118
Cumulative person-years	33908	100777	166273	230393	292223	341975	371833	34210	102191	169354	235475	299372	350870	381574
Usual care group														
Cumulative cancers	13	45	83	113	146	167	176	0	9	28	50	69	90	100
Cumulative person-years	33994	101279	167980	232046	294424	344734	374976	34260	102344	169617	235836	299903	351557	382502

Y-axis shown in blue indicates range of 0 to 120 cumulative events.

Prevention (Protective factors)



Oral contraceptives

- Prolonged use of oral contraceptive reduces the risk of ovarian cancer.
- Many studies was associated with statistically significant reduction in risk of developing ovarian cancer (RR 0.73 for 2 years of use and reduced by 20% for each 5 years of use, and by 50% if used for 15 years.
- The use of both oral contraceptive and tubal ligation reduced the risk of ovarian cancer by 72 %

- Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, Hermon C, Peto R, Reeves G, Lancet. 2008;371(9609):303.

Oral contraceptive and risk of ovarian cancer

Author	Date	Type of Study	Cases	Controls or Cohort Size	Odds Ratio or Relative Risk	95% CI
Ness et al.[14]	2001	Case-control	727	1,360	0.6	0.5 – 0.8
Siskind et al.[15]	2000	Case-control	794	853	0.57	0.4 – 0.82
Narod et al.[16]	1998	Case-control	207	161	0.5	0.3 – 0.8
Vessey and Painter[17]	1995	Cohort	42	15,292	0.3	0.1 – 0.7
Hankinson et al.[18]	1995	Cohort	260	121,700	0.65	0.4 – 1.05
Rosenberg et al.[19]	1994	Case-control	441	2,065	0.6	0.4 – 0.8
John et al.[20]	1993	Case-control	110	246	0.62	0.24 – 1.6
Parazzini et al.[21]	1991	Case-control	505	1,375	0.7	0.5 – 1.0
Franceschi et al.[22]	1991	Case-control	971	2,258	0.6	0.4 – 0.8
Parazzini et al.[23]	1991	Case-control	91	237	0.3	0.2 – 0.6
Gwinn et al.[24]	1990	Case-control	436	3,833	0.5	0.5 – 0.7
CASH Group[25]	1987	Case-control	546	4,228	0.6	0.5 – 0.7
Tzonou et al.[26]	1984	Case-control	150	250	0.4	0.1 – 1.1
La Vecchia et al.[27]	1984	Case-control	209	418	0.6	0.3 – 1.0
Rosenberg et al.[28]	1982	Case-control	136	187	0.6	0.4 – 0.9
Cramer et al.[29]	1982	Case-control	144	139	0.11	0.04 – 0.33
Willett et al.[30]	1981	Case-control	47	464	0.8	0.4 – 1.5

Barnes et at, CA cancer J clinical, 2002

Summary

- Ovarian cancer is the second most common gynecologic malignancy in the United States, the most common cause of death among women with gynecologic cancer, and the fifth leading cause of cancer death in all women. The annual incidence of ovarian cancer in the United States is 12.7 per 100,000 women. The lifetime risk of ovarian cancer in the general population is 1.4 percent.

- Risk factors for ovarian cancer include increasing age, nulligravida, infertility, endometriosis, and hereditary ovarian cancer syndromes (BRCA gene mutations, Lynch syndrome).

- Protective factors include oral contraceptives, salpingo-oophorectomy, tubal ligation, hysterectomy, and breastfeeding.

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- Canadian cancer society

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Intratypic HPV Variants and Cervical Cancer Risk

EPIB 671: Cancer Epidemiology
June 20, 2014

HPV and cervical cancer

- HPV is a necessary, yet not sufficient, cause for cervical cancer
- HPV types 16 and 18 in ~70% invasive cervical cancer cases
  - Current vaccine target
- Other high risk HPV types (31, 33, 35, 45, 52, and 58)

