McGill EPIB-671 Symposium - 2015

Scientific Program, Wednesday, June 17

Time	Presenter	Title
12:30 - 12:45	Host	Introduction to the Symposium and Instructions
12:45 - 13:00	Camille Loranger	Ultraviolet light exposure and cutaneous squamous cell cancer
13:00 - 13:15	Anwar Shams	Dietary risk factors for colorectal cancer
13:15 - 13:30	Ziad Fawaz	Trends in brain cancer incidence and survival
13:30 - 13:45	Jessica McNeil	Physical activity and prevention of cancer recurrence
13:45 - 14:00	Maryam Ajikobi	Risk factors for ovarian cancer
14:00 - 14:15	Linnea Duke	Epidemiology of testicular cancer
14:15 - 14:30	Sara Soldera	Breast cancer screening for women aged 50-69 years
14:30 - 14:45	Zoe Greenwald	Cervical cancer screening in developing countries
14:45 - 15:00	***Coffee Break***	
15:00 - 15:15	Elena Netchiporouk	Epidemiology of cutaneous lymphoma
15:15 - 15:30	Muhammad Mujammami	Epidemiology of thyroid cancer
15:30 - 15:45	Lukas Tamayo Orrego	Epidemiology of medulloblastoma
15:45 - 16:00	Pylyp Zolotarov	Cancer risk following the 1986 Chernobyl disaster
16:00 - 16:15	Lidija Latifovic	Flame retardant compounds and breast cancer risk
16:15 - 16:30	Joice Rocha Cury	Chemoprevention of prostate cancer
16:30 - 16:45	Huda Altoukhi	PSA testing for prostate cancer screening
16:45 - 17:00	Final remarks, exam, and end of course: Have a Happy Summer!	

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

UV EXPOSURE AND CUTANEOUS SQUAMOUS CELL CARCINOMA

Camillle Loranger

EPIB-671

June 2015

BACKGROUND OF ULTRAVIOLET

- UV spectrum (100-400 nm)
  - UVA1 (320-340); UVA2 (340-400)
  - UVB (290-320)
  - UVC (100-290) (all absorb by ozone layer)
- Solar Radiation is the major source of UV
  - 95% of UVA and 5% of UVB reaches the earth
- Additional artificial sources
  - Phototherapy (PUVA; UVA; UVB)
  - Tanning beds (UVA mainly)
- ***Group I carcinogen***; initiator and promoter for skin cancer *(IARC monograph, 2009)*

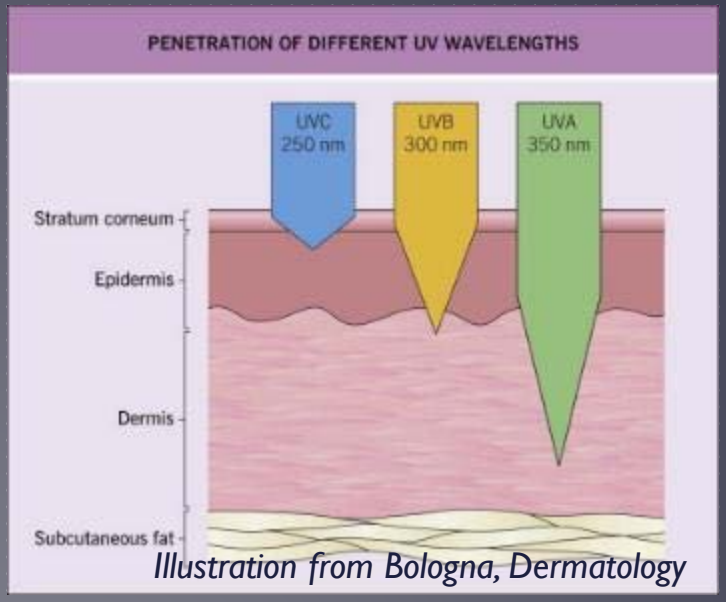
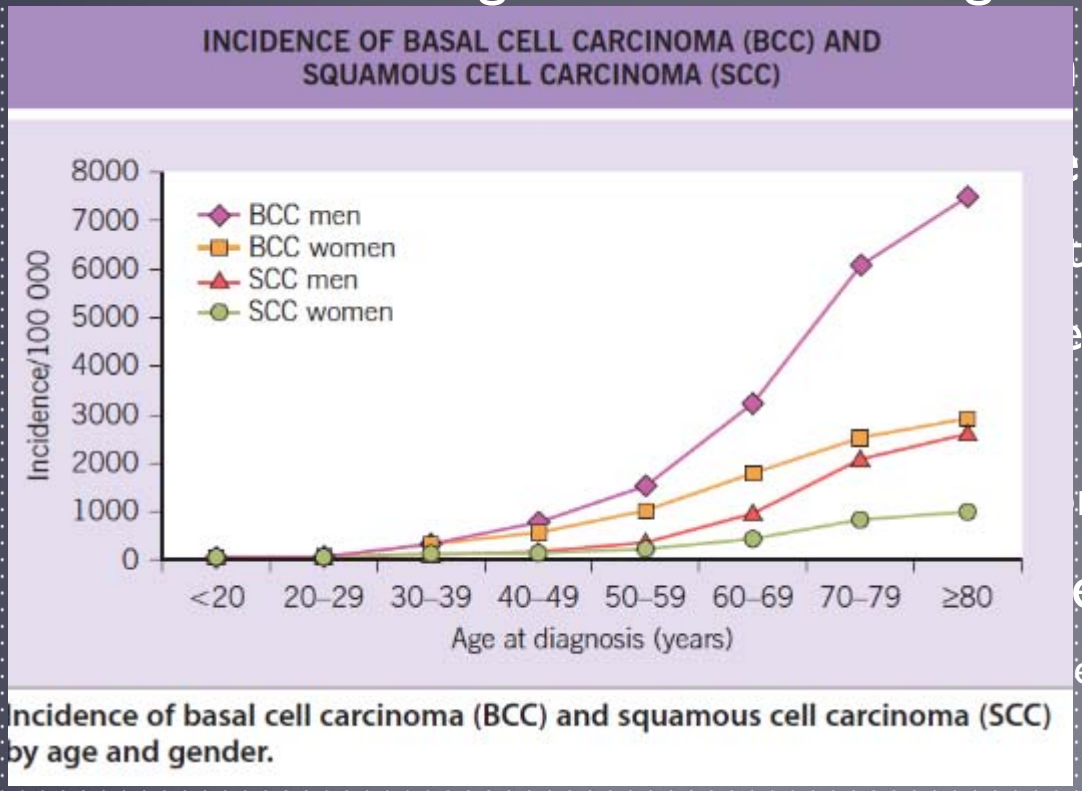


Illustration from Bologna, Dermatology

EPIDEMIOLOGY OF CUTANEOUS SCC

- Incidence rising worldwide and significantly ↑ after 60



Incidence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) by age and gender.

ned population after BCC

erestimated

tosis, SCC in situ)

es

r SCC (5 %) *

ears

eath

Canadian Cancer Society : Canadian Cancer Statistics 2014

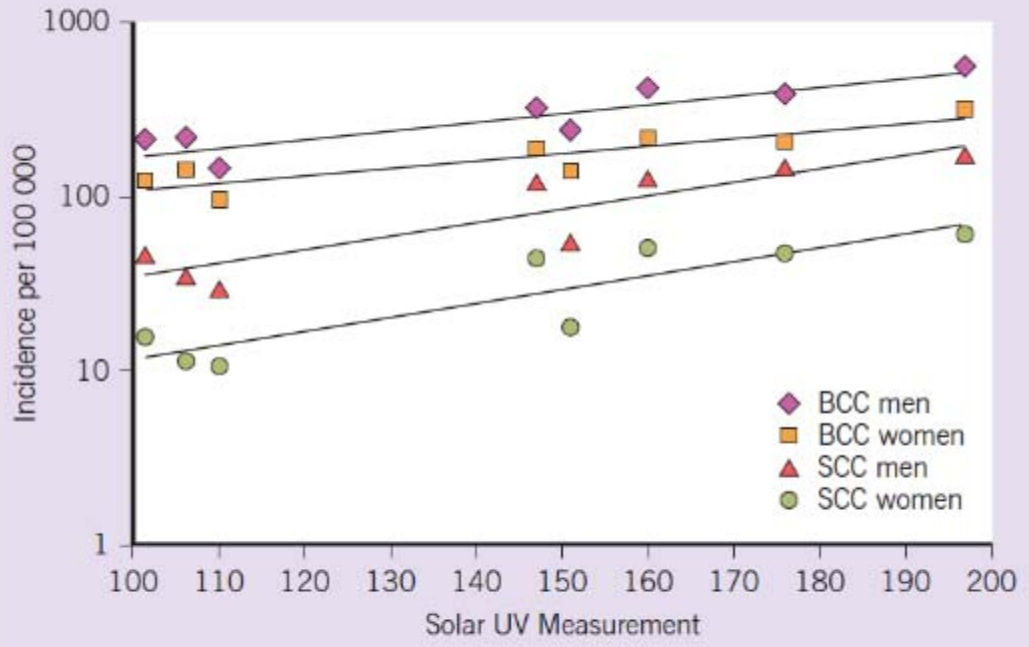
illustration from Bologna, Dermatology 2013

UVR : GREATEST RISK FACTOR FOR SCC

COMPARISON OF LATITUDE AND INCIDENCE (PER 100 000) CARCINOMA (BCC) AND SQUAMOUS CELL CARCINO

Geographic area (year of report)	Latitude	BCC male/ female	SCC male/ female	
Townsville, Australia (1998)	19° S	2058/1195	1332/755	
Nambour, Australia (1996)	27° S	2074/1579	1035/472	
Nambour, Australia (2006)	27° S	1813/1269	–	
Arizona (2001)	31° N	936/497	270/112	
New Hampshire (1999)	42° N	310/165	97/32	
Rochester, MN (1997/1990)	43° N	175/124	155/71	
Vaud, Switzerland (2001)	46° N	75/66	29/17	
British Columbia, Canada (1990)	49° N	120/92	31/7	
West Glamorgan, Wales (2000)	51° N	128/105	25/9	
Netherlands (1991)	52° N	46/32	11/3	
Hull, England (1994)	53° N	116/103	29/21	145/124
Finland (1999)	62° N	49/45	7/4	56/49

RELATIONSHIP OF INCIDENCE RATES OF BASAL CELL CARCINOMA (BCC) AND SQUAMOUS CELL CARCINOMA (SCC)



Relationship of incidence rates of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) to estimated ambient erythemal UV radiation as measured in ten cities in the US. *From Armstrong BK, Kricker A. J Photochem Photobiol B. 2001;63:8–18.*

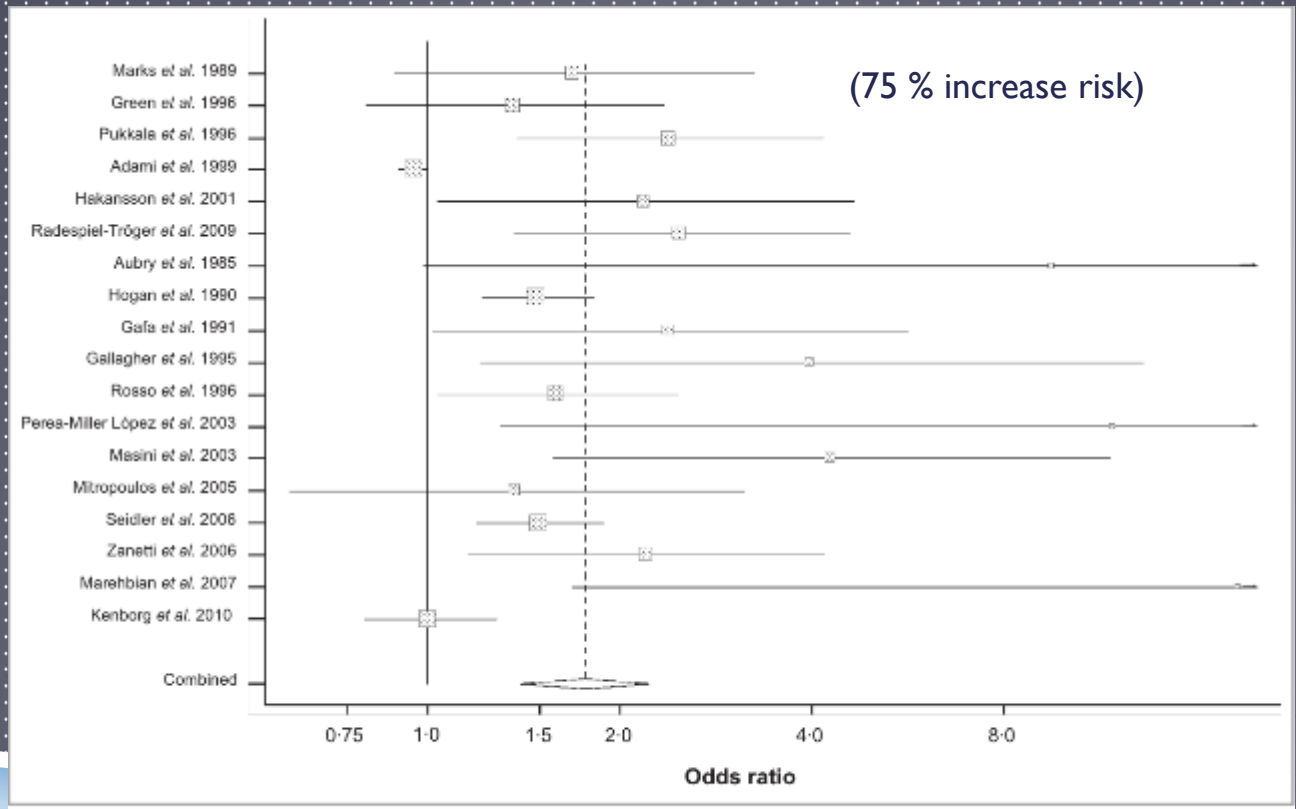
**Illustration from Bologna*

CLINICAL AND LABORATORY INVESTIGATIONS

BJD
British Journal of Dermatology

Occupational ultraviolet light exposure increases the risk for the development of cutaneous squamous cell carcinoma: a systematic review and meta-analysis

J. Schmitt, A. Seidler,* T.L. Diepgen† and A. Bauer



(75 % increase risk)

g 2. Results of random-effects meta-analysis for squamous cell carcinoma of the skin of individuals with outdoor occupation/occupational ltraviolet (UV) exposure vs. indoor occupation/no occupational UV exposure.

OTHER

SKIN

RISK FACTORS FOR THE DEVELOPMENT OF BASAL CELL CARCINOMAS (BCCS) AND SQUAMOUS CELL CARCINOMAS (SCCS)

	SCC	BCC
ENVIRONMENTAL EXPOSURES		
Cumulative/occupational sun exposure	+	
Intermittent/recreational sun exposure		+
Other exposures to UV light (PUVA, tanning beds)	+	+
Ionizing radiation	+	+
Chemicals (arsenic)	+	(+)
HPV	+	
Cigarette smoking	+	
PIGMENTARY PHENOTYPE		
Fair skin	+	+
Always burns, never tans	+	+
Freckling	+	+
Red hair	+	+
GENETIC SYNDROMES		
Xeroderma pigmentosum	+	+
Oculocutaneous albinism	+	(+)
Epidermodysplasia verruciformis	+	
Dystrophic epidermolysis bullosa (primarily recessive)	+	
Ferguson–Smith syndrome	+	
Muir–Torre syndrome	+*	(+)*
Nevoid basal cell carcinoma syndrome		+
Bazex and Rombo syndromes		+
PREDISPOSING CLINICAL SETTINGS		
Chronic non-healing wounds	+	
Longstanding discoid lupus erythematosus, lichen planus (erosive) or lichen sclerosus	+	
Porokeratosis (especially linear)	+	
Nevus sebaceus		+†
IMMUNOSUPPRESSION		
Organ transplantation	+	(+)
Other (e.g. chronic lymphocytic leukemia treated with fludarabine, AIDS patients with HPV infection)	+	

*Both SCCs (keratoacanthoma type) and BCCs typically have sebaceous differentiation.
†More often trichoblastomas.

Illustration Bologna

EVIDENCE FOR CIGARETTE SMOKING AND SCC DEVELOPMENT

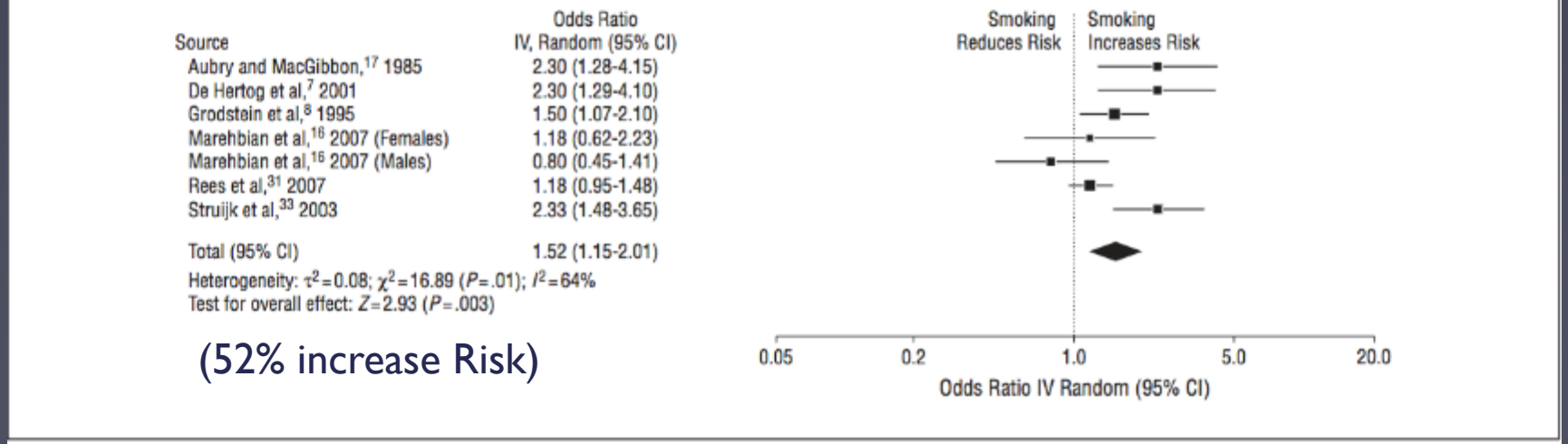
EVIDENCE-BASED DERMATOLOGY: REVIEW

ONLINE FIRST

Smoking and the Risk of Nonmelanoma Skin Cancer

Systematic Review and Meta-analysis *(ArchDermatolog, Aug 2012)*

Jo Leonardi-Bee, PhD; Thomas Ellison, BMedSci; Fiona Bath-Hextall, PhD



(52% increase Risk)

Figure 3. Smoking and the risk of cutaneous squamous cell carcinoma. Squares indicate the odds ratio for the individual study with horizontal lines indicating the 95% CIs. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using the random-effects model. Diamond indicates the pooled odds ratio with 95% CIs. IV indicates inverse variance.

Table 2. Summary of the Evidence and Quality of Evidence-Based Recommendations for Clinical Practice

Grade of Recommendation[a]	Quality of Evidence[a]	Evidence Summary	Recommendation	Sources
1	A	There is a clear, consistent, increased risk of cutaneous SCC associated with smoking (pooled OR, 1.52; 95% CI, 1.15-2.01); however, smoking status does not appear to be significantly associated with risk of BCC	Clinicians need to consider the increased risk of cutaneous SCC associated with smoking status. Thus, it is important for clinicians to actively survey current smokers to identify early skin cancers	7, 8, 16, 17, 29, 31-33

UVR FROM TANNING BEDS (UVA)

- First Tanning Beds in 1970s emitted both UVA and UVB
  - UVB emission subsequently reduce to reduce risk of skin cancer
  - UVB increase again recently to produce longer lasting tans
- UVA produces immediate pigment darkening due to oxidation and redistribution of existing melanin *(not as protective for future sun exposure as UVB tanning)*
- Recent meta-analysis on no vs any use of tanning bed *
  - OR of 2.25 for risk of SCC *after adjustment for sun exposure and sun sensitivity*
- IARC upgraded its classification from probable carcinogen to ***group 1 carcinogen*** **in 2009**

* *Karagas, J Nat cancer, 2002 Int J Cancer , 120: 1116–1122.*

PUVA PHOTOTHERAPY

- Used as a standard treatment for psoriasis
- Psoralen (photosensitizing agent) followed by controlled dose of irradiation with UVA
- Dose dependant increased risk of SCC
  - > 350 PUVA treatment High increase
  - < 150 PUVA treatment Modest increase
- No evidence of increase risk of NMSC phototherapy only

Table VIII. Kaplan Meier estimates of adjusted* hazard ratio and 95% confidence interval for development of one or more skin cancers in a year by type and exposure to psoralen plus ultraviolet A (Cox proportional hazard models with multiple failures)

	Squamous cell cancer		Basal cell cancer	
	Adjusted HR	95% CI	Adjusted HR	95% CI
PUVA exposure				
<50	1		1	
51-150	1.90	1.39-2.59	1.24	0.94-1.62
151-250	3.87	2.84-5.28	2.07	1.59-2.72
251-350	5.79	4.21-7.97	2.47	1.85-3.29
351-450	9.06	6.54-12.56	2.59	1.88-3.56
>450	14.33	10.49-19.60	3.56	2.66-4.77

CI, Confidence interval; *HR*, hazard ratio; *PUVA*, psoralen plus ultraviolet A.
*Adjusted for age, gender, residence, exposure to tar, radiation exposure, and skin type.

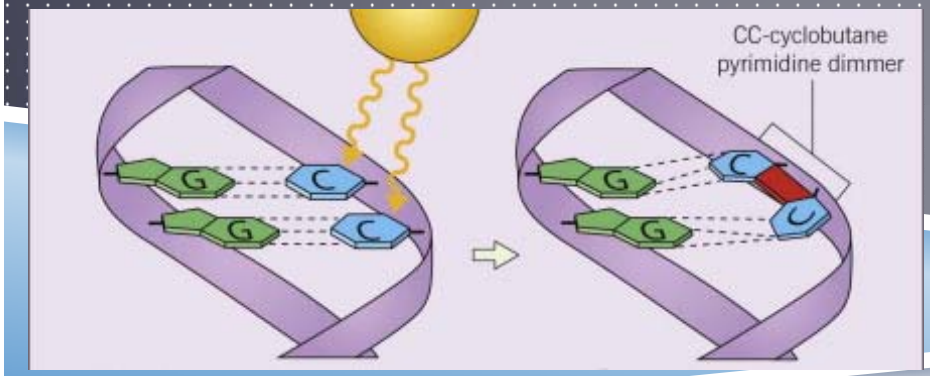
ORIGINAL ARTICLES

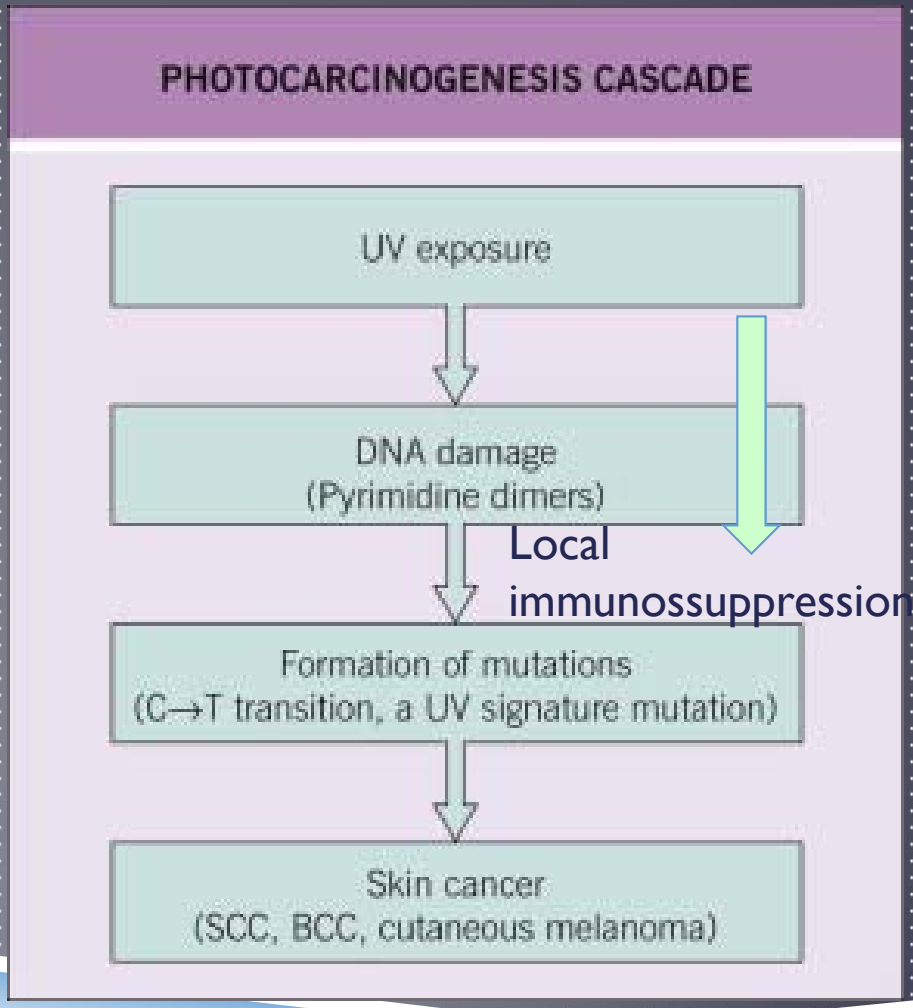
The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: A 30-year prospective study

Robert S. Stern, MD, for the PUVA Follow-Up Study
Boston, Massachusetts

MECHANISM OF PHOTO CARCINOGENESIS

- In 1980s, most damage attributed to UVB.
- **UVB** induces **direct DNA** damage by causing formation of pyrimidine dimers
- **UVA** induces both **direct** and **indirect** (via photosensitizers) **DNA** damage (less mutagenic) by producing oxidative products





UV ASSOCIATED MUTATION FORMATION

Unrepaired UV-induced DNA damage can result in mutation formation

Inherited UV-mutation

- Inherited defect in DNA repair pathways introduces more mutations in critical genes with UV-induced DNA damage
- XP (Xeroderma Pigmentosum)

Acquired UV-mutation

- **UV signature mutation**

C-T and CC-TT transition in P53 tumor suppressor gene found in most cutaneous SCCs and AK (precursor lesion) indicating **early event in pathogenesis of SCC**

P53 – critical role in DNA damage response pathways and cell cycle regulation

IMMUNOSUPPRESSION AND CUTANEOUS SCC

- UV has **local immunosuppressive properties**
  - Affects adaptive immune mechanism in skin
  - Impairs surveillance against cells infected with oncogenic virus
- Important cofactor in already immunosuppressed patient for SCC risk development
  - HIV, Organ transplant patients, Chronic immunosuppressive drugs
    - Risk of SCC directly related to **length of immunosuppressive drug**
  - Inherited genetic syndromes

Apoptosis of T lymphocytes and Langerhans cells
Induction of T regs

ORGAN TRANSPLANT PATIENTS

- Higher risk than general population with reversal of usual BCC : SCC ratio.
- 40% will develop SCC within 15 years of immunosuppression
- Many cofactors :
  - **UV light exposure**
  - Chronic immunosuppression
  - HPV infection (oncogenic virus)
    - Prevalence rates of all types of HPV-DNA is higher in AK & SCC from organ transplant than general population
      - Mainly β and γ HPV but also α type
  - Direct carcinogenic effects of some immunosuppressive medication

ASSOCIATION BETWEEN HPV, **UVR** AND DEVELOPMENT OF SCC

- First evidence : β-HPVs association with SCC in epidermodysplasia verruciformis (EV)
  - Rare genetic condition associated with early development of SCC by fourth decade (30-60%) in sun-exposed areas
  - β HPV 5 & 8 identified in 90% of SCCs in EV
  - β HPV 5 & 8 classified as "**possibly carcinogenic**"
  - Co-carcinogens in conjunction with UVR and immunosuppression
- β HPVs also likely an etiologic agent of SCCs that arise in chronically immunosuppressed patients
- Association of β HPV infection to SCC in general population is area of debate

Seminar in Oncology, Vol 43, No 2, April 2015, pp 284-290

SUMMARY OF CONCLUSIONS

- UVR : Group I carcinogen for all skin cancers and from different sources of exposure (tanning beds, solar, PUVA)
- Chronic cumulative exposure important factor in cutaneous SCC development
- Different mechanism of carcinogenesis between UVA and UVB
- Other questions of interest in epidemiology of cutaneous SCC
  - Role of HPV in cutaneous SCC in chronic immunosuppressed patients
  - HPV vaccination in organ transplant patient as a preventive measure for SCC
  - Specific role of UVB vs UVA in photo carcinogenesis
    - Evidence for skin cancer laterality and UVA exposure while driving

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- *Bologna, Dermatology, Section 18, chap108 : 1773-1793*
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- *Jo-Leonardi & al. Smoking and risk of non melanoma skin cancer. Archives of Dermatology, August 2012; 148(8): 939-46*
- *Karagas MR, Stannard VA, Mott LA, et al. Use of tanning devices and risk of basal cell and squamous cell skin cancers. J Natl Cancer Inst. 2002;94:224–6.*
- *IARC, The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers : A systematic review. Int J Cancer 2006 , 120: 1116–1122.*
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- *Margaret E. Mclaughlin, Human papillomavirus and Non Melanoma Skin Cancer; Semin Oncol 42:284-290*

Dietary risk factors for Colorectal cancer

Anwar Shams

R1-Radiation Oncology

Outlines

- Epidemiology of CRC
- Risk factors
- Diet associated CRC
- Summary

Epidemiology of CRC

FIGURE 1.2 Percent distribution of estimated new cancer cases, by sex, Canada, 2015

Prostate	23.9%	Breast	25.9%
Colorectal	13.9%	Lung	13.5%
Lung	13.5%	Colorectal	11.5%
Bladder	6.1%	Body of uterus	6.5%
Non-Hodgkin lymphoma	4.5%	Thyroid	5.0%
Kidney	3.9%	Non-Hodgkin lymphoma	3.8%
Melanoma	3.6%	Melanoma	3.2%
Leukemia	3.5%	Ovary	2.9%
Oral	2.9%	Leukemia	2.8%
Pancreas	2.4%	Pancreas	2.5%
Stomach	2.1%	Kidney	2.4%
Brain/CNS	1.7%	Bladder	2.1%
Esophagus	1.7%	Cervix	1.5%
Liver	1.7%	Oral	1.5%
Multiple myeloma	1.5%	Brain/CNS	1.3%
Thyroid	1.4%	Stomach	1.3%
Testis	1.0%	Multiple myeloma	1.2%
Larynx	0.9%	Liver	0.6%
Hodgkin lymphoma	0.5%	Esophagus	0.5%
Breast	0.2%	Hodgkin lymphoma	0.5%
All other cancers	9.0%	Larynx	0.2%
		All other cancers	9.3%

CNS=central nervous system

Note: The complete definition of the specific cancers listed here can be found in Table A10.

Analysis by: Surveillance and Epidemiology Division, CCDP, Public Health Agency of Canada
Data sources: Canadian Cancer Registry database at Statistics Canada and Quebec Cancer Registry (2008–2010)

FIGURE 3.2 Percent distribution of estimated cancer deaths, by sex, Canada, 2015

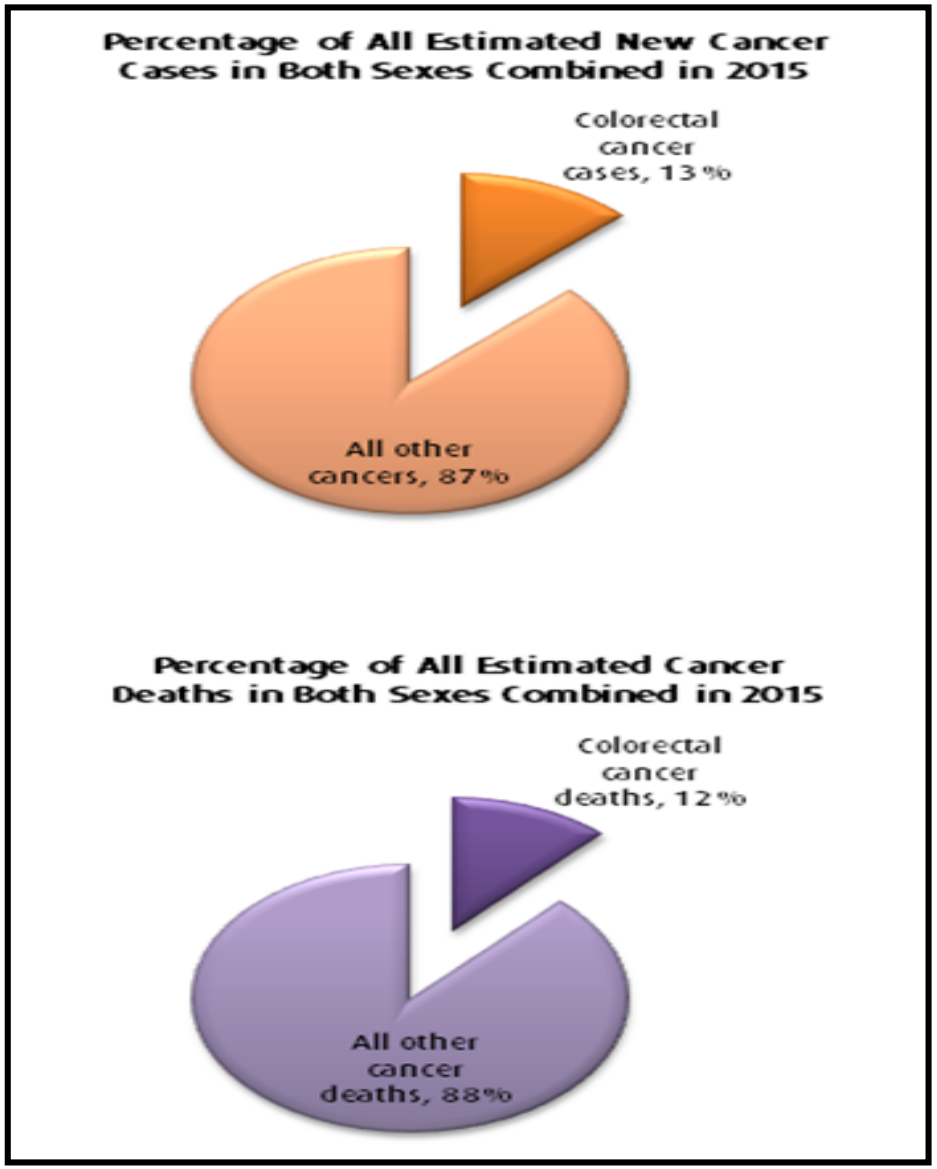
Lung	26.6%	Lung	27.0%
Colorectal	12.4%	Breast	13.6%
Prostate	10.1%	Colorectal	11.5%
Pancreas	5.6%	Pancreas	6.2%
Bladder	4.0%	Ovary	4.7%
Esophagus	3.9%	Non-Hodgkin lymphoma	3.3%
Leukemia	3.8%	Leukemia	3.1%
Non-Hodgkin lymphoma	3.5%	Body of uterus	2.8%
Stomach	3.1%	Brain/CNS	2.3%
Brain/CNS	3.0%	Stomach	2.1%
Kidney	2.7%	Bladder	1.8%
Liver	2.1%	Kidney	1.8%
Oral	2.0%	Multiple myeloma	1.7%
Melanoma	1.8%	Esophagus	1.2%
Multiple myeloma	1.8%	Melanoma	1.1%
Larynx	0.8%	Oral	1.1%
Breast	0.1%	Cervix	1.0%
All other cancers	12.5%	Liver	0.7%
		Larynx	0.2%
		All other cancers	12.8%

CNS=central nervous system

Note: The complete definition of the specific cancers listed here can be found in Table A10.

Analysis by: Surveillance and Epidemiology Division, CCDP, Public Health Agency of Canada
Data source: Canadian Vital Statistics Death database at Statistics Canada

Colorectal cancer statistics



Canadian Cancer Statistics 2015

Risk factors of CRC

- Hereditary CRC syndrome
- Family & Personal history
- IBD
- Sedentary life style
- Obesity
- Diet high in red meat & processed meat
- Diet low in fiber
- Cooking meat at high temperatures
- Alcohol
- Smoking
- Diabetes
- Exposure to ionizing radiation

DIATERY RISK FACTOR FOR CRC

Two general dietary patterns were found to play a role in colorectal adenoma and cancer risk.

A healthier pattern, also named ,prudent pattern ,fruits and vegetables pattern, (high consumption of fruits and vegetables, fibers, fish and poultry, calcium and vitD3, and lower intakes of red and processed meat, beers and alcohol) found to be protective against colorectal adenoma and cancer incidence.

A less healthy pattern, also named western pattern , meat and potato pattern , (red and processed meat, potatoes , refined carbohydrates, trans and saturated fat, candies, cookies, dessert, beers and alcohol , and fast food) may increase risk of CRC.

Paige E. Miller et al … 2010

In prospective study done by Willett et al. in 1990 of 150 colorectal cancer patients in the Nurses'Health Study, found high intake of red meat but not of chicken or fish might be associated with increased colon cancer

Willett et al. in 1990

Fruit and Vegetable Pattern

In a population-based case-control : statistically significant inverse association between a dietary pattern ("Salad") and colon cancer risk among women (OR = 0.73, 95% CI = 0.60–0.89; 223 controls,223 cases) .

In the same study they identified a "Light" dietary pattern among women (lemons, limes, hard cheese, fish, yogurt, and some fruits and vegetables) was inversely associated with colon cancer risk (OR = 0.77, 95% CI = 0.63–0.93).

Randall E et al … 1992,

Another statistically significant reduction in colorectal cancer risk associated with fruits and vegetables pattern in both men and women, men (RR: 0.82; 95% CI: 0.72-0.94) and women (RR: 0.87; 95% CI: 0.71-1.07) was from the NIH-AARP Diet and Health prospective cohort Study .

Paige E. Miller et al … 2010

Meat and Potatoes Pattern

An elevated colon cancer risk was observed in 3 dietary patterns among men, included :

"Traditional" : beef, potatoes, cakes, pies, and some vegetables (green beans) (OR = 1.28, 95% CI = 1.04–1.57);

"Snacks" : cookies, candy, crackers, pastries, hamburgers, ice cream, and baked beans (OR = 1.31,95% CI = 1.07–1.60); and a

"High Fat" : eggs, bacon, sausage, steak, salami, pepperoni, beer, and other alcohol (OR = 1.28, 95% CI = 1.05–1.58).

Randall E et al … 1992,

Both men and women who had higher scores on "Western" dietary pattern had ORs of 1.80 (95% CI= 1.28–2.15) and 1.49 (95% CI = 1.05–2.12) for risk of colon cancer, respectively.

Slattery et al … 1998

In European Prospective Investigation into Cancer and Nutrition (1993–2000) , four dietary patterns were identified :

Healthy:(vegetables, fruit, yogurt, sea products, and olive oil)

Western: (potatoes, pizzas and pies, sandwiches, sweets, cakes, cheese, cereal products, processed meat, eggs, and butter);

Drinker:(sandwiches, snacks, processed meat, and alcoholic beverages)

Meat eaters:(meat, poultry, and margarine).

An increased risk of adenoma was observed with high scores of the Western pattern (RR 1.39, 95% CI: 1.00- 1.94) and the drinker pattern (RR 1.42, 95%CI: 1.10- 1.83).

The meat-eaters pattern was positively associated with colorectal cancer risk (RR 1.58, 95% CI: 0.98- 2.53).

Kesse et al …2006

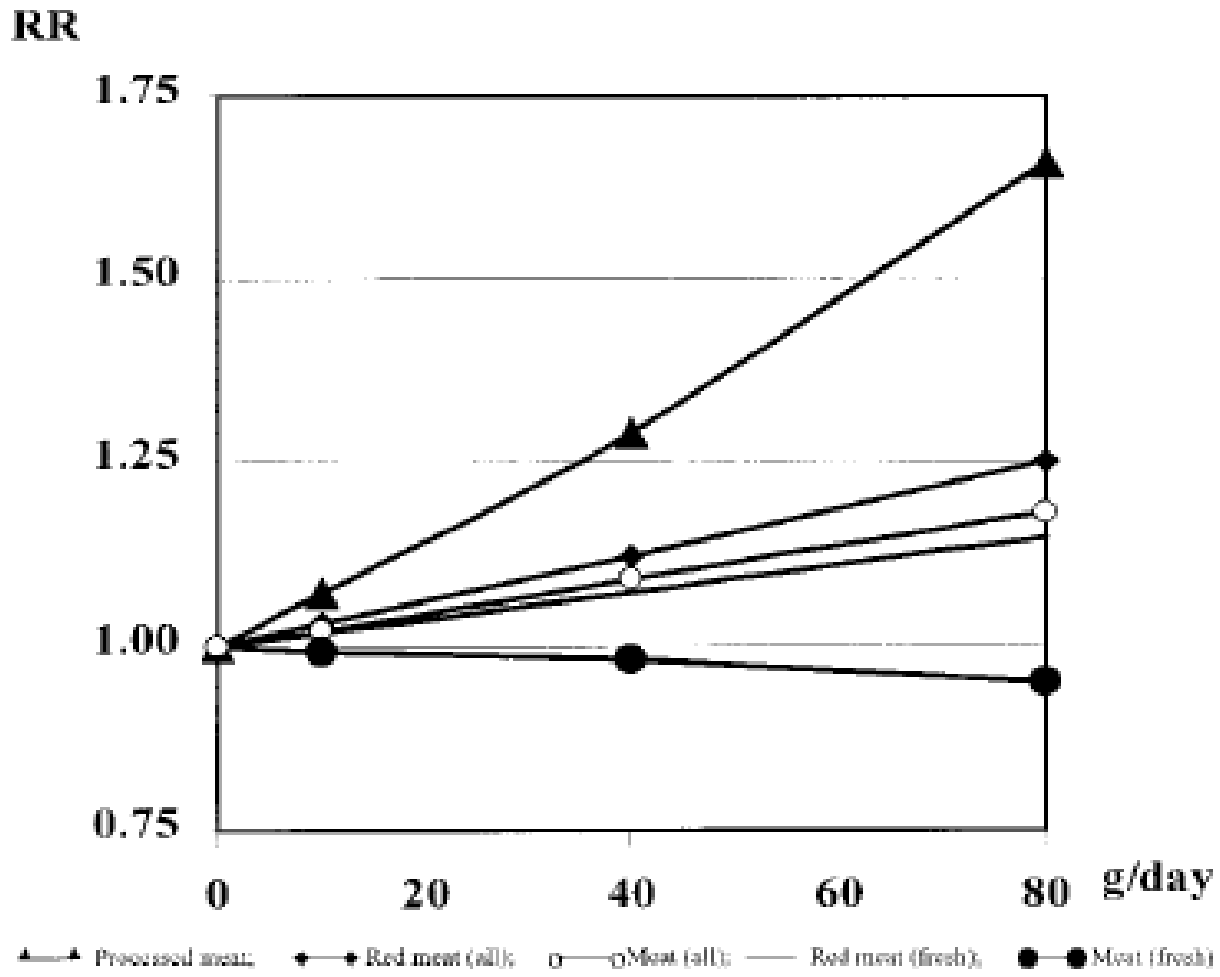


FIGURE 4 – Dose-response analysis of relative risk of colorectal cancer for meat consumption.

Prossed meat

Red meat(all)

Meat(all)

Red meat (fresh)

Meat (fresh)

Norat T et al …2002

Potential mechanisms for carcinogenicity

1. Fat can increase the excretion of bile acids, which may act as tumour promoters.
2. Diacylglycerides, could selectively induce mitogenesis of adenomas and some carcinoma cells.
3. Fat could reduce the number and activity of insulin receptors.
4. Hyperinsulinemia could act as a growth factor and tumor promoter .
5. Dietary protein is broken down into amino acids then degraded to ammonia, which may be carcinogenic to the colon.
6. Dietary iron enhances lipid peroxidation in the mouse colon and augments dimethylhydrazine-induced colorectal tumours in mice and rats but the results of epidemiological studies are still insufficient .
7. Red meat enhances the production of endogenous promoters and possible carcinogens such as N-nitroso compounds (NOC), yet the same effect has not been observed with white meat.
8. Supplements of nitrate have been shown to elevate NOC levels .
9. Formation of heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH) in meat when it is cooked at high temperature for a long time or over an open flame.

Teresa Norat et al …2002

On the other hand …

Dietary fiber may exert its anti carcinogenic effect through decreases transit time in the GIT, increases binding of carcinogens, increases production of short-chain fatty acids, and decreases concentrations of secondary bile acids .

Antioxidants: enhance DNA repair, and inhibit activation of carcinogens such as NOCs .

The active form of vitamin D, 1,25-dihydroxycholecalciferol: promote cell differentiation and apoptosis while inhibiting cell proliferation in colonic mucosa.

Paige E. Miller et al … 2010

Summary

- CRC is the 2nd common cancer and cause of mortality among male, and it is account the 3rd rank among female regarding the incidence and mortality rate.

- Healthy pattern diet appeared to be protective against colorectal adenoma and cancer incidence.

- Western pattern diet found to be associated with increase the risk of CRC.

- Greater consumption of red meat ,particularly processed meat, in a dose-response manner found to increase the risk of CRC.

- Different explanations behind both harmful and protective effects of western and prudent diets have been suggested .

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Trends in Brain Cancer Incidence and Survival

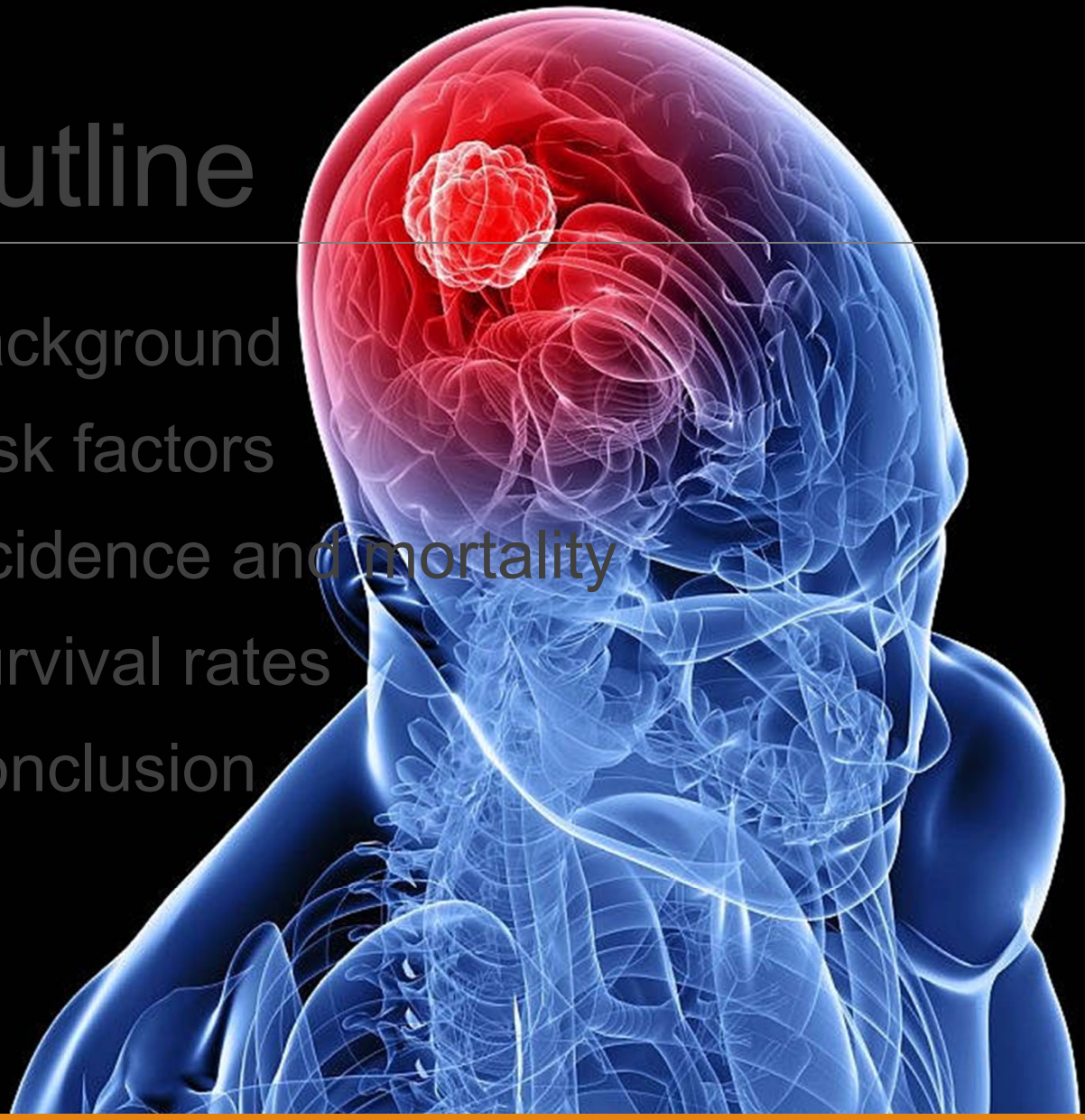
ZIAD SIMON FAWAZ, M.D.

R1 RADIATION ONCOLOGY

M.SC. CANDIDATE EXP. MED.

Outline

- Background
- Risk factors
- Incidence and mortality
- Survival rates
- Conclusion



How many Canadian women are expected to develop brain cancer during their lifetime?

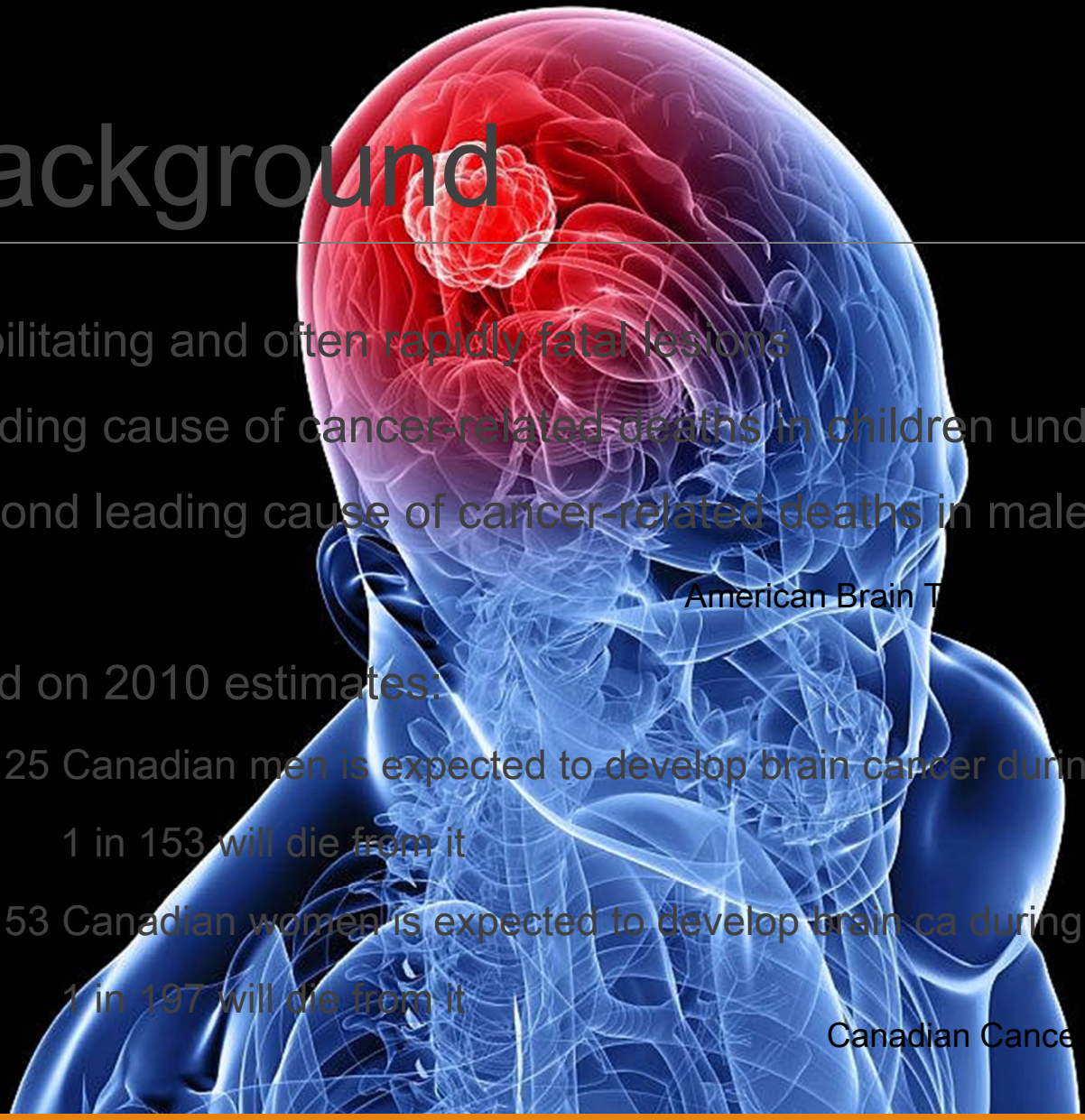
a) 1/500

b) 1/350

c) 1/150

d) 1/50

Background



- Debilitating and often rapidly fatal lesions
- Leading cause of cancer-related deaths in children under 20
- Second leading cause of cancer-related deaths in males 20-39

American Brain T

Based on 2010 estimates:

- 1 in 125 Canadian men is expected to develop brain cancer during his lifetime
  1 in 153 will die from it
- 1 in 153 Canadian women is expected to develop brain ca during her lifetime
  1 in 197 will die from it

Canadian Cance

Risk Factors

- Little consensus about nature and magnitude of risk factors for primary brain cancer
- Proven causes of brain tumors account for a small proportion of cases
- Multiple risk factors studied

Table 2. Factors studied in relationship to risk of primary brain tumors of neuroepithelial tissue or meninges

Hereditary syndromes[a]: tuberous sclerosis, neurofibromatosis types 1 and 2, nevoid basal cell carcinoma syndrome, and adenomatous polyposis syndromes, Li-Fraumeni cancer family syndrome (inherited *p53* mutations)

Family history of brain tumors

Constitutive polymorphisms in glutathione transferases, cytochrome p450 *2D6* and *1A1*, *N*-acetyltransferase, *ERCC1* and *ERCC2*, other carcinogen metabolizing, DNA repair, and immune function genes

Lymphocyte mutagen sensitivity to gamma radiation

Prior cancers

Infectious agents or immunologic response: viruses (common colds, influenza, varicella zoster virus, BK virus, JC virus, others), *Toxoplasma gondii*

Allergies

Head trauma

Epilepsy, seizures, or convulsions

Drugs and medications

Diet and vitamins: nitrosamine/nitrosamide/nitrate/nitrite consumption, calcium, food frequency, cured foods

Tobacco smoke exposures

Alcohol

Hair dyes and sprays

Traffic-related air pollution

Occupations and industries: synthetic rubber manufacturing, vinyl chloride, petroleum refining/production work, licensed pesticide applicators, agricultural work, others (see text), parental workplace exposures

Ionizing radiation: therapeutic[a]; diagnostic and other sources

Cellular telephones

Other radio frequency exposures

Power frequency electromagnetic field

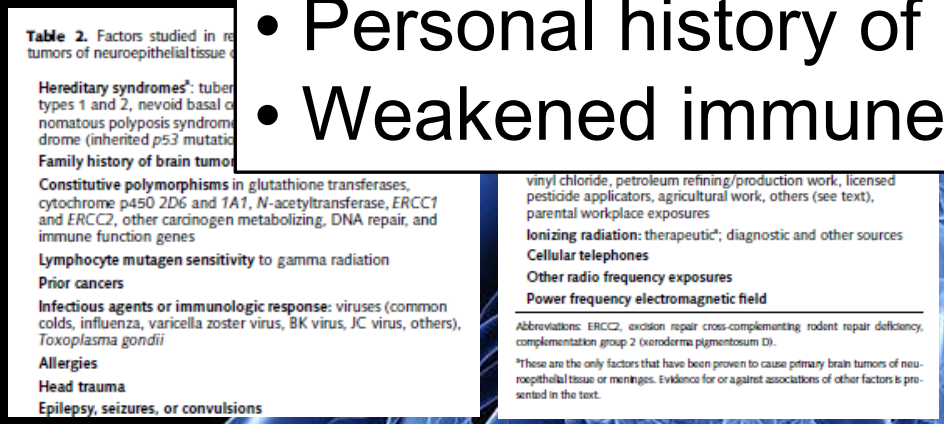
Abbreviations: ERCC2, excision repair cross-complementing rodent repair deficiency, complementation group 2 (xeroderma pigmentosum D).

[a]These are the only factors that have been proven to cause primary brain tumors of neuroepithelial tissue or meninges. Evidence for or against associations of other factors is presented in the text.

M., et al., Epidemiology of primary brain tumors: current concepts and review of th
ncol, 2002. 4(4): p. 278-99.

Risk Factors

- Radiation exposure
- Inherited conditions
- Family history of brain tumors
- Personal history of childhood cancer
- Weakened immune system



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vinyl chloride, petroleum refining/production work, licensed pesticide applicators, agricultural work, others (see text), parental workplace exposures
Ionizing radiation: therapeutic[a]; diagnostic and other sources
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Incidence and Mortality

n cancer incidence and survival in the United State
Program, 1973 to 2001. Neurosurg Focus, 2006. 2

National Cancer Institute's SEER Program
- Population-based incidence data and survival data

38 453 patients
Diagnosed malignant brain tumor
Period between 1973 and 2001
- Exclusion: patients with multiple primary tumors

Divied into
- Children: < 20 years old at dx
- Young/middle-aged adults: 20-65 years old
- Elderly adults: > 65 years old

Classified into
- Metropolitan
- Nonmetropolitan

Classified by grouping ICD-O

Incidence and Mortality

Bimodal: 2 peaks –
early childhood and elderly

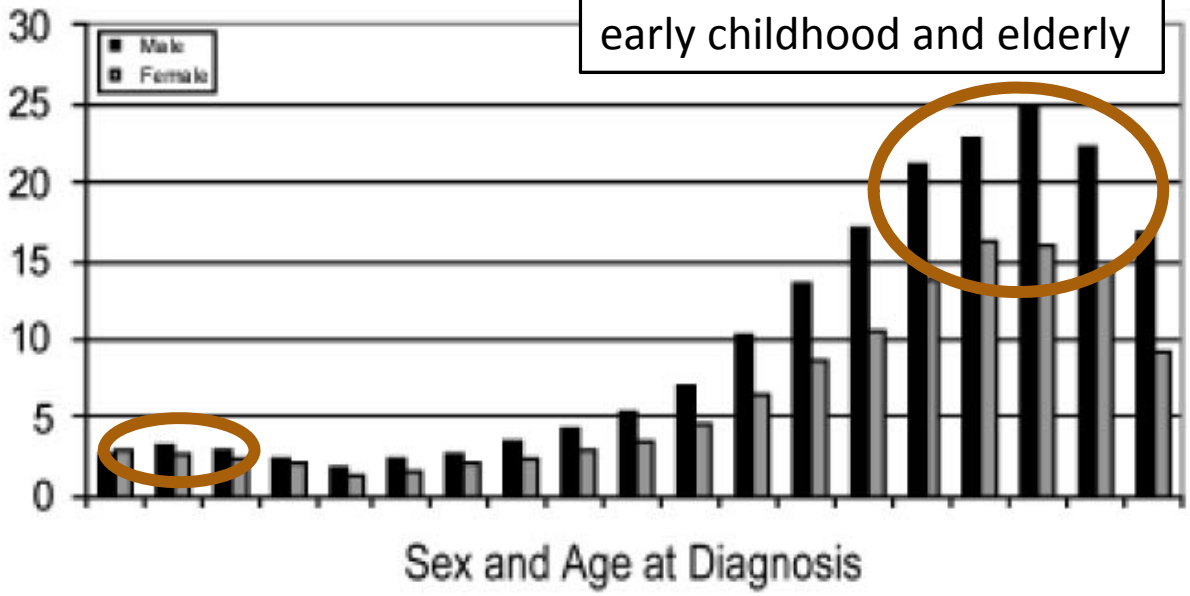


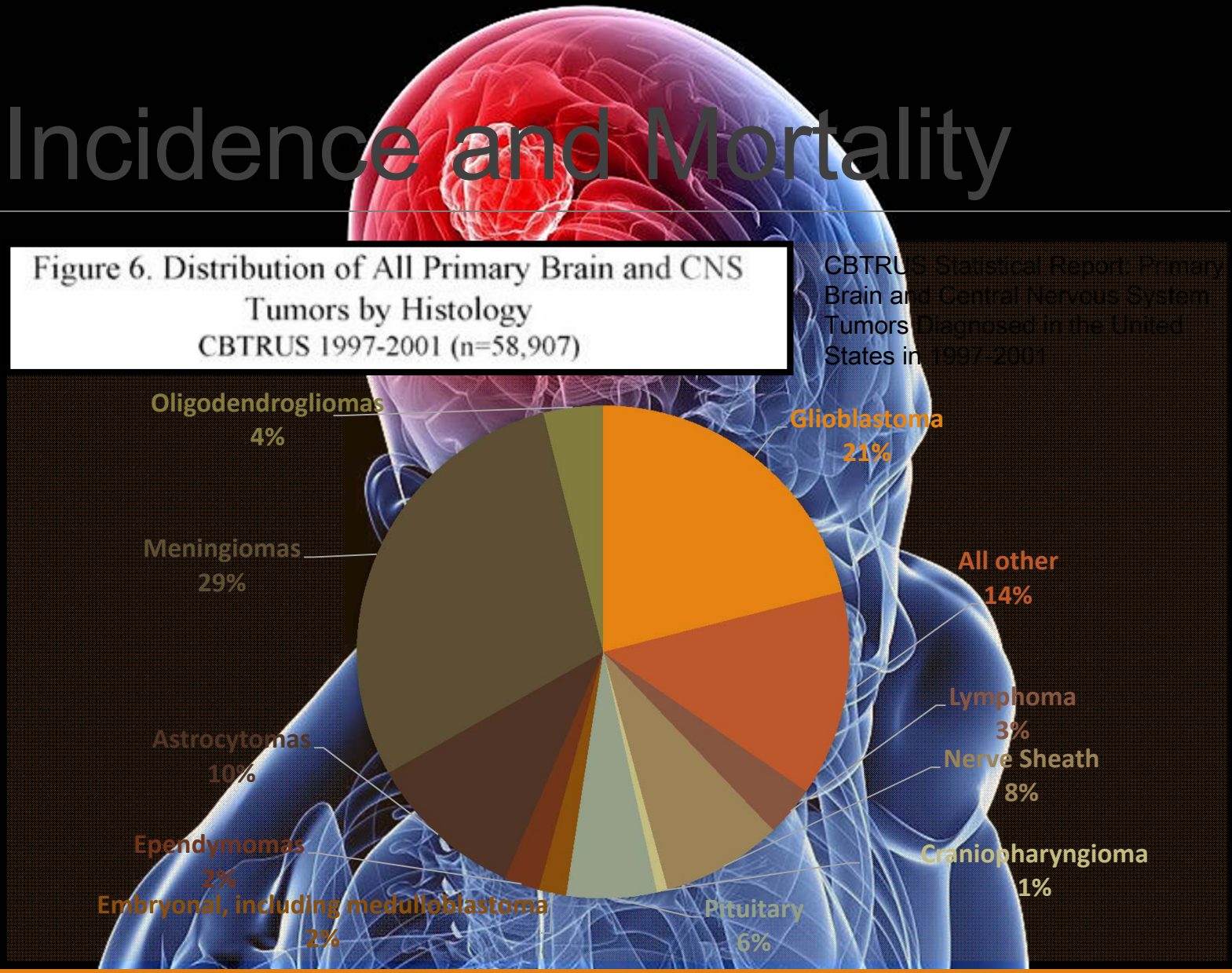
FIG. 1. Bar graph showing brain cancer incidence per 100,000; population based on data from the nine standard SEER registries (1973–2001) depicted by sex and age.