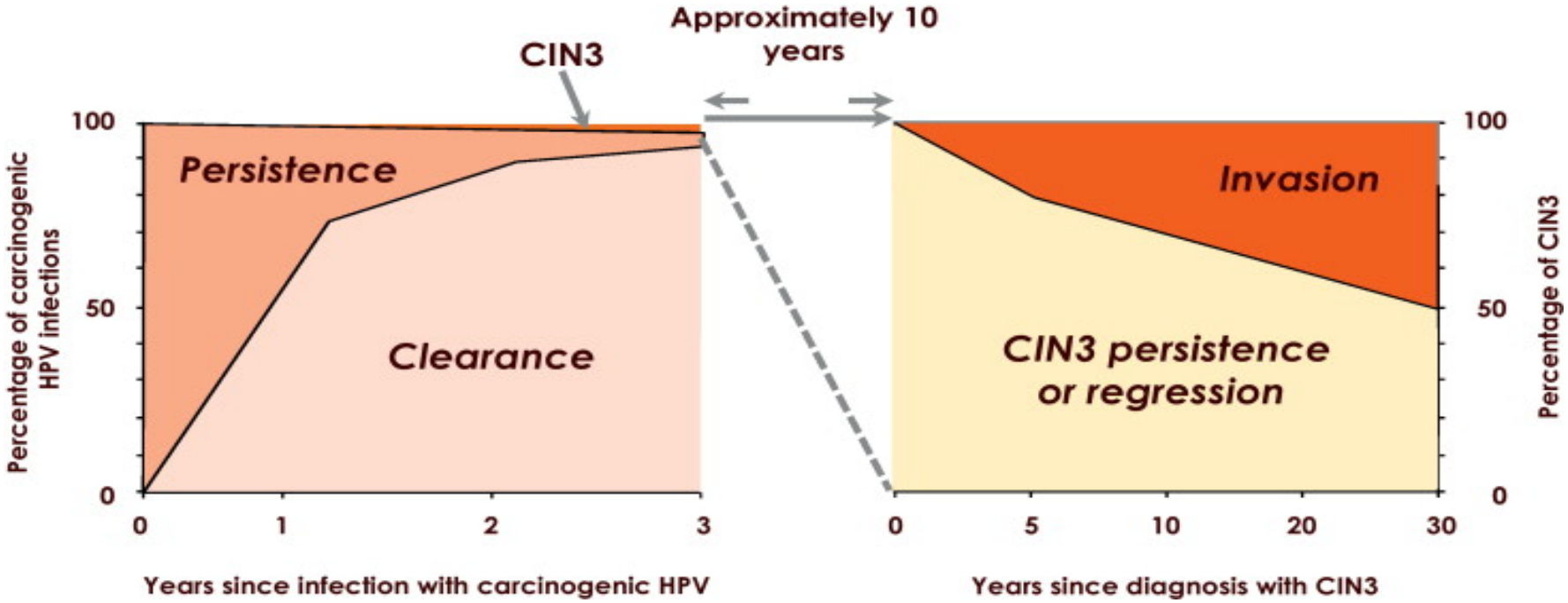

Image: Moscicki et al. (2012)

- How can we predict cases that are at the highest risk?
  - Age
  - Ethnicity
  - Multiple HPV types (co-infection)
  - HPV genetic differences

Classification

- L1 gene variability
  - Type: >10%
  - Subtype: 2–10%
  - Variant: <2%
    - or 5% in a less conserved area