, et al., Trends in brain cancer incidence and survival in the United States: Surveil
ogy, and End Results Program, 1973 to 2001. Neurosurg Focus, 2006. 20(4): p. E1

Incidence and Mortality

Figure 6. Distribution of All Primary Brain and CNS Tumors by Histology
CBTRUS 1997-2001 (n=58,907)

CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 1997-2001



Incidence and Mortality

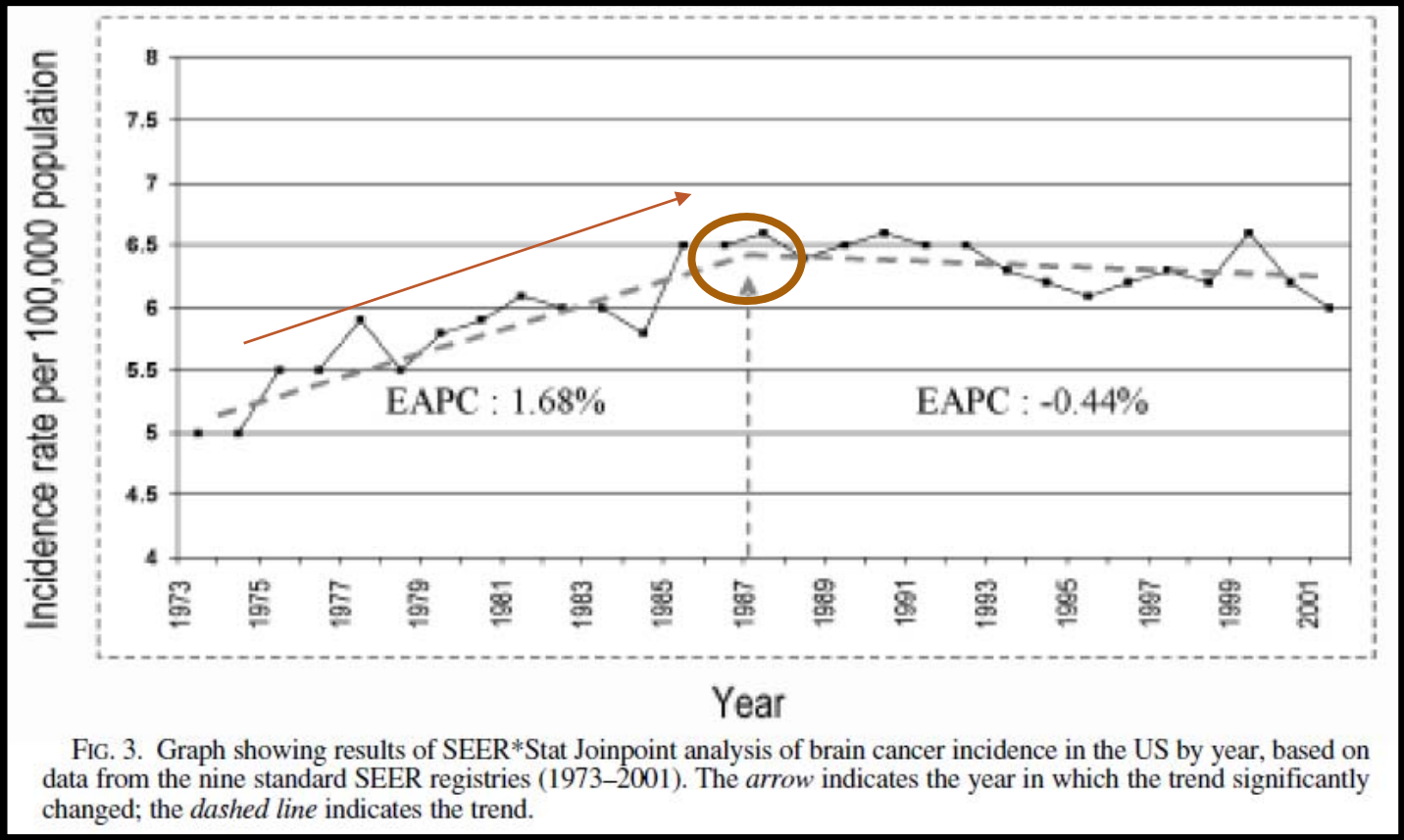


FIG. 3. Graph showing results of SEER*Stat Joinpoint analysis of brain cancer incidence in the US by year, based on data from the nine standard SEER registries (1973–2001). The *arrow* indicates the year in which the trend significantly changed; the *dashed line* indicates the trend.

Incidence and Mortality

	RR of brain cancer
Men:Women	1.48 (95% CI 1.45-1.51)
Elderly:Young adults	3.18 (95% CI 3.09-3.22)
Caucasian:African-American	1.86 (95% CI 1.78-1.94)
Metropolitan:Nonmetropolitan	1.35 (95% CI 1.31-1.38)

, et al., Trends in brain cancer incidence and survival in the United States: Surveil
ogy, and End Results Program, 1973 to 2001. Neurosurg Focus, 2006. 20(4): p. E1

Survival Rates

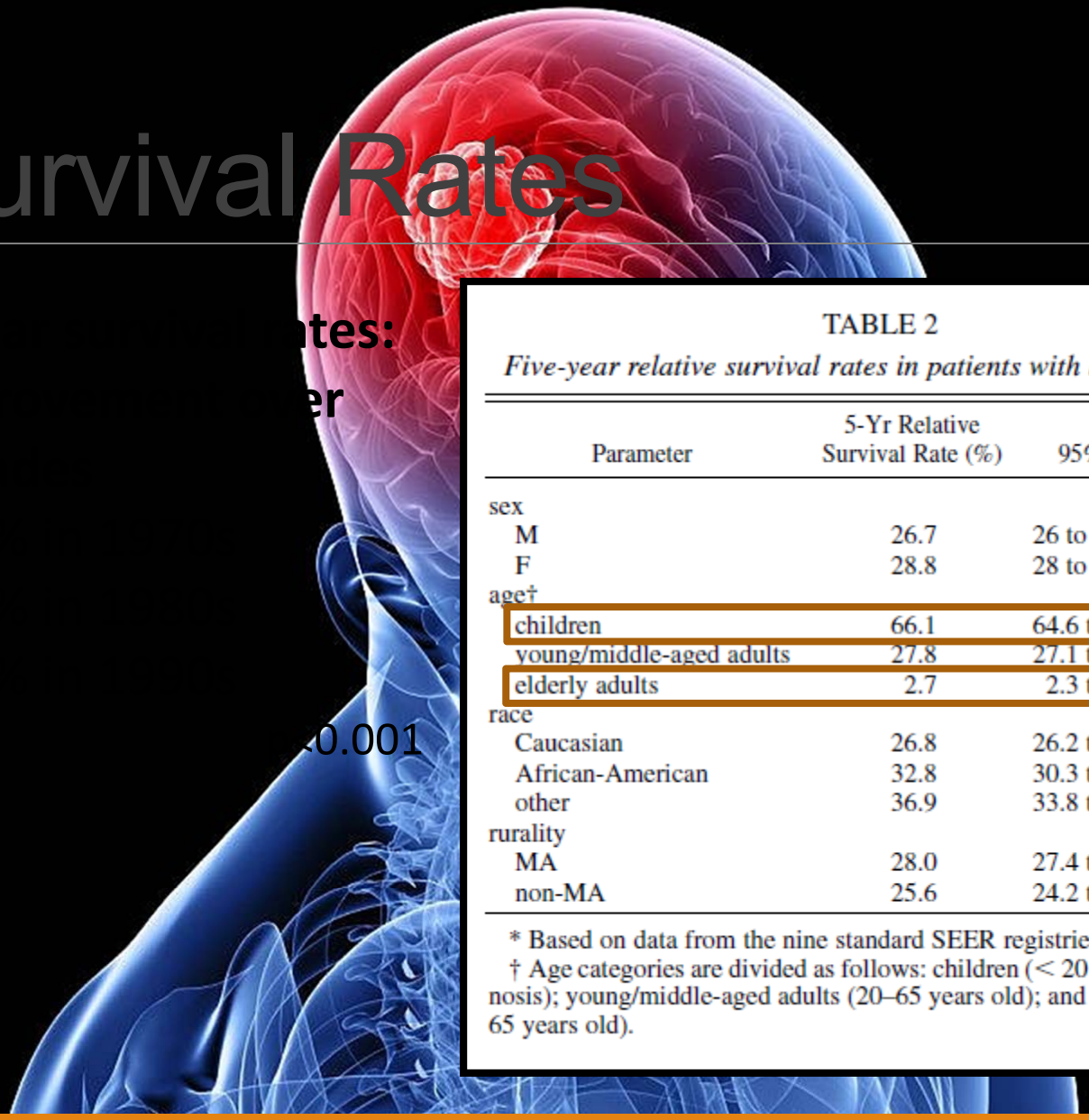


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TABLE 2

*Five-year relative survival rates in patients with brain tumors**

Parameter	5-Yr Relative Survival Rate (%)	95% CI	p Value
sex			
M	26.7	26 to 27.4	<0.001
F	28.8	28 to 29.6	
age†			
children	66.1	64.6 to 67.6	<0.001
young/middle-aged adults	27.8	27.1 to 28.5	
elderly adults	2.7	2.3 to 3.1	
race			
Caucasian	26.8	26.2 to 27.4	<0.001
African-American	32.8	30.3 to 35.3	
other	36.9	33.8 to 40.0	
rurality			
MA	28.0	27.4 to 28.6	<0.001
non-MA	25.6	24.2 to 27.0	<0.001

* Based on data from the nine standard SEER registries (1973–2001).
† Age categories are divided as follows: children (< 20 years old at diagnosis); young/middle-aged adults (20–65 years old); and elderly adults (> 65 years old).

Survival Rates

Type of Tumor	5-Year Relative Survival Rate		
	Age		
	20-44	45-54	55-64
Low-grade (diffuse) astrocytoma	65%	43%	21%
Anaplastic astrocytoma	49%	29%	10%
Glioblastoma	17%	6%	4%
Oligodendroglioma	85%	79%	64%
Anaplastic oligodendroglioma	67%	55%	38%
Ependymoma/anaplastic ependymoma	91%	86%	85%
Meningioma	92%	77%	67%

an Cancer Society 2015

GBM, im
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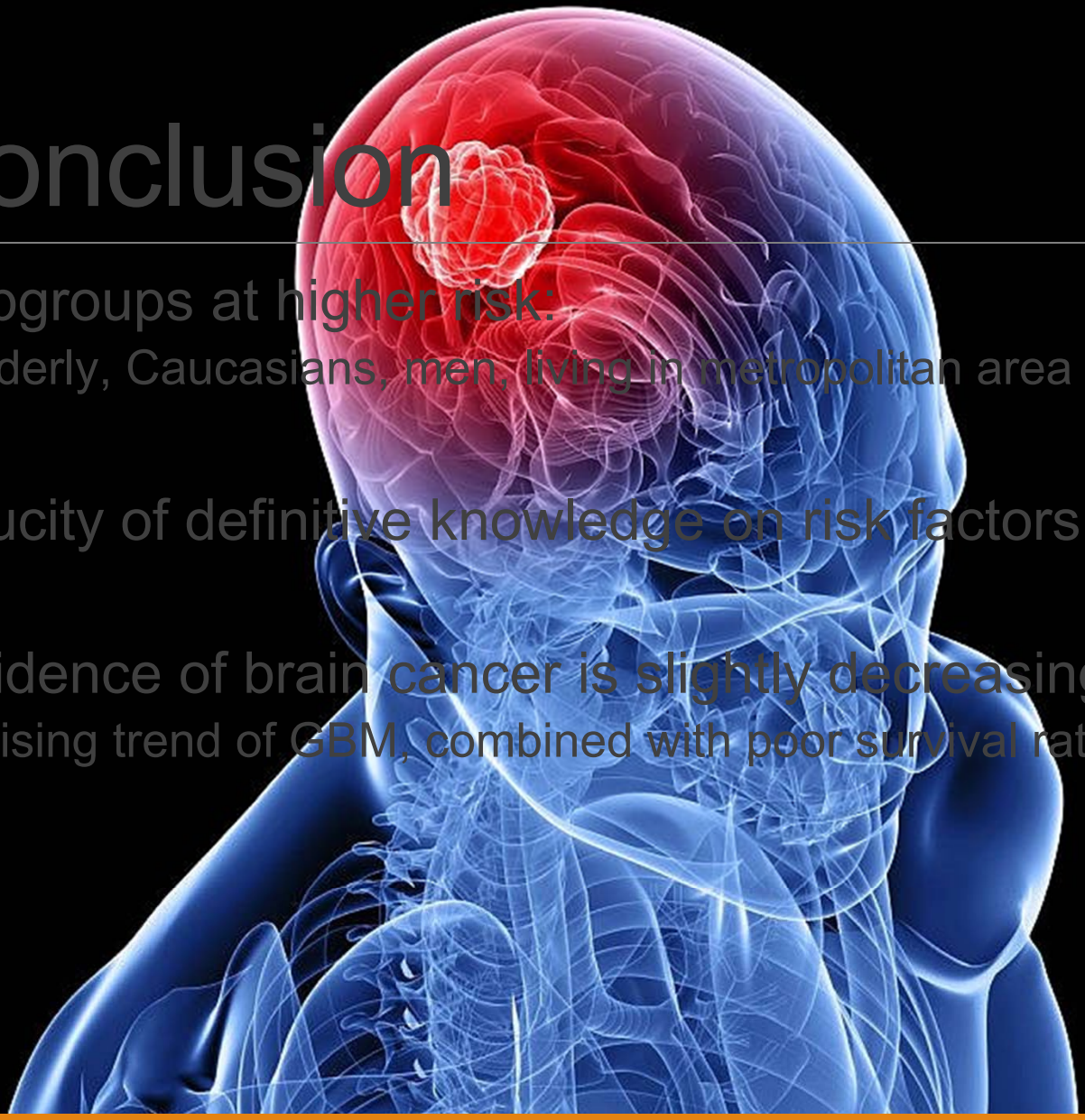
28% vs 3

No statistical
improvement
the 1980s

Conclusion



- Subgroups at higher risk:
  - Elderly, Caucasians, men, living in metropolitan area
- Paucity of definitive knowledge on risk factors
- Incidence of brain cancer is slightly decreasing
  - Rising trend of GBM, combined with poor survival rates

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Physical activity and prevention of cancer recurrence

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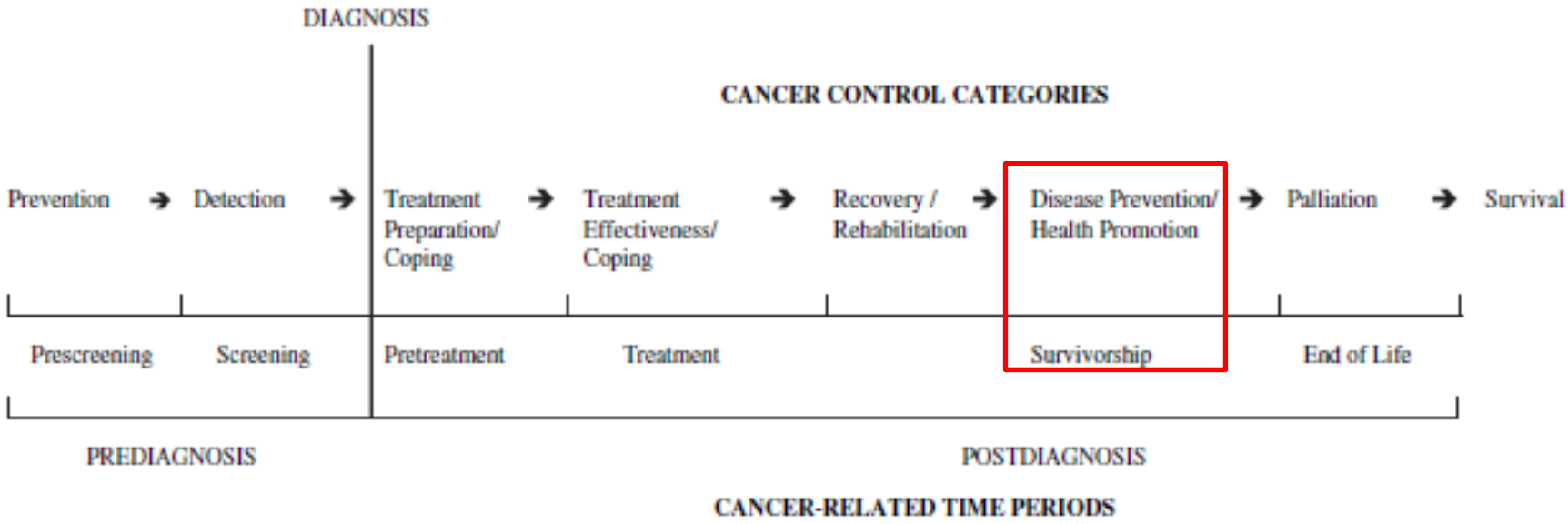
School of Human Kinetics
University of Ottawa

Student Symposium – EPIB671 – June 2015

Cancer survivorship



The 5-year relative survival rate now stands at **68%** (American Cancer Society, 2014).

This rate **can go up to 90%** for certain cancers (e.g. prostate, colon and breast) if they are detected early (Courneya et al., Cancer Therapy, 2004).

Physical activity

Similar (if not identical) PA guidelines are recommended for individuals with chronic illnesses (e.g. CVD, diabetes, cancer; ACSM, 3rd eddition, 2009).

Old vs. new PA guidelines for cancer survivors…

(American Cancer Society, 2010 Biennial Conference).

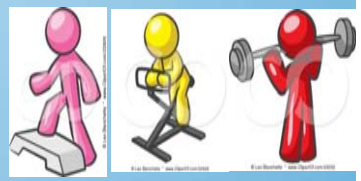
Physical activity, cancer recurrence…and Epidemiology!

Level

1 Observational studies assessing the associations between PA and cancer recurrence

2 Meta-analyses of the associations between PA and cancer recurrence

3 RCT with exercise as an intervention and the main outcomes include biomarkers of cancer recurrence



4 RCT with exercise as an intervention and the main outcomes include cancer recurrence

Level 1 studies

Nurses' Health Study (2987 women with stage 1-3 breast cancer)

		Physical Activity After Diagnosis, MET-h/wk					
	Total (N = 2987)	<3 (n = 959)	3-8.9 (n = 862)	9-14.9 (n = 335)	15-23.9 (n = 428)	≥24 (n = 403)	*P* for Trend
Total deaths	463	188	126	38	51	60	
Age-adjusted RR (95% CI)		1.00	0.69 (0.55-0.87)	0.53 (0.37-0.75)	0.56 (0.41-0.77)	0.67 (0.50-0.90)	.004
Multivariable-adjusted RR (95% CI)*		1.00	0.71 (0.56-0.89)	0.59 (0.41-0.84)	0.56 (0.41-0.77)	0.65 (0.48-0.88)	.003
Breast cancer deaths	280	110	84	20	32	34	
Age-adjusted RR (95% CI)		1.00	0.79 (0.60-1.06)	0.47 (0.29-0.76)	0.60 (0.41-0.89)	0.64 (0.44-0.94)	.01
Multivariable-adjusted RR (95% CI)*		1.00	0.80 (0.60-1.06)	0.50 (0.31-0.82)	0.56 (0.38-0.84)	0.60 (0.40-0.89)	.004
Recurrence	370	137	108	29	45	51	
Age-adjusted RR (95% CI)		1.00	0.82 (0.64-1.06)	0.53 (0.35-0.79)	0.66 (0.47-0.93)	0.76 (0.55-1.04)	.05
Multivariable-adjusted RR (95% CI)*		1.00	0.83 (0.64-1.08)	0.57 (0.38-0.85)	0.66 (0.47-0.93)	0.74 (0.53-1.04)	.05

Abbreviations: CI, confidence interval; MET, metabolic equivalent task; RR, relative risk.

*Adjusted for age (months); interval between diagnosis and physical activity assessment (28-33, 34-40, ≥41 mo); smoking status (never, current, past); body mass index (<21, 21-22.9, 23-24.9, 25-28.9, ≥29), which was calculated as weight in kilograms divided by the square of height in meters; menopausal status and hormone therapy use (premenopausal, postmenopausal, and never use; postmenopausal and current use; postmenopausal and past use; uncertain menopausal status; missing); age at first birth and parity (nulliparous, <25 y and 1-2 births, <25 y and ≥3 births, ≥25 y and 1-2 births, ≥25 y and ≥3 births); oral contraceptive use (never, ever, missing); energy intake (quintiles); energy-adjusted protein intake (quintiles); disease stage (I, II, III); radiation treatment (yes or no); chemotherapy (yes or no); and tamoxifen treatment (yes or no).

Holmes et al., JAMA, 2005

Level 1 studies

CALGB trial (832 patients with stage 3 colon cancer)

Outcome	Total MET-Hours per Week										*P* for Trend
	< 3		3-8.9		9-17.9		18-26.9		≥ 27		
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
Cancer recurrence or death from any cause (disease-free survival)											
No. of events	67		42		30		11		22		
No. at risk	273		187		137		84		151		
Unadjusted	Referent		0.94	0.64 to 1.38	0.89	0.58 to 1.37	0.51	0.27 to 0.97	0.58	0.36 to 0.94	.01
Adjusted*	Referent		0.87	0.58 to 1.29	0.90	0.57 to 1.40	0.51	0.26 to 0.97	0.55	0.33 to 0.91	.01
Cancer recurrence (recurrence-free survival)											
No. of events	62		38		27		10		22		
No. at risk	273		187		137		84		151		
Unadjusted	Referent		0.92	0.61 to 1.37	0.87	0.55 to 1.37	0.50	0.26 to 0.98	0.63	0.39 to 1.02	.03
Adjusted*	Referent		0.86	0.57 to 1.30	0.89	0.55 to 1.42	0.51	0.26 to 1.01	0.60	0.36 to 1.01	.03
Overall mortality											
No. of events	33		21		13		8		9		
No. at risk	273		187		137		84		151		
Unadjusted	Referent		0.93	0.53 to 1.60	0.75	0.39 to 1.43	0.79	0.37 to 1.72	0.50	0.24 to 1.04	.05
Adjusted*	Referent		0.85	0.49 to 1.49	0.71	0.36 to 1.41	0.71	0.32 to 1.59	0.37	0.16 to 0.82	.01

Abbreviations: MET, metabolic equivalent task; HR, hazard ratio; CEA, carcinoembryonic antigen.
*Adjusted for sex, age, depth of invasion through bowel wall (T1-2 *v* T3-4), number of positive lymph nodes (one to three *v* four or more), presence of clinical perforation at time of surgery, presence of bowel obstruction at time of surgery, baseline CEA (≤ 5 *v* > 5 ng/dL), grade of tumor differentiation (poorly or undifferentiated *v* well or moderately), baseline performance status (0 *v* 1-2), treatment arm, weight change between first and second questionnaire, body mass index at time of second questionnaire, and time between study entry and completion of second questionnaire.

Meyerhardt et al., J Clin Oncol, 2006

Level 1 studies

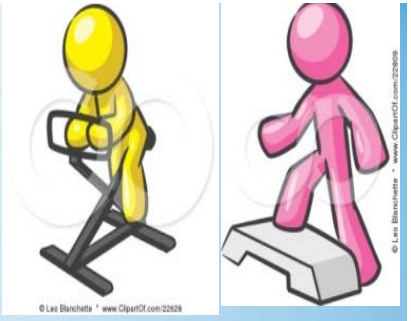
LACE trial (1970 women with stage 1-3 breast cancer)

	Recurrence (n = 225)		Breast cancer mortality (n = 102)		All-cause mortality (n = 187)	
	Model I*	Model II †	Model I*	Model II ‡	Model I*	Model II§
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total activity, MET-h/wk						
Q1 (<29)	Ref	Ref	Ref	Ref	Ref	Ref
Q2 (29-<44)	0.65 (0.44-0.97)	0.76 (0.51-1.13)	0.83 (0.49-1.40)	1.01 (0.57-1.78)	0.70 (0.47-1.04)	0.89 (0.59-1.33)
Q3 (44-<62)	0.82 (0.57-1.19)	0.87 (0.59-1.29)	0.71 (0.41-1.24)	0.70 (0.38-1.29)	0.67 (0.45-1.00)	0.82 (0.54-1.25)
Q4 (≥62)	0.79 (0.54-1.15)	0.91 (0.61-1.36)	0.68 (0.39-1.18)	0.87 (0.48-1.59)	0.58 (0.38-0.88)	0.76 (0.48-1.19)
P for trend	0.40	0.78	0.14	0.41	0.01	0.20
Moderate-vigorous activity, MET-h/wk						
Q1 (<5.3)	Ref	Ref	Ref	Ref	Ref	Ref
Q2 (5.3-<15)	0.67 (0.46-0.97)	0.73 (0.49-1.09)	0.68 (0.41-1.15)	0.77 (0.44-1.34)	0.63 (0.43-0.93)	0.71 (0.48-1.07)
Q3 (15-<27)	0.62 (0.42-0.91)	0.75 (0.50-1.12)	0.47 (0.26-0.85)	0.47 (0.24-0.91)	0.49 (0.32-0.74)	0.58 (0.37-0.90)
Q4 (≥27)	0.84 (0.59-1.20)	1.00 (0.68-1.46)	0.68 (0.41-1.15)	0.90 (0.51-1.58)	0.56 (0.38-0.83)	0.74 (0.49-1.13)
P for trend	0.31	0.95	0.07	0.38	0.001	0.06
H/wk of moderate activity						
<1	Ref	Ref	Ref	Ref	Ref	Ref
1-<3	0.76 (0.53-1.09)	0.81 (0.55-1.18)	0.51 (0.29-0.89)	0.65 (0.36-1.16)	0.59 (0.40-0.87)	0.71 (0.48-1.06)
3-<6	0.80 (0.56-1.13)	0.86 (0.60-1.25)	0.69 (0.42-1.13)	0.69 (0.40-1.19)	0.57 (0.39-0.84)	0.66 (0.44-1.00)
≥6	0.66 (0.44-0.97)	0.81 (0.54-1.22)	0.56 (0.32-0.98)	0.73 (0.40-1.33)	0.51 (0.34-0.79)	0.66 (0.42-1.03)
P for trend	0.05	0.36	0.07	0.26	0.001	0.04
Hours/wk of vigorous activity						
0	Ref	Ref	Ref	Ref	Ref	Ref
>0-<1	0.88 (0.61-1.28)	0.91 (0.62-1.36)	0.72 (0.40-1.28)	0.79 (0.42-1.48)	0.74 (0.48-1.15)	0.90 (0.57-1.41)
≥1	1.06 (0.78-1.44)	1.12 (0.81-1.56)	0.85 (0.53-1.36)	1.10 (0.68-1.80)	0.87 (0.61-1.23)	1.02 (0.70-1.47)
P for trend	0.80	0.58	0.40	0.82	0.33	1.0
Selected activities, MET-h/wk						
<9	Ref	Ref	Ref	Ref	Ref	Ref
≥9	1.00 (0.76-1.31)	1.16 (0.87-1.55)	0.91 (0.61-1.36)	1.19 (0.78-1.84)	0.78 (0.57-1.06)	0.98 (0.71-1.35)

HR, hazard ratio; 95% CI, 95% confidence interval.
*Adjusted for age.
†Adjusted for age, number of positive nodes, stage and weight at 18 y.
‡Adjusted for age, number of positive nodes, stage, weight at 18 y, type of treatment (chemotherapy/radiation) and type of surgery (mastectomy or conserving).
§Adjusted for age, number of positive nodes, stage, weight at 18 y, education level and smoking status.

Sternfeld et al., Cancer Epidemiol Boimarkers Prev, 2009

Level 2 studies



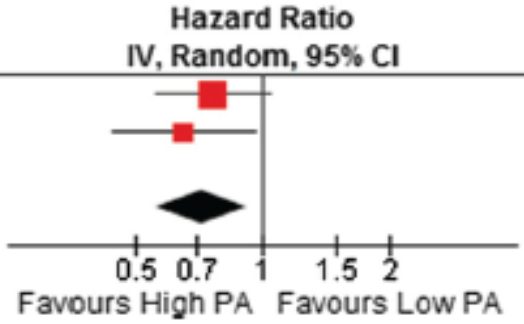
Meta-analysis (123 574 women with breast cancer; 5462 cancer-related deaths or recurrence)

Pre-diagnosis (A) and post-diagnosis (B) PA and cancer recurrence

A

Study or Subgroup	Weight	Hazard Ratio IV, Random, 95% CI	Year
Friedenreich et al. 2009	61.4%	0.76 [0.56, 1.04]	2009
Schmidt et al. 2013	38.6%	0.65 [0.44, 0.97]	2013
Total (95% CI)	**100.0%**	**0.72 [0.56, 0.91]**	

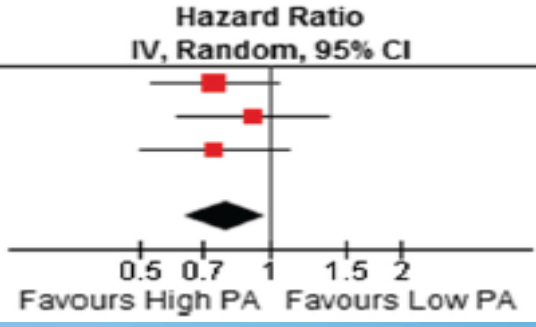
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.37$, df = 1 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 2.67 (P = 0.008)



B

Study or Subgroup	Weight	Hazard Ratio IV, Random, 95% CI	Year
Holmes et al. 2005	41.0%	0.74 [0.53, 1.04]	2005
Sternfield et al. 2009	29.0%	0.91 [0.61, 1.36]	2009
Bertram et al. 2011	30.0%	0.74 [0.50, 1.10]	2011
Total (95% CI)	**100.0%**	**0.79 [0.63, 0.98]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.73$, df = 2 (P = 0.70); $I^2 = 0\%$
Test for overall effect: Z = 2.19 (P = 0.03)



Lahart et al., Acta Oncologica, 2015

Level 3 studies

Yale Exercise and Survivorship Study (75 postmenopausal breast cancer survivors)

Exercise group: 150 MVPA per week
Usual care: Maintain current PA levels

	Baseline			6 mo			Change over 6 mo*		
	Exercisers	Usual care	*P*	Exercisers	Usual care	*P*	Exercisers	Usual care	*P*
Insulin (μU/mL)	24.57 (3.85)	25.69 (4.21)	0.84	22.92 (3.25)	31.98 (5.46)	0.16	−1.75 (2.32)	3.49 (2.46)	0.089
IGF-I (ng/mL)	213.34 (12.57)	232.34 (18.65)	0.40	207.14 (11.20)	243.73 (18.47)	0.10	−7.36 (6.02)	12.70 (6.39)	0.026
IGFBP-3 (μg/mL)	4.15 (0.16)	4.48 (0.17)	0.16	3.98 (0.16)	4.61 (0.18)	0.011	−0.19 (0.08)	0.15 (0.10)	0.006

*Adjusted for baseline value.

Irwin et al., Cancer Epidemiol Biomarkers Prev, 2009

Level 4 studies

There are currently **no** RCTs that have evaluated the effects of an exercise intervention on cancer recurrence as an outcome.

However, there are currently RCTs **underway** which may be able to answer this question:

-The CHALLENGE trial (Multinational trial in Canada and Australia; Courneya et al., Curr Oncol 2008)
A 3-year structured and supervised PA intervention on disease outcomes (e.g. disease free survival, biological markers, health-related fitness) in 962 high-risk stage II-III colon cancer survivors.
-DIANA-5 trial (Multi-institution trial in Italy; Villarini et al., Tumori, 2012).
Effectiveness of a Mediterranean diet + moderate PA in reducing breast cancer events in 1208 women with early stage invasive breast cancer at high risk of recurrence because of metabolic or endocrine milieu.

"If we knew what it was we were doing, it would not be called research, would it?" *–Albert Einstein*

In summary

Good (but could be better...) number of observational studies which demonstrate an association between habitual PA participation and prevalence of cancer recurrence.

Good number of RCTs with exercise as an intervention and biomarkers of cancer recurrence as outcomes, which demonstrate benefits of PA participation on these numerous markers.

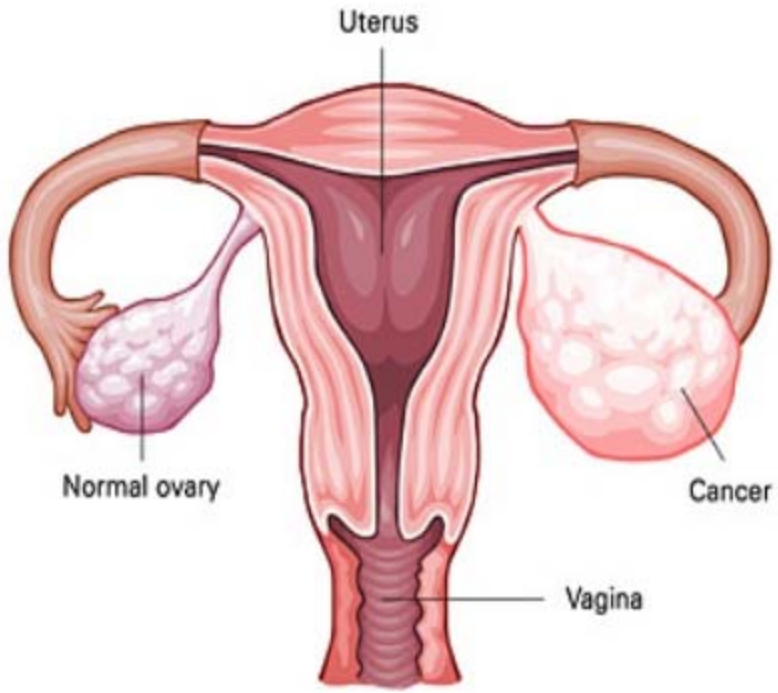
No current results (but trials underway) of RCTs with exercise and cancer recurrence as an outcome

Future direction

EPI 671
RISK FACTORS FOR OVARIAN CANCER

Maryam Ajikobi

June 17TH 2015



Ovarian cancer statistics

- Ovarian cancer is the seventh most common cancer in women worldwide (18 most common cancer overall), with 239,000 new cases diagnosed in 2012.
- Ovarian cancer often has no symptoms at the early stages, so the disease is generally advanced when it is diagnosed.
- The 5-year survival rate (which compares the 5-year survival of people with the cancer to the survival of others at the same age who do not have cancer) ranges from approximately 30 to 50 per cent.

International Agency for Research on Cancer; 2014.

Increases risk ('sufficient' or 'convincing' evidence)	May increase risk ('limited' or 'probable' evidence)	Decreases risk ('sufficient' or 'convincing' evidence)	May decrease risk ('limited' or 'probable' evidence)
•Asbestos •Hormone replacement therapy (oestrogen-only) •Tobacco smoking	•Talc-based body powder (perineal use) •X-radiation, gamma radiation •Adult-attained height	•Oral contraceptives	•Breastfeeding •Non-starchy vegetables (not salted or pickled)

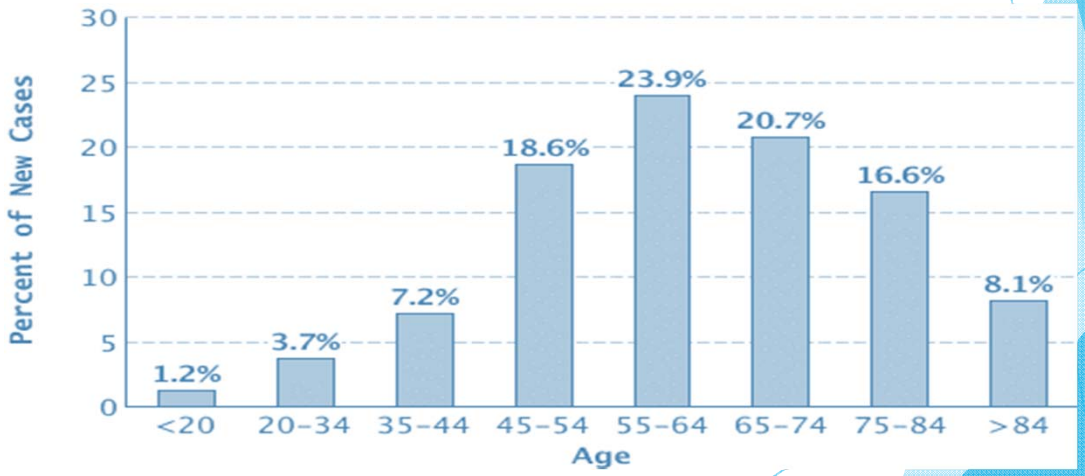
- International Agency for Research on Cancer (IARC) and The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) classifications.

Overview

- Age
- Reproductive and hormonal factors: Overall
- Reproductive and hormonal factors: Hormone Replacement Therapy (HRT).
- Tobacco
- Occupational exposures: Asbestos
- Family history of ovarian cancer
- Family history of other cancers
- Genetic conditions BRCA1/2 mutations
- What can be done to reduce the risk.

Age

- The risk of developing ovarian cancer gets higher with age.
- Ovarian cancer is rare in women younger than 40.
- Most ovarian cancers develop after menopause. Half of all ovarian cancers are found in women 63 years of age or older.



- www.cancer.org.03/12/2015

Reproductive and hormonal factors: overall

- Ovarian cancer risk is associated with factors affecting lifetime number of (and breaks between) ovulations, and/or sex hormone levels (oestrogen, progesterone and androgens).

- Ovulation causes structural changes to the ovary which may stimulate cancer development, and hormonal factors may compound this or have their own independent effects.

Jayson GC, Kohn EC, Kitchener HC, et al. Lancet 2014

Reproductive and hormonal factors hormone replacement therapy (HRT)

- Hormone replacement therapy (HRT) was significantly associated with an increased risk for ovarian cancer in postmenopausal women, according to an extensive meta-analysis from the Collaborative Group on Epidemiological Studies of Ovarian Cancer
- Ovarian cancer risk is 53% higher in long-term (5+ years) current oestrogen-only HRT users, compared with never users
- Ovarian cancer risk is 20% higher in long-term (5+ years) oestrogen-progesterone HRT users, compared with never users.

(Jayson GC, Kohn EC, Kitchener HC, et al. Lancet 2014)

Tobacco

- Ovarian mucinous cancer risk is 31-49% higher in current smokers compared with never-smokers, meta- and pooled analyses have shown.
- Risk increases with smoking duration.
- Ovarian mucinous borderline malignant tumor risk is 83-125% higher in current versus never-smokers.

(Faber MT, Kjær SK, Dehlendorff C, et al 2013. & Brinton L, Marchbanks P, Negri E, et al.2013)

Occupational exposure: Asbestos

- Ovarian cancer mortality risk is higher in women occupationally exposed to asbestos.
- meta-analyses have shown; however the evidence is limited by erroneous inclusion of peritoneal mesothelioma with ovarian cancer cases, potential confounding by other risk factors, and lack of evidence for an association with ovarian cancer incidence.
- When all studies were included in a meta-analysis, the effect size was 1.75 (95% CI, 1.45-2.10) attenuating to 1.29 (95% CI, 0.97-1.73) in studies with confirmed ovarian cancers.

Reid A, de Klerk N, Musk AW. Cancer Epidemiol Biomarkers Prev 2011;20(7):1287-95.&

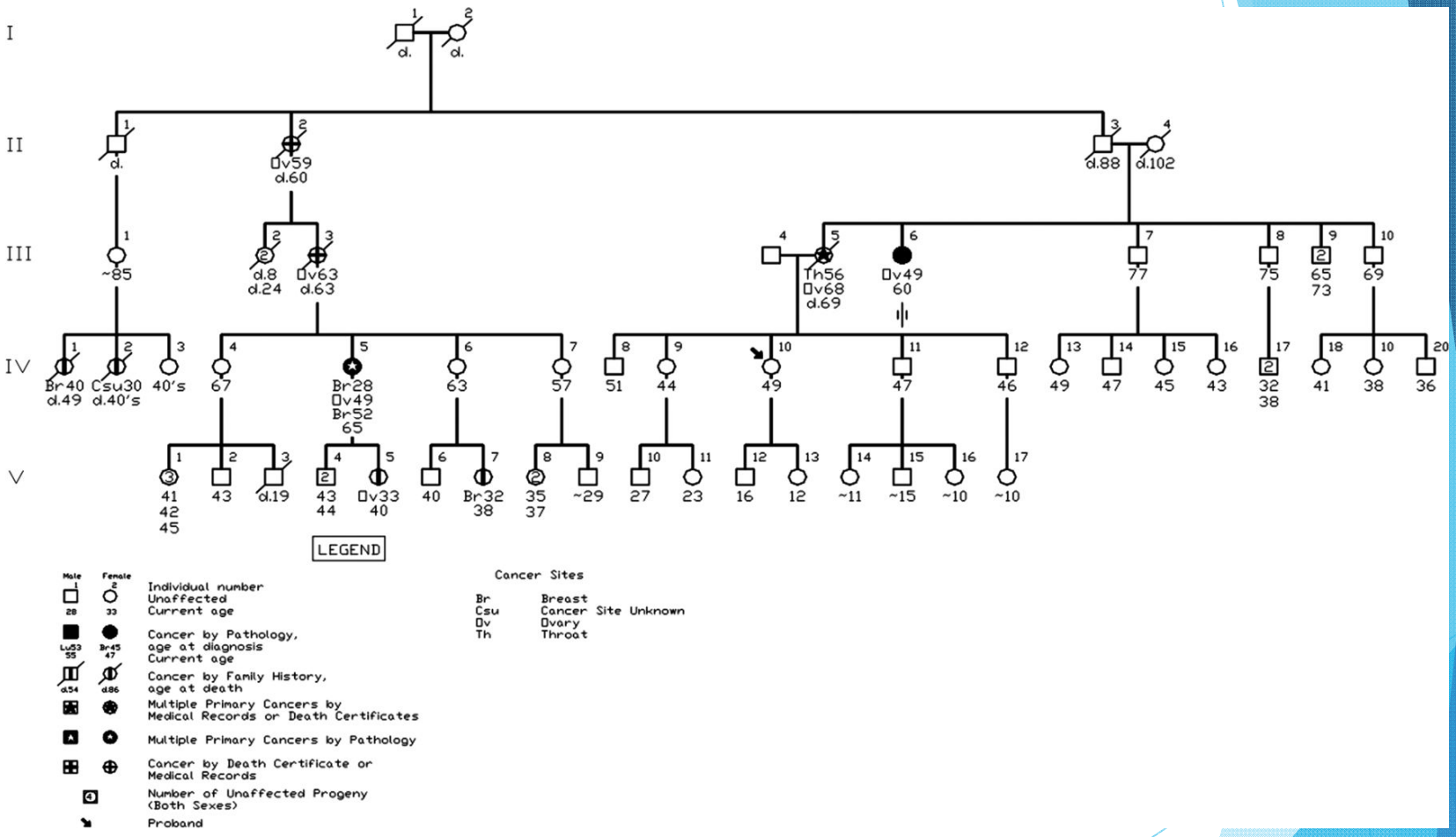
Camargo MC, Stayner LT, Straif K, et al.Environ Health Perspect 2011;119(9):1211-7.

Family history of ovarian cancer

- Around 3% of ovarian cancer cases occur in women with a family history of ovarian cancer, a cohort study showed.(Br J Cancer 2008).

- Ovarian cancer risk is 2.7-3.5 times higher in women whose mother or sister has/had ovarian cancer, compared with women with no such family history, cohort studies have shown; risk may be higher if the affected relative was diagnosed at a younger age.(American Society of Clinical Oncology (ASCO 2015)

Pedigree of a family with a strong history of ovarian cancer (OC) through four generations.



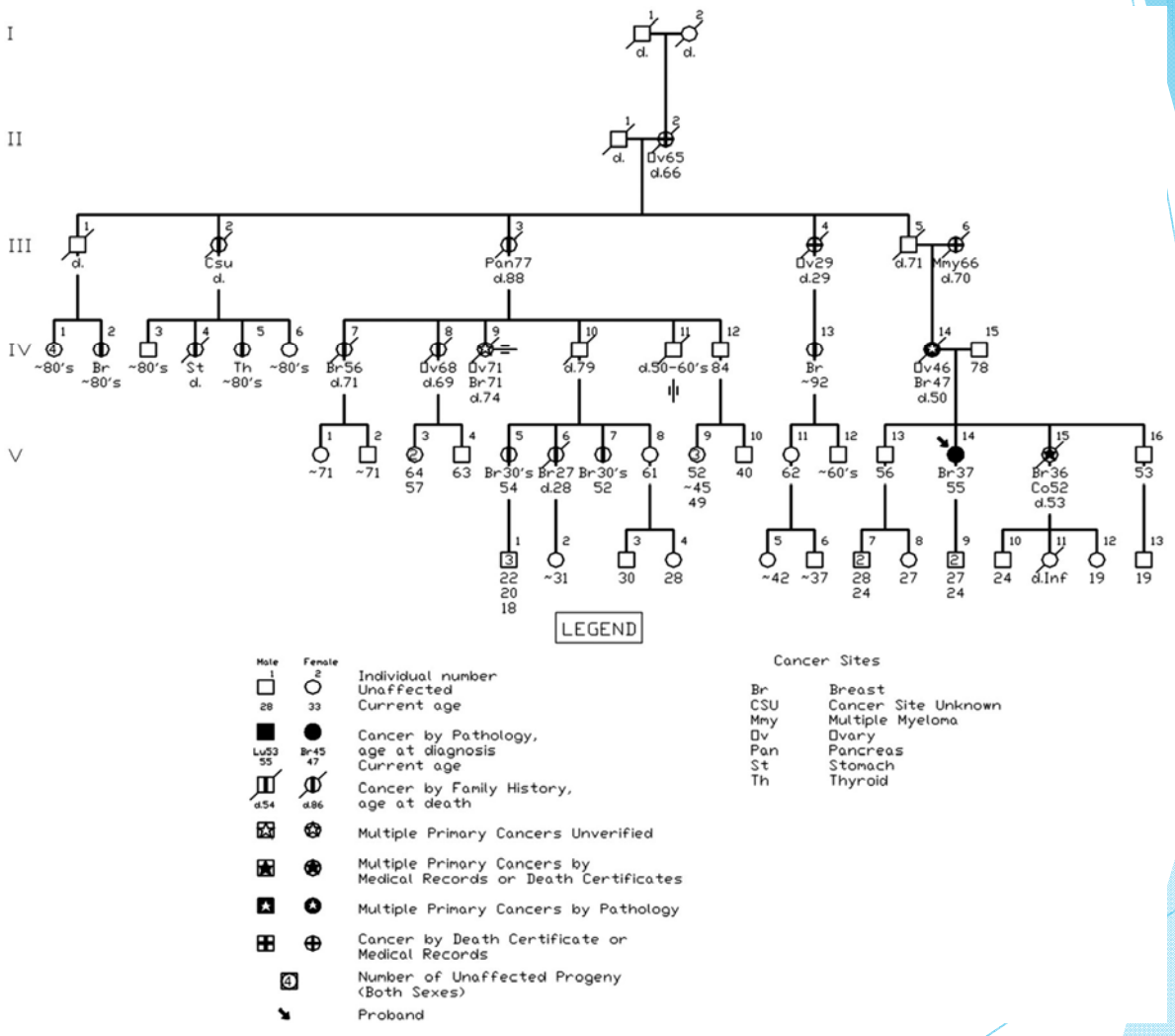
H. T. Lynch et al. Ann Oncol 2013;24:viii83-viii95

Annals of Oncology

Family history of other cancers

- Ovarian cancer risk is higher in women whose sibling has/had stomach, liver, breast, prostate, or connective tissue cancer, or melanoma; or whose parent has/had breast or liver cancer, a cohort study showed(Hemminki K, Sundquist J, Brandt A.2011)
- Ovarian cancer risk is higher in families with a history of breast cancer compared with the general population, even when when BRCA1 or BRCA2 mutations are not present, a cohort study showed.(Jervis S, Song H, Lee A, et al.2014).

Pedigree of a HBOC family with varying ages of ovarian (OC) and breast cancer (BC) onset.



H. T. Lynch et al. Ann Oncol 2013;24:viii83-viii95

Annals of Oncology

Genetics conditions BRCA1/2

- Inherited conditions account for 5-15% of ovarian cancer cases; the majority of these hereditary cases are linked with BRCA1/2 mutations.(Lynch HT, Snyder C, Casey MJ.2013).
- Ovarian cancer risk is up to 65% higher in women with BRCA1 mutation, and up to 35% higher in women with BRCA2 mutation, versus women without these genes.(Ingham SL, Warwick J, Buchan I, et al.2013 & Mavaddat N, Peock S, Frost D, et al.2013).

Conclusion

- **What Can You (and Yours) Change?**
- Use oral conceptive
- Pregnancies and breast feeding
- Consumption of non-starchy vegetables
- Tubal ligation
- Salpingoo-ophorectomy
- hysterectomy

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- www.cancer.org.03/12/2015
- The European Society for Medical Oncology 2013

EPIDEMIOLOGY OF TESTICULAR CANCER

EPIB 671 Student Symposium June 17, 2015

Linnea Duke

Introduction: Testicular Cancer (TC)

- Most common cancer in young men, but rare compared to other cancers overall
  - ~1% of all cancers
- Peak incidence occurs between 25 – 35 years
    - A second, much smaller peak, > 80 years of age
- Most are germ cell tumors which can be divided, according to histology, into seminoma and non-seminoma subtypes
  - Seminoma more common (~ 60%)
- Relative to other cancers, death from TC is rare
  - 5 year survival rates are approximately 95% → overall high survival can mask ethnic disparities

Garner *et al.* (2005); Sarfati *et al.* (2010); Stephenson and Gilligan (2012)

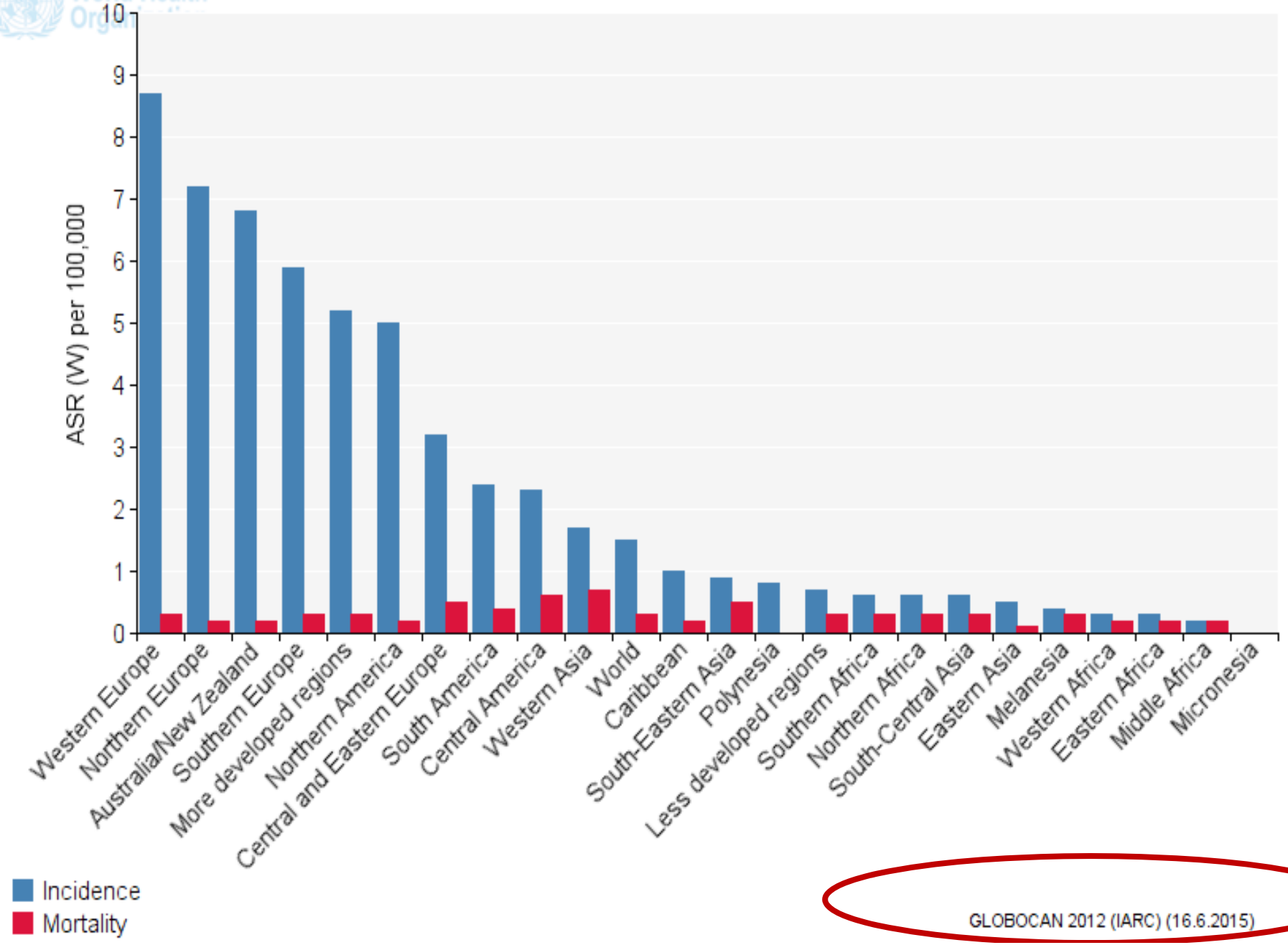
Introduction: Testicular Cancer

- **Four well-established risk factors:**
  - Cryptorchidism (= undescended testicles)
  - Family history of TC
  - Personal history of TC
  - Presence of intratubular germ cell neoplasia (ITGCN) → precursor lesion

- Increases in the incidence of TC in developed countries has be attributed to **birth-cohort effects**
  - Implies environmental factors play a role
    - ??Prenatal exposures (e.g. excess of endogenous maternal hormones, primarily estrogen, increased parity)

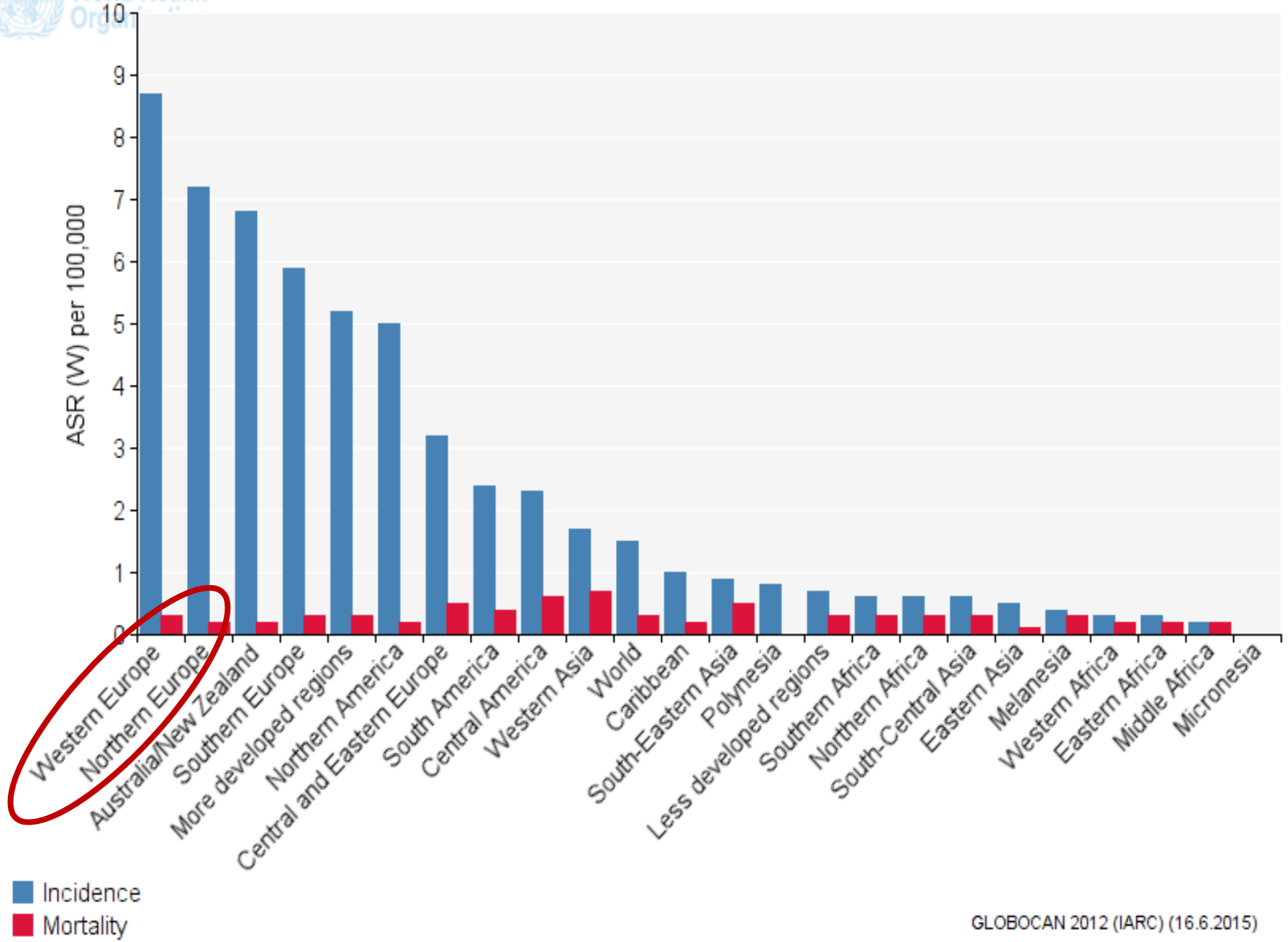
Garner *et al.* (2005); Stephenson and Gilligan (2012)

Testis, all ages



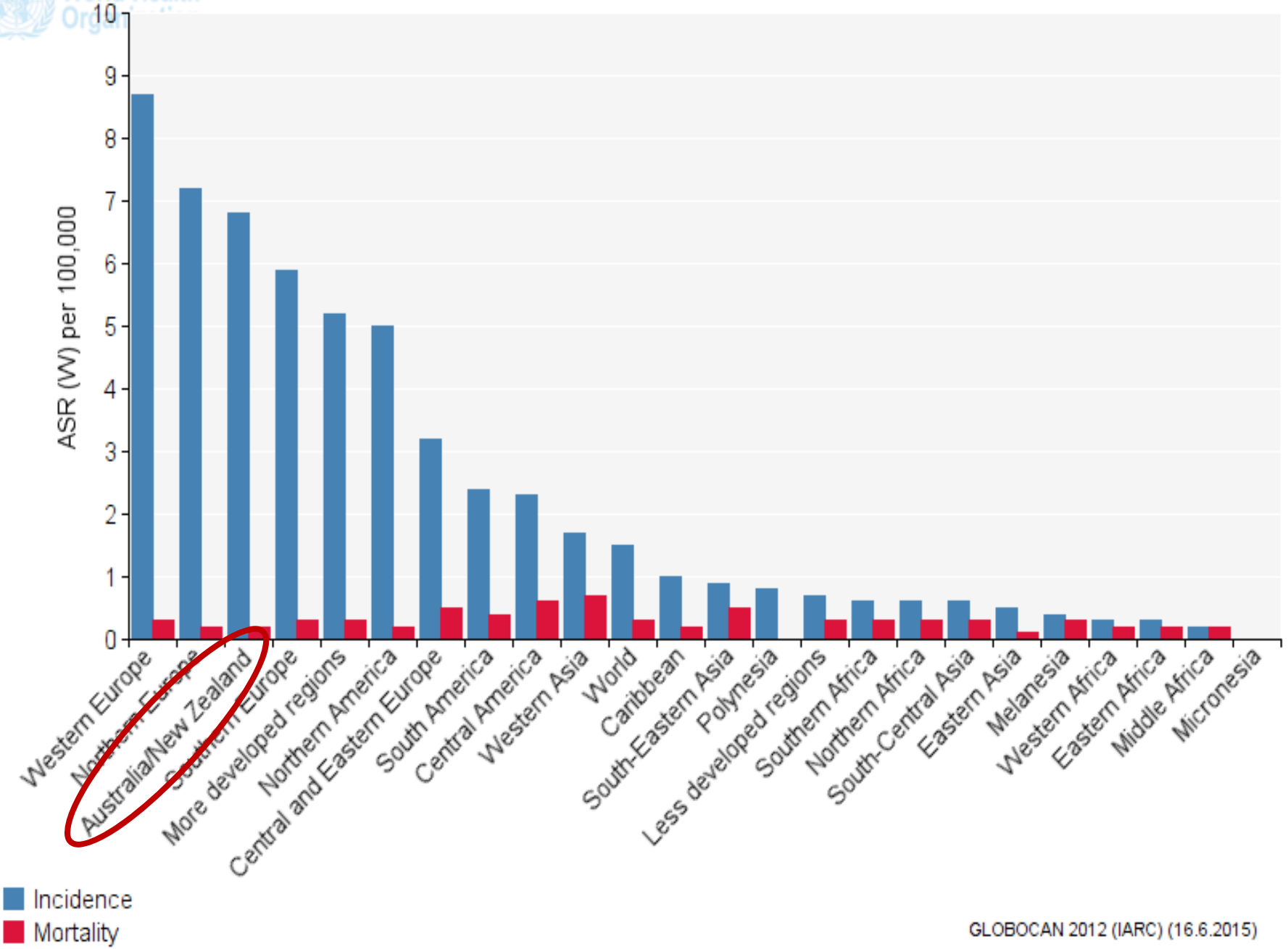
GLOBOCAN 2012 (IARC) (16.6.2015)

Testis, all ages



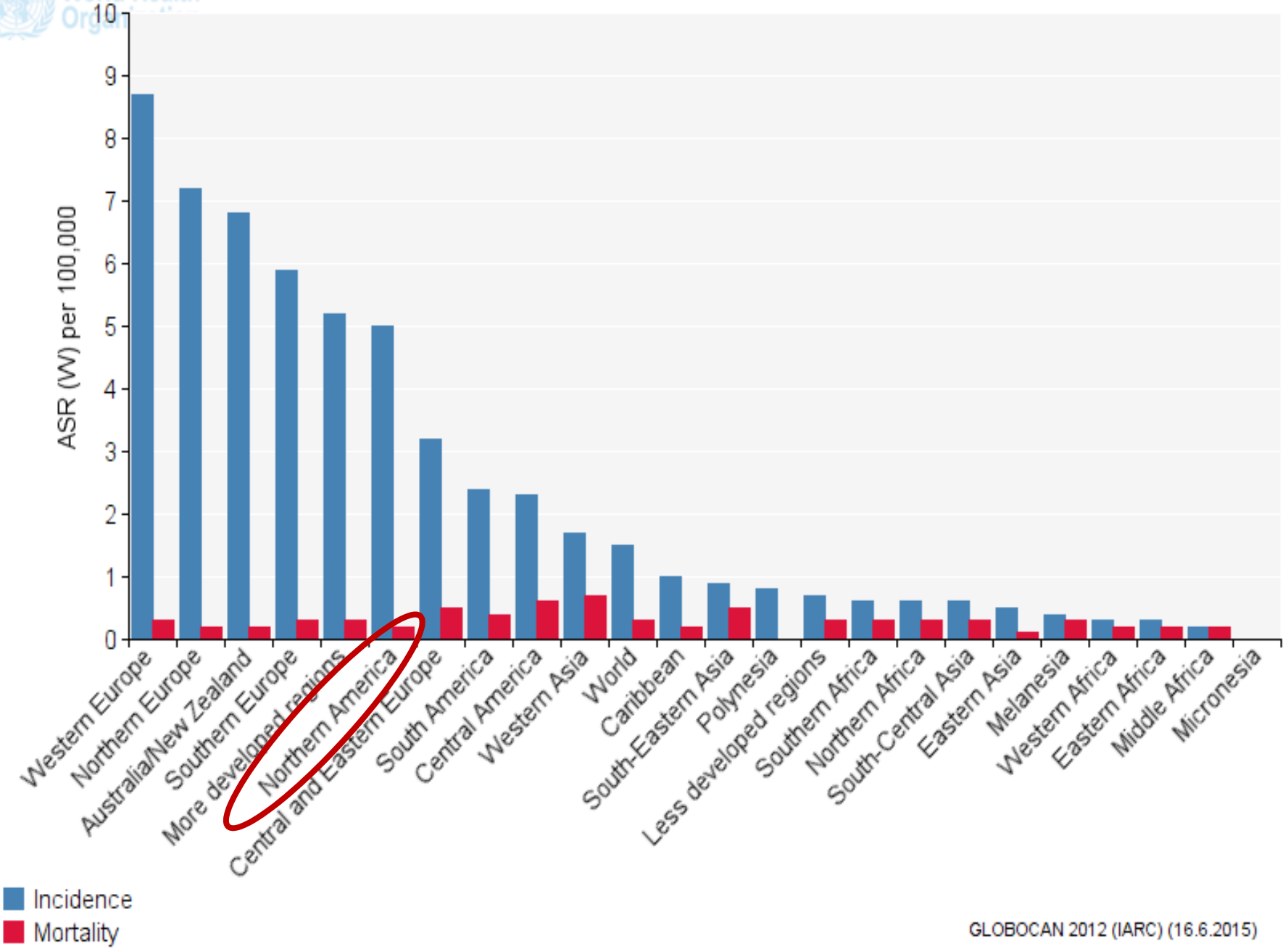
GLOBOCAN 2012 (IARC) (16.6.2015)