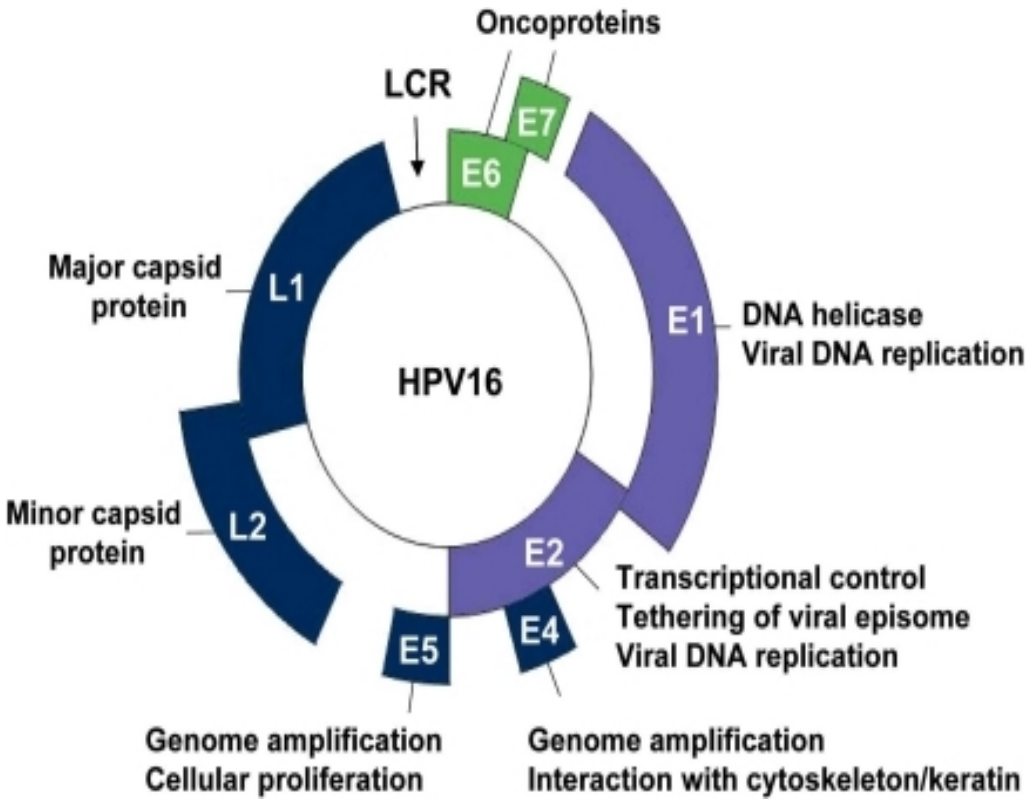

Image: D'Abramo et al. (2004)

HPV genome

- E6 and E7: proteins promote cell cycle and proliferation of cervical cancer cells
  - inhibit p53 and RB
- LCR (long control region): regulates transcription

Why look at HPV variants?

- Natural history of HPV
  - Transmission, persistence, and progression to cancer
- Molecular mechanism
  - Differences in cervical cancer potential
- Prediction of cervical cancer risk

à Use to decide treatment?