Testis, all ages



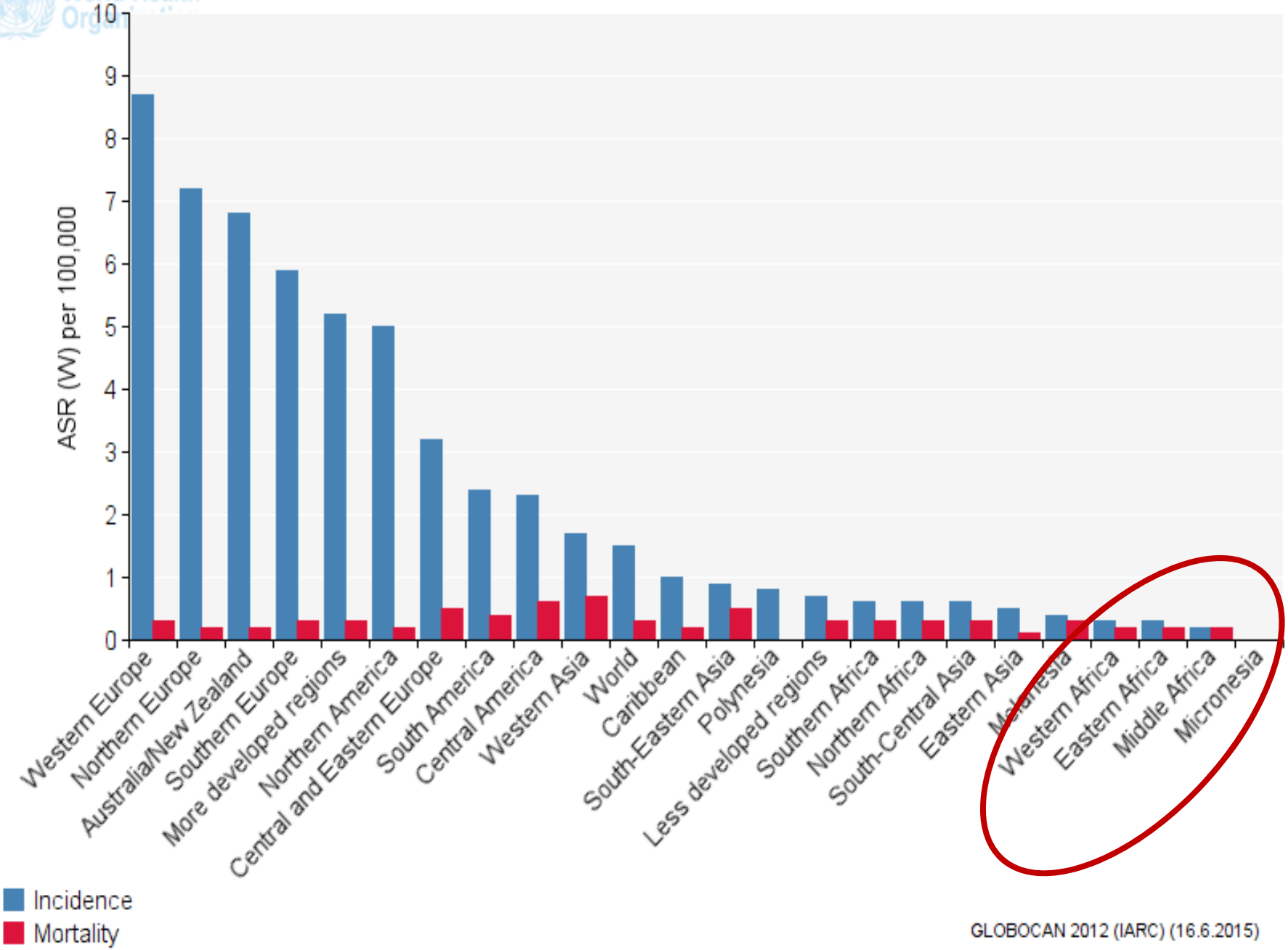
GLOBOCAN 2012 (IARC) (16.6.2015)

Testis, all ages



GLOBOCAN 2012 (IARC) (16.6.2015)

Testis, all ages



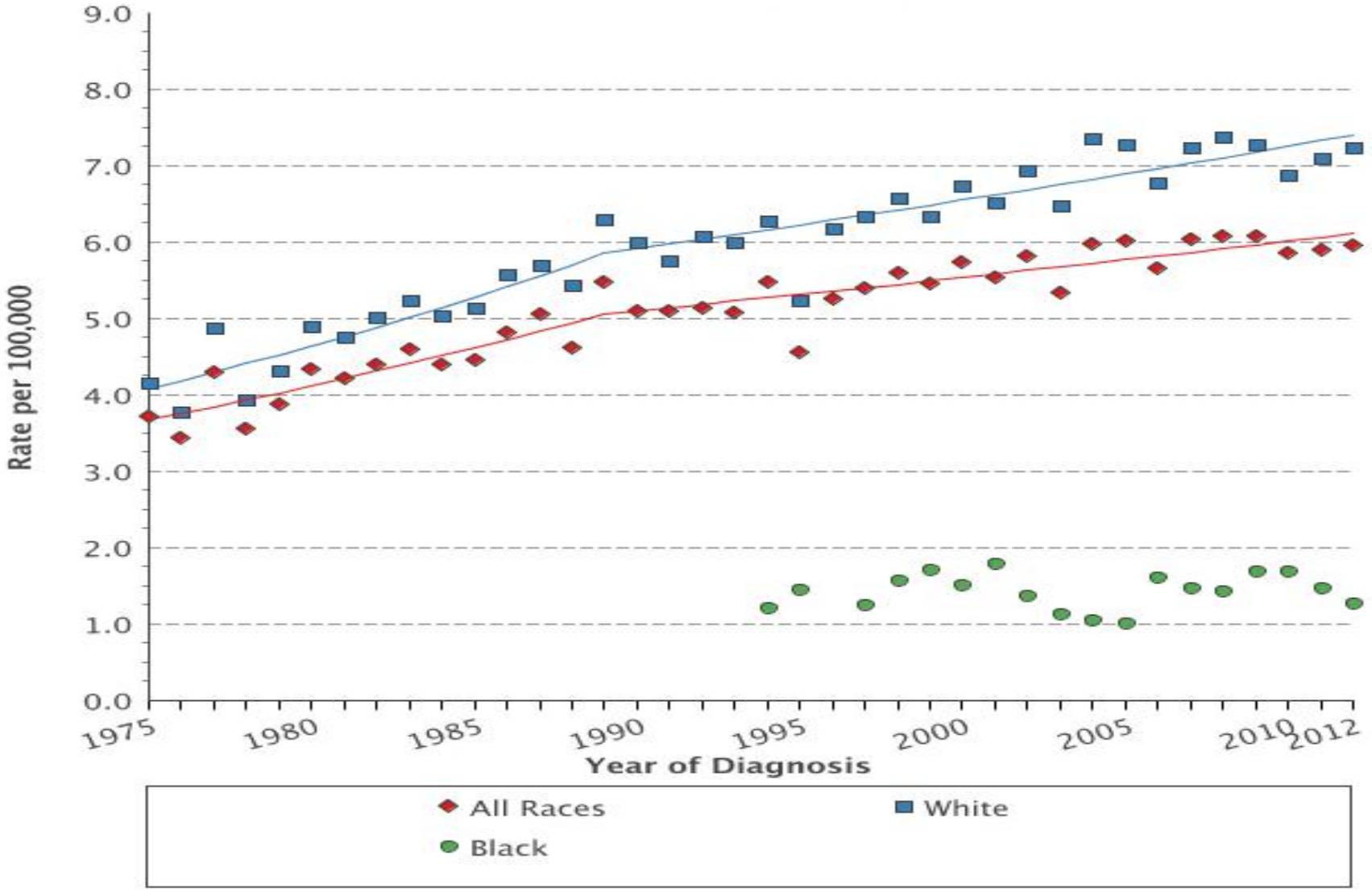
GLOBOCAN 2012 (IARC) (16.6.2015)

Testicular Cancer and Issue of Ethnic Disparity

- **A consistent finding in TC:**
  - In most countries, the population of European descent has the highest specific incidence rate of TC (Sarfati *et al.*, 2010)

Quote from: Gurney et al. (2015:561).

Age-Adjusted SEER Incidence Rates by Race/Ethnicity for Testicular Cancer (1975 – 2012)



Testicular Cancer in New Zealand "Obscure Etiology, Unusual Disparity"

- **Exception:** New Zealand (NZ):
  - In NZ the Māori consistently demonstrate **significantly higher TC rates than European counterparts**
    - Sarfati *et al.* (2010); Gurney *et al.* (2013, 2015)
  - Only example where a non-European population holds the greatest relative risk of TC
- **Why do we care that the epidemiology of TC in NZ is different?:**
  - Understanding this disparity in NZ can provide insight into important exposures involved in the etiology of TC

Quote from: Gurney et al. (2015:561).

Testicular Cancer in New Zealand: Gurney *et al.* (2015)

- Māori males aged 15-44 were 80% more likely to be diagnosed with TC than European/Other males between 2000 - 2011
  - **Age standardized RR 1.80, 95% CI 1.58 – 2.05**

- **Key findings from Gurney *et al.* (2015):**

  - Differential histology (i.e. Different TC subtype) not an explanation for the ethnic difference in TC incidence

  - Māori TC patients more likely to die of their cancer compared to European/Other patients
    - **Cancer-specific adjusted HR 2.29, 95% CI 1.14 – 4.59** (adjusted for age, stage, deprivation and rurality)

Testicular Cancer in New Zealand: Gurney *et al.* (2015)

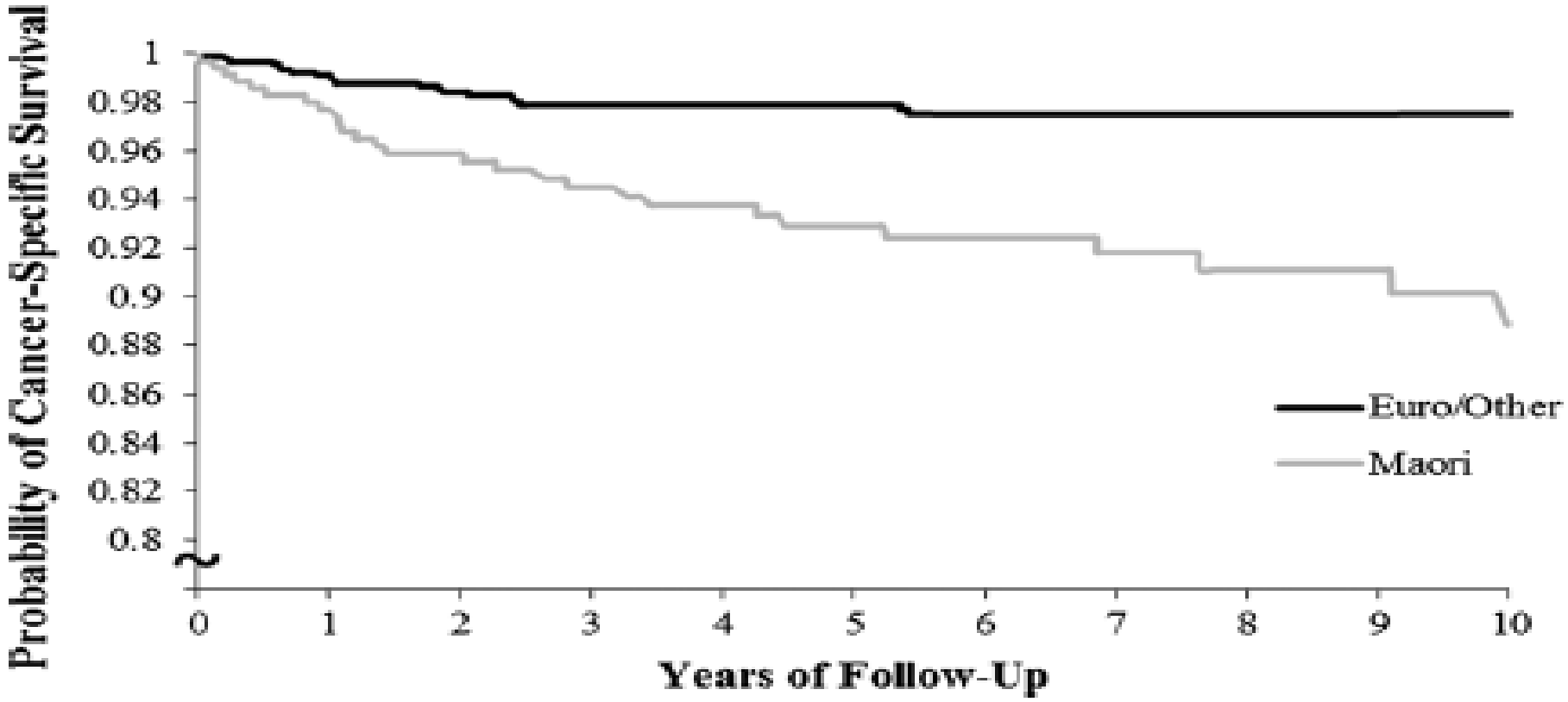
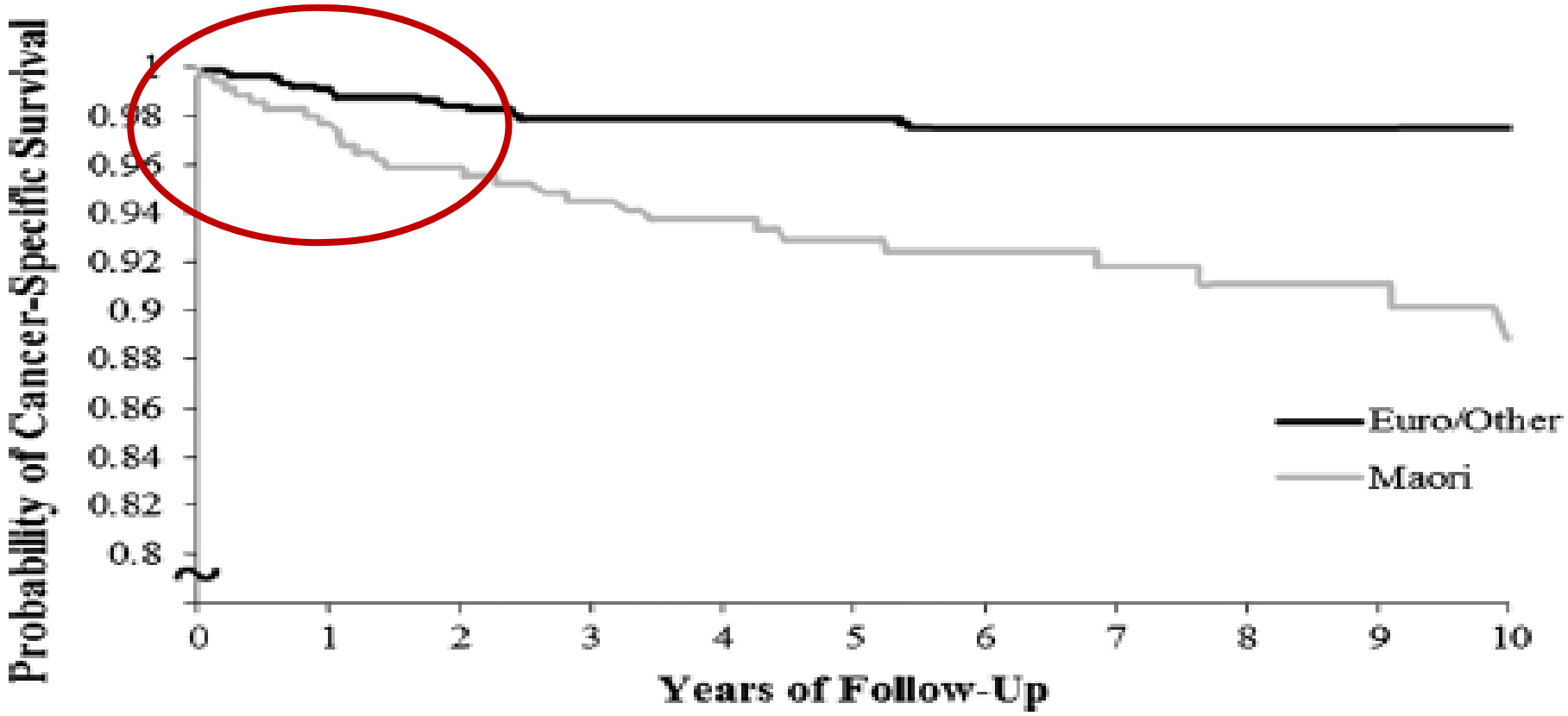


Fig. 1 Crude Kaplan–Meier curve, comparing 10-year cancer-specific survival between Māori and European/Other ethnic groups (15–44-year-olds)

Source: Gurney *et al.* (2015: *567*)

Testicular Cancer in New Zealand: Gurney *et al.* (2015)



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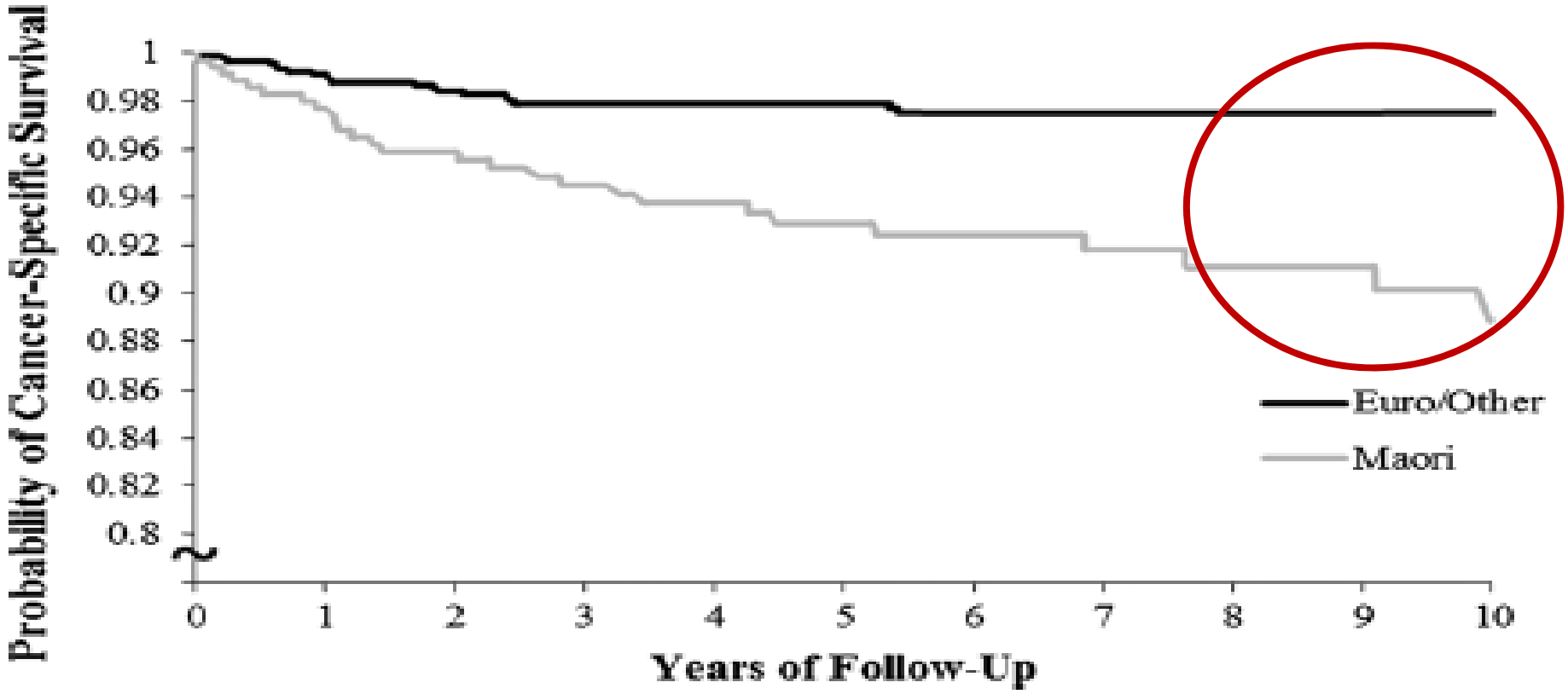
Source: Gurney *et al.* (2015: 567)

Testicular Cancer in New Zealand: Gurney *et al.* (2015)



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Source: Gurney *et al.* (2015: 567)

Cryptorchidism in New Zealand: Gurney *et al.* (2013)

- Would expect that the **prevalence of cryptorchidism would show similar disparity**
  - Most studies have not reported a major difference in risk (e.g. McGlynn *et al.*, 2006)
    - **US Collaborative Perinatal Study:** cryptorchidism was more common in white children compared to black children **(1.90% *vs* 1.55%; P = 0.04)**
    - Difference is not compatible with the **5-fold difference in TC rates → not the only mediating factor**
  - **Results do not support the hypothesis that the risk factors for cryptorchidism vary dramatically by ethnicity**
    - Collected data up to 7 years, did not look at cryptorchidism as a function of age

Cryptorchidism in New Zealand: Gurney *et al.* (2013)

- Māori demonstrated a more sustained incidence rate of cryptorchidism up to 7 years of age
  - **1.93 per 1000 PYs, 95% CI 1.81 – 2.02 for Māori *vs.***
  - **1.55 per 1000 PYs, 95% CI 1.48 – 1.62 for European/Other**

- **Suggests a few possibilities (non-mutually exclusive):**
  - Māori children have poorer access to health care → later diagnosis
  - Māori children are more likely to acquire cryptorchidism later in childhood
  - **??? Late detection and late correction → increased incidence of TC among Māori populations later in life**

Cryptorchidism in New Zealand: Gurney *et al.* (2013)

Table 2. *Crude and adjusted RR (95% CI) for incidence of orchiopexy confirmed cryptorchidism by ethnicity*

	Crude	Short Gestation	Small for Gestational Age
European/other	Referent	Referent	Referent
Māori	1.24 (1.15-1.34)	1.24 (1.15-1.34)	1.20 (1.11-1.30)
Pacific	0.88 (0.79-0.98)	0.89 (0.8-0.99)	0.89 (0.8-0.99)
Asian	0.71 (0.61-0.82)	0.71 (0.62-0.82)	0.68 (0.59-0.79)

Source: Gurney *et al.* (2013: 1855)

Cryptorchidism in New Zealand: Gurney *et al.* (2013)

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Asian	0.71 (0.61-0.82)	0.71 (0.62-0.82)	0.68 (0.59-0.79)

Source: Gurney *et al.* (2013: 1855)

Conclusions

- Testicular Cancer (TC) remains perplexing....reasons behind the ethnic disparities unknown
- In NZ, the pattern of cryptorchidism by ethnic group demonstrated the same pattern as that of TC in the same population
  - Similar pattern of cryptorchidism seen in the US between black and white populations
  - Extent of ethnic disparity in cryptorchidism not sufficient to explain ethnic disparities in TC
  - Supports hypothesis that principal factors responsible for ethnic differences in TC incidence occur prenatally/*in utero*
- Suggests that future research should be directed to environment and genetic exposures that could impair normal testicular development

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Breast Cancer Screening

for women aged 50 to 69 years

Sara Soldera, MD, FRCPC

EPIB 671

June 17, 2015

Agenda

- Current Guidelines
- Screening Programs Requirements
- Trends in Incidence and Mortality
- Observational Trials
- Randomized Controlled Trials
- Overdiagnosis and Harm
- Summary

Current Guidelines

- Lack of consensus
  - Age 50-69, q 2-3 years (CTFPHC)
    - Weak recommendation; moderate quality evidence
  - Age 50-74, q 2 years (USPSTF)
    - Grade B
  - Age 50-69, q 2 years* (WHO)
    - Strong recommendation based on moderate quality evidence, interval based on low quality evidence
  - Not recommended (SMB)

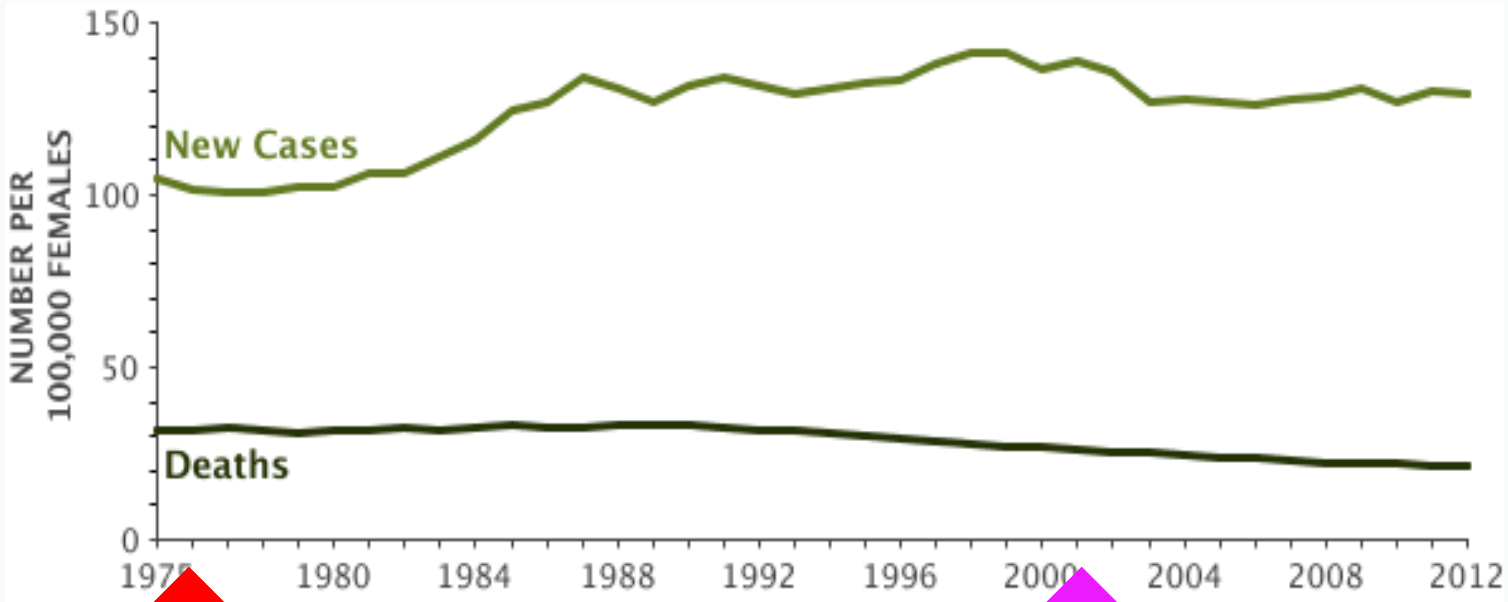
- Mammography, but then what?
  - DCIS ➔ lumpectomy ± radiation vs mastectomy
  - Invasive cancer ➔ lumpectomy/radiation vs mastectomy ± chemotherapy ± endocrine therapy

Screening Program Requirements

- Disease related factors
  - Important health issue
  - Recognized pre-clinical/early stage
  - Recognized mechanism of progression (pre-clinical ➔ advanced)
- Test related factors
  - Suitable
  - Acceptable
- Treatment related factors
  - Accepted treatment
  - Available facilities, personnel and protocol for dx and treatment
  - Acceptable global cost

Incidence and Mortality Rates

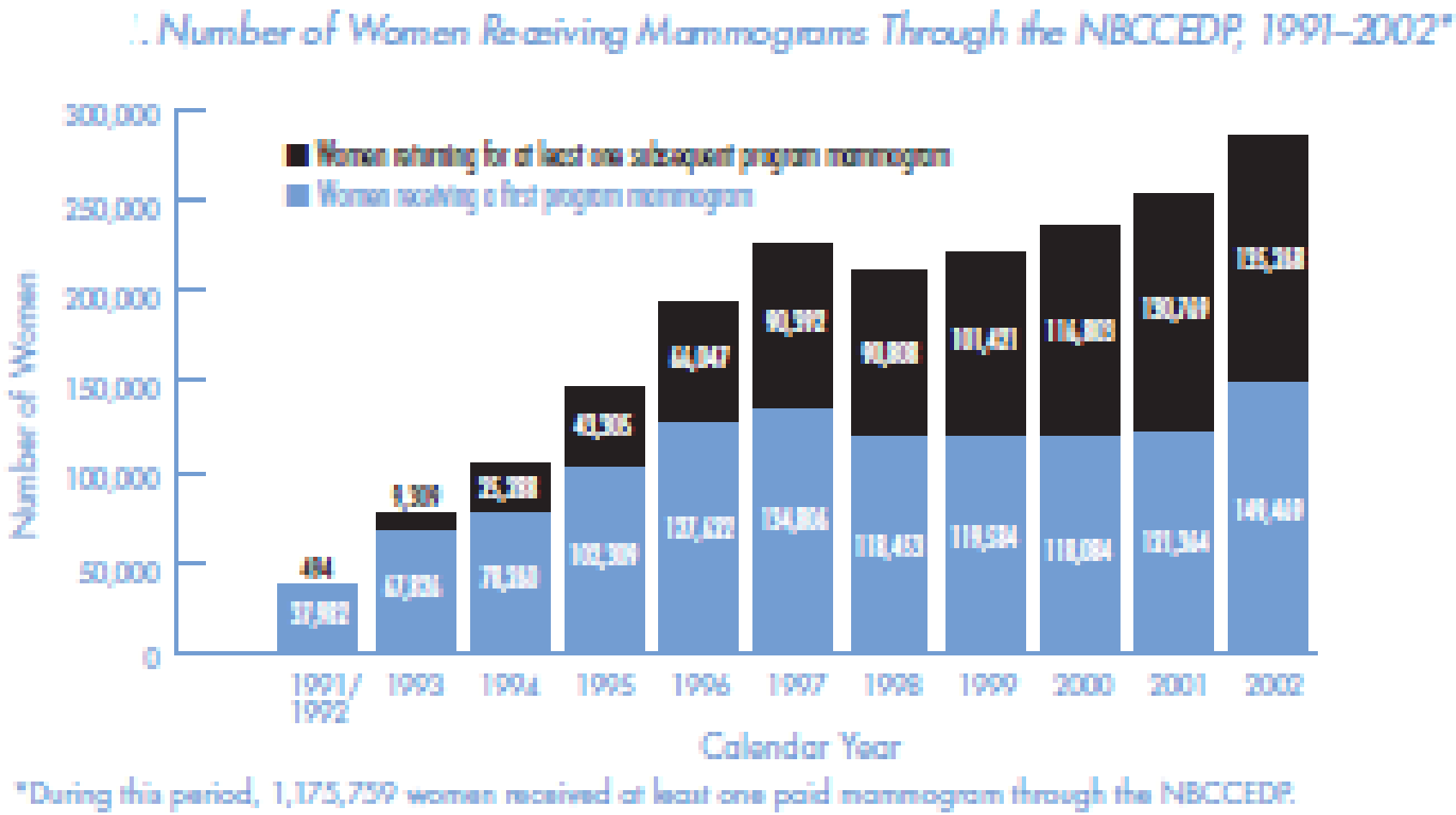
New Cases, Deaths and 5-Year Relative Survival View Data Table



Year		1980	1985	1990	1995		2003	2007
5-Year Relative Survival	7	74.8%	78.4%	84.6%	86.8%	%	89.7%	91.0%

SEER 9 Incidence & U.S. Mortality 1975-2012, All Races, Females. Rates are Age-Adjusted.

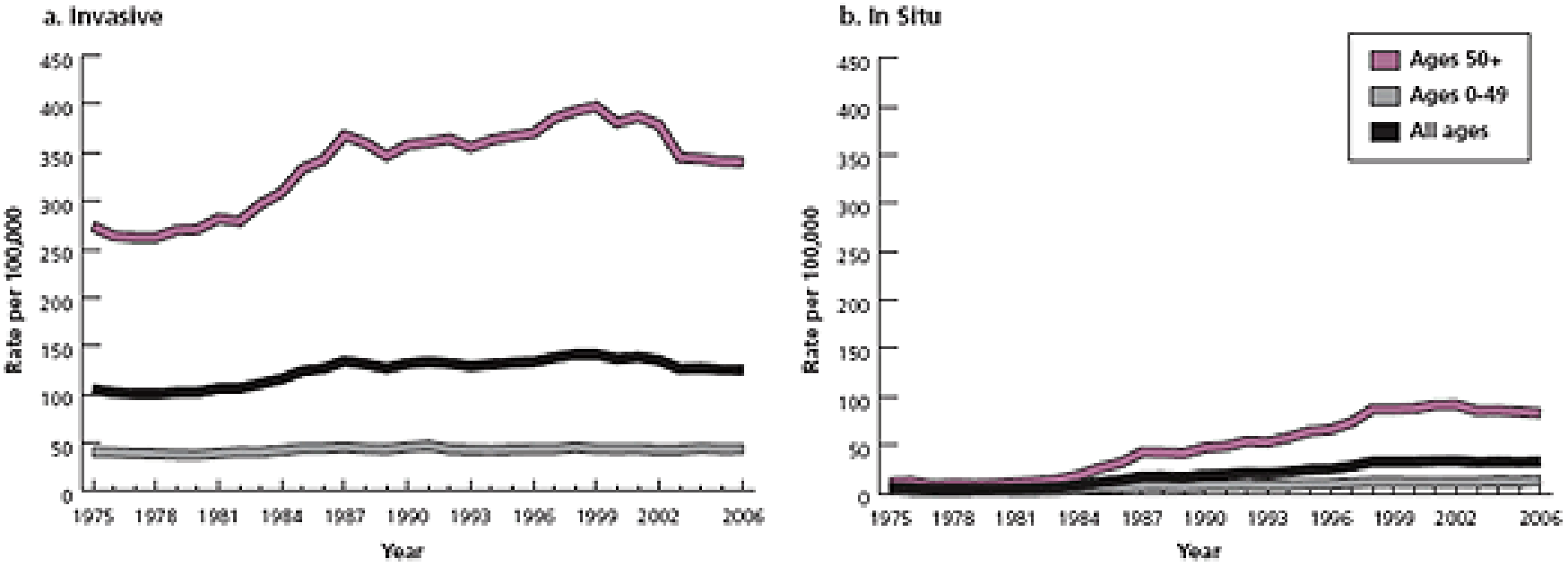
Mammography Use



Breast Cancer Screening. U. S. Department of Health and Human Services Health Resources and Services Administration. 2002.

Age-Specific Incidence Rate

Figure 3. Incidence Rates* of Invasive and In Situ Female Breast Cancer by Age, Adjusted for Delayed Reporting, US, 1975-2006

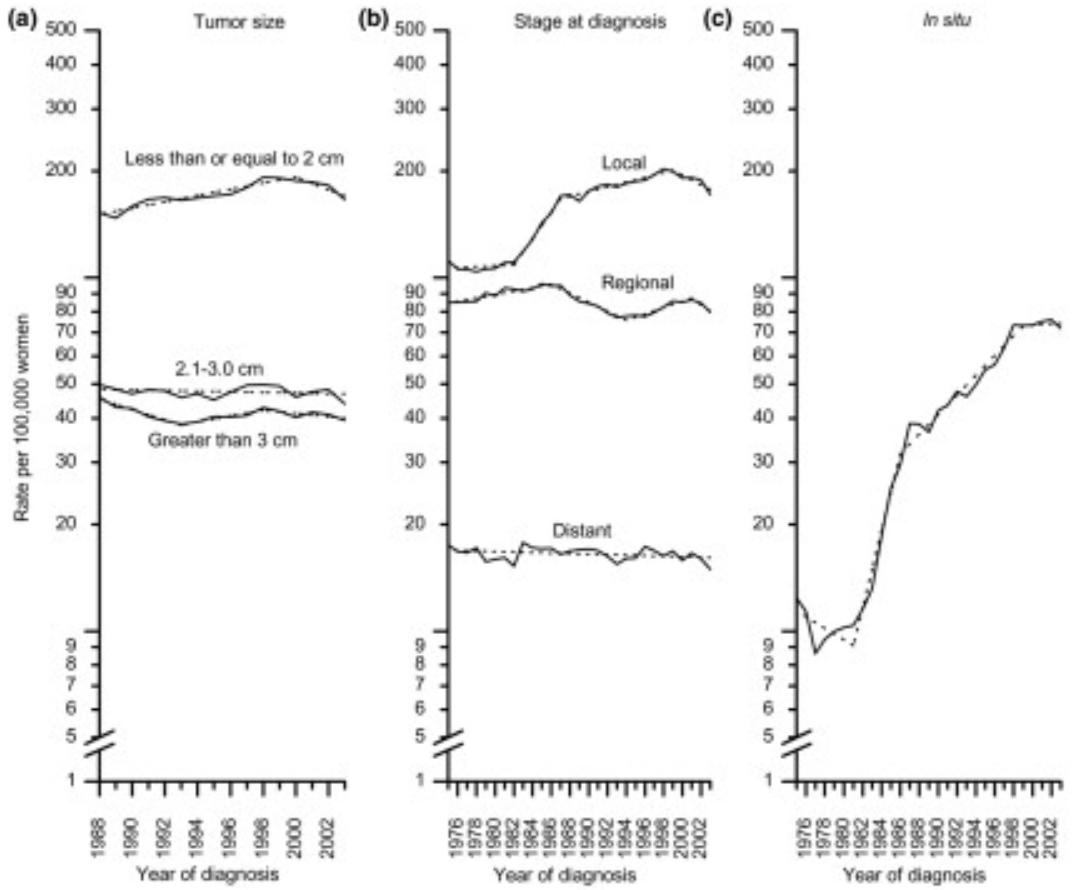


*Rates are age-adjusted to the 2000 US standard population within each age group.

Data source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 9 Registries, 1973-2006, Division of Cancer Control and Population Science, National Cancer Institute, 2009.

American Cancer Society, Surveillance Research, 2009

Stage-Specific Incidence Rate



Trends in age-standardized invasive breast cancer rates among women 40 years old and above. **(a)** Trend by tumor size (1988 to 2003). **(b)** Trend by stage (1975 to 2003). **(c)** Trend for *in situ* breast cancer rates (1975 to 2003). Solid lines represent observed rates and dashed lines fitted rates.

Jemal *et al. Breast Cancer Research* 2007 **9**:R28 doi:10.1186/bcr1672

Evidence: Observational Trials

- Numerous observational trials and multiple systematic reviews
  - Ecologic studies
    - Time-trend analyses
    - Incidence-based studies
  - Case-control studies (roughly RR 0.50)
  - Cohort studies (few, RR 0.83-0.87)

- Wide range of quoted RR 0.30- 0.92
  - more recent trials 0.83-0.87

- Inherent biases
  - Volunteer bias (selection of the most healthy)
  - Lead-time bias
  - Length-time bias

Evidence: Randomized Controlled Trials

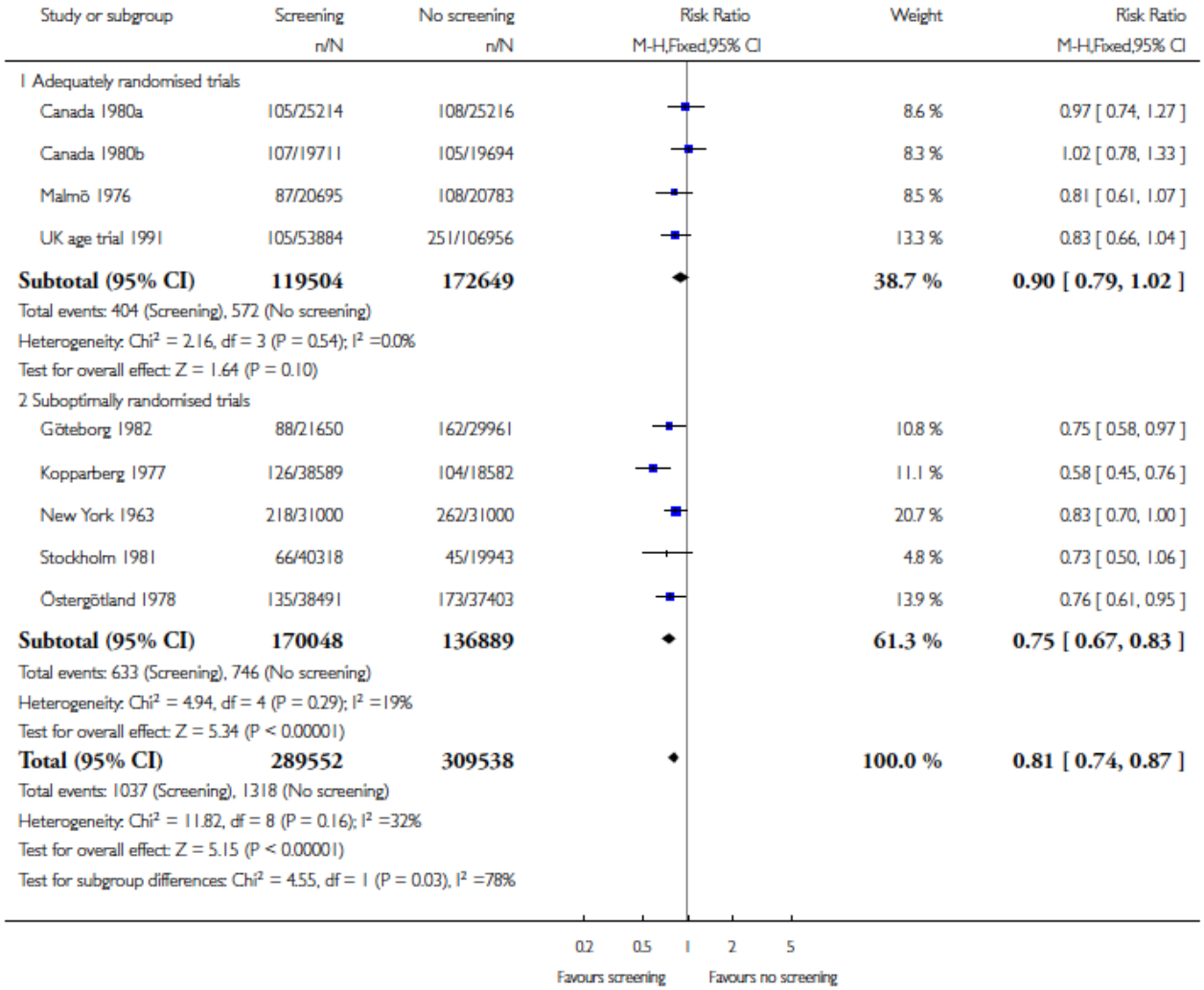
- 8 RCT with variable methodologies
  - n = > 600 000
  - Canada, UK, Scotland (Edinburgh), Sweden (4) and USA (New York)
  - Start date 1963- 1982
  - Women aged ≥ 39 years (most 45-64 years)
  - Variable screening
    - 2- 9 cycles
    - 1- 3 year interval
    - 4- 7 year screening period
  - Primary outcomes: breast cancer mortality
    - Surgical interventions, radiation therapy, chemotherapy and total mortality

Analysis 1.2. Comparison 1 Screening with mammography versus no screening, Outcome 2 Deaths ascribed to breast cancer, 13 years follow up.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 2 Deaths ascribed to breast cancer, 13 years follow up



Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. *Cochrane Database of Systematic Reviews* 2013.

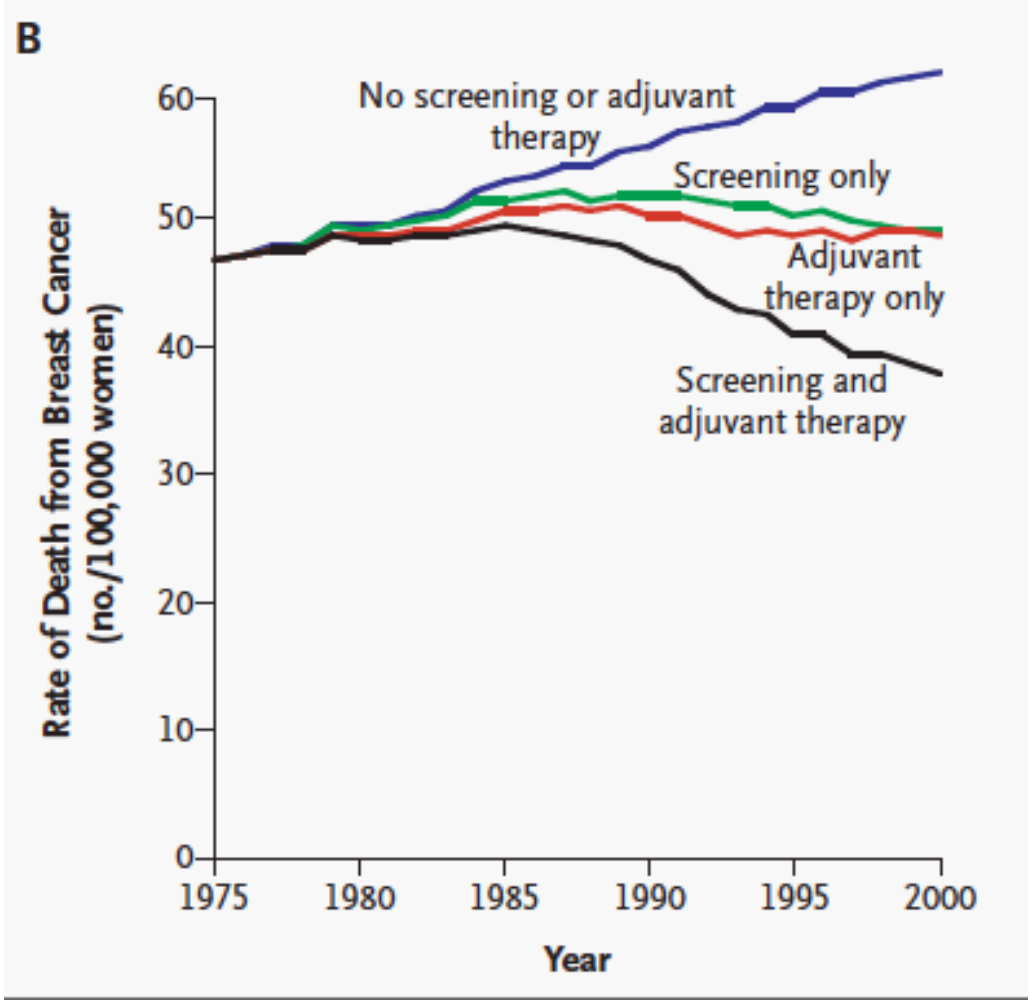
Discussion

- Selection bias
  - Screening arm invited for screening, while control enrolled through variable methods (confounding by indication)
- Randomization
  - Post-randomization differential exclusion due to previous breast cancer diagnosis (screening > control)
  - Quality of randomization
    - Baseline characteristics not reported
    - Unbalanced groups (SES/age distribution favoring screening)
    - Unjustified post-randomization changes in study group allocation
    - Differing breast cancer mortality rates amongst control groups (Two-County trial)
- Differential misclassification of cause of death
  - Unblinded assignment
  - Local treatment of breast cancer potentially reducing cancer deaths attributed to breast primary (normal breast exam at time of death)

Discussion (2)

- Breast cancer mortality as an endpoint
  - Does not necessarily translate into an overall survival benefit: harm related to interventions?
  - Overall mortality unchanged*
- Greatest benefit reported in trials with fewer screening cycles, poor equipment and high rate of screening in control group
- True screening program?
  - Few cycles of screening
  - Subsequent screening of control group (contamination)
- External Validity?
  - Outdated treatments
  - Efficacy vs effectiveness

Combination Screening and Modern Therapies



Berry D, et al. NEJM. 2005

Overdiagnosis and Harm

- Overdiagnosis
  - Wide range (0 to 54%)
    - Screening in control group dampens magnitude
    - Choice of denominator
- Treatment related harm
    - Radiation: 27% and 78% excess mortality from heart disease and lung cancer, respectively
    - Chemotherapy: 2% cardiotoxicity and 1-2% leukemia
    - Hormonal therapy: bone related events
- False-positive rate
  - 10.7%/ mammogram
  - 49% after 10 mammograms ➔ 19% biopsy
  - Higher in younger age groups
- Psychological distress, health-related QOL, overtreatment and DALYs?

Table 2: Estimated number of women with adverse outcomes following screening mammography[12]

Adverse outcome	Women affected by age range, no.		
	40–49 yr	50–69 yr	70–74 yr
Per 1000 women screened			
False-positive result on mammogram	327	282	212
Unnecessary biopsy	36	37	26
Per single death prevented			
Number needed to screen	2108	721	451
False-positive result on mammogram	690	204	96
Unnecessary biopsy*	75	26	11

Note: Results are expressed per thousand women screened for a median of 11 yr (estimated as a total of 4 screening mammograms per woman assuming a screening interval of 2–3 yr). The period of 11 yr was chosen because it was the approximate median duration of follow-up during the randomized trials included in the systematic review. Data assume that rescreening rates stay constant over time.
*Percutaneous or surgical biopsies of the breast that were subsequently found not to have cancer.

The Canadian Preventative Task Force. CMAJ. 2011.

Summary

- Breast cancer is an important source of morbidity and cancer related mortality amongst women
- Screening programs contributing to rising incidence, but mostly early stage
- Effect on cancer-related and overall mortality still controversial due to lack of good quality evidence
- Further epidemiologic trials needed to investigate use of screening at extreme of ages, overdiagnosis and net-effect of screening programs
- Basic science research to further elucidate mechanism of progression from pre-malignant to invasive disease

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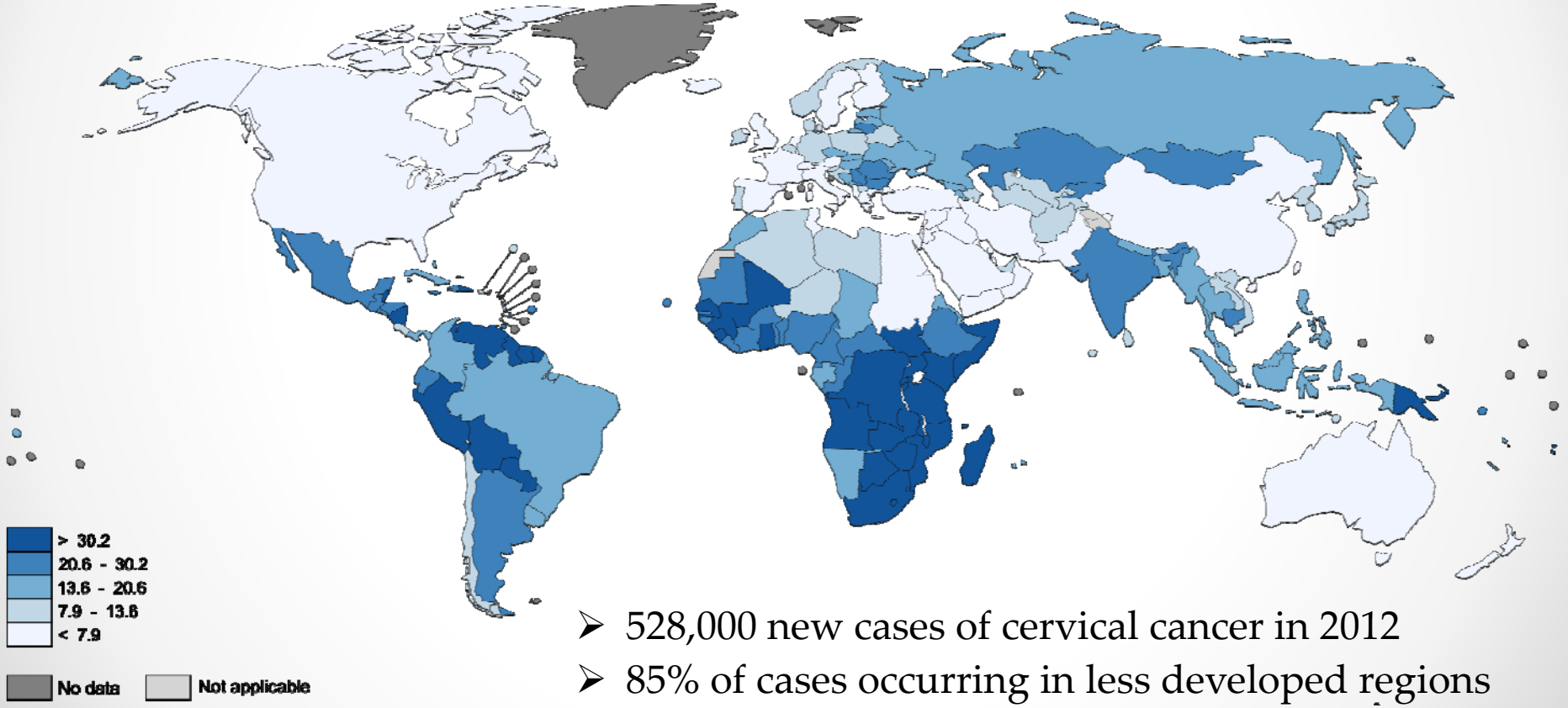
Cervical Cancer Prevention In Developing Countries

Zoë Greenwald
MSc1 Epidemiology
EPIB 671: Cancer Epidemiology & Prevention
June 17, 2015

Cervical cancer **incidence** worldwide (2012)

Age-standardized incidence rates per 100,000

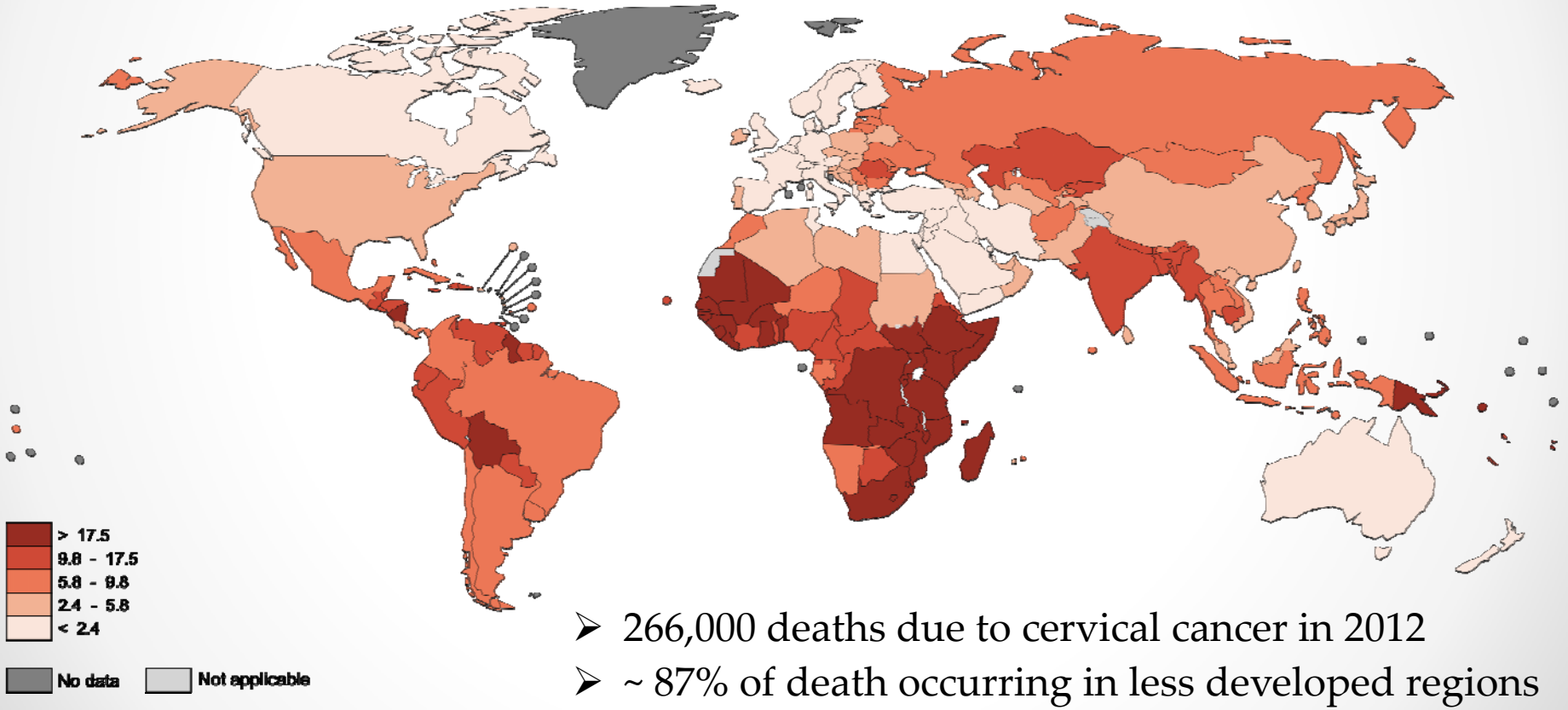


- 528,000 new cases of cervical cancer in 2012
- 85% of cases occurring in less developed regions

Source: IARC, Globocan (2012)

Cervical cancer **mortality** worldwide (2012)

Age-standardized mortality rates per 100,000



- 266,000 deaths due to cervical cancer in 2012
- ~ 87% of death occurring in less developed regions
- 5-year survival rate in developing countries <50%

Source: IARC, Globocan (2012); Franco & Ferenczy (2005)

Risk factors: Cervical Cancer

-- HPV is a necessary cause of Cervical Cancer --

Initiation: Sexual activity mediates exposure to HPV infection via:

- Age at sexual onset
- Number of sexual partners

Promotion: co-factors associated with disease progression:

- Parity, smoking, HIV infection, immune response (HLA mediated), oral contraceptives, dietary factors

Detection of precursors

- Precursors to invasive squamous cell cervical cancer are intra-epithelial lesions (CIN1/2/3, LSIL/HSIL)
- Precursor to adenocarcinoma arise from the columnar epithelium as *adenocarcinoma in situ (AIS)*

Source: Franco & Ferenczy (2005)

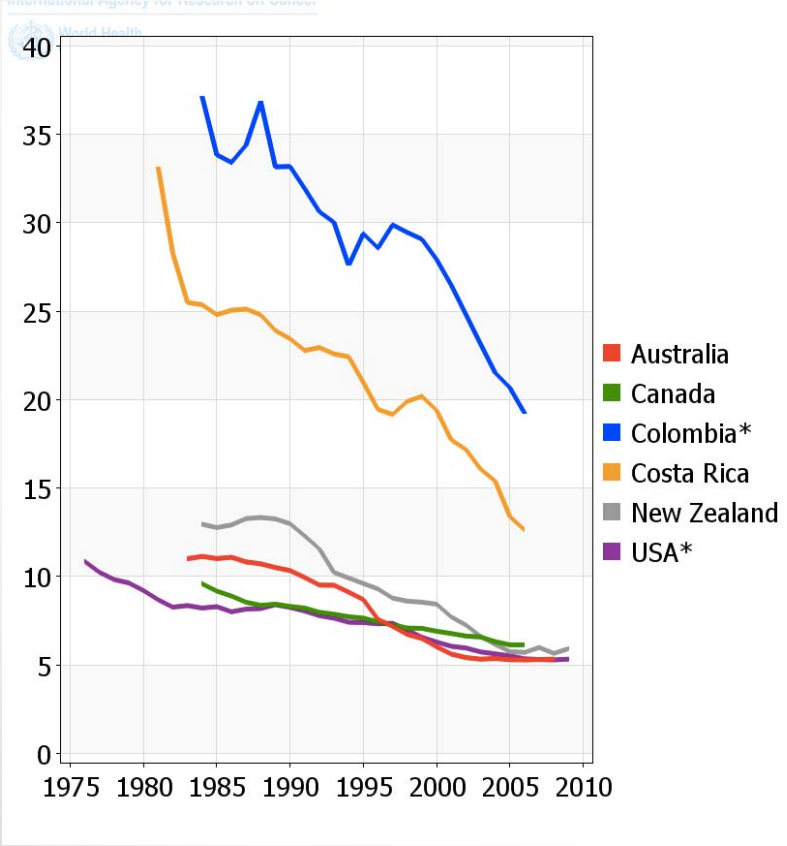
Cervical cancer prevention

- **1960-70s**: early evidence that screening for cervical squamous intraepithelial lesions by cytological test (Pap smear) can prevent development of invasive cervical cancers
- **1985**: IARC & UICC monograph on cervical cancer screening promoted the development of organized screening programs → ***Secondary prevention***
- **1992**: Identification of Human Papillomarivus (HPV) as the major cause of cervical cancer
- **2005**: Vaccines against oncogenic HPV types → ***Primary prevention***

Source: IARC (2005) IARC Handbooks of Cancer Prevention Volume 10, Cervix Cancer Screening.

Success story of secondary prevention

Trends in Cervical Cancer Incidence
Age-standardized rate per 100,000



Country	State of cervical cancer screening program
Australia	Cytological screening available opportunistically since 1960s. Organized screening since 1991
Colombia	Organized screening program began in 1989. Recommends screening for women 25-64y (every 3 years)

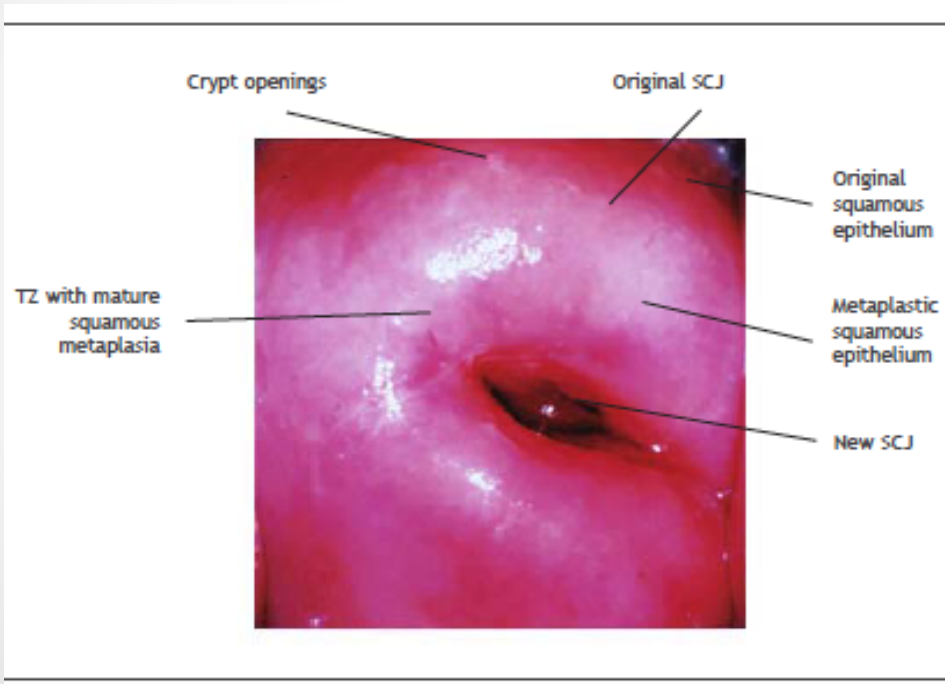
Source: IARC, Globocan (2012); IARC (2005) IARC Handbooks of Cancer Prevention Volume 10, Cervix Cancer Screening.