HPV 16 & 18 variants

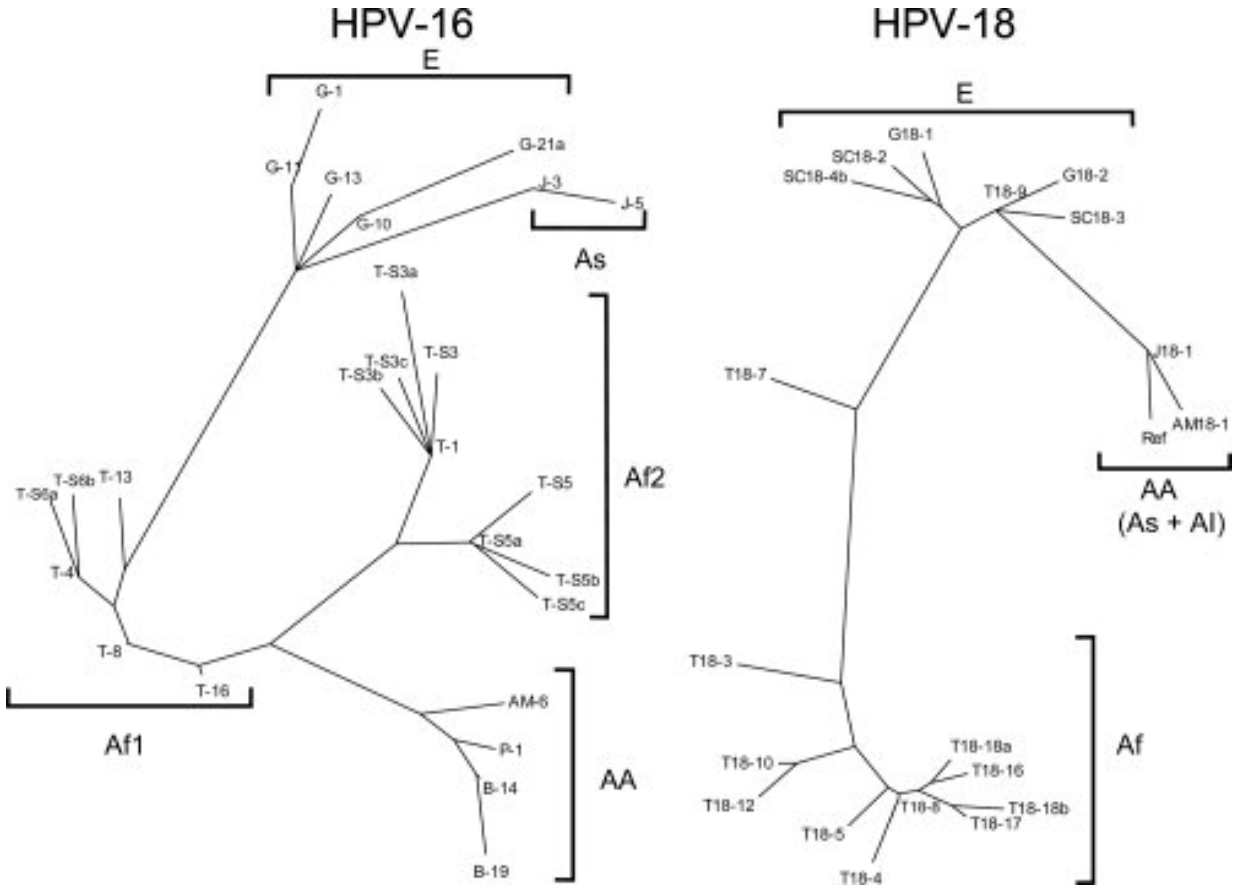

Image: Bernard et al. (2006)