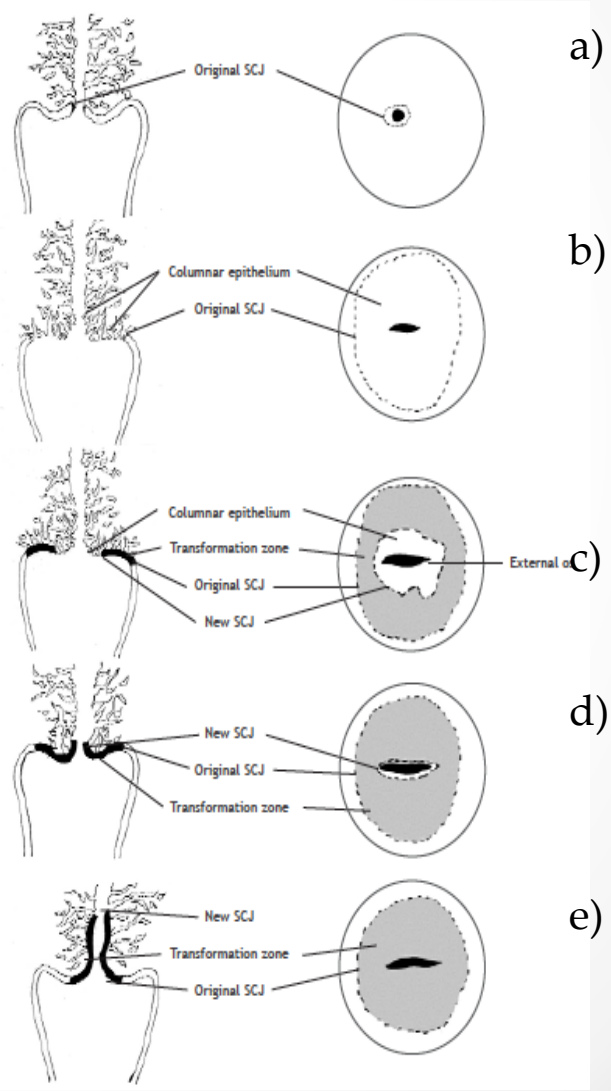
Screening Test	Procedure	Strengths	Weaknesses
Cervical cytology* (Pap smear)	Sample of cells taken from cervix. Laboratory analysis by cytology.	Specificity=98% (95%CI: 0.97-0.99) Few false positives	Sensitivity=51% (95%CI: 0.37-0.66) - Many false negatives - Poor inter-rater reliability - Not cost-effective
Visual Inspection*	Visualization of cervix after staining with 5% Acetic Acid (VIA) or Lugol's Iodine (VILI)	-Inexpensive, safe acceptable -less infrastructure need than with lab-based tests	Comparable sensitivity for detecting LSIL/HSIL, but lower specificity leads to higher rate of colposcopy referrals
Cervicography*	Photograph of cervix taken after application of 5% acetic acid	Can be evaluated by specialist at a remote site	Low specificity, high rate of colposcopy referrals
HPV DNA testing	DNA Hybridization Techniques: Hybrid Capture (HC) assay and polymerase chain reaction (PCR)	-Reproducible -High sensitivity	- Expensive to implement - Lower specificity than cytology
Colposcopy**	Microscopic visualization of cervix following application of saline, 3-5% acetic acid, Lugol's iodine	Essential for obtaining directed biopsies (diagnostic test)	-Subjective -Lower sensitivity for low-grade lesions

Source: *Franco & Ferenczy (2002); **Sellors & Sankaranarayanan (2003)

The healthy cervix

As visualized by colposcopy under saline application





a) Before Menarche

b) After puberty, early reproductive age

c) In a woman in her 30s

d) In a peri-menopausal woman

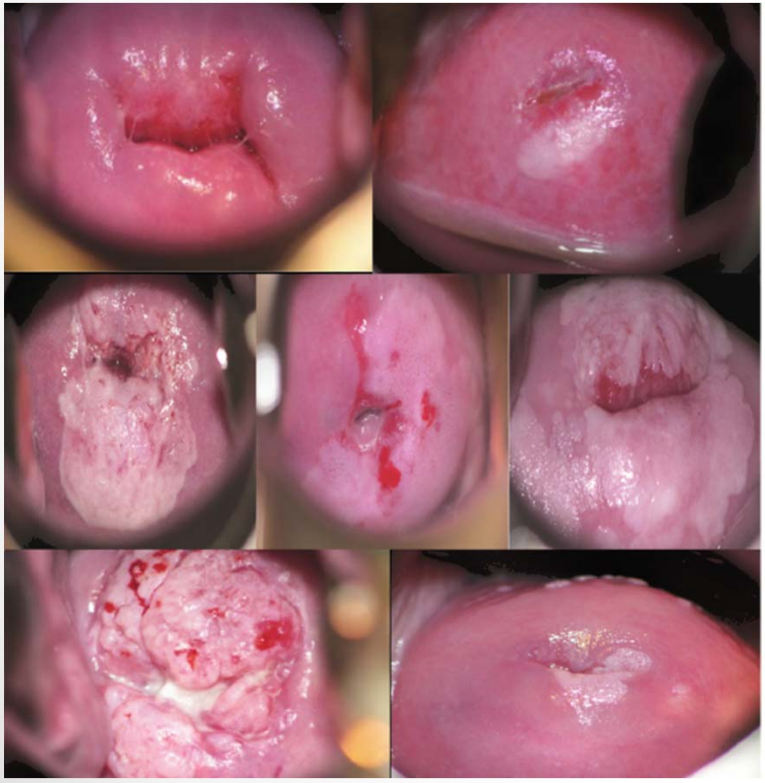
e) In a post-menopausal woman

Source: Sellors & Sankaranarayanan (2003)

Visual Inspection

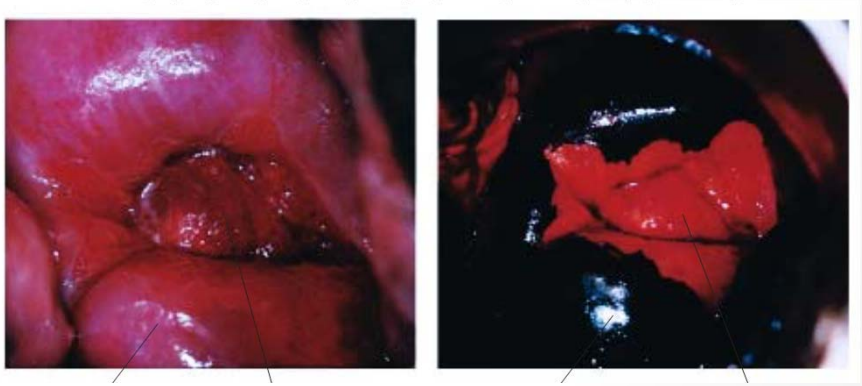
5% Acetic Acid (VIA)

Lesions turn aceto-white



Lugol's Iodine (VILI)

Lesions are iodine-negative



VIA based screening, augmented by cervography in Lusaka Province, Zambia

Source: Parham et al. (2015), Sellors & Sankaranarayanan (2003)

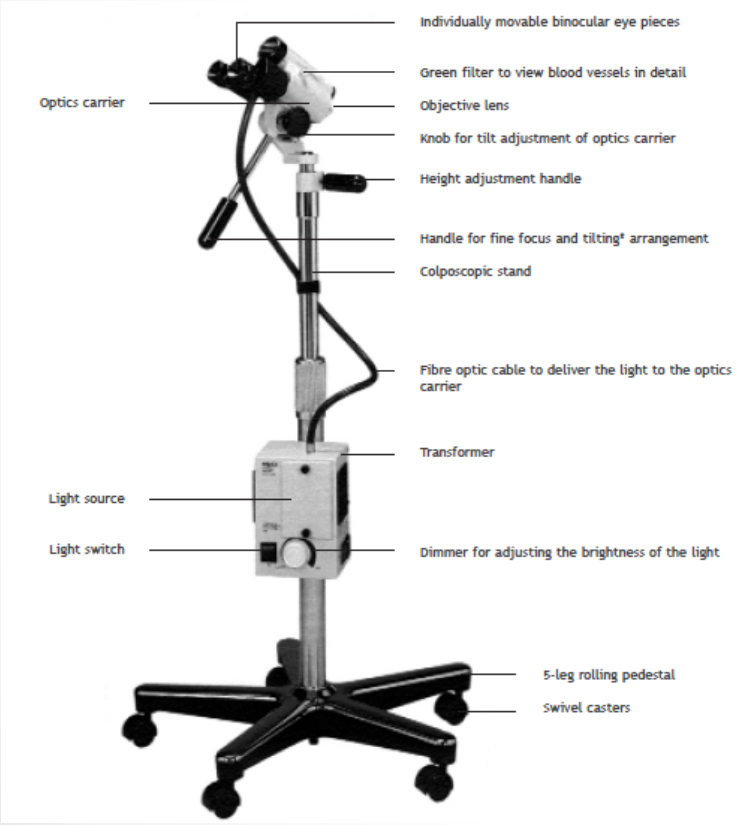
HPV DNA Testing

- The Hybrid Capture™ (HC) assay most widely used in clinical and screening settings
- *Care*HPV test (QIAGEN) designed for use in low-resources settings
- Qualitative detection of HPV DNA in cervical specimens of 13 high-oncogenic risk genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68
- Combination of primary screening with HPV-DNA tests followed by cytological triage of HPV-positive results in nearly 100% sensitivity and negative predictive values

Source: Franco & Ferenczy (2007), Jeronimo et al (2014)

Colposcopy

The Colposcope



- Indications for colposcopy:
  - Suspicious-looking cervix
  - CIN 2 or CIN 3 on cytology
  - Persisting CIN 1on cytology (>12m)
  - Acetopositivity on VIA
  - Positivity on VILI
  - Infection with oncogenic HPV
- IARC 2004 Colposcopy report:
  - Recommends that women in developing countries with any grade of CIN on cytology by referred for colposcopy
  - justification: possibility of reporting misclassification and challenges in follow-up

Source: Sellors & Sankaranarayanan (2003) IARC

Comparison of *care*HPV test, VIA and Pap smear in the detection of cervical cancer

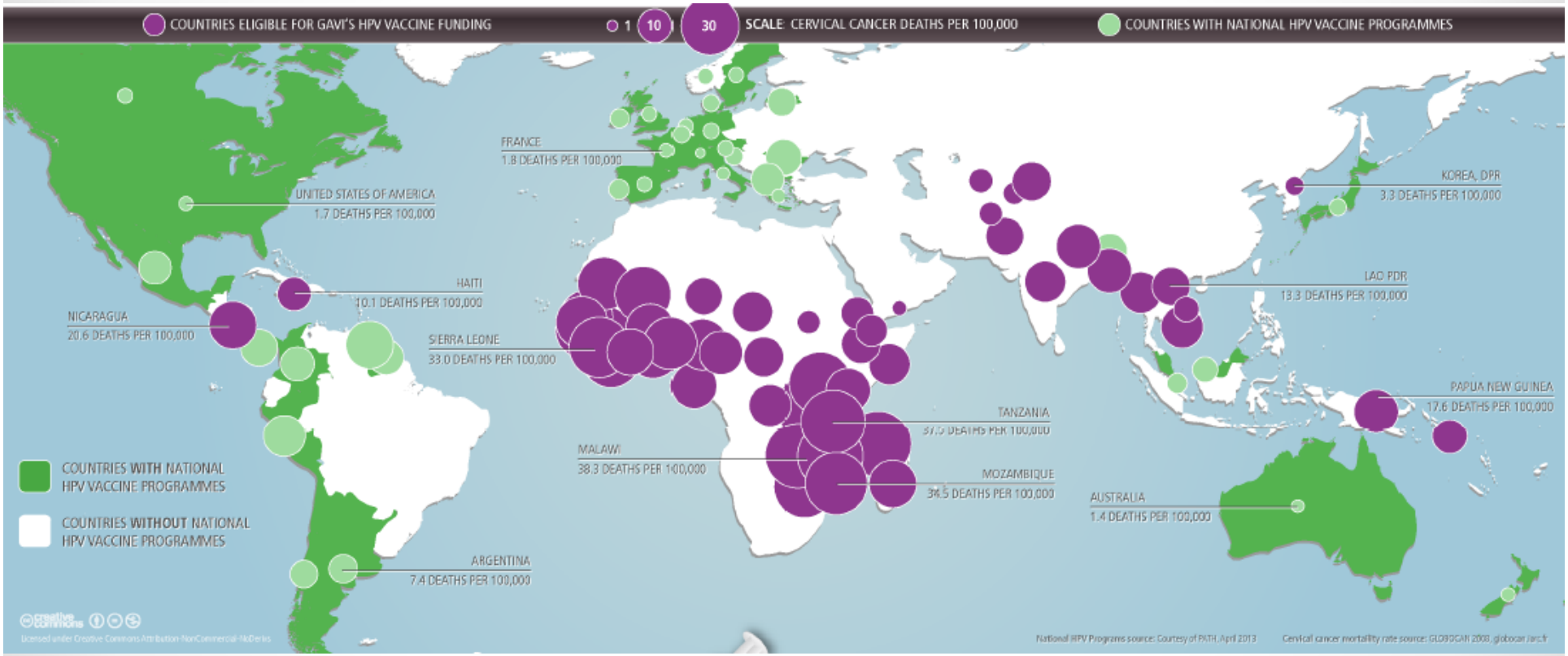
TABLE 3. Overall (4 clinical sites combined) clinical performance (sensitivity, specificity, PPV, NPV, and test positivity) for detection of CIN2+ and CIN3+

	CIN2+	CIN3+
No. cases	286	150
Positivity, %		
Vaginal *care*HPV	10.08	
Cervical *care*HPV	9.67	
VIA	16.55	
Papanicolaou test	13.08	
Sensitivity, % (95% CI)		
Vaginal *care*HPV	69.6 (63.9, 74.9)	71.3 (63.4, 78.4)
Cervical *care*HPV	81.5 (76.5, 85.8)	85.3 (78.6, 90.6)
VIA	59.8 (53.9, 65.5)	62.7 (54.4, 70.4)
Papanicolaou test	58.4 (52.4, 64.2)	62.7 (54.4, 70.4)
Specificity, % (95% CI)		
Vaginal *care*HPV	90.9 (90.5, 91.4)	90.5 (90.0, 90.9)
Cervical *care*HPV	91.6 (91.1, 92.0)	91.0 (90.6, 91.4)
VIA	84.2 (83.6, 84.7)	83.9 (83.3, 84.4)
Papanicolaou test	87.7 (87.2, 88.2)	87.4 (86.8, 87.9)
PPV, % (95% CI)		
Vaginal *care*HPV	11.7 (10.2, 13.3)	6.3 (5.2, 7.5)
Cervical *care*HPV	14.2 (12.6, 16.0)	7.8 (6.6, 9.2)
VIA	6.1 (5.2, 7.1)	3.4 (2.7, 4.1)
Papanicolaou test	7.5 (6.5, 8.7)	4.2 (3.4, 5.2)
NPV, % (95% CI)		
Vaginal *care*HPV	99.4 (99.3, 99.5)	99.7 (99.6, 99.8)
Cervical *care*HPV	99.7 (99.6, 99.7)	99.9 (99.9, 99.9)
VIA	99.2 (99.0, 99.3)	99.6 (99.5, 99.7)
Papanicolaou test	99.2 (99.0, 99.3)	99.6 (99.5, 99.7)

- Feasibility and performance study in India, Nicaragua and Uganda
- 16,591 women screened by all four methods
- Results: HPV DNA testing (using clinician collected or self-collected specimens) had better clinical performance than subjective tests (VIA & Pap)

Source: Jeronimo et al. IJGC (2014)

Global Alliance Vaccine Initiative (GAVI) for primary prevention via HPV Vaccination



- Achieved new price of US $4.50 per dose
- Since 2013, 20 countries have introduced HPV vaccines with GAVI support
- Goal: by 2020, vaccinate 30 million girls in over 40 countries

Source: GAVI alliance (2014) http://www.gavi.org/support/nvs/hpv/hpv-vaccine-infographic/

Thank You!

Questions? Comments?

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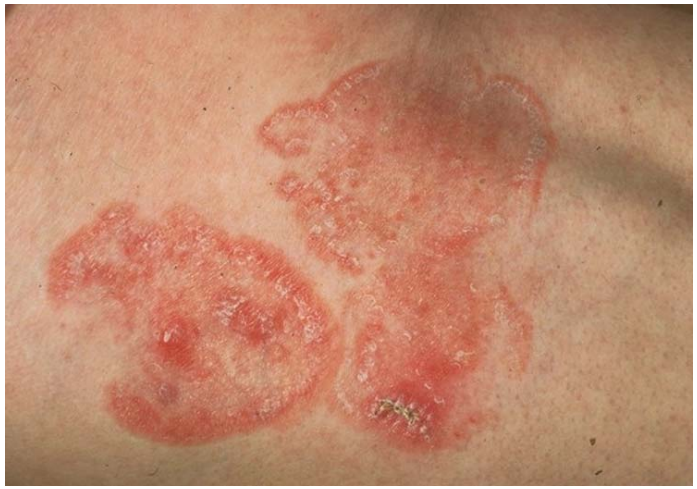
Epidemiology of mycosis fungoides



Elena Netchiporouk

PGY-3, Dermatology resident

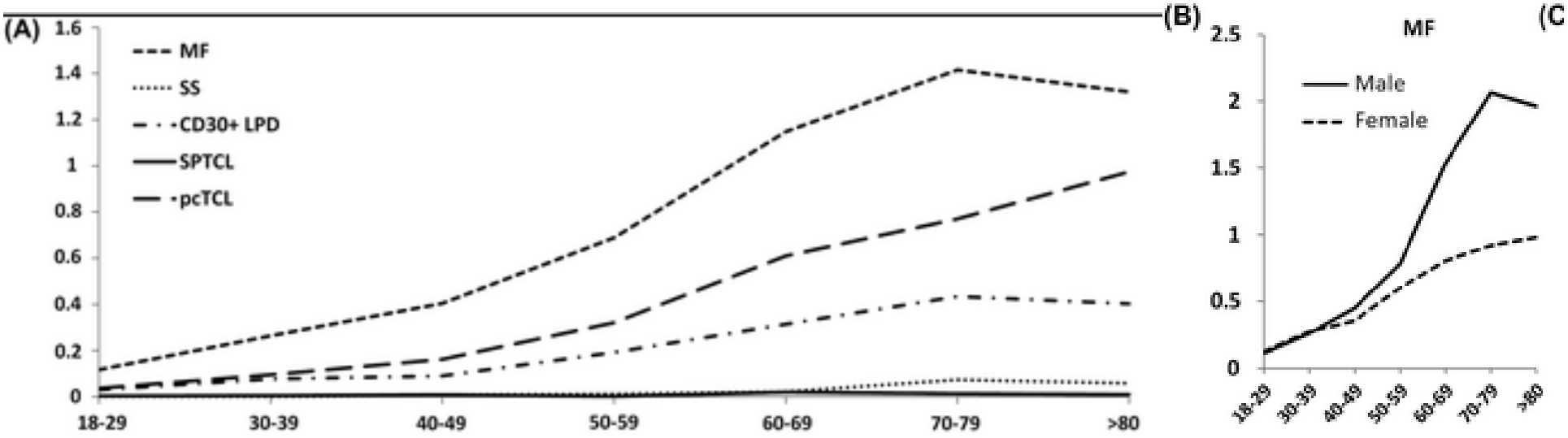
MSc Candidate, Experimental Medicine

Introduction Cutaneous Lymphoma

- Primary cutaneous lymphomas belong to the group of **extranodal non-Hodgkin lymphomas.**
- Skin is the **second** most commonly involved organ after the GI tract.
- In contrast to nodal lymphoma, ¾ of primary cutaneous lymphomas are **T-cell** derived and termed Cutaneous T cell Lymphomas (**CTCL**).
- The incidence of CTCL is currently ~ 10.2 per million persons.
- More common in men, African American race and advanced age.
- **Mycosis fungoides** (MF) and its leukemic variant, **Sézary Syndrome** (SS), comprise 2/3 of all CTCL.
- Clinical presentation is highly variable. Itching is often significant and profoundly affects the QOL. With disease progression, increased incidence of opportunistic infections, alopecia and involvement of other organs.
- Disease of skin homing memory cell – 50% of patients succumb to infectious complications.

Wilcox, R. A. (2014), Cutaneous T-cell lymphoma: 2014 Update on diagnosis, risk-stratification, and management. Am. J. Hematol., 89: 837–851. doi: 10.1002/ajh.23756
Megan Desai et al. (2015), Clinical characteristics, prognostic factors, and survival of 393 patients with mycosis fungoides and Sézary syndrome in the southeastern United States: A single-institution cohort. JAAD., 72, 276–285, doi:10.1016/j.jaad.2014.10.019

Age-adjusted incidence rates of CTCL by age-groups and gender

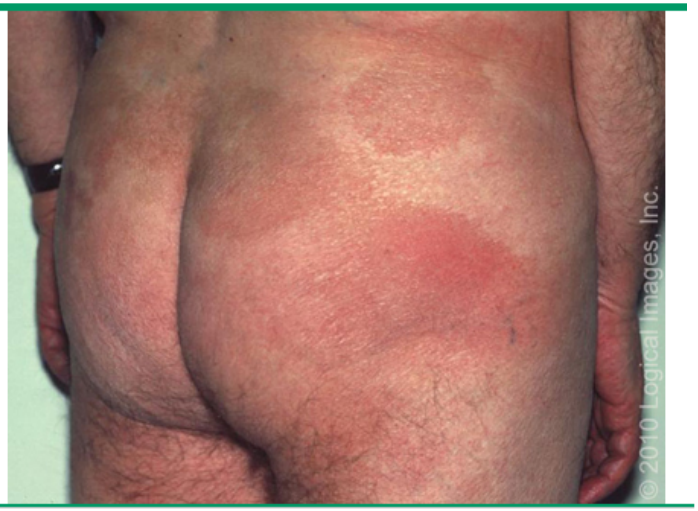


Hassaan Imam, et al. (2013), Incidence and survival patterns of cutaneous T-cell lymphomas in the United States. Leukemia & Lymphoma, 54, 4, 752-759, doi:10.3109/10428194.2012.729831

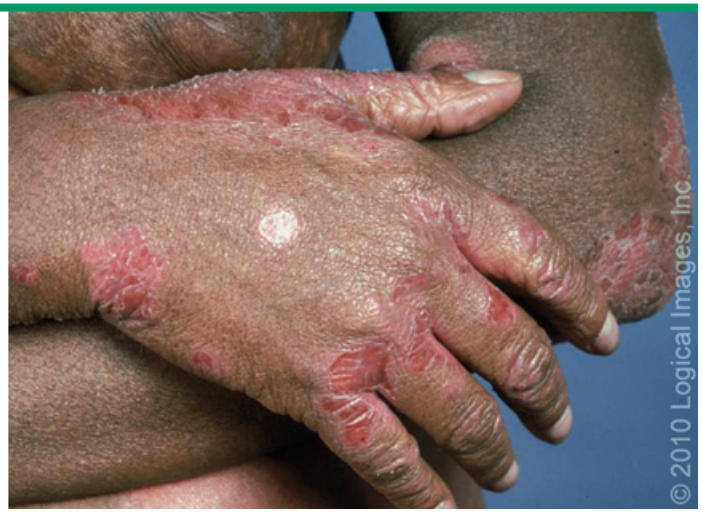
Staging

Early disease (T1-T2)

Mycosis fungoides - patch stage

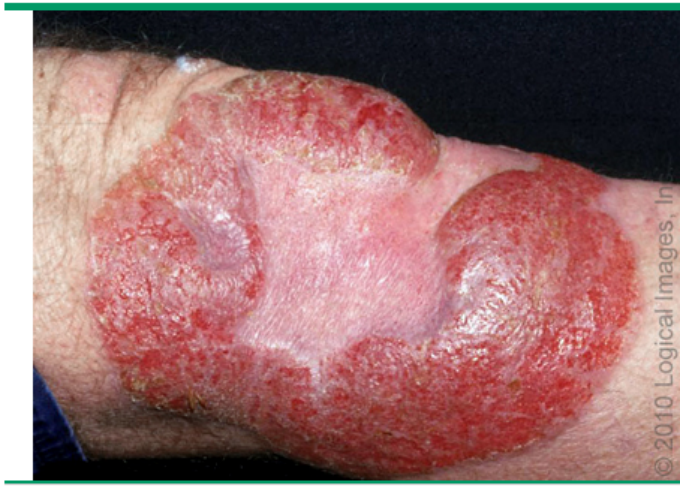


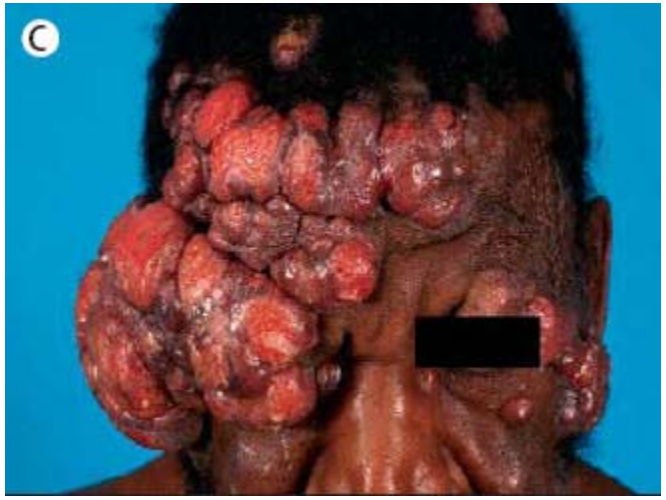
Mycosis fungoides - plaque stage



Advanced disease (T3)

Mycosis fungoides - tumor stage

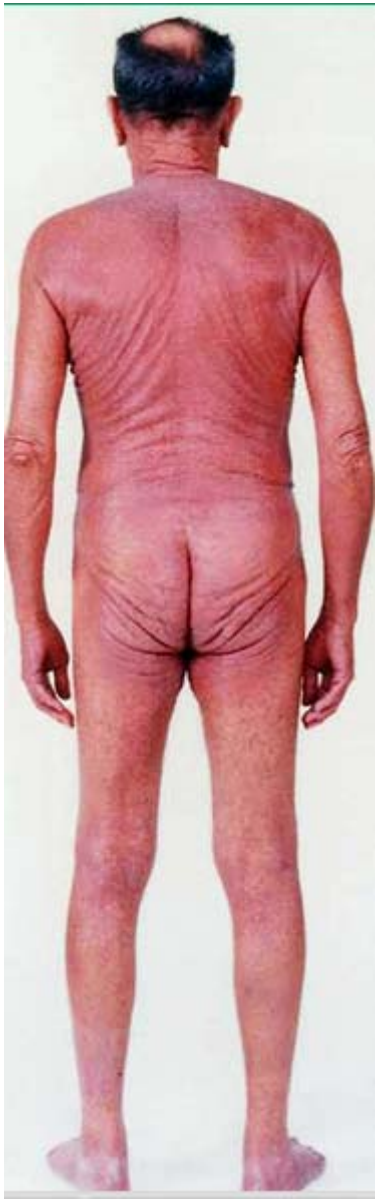




UptoDate and Lancet 2008; 371: 945–57

Advanced disease (T4)

Erythroderma in Sézary syndrome



Survival

Table 1. ISCL/EORTC Staging

Stage	TNMB classification				Median OS (years)	10-Year(6)		
	T	*N*	*M*	*B*		OS (%)	DSS (%)	RDP (%)
IA	1	0	0	0,1	35.5	88	95	12
IB	2	0	0	0,1	21.5	70	77	38
IIA	1,2	1	0	0,1	15.8	52	67	33
IIB	3	0–2	0	0,1	4.7	34	42	58
IIIA	4	0–2	0	0	4.7	37	45	62
IIIB	4	0–2	0	1	3.4	25	45	73
IVA1	1–4	0–2	0	2	3.8	18	20	83
IVA2	1–4	3	0	0–2	2.1	15	20	80
IVB	1–4	0–3	1	0–2	1.4	18 (5 year)	18 (5 year)	82 (5 year)

DSS: disease-specific survival; OS: overall survival; RDP: risk of disease progression.

Wilcox, R. A. (2014), Cutaneous T-cell lymphoma: 2014 Update on diagnosis, risk-stratification, and management. Am. J. Hematol., 89: 837–851. doi: 10.1002/ajh.23756

Fortunately,…

Table II. Differences in baseline characteristics at presentation across race.

CTCL characteristic	White (W)		Black (B)		Other (O)		*p*-Value*	
	Count	%	Count	%	Count	%	W vs. B	W vs. O
Age, years								
Mean	61		54		55		< 0.001	< 0.001
Median	63		53		54			
IQR	50–74		44–65		42–69			
18–59	858	43.29	198	63.26	90	62.07	< 0.001	< 0.001
60–79	843	42.53	97	30.99	40	27.59		
≥ 80	281	14.18	18	5.75	15	10.34		
Male sex	1183	59.69	143	45.69	84	57.93	< 0.001	0.677
Stage (MF/SS only)†								
IA	520	51.13	77	40.53	49	55.68	< 0.001	0.829
IB	86	8.46	20	10.53	10	11.36		
IIA	12	1.18	10	5.26	0	0.00		
IIB	60	5.90	9	4.74	5	5.68		
III	42	4.13	12	6.32	5	5.68		
IVA	14	1.38	10	5.26	1	1.14		
IVB	27	2.65	6	3.16	1	1.14		
Unknown	256	25.17	46	24.21	17	19.32		

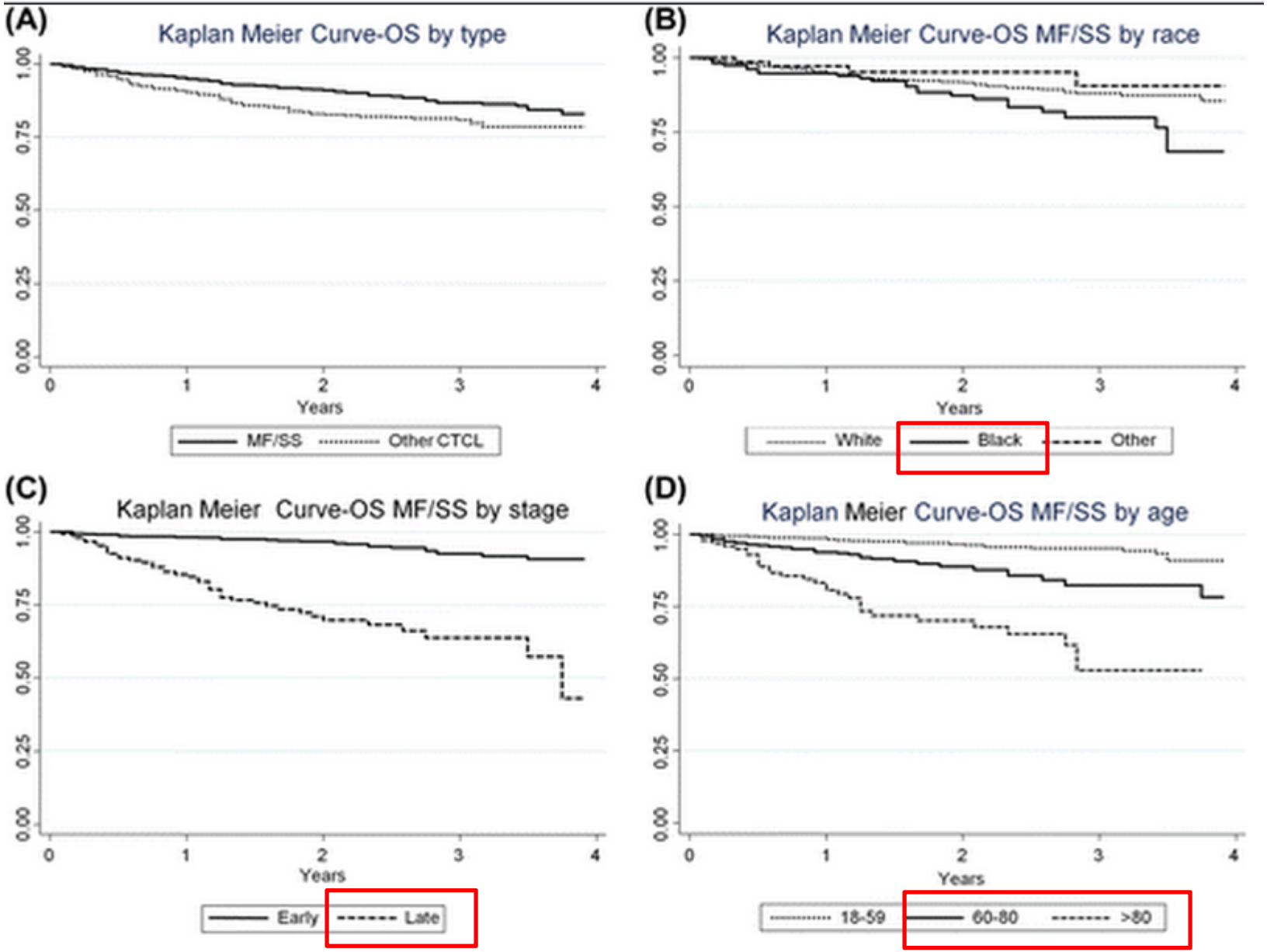
IQR, inter-quartile range; CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; SS, Sézary syndrome.