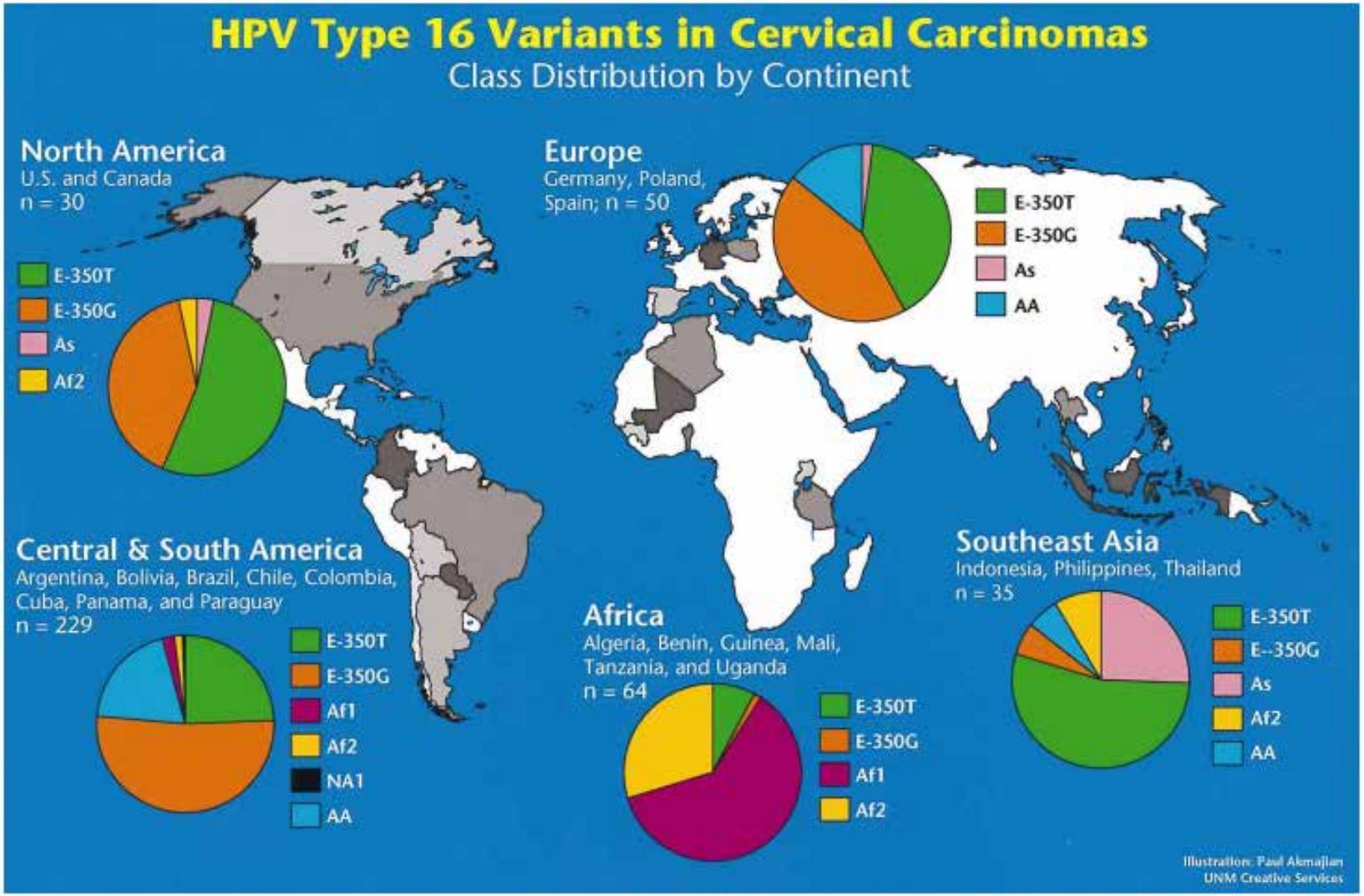

FIG. 5. Global distribution of major HPV-16 classes and subclasses. The assignments of major HPV-16 variants including E, As, Af-1, Af-2, and AA are shown. The European prototype (E) has been divided into variants demonstrating a nucleotide variation within the E6 coding region at nt 350. This E class distinction is represented by E-350T and E-350G categories and excludes As variants. HPV-16 variants sampled in this study were from countries that are shaded.

Image: Yamada et al. (1997)

Types of studies

- Phylogeny
- Cervical cancer risk
  - Proxy outcome:
    - Persistence
    - Abnormal Pap smear findings

Villa et al. 2000

- Ludwig-McGill cohort (Brazil)
- 2528 enrolled: 443 HPV positive
  - 97 isolates of HPV-16 (54 subjects)
  - 25 HPV-18 (12 subjects)
- PCR
  - molecular variants characterized by
    - sequence analysis of the LCR
    - dot blot hybridization of the E6 and L1 genes

Table 3. Age- and race-adjusted OR (and respective 95% CI) of prevalent cervical lesions by HPV-infection status at enrolment and in first year follow-up visits

OR and CI values are calculated by logistic regression analysis. Models for any grade SIL exclude atypical squamous cells of undetermined significance (ASCUS) and models for HSIL exclude ASCUS and LSIL. Calculated values exclude untested HPV-16 and -18 isolates. HPV-18 infections were included among other oncogenic types when variants were considered only for HPV-16. Variants of HPV-16 and -18 are grouped according to branches of geographical relatedness.

Lesion outcome, ascertainment method	HPV-infection status (no. cases/subjects)	OR (95% CI)	
		HPV-16 and -18 variants combined	HPV-16 variants only
Any grade SIL, cytology only	Negative (10/1211)	1·0 (reference value)	1·0 (reference value)
	E branch (12/44)	45·48 (18·3–113·3)	55·47 (21·5–143·3)
	AA/Af/As branches (5/23)	99·65 (32·1–308·9)	110·05 (34·9–347·1)
	Other oncogenic types (46/164)	48·06 (23·4–98·9)	44·95 (22·0–92·0)
	Only non-oncogenic types (12/159)	9·08 (3·8–21·8)	9·06 (3·9–21·7)
HSIL, cytology only	Negative (2/1203)	1·0 (reference value)	1·0 (reference value)
	E branch (7/39)	151·25 (29·7–771·3)	173·94 (32·8–923·5)
	AA/Af/As branches (6/16)	529·81 (88·6–3167)	573·30 (95·1–3457)
	Other oncogenic types (12/130)	74·79 (16·2–345·6)	71·49 (15·6–326·7)
	Only non-oncogenic types (3/150)	8·90 (1·2–63·9)	8·88 (1·2–63·7)
HSIL, cytology or cervicography	Negative (7/1203)	1·0 (reference value)	1·0 (reference value)
	E branch (8/40)	46·31 (15·5–138·0)	54·89 (17·5–172·0)
	AA/Af/As branches (7/17)	172·24 (47·1–630·1)	186·21 (50·2–690·1)
	Other oncogenic types (13/131)	21·62 (8·3–56·6)	20·59 (8·0–53·1)
	Only non-oncogenic types (3/150)	2·51 (0·5–12·2)	2·50 (0·5–12·2)

Villa et al. (2000)

There are other high risk types!

HPV SPECIES (alpha)	HPV GENOTYPE	RISK
9	HPV 52	High
	HPV 67	Undetermined
	HPV 33	High
	HPV 58	High
	HPV 16	High
	HPV 31	High
	HPV 35	High
11	HPV 34	Undetermined
	HPV 73	Probably high
7	HPV 59	High
	HPV 18	High
	HPV 45	High
	HPV 70	Low
	HPV 39	High
	HPV 68	Probably high
	HPV 85	Undetermined
5	HPV 26	Probably high
	HPV 69	Undetermined
	HPV 51	High
	HPV 82	Probably high
6	HPV 30	Undetermined
	HPV 53	Probably high
	HPV 56	High
	HPV 66	Probably high

HPV SPECIES (alpha)	HPV GENOTYPE	RISK
10	HPV 6	Low
	HPV 11	Low
	HPV 13	Low
	HPV 74	Undetermined
	HPV 44	Low
	HPV 55	Undetermined
8	HPV 91	Undetermined
	HPV 7	Undetermined
	HPV 40	Low
	HPV 43	Low
1	HPV 32	Undetermined
	HPV 42	Low
13	HPV 54	Low

HPV SPECIES (alpha)	HPV GENOTYPE	RISK
4	HPV57	Undetermined
	HPV 2a	Undetermined
	HPV 27	Undetermined
15	HPV 71	Undetermined
	HPV 90	Undetermined
3	HPV 61	Low
	HPV 72	Low
	HPV 62	Undetermined
	HPV 81	Low
	HPV 83	Undetermined
	HPV 89	Low
	HPV 84	Undetermined
	HPV 86	Undetermined
	HPV 87	Undetermined
2	HPV 28	Undetermined
	HPV 3	Undetermined
	HPV 10	Undetermined
	HPV 29	Undetermined
	HPV 77	Undetermined

Image: Munoz et al. (2006)

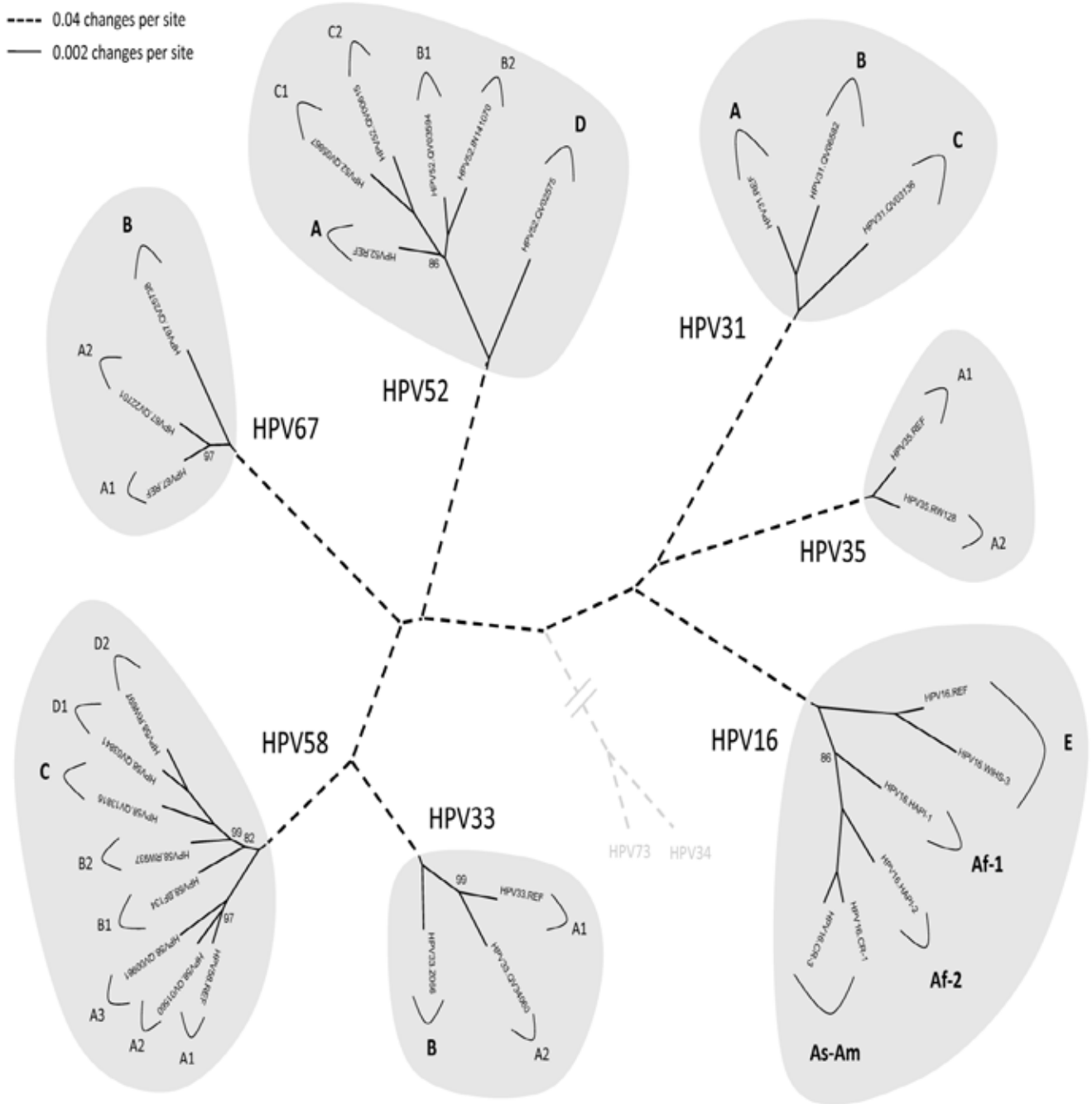

Image: Chen et al. (2011)

Other HR-HPV Variants

- **[Raiol et al., 2009]:** types 31, 33, 35, and 58 do not show geographical clustering
  - Two branches of HPV-52 could be Asian and European
- **[Schiffman et al., 2010]:** tested families α-9, 11, 7, 5, and 6. Only type 35 (in addition to HPV-16) showed differences in odds
  - Persistence : OR = 3.71
  - CIN3+: OR= 6.35
- **[Xi et al., 2013]:** type 31 (reference C)
  - Clearance:
    - A: HR = 1.2 [0.7, 2.1]
    - B: HR = 2.1 [1.2, 3.5]

Difficulties and limitations

- Limited number of samples within each exposure category
- Even more limited numbers of cervical cancer cases
  - Using proxy outcomes not entirely accurate
- Latent virus may be missed with molecular testing

Potential implications

- Would it be possible or useful to use variant information in screening?
  - Self-screening
- Could this information help with designing therapeutic measures?

Summary

- HPV can be classified by type and intratypic variant
- Different variants may differ in terms of cervical cancer risk
- Understanding intratypic variants may be useful in secondary prevention

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Thank you!

Questions?