*Cases with unknown data were excluded when calculating the *p*-value.

Cases of MF/SS were staged according to the Mycosis Fungoides Cooperative Group staging system.

Hassaan Imam, et al. (2013), Incidence and survival patterns of cutaneous T-cell lymphomas in the United States. Leukemia & Lymphoma, 54, 4, 752-759, doi:10.3109/10428194.2012.729831

Markers of adverse prognosis



Why is it a disease of interest?

- 5 fold increase in incidence since 1972

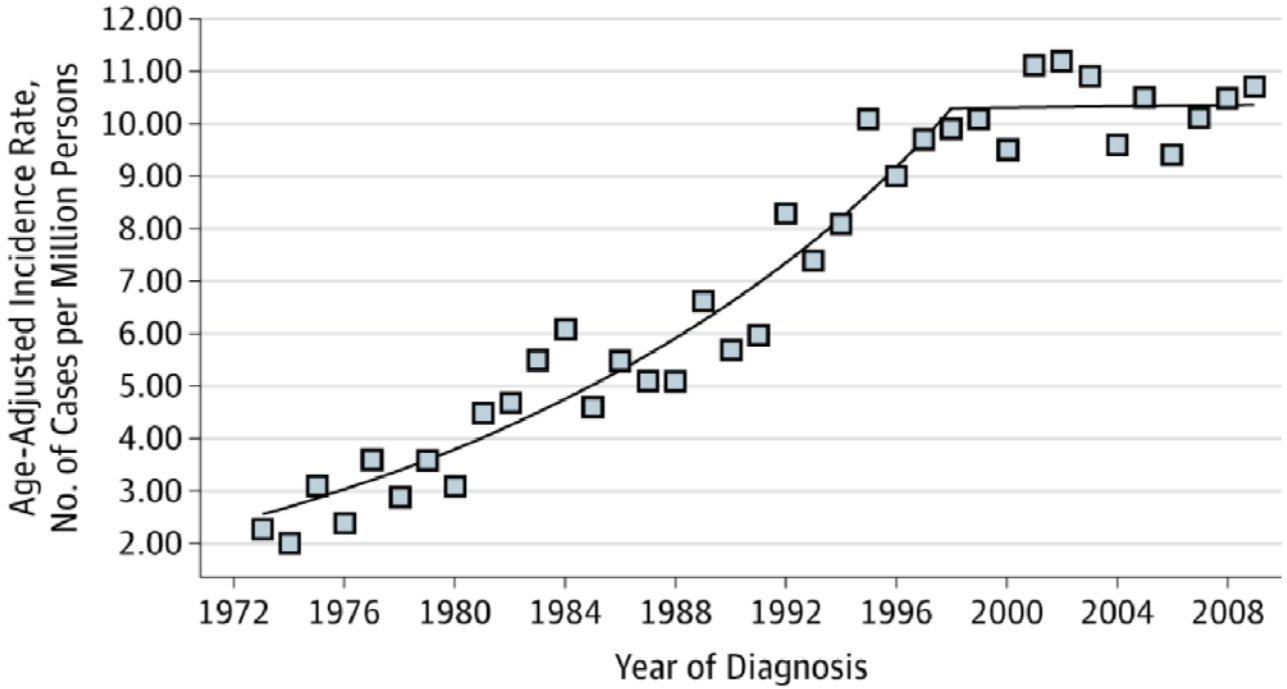
- Etiology unclear MF, but believed to result from **chronic antigenic stimulation that leads to uncontrolled clonal expansion and the accumulation of T helper memory cells** in the skin

- Most skin cancers are caused by external and occasionally preventable agents such as viruses (HPV, Merkel cell polyomavirus, HHV8); or environmental exposure (sun, arsenic, or radiation).

- Mycosis Fungoides has been reported to occur in married couples and/or in families and clusters in geographic areas, which argues for an **exogenous cause**.

From: **Changing Incidence Trends of Cutaneous T-Cell Lymphoma**

JAMA Dermatol. 2013;149(11):1295-1299. doi:10.1001/jamadermatol.2013.5526



Almost 5 fold increase in incidence since 1972 with plateauing in 2000. Trend is consistent across subgroups of race, sex, age, diagnosis, and location.

Overall CTCL Incidence Between 1973 and 2009 From 9 Surveillance, Epidemiology, and End Results Registries, Including Original Data Points and Incidence Trends

Geographic disease variation and clustering

- Population based US study
  - Highest incidence in San Francisco
- Texas study
  - Age and gender adjusted incidence 9-35 times higher in 3 communities within Houston metropolitan area compared to state statistics. Possible areas of oil refinery/radioactive pollution.
  - Cold spots in hot desert climate near El Paso, Texas. No cases in a population of ~150,000 individuals despite University Center and 13 Dermatologists.
- Pittsburg study
  - Urban hot spot with 3 fold increased incidence
- Clustering in Sweden
- Earlier age of onset in Middle East (thirties versus sixties)

Litvinov, I. V., Tetzlaff, M. T., Rahme, E., Habel, Y., Risser, D. R., Gangar, P., Jennings, M. A., Pehr, K., Prieto, V. G., Sasseville, D. and Duvic, M. (2015), Identification of geographic clustering and regions spared by cutaneous T-cell lymphoma in Texas using 2 distinct cancer registries. Cancer, 121: 1993–2003. doi: 10.1002/cncr.29301

Moreau JF, Buchanich JM, Geskin JZ, Akilov OE, Geskin LJ. Non-random geographic distribution of patients with cutaneous T-cell lymphoma in the Greater Pittsburgh Area. *Dermatol Online J*. 2014;**20**(7). pii: 13030/qt4nw7592w.

Gip L, Nilsson E. Clustering of mycosis fungoides in the County of Vasternorrland [in Swedish]. *Lakartidningen*. 1977;**74**:1174-1176.

Criscione V, Weinstock M. Incidence of Cutaneous T-Cell Lymphoma in the United States, 1973-2002. *Arch Dermatol.* 2007;143(7):854-859. doi:10.1001/archderm.143.7.854.

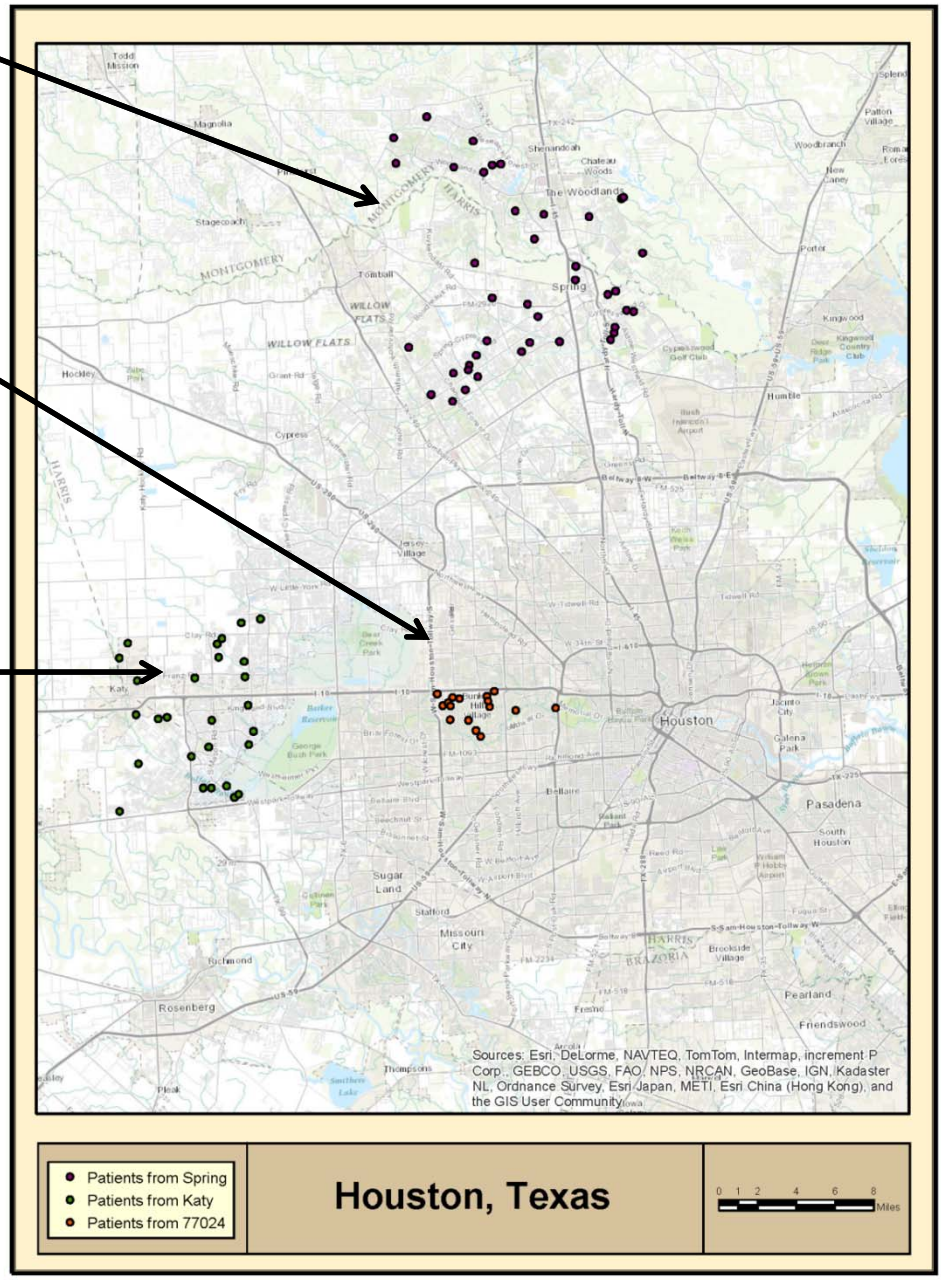
Spring, Texas:
40 Cases
(Population: 54,298)

Houston Memorial
Area (Zip Code 77024)
16 Cases:
(Population: 34,775)

Katy, Texas:
25 Cases
(Population: 14,102)

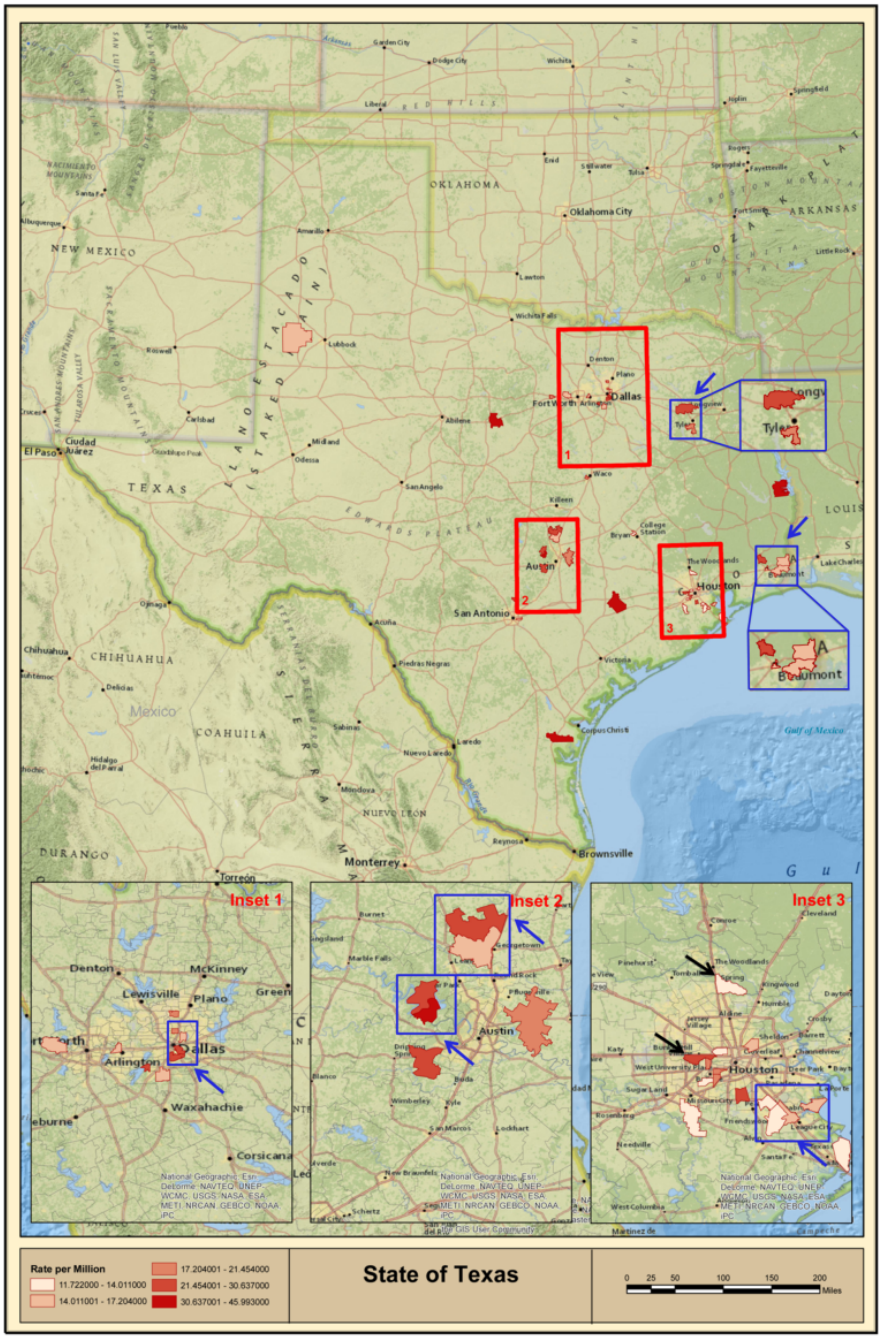
Based on statistics alone (~8-10 cases per million per year), if you have seen 1 case of CTCL from Katy, TX then you should not see another case for the next 10 years (!)

2000-2012 Cases of CTCL



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Texas Cancer Registry



TCR Database	Zip codes	Incidence rate (1996-2010) [95% CI]
Beaumont area	77630	14.42 [6.48, 32.11]
	77632	14.99 [6.23, 36.02]
	77651	20.02 [7.54, 53.35]
	77657	22.84 [10.26, 50.83]
	77701	17.14 [6.43, 45.67]
	77659	28.11 [7.03, 112.4]
Tyler/Lindale area	75703	17.75 [9.24. 34.11]
	75771	28.69 [13.68, 60.18]
Dallas	75115	15.39 [8.28, 28.60]
	75214	15.57 [7.79, 31.13]
	75215	27.96 [13.33, 58.65]
	75216	22.87 [14.22, 36.79]
	75225	19.41 [8.72, 43.21]
	75248	18.07 [9.40, 34.73]
	75249	23.64 [8.87, 63.99]
North Austin	78628	16.13 [7.25, 35.91]
	78633	24.12 [11.50, 50.59]
West Austin	78645	30.64 [11.50, 81.63]
	78734	34.88 [17.44, 69.75]
Central Houston	77008	13.53 [6.08, 30.11]
	77024	23.70 [13.46, 41.73]
	77056	20.38 [8.48, 48.98]
	77025	21.45 [10.73, 42.90]
	77096	14.01 [6.68, 29.39]
	77005	19.10 [9.11, 40.06]
Southeast Houston	77048	22.55 [9.39, 54.18]
	77089	12.53 [6.27, 25.05]
	77546	12.32 [6.16, 24.64]
	77598	15.61 [6.50, 37.50
	77586	16.76 [6.98, 40.27]
All Texas		5.77 [5.52; 6.03]

TCR Database	Zip codes	Population	Incidence rate (1996-2010) [95% CI]
Texas Coldspots	79936	101,500	0 [0, 2.52]
	79928	49,500	0 [0, 5.17]
	78596	57,500	0 [0, 4.45]
	78240	47,500	0 [0, 5.37]
	78046	54,000	0 [0, 4.73]
	77573	56,500	0 [0, 4.52]

Familial clustering

- Disease clustering in non related married couples
- 6 cases of familial MF in Israeli study (300 patients)

Hazen PG, Michel B. Hodgkin's disease and mycosis fungoides in a married couple. *Dermatologica*. 1977;**154**:257-260.
Hodak E, Klein T, Gabay B, et al. Familial mycosis fungoides: report of 6 kindreds and a study of the HLA system. *J Am Acad Dermatol*. 2005;**52**(3 pt 1):393-402.
Schmidt AN[1], Robbins JB, Greer JP, Zic JA. Conjugal transformed mycosis fungoides: the unknown role of viral infection and environmental exposures in the development of cutaneous T-cell lymphoma. *J Am Acad Dermatol*. 2006 May;54(5 Suppl):S202-5.
Dupin M[1], Darie H, Jumbou O, Veran Y, Gros P, Dreno B, Dormont D, Millet P. [Conjugal mycosis fungoides]. Ann Dermatol Venereol. 1995;122(9):595-8.

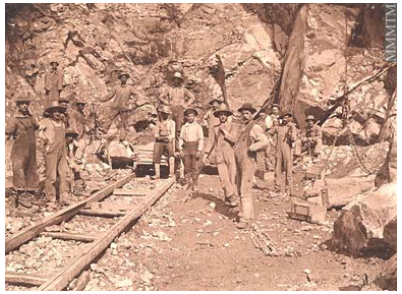
Possible explanation

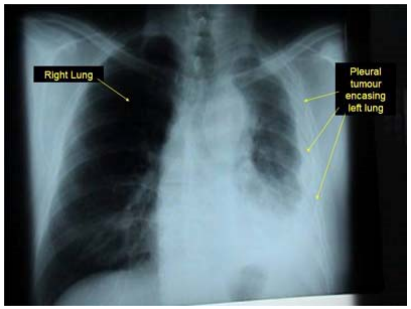
- Etiologic factor(s) remains to be discovered, many hypotheses
- Weak evidence for infectious agents (*Staphylococcus aureus*, tinea, HTLV-1, CMV, EBV)
- Drugs – large case series suggesting association with HCTZ. 28.8% of pts experiences CR after drug discontinuation.
- Environmental and occupational exposures:
  - Multicenter case control study suggesting increased risk with exposure to aromatic halogenated hydrocarbons (OR 4.6 in men) and pesticides specifically (OR 6.8 for men and 2.4 for women).
- InterLymph study pooling results from 14 case-control studies from Europe, North America and Australia (324 MF/SS cases and 17217 controls) found positive associations
  - Obesity (OR 1.57, 1.03 to 2.40)
  - Cigarette smoking for 40 years or more (OR 1.55, 1.04 to 2.31)
  - Eczema (OR 2.38, 1.73 to 3.29)
  - Family history of multiple myeloma (OR 8.49, 3.31 to 21.80)
  - Occupations such as farmers (OR 2.37, 1.14 to 4.92), painters (OR 3.71, 1.94 to 7.07), woodworkers (OR 2.20, 1.18 to 4.08), and general carpenters (OR 4.07, 1.54 to 10.75).
  - Reduced risk associated with physical activity (OR 0.46, 0.22 to 0.97).

Morales-Suárez-Varela MM et al. Occupational exposures and mycosis fungoides. A European multicentre case-control study (Europe). Cancer Causes Control. 2005 Dec;16(10):1253-9.
Briseis Aschebrook-Kilfoy et al. Medical History, Lifestyle, Family History, and Occupational Risk Factors for Mycosis Fungoides and Sézary Syndrome: The InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr (2014)2014 (48): 98-105.doi:10.1093/jncimonographs/lgu008
Richard R. Jahan-Tigh et al. Hydrochlorothiazide and cutaneous T cell lymphoma, Prospective analysis and case series. Cancer Volume 119, Issue 4, pages 825–831, 15 February 2013, DOI: 10.1002/cncr.27740

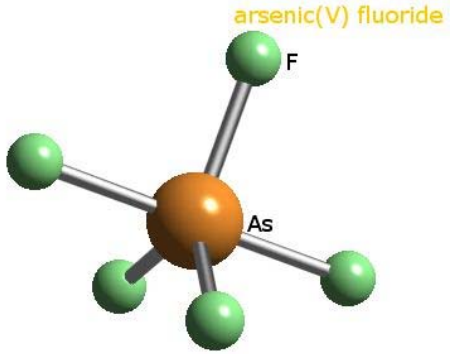
Historic note…

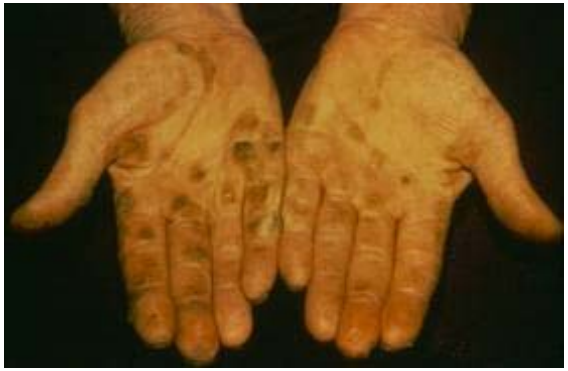
- After studying the prevalence of **mesotheliomas** in asbestos mines of South Africa and in Quebec, Canada, asbestos was established as a critical factor responsible for this deadly disease.

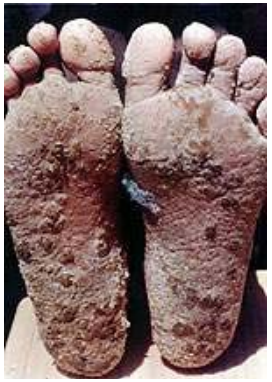




- A study of a small arsenic mining town in Prussia in 1898, where chronic poisoning took place through the use of contaminated drinking water helped establish the link between arsenic and the occurrence of **arsenical keratoses** and **skin squamous cell carcinomas**.







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4. Briseis Aschebrook-Kilfoy et al. Medical History, Lifestyle, Family History, and Occupational Risk Factors for Mycosis Fungoides and Sézary Syndrome: The InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr (2014)2014 (48): 98-105.doi:10.1093/jncimonographs/lgu008
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14. UptoDate
15. Lancet 2008; 371: 945–57

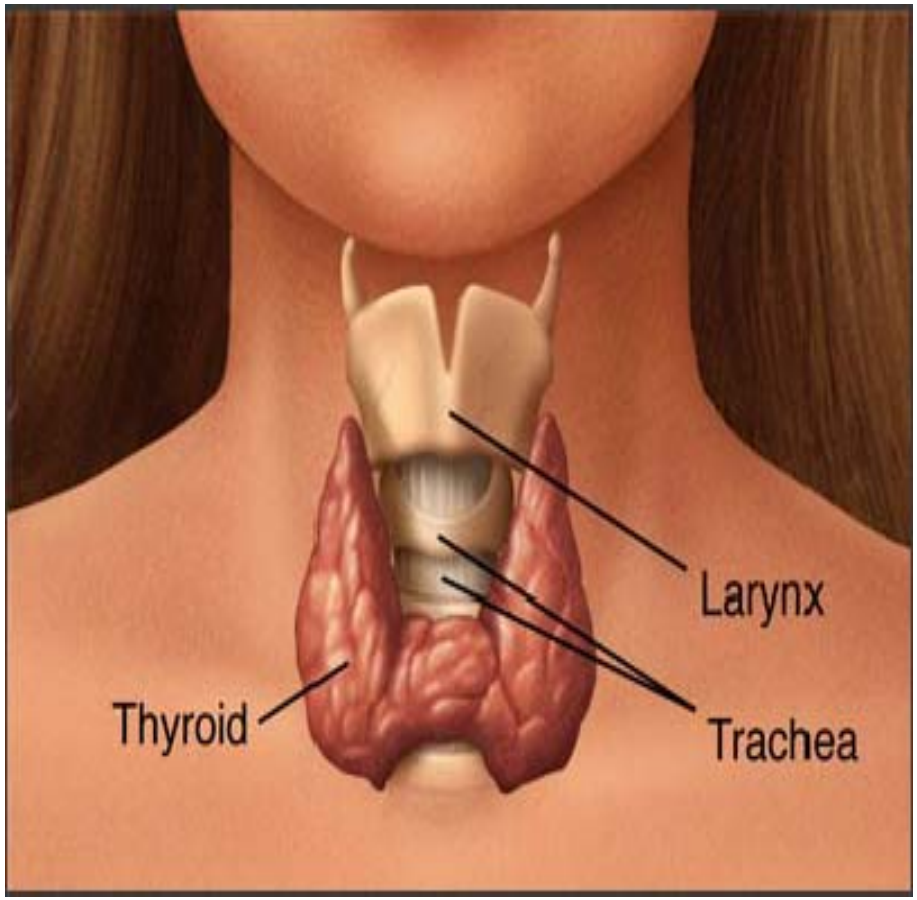
Epidemiology
of
Thyroid Cancer

Muhammad Mujammami, MD

Cancer Epidemiology and Prevention
Course EPIB 671

June 17, 2015

Thyroid Gland



- Derived from endodermal tissue at base of tongue

- Named after the thyroid cartilage **(Greek: Shield)**
- 1st gland to develop – **day 24**

Wharton 1656:

"purpose is to… beautify the neck…particularly in females to whom for this reason a larger gland.."

Solitary Nodular Thyroid Disease

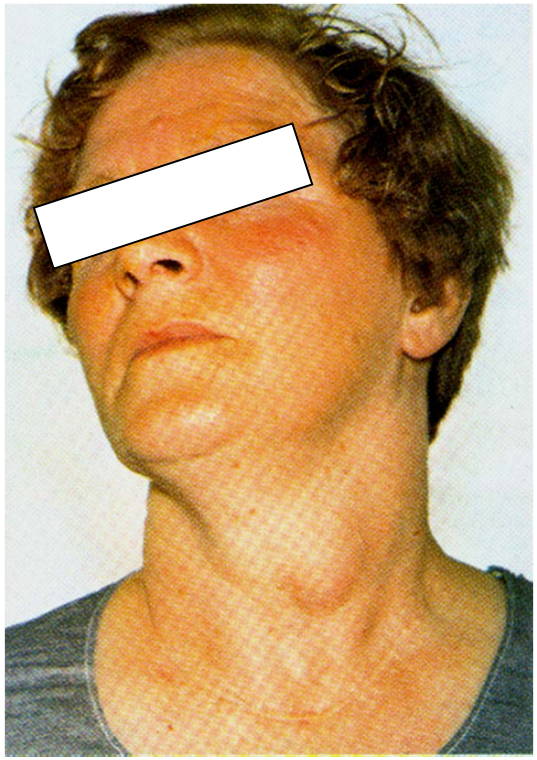
Neoplastic Lesions

Adenoma

- Macrofollicular
- Microfollicular
- Atypical

Carcinoma

- Papillary (80%)
- Follicular (10%)
- Medullary (4%)
- Hurthle cell (3%)
- Anaplastic (<2%)
- Lymphoma (<1%)
- Metastases (<1%)



Hyperplastic Lesions

Colloid Nodules

- Unrecognized MNG

Hypercellular

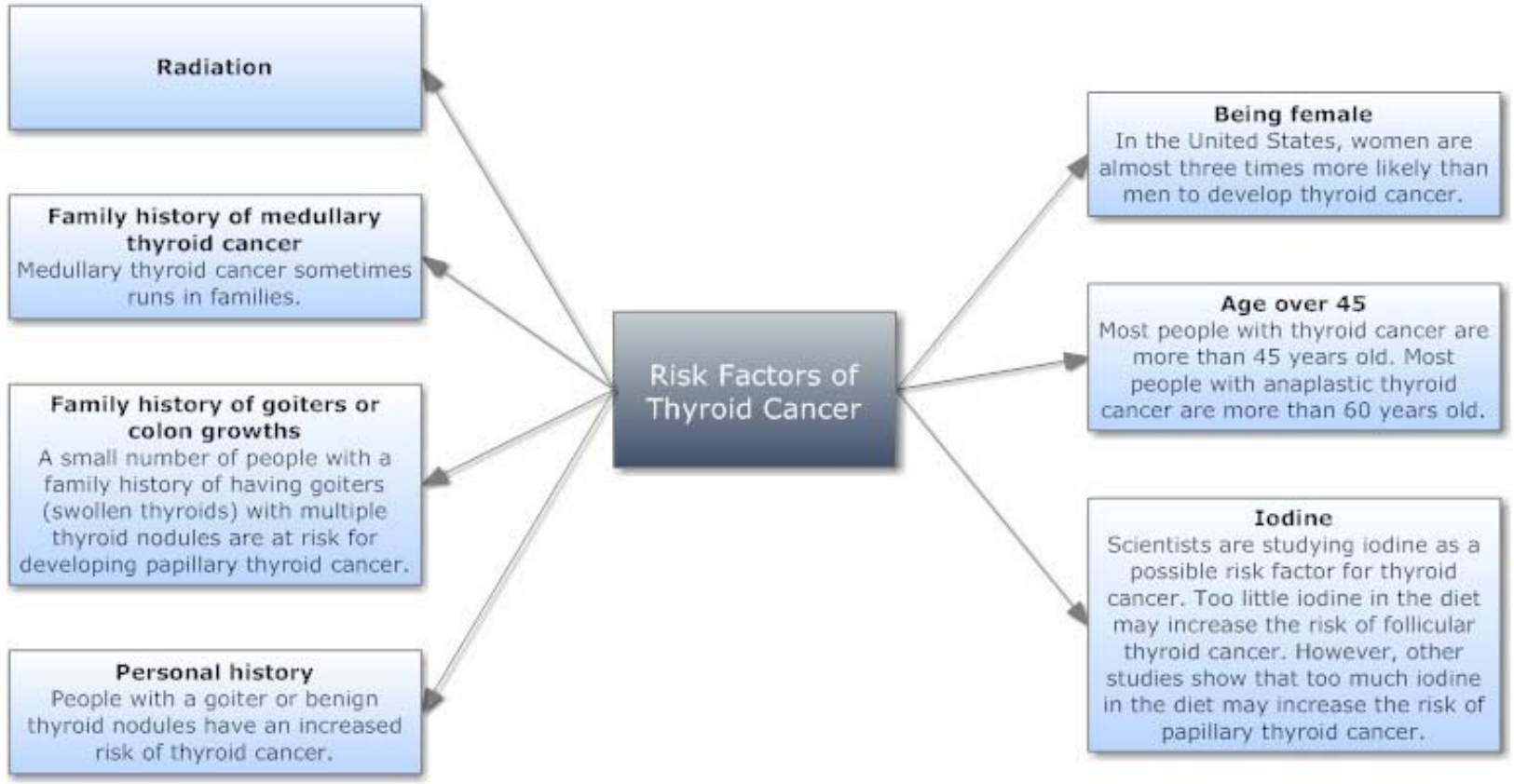
- Adenomatoid nodules
- Hyperplastic nodules

Cystic Lesions

Simple cysts
Hemorrhagic tumors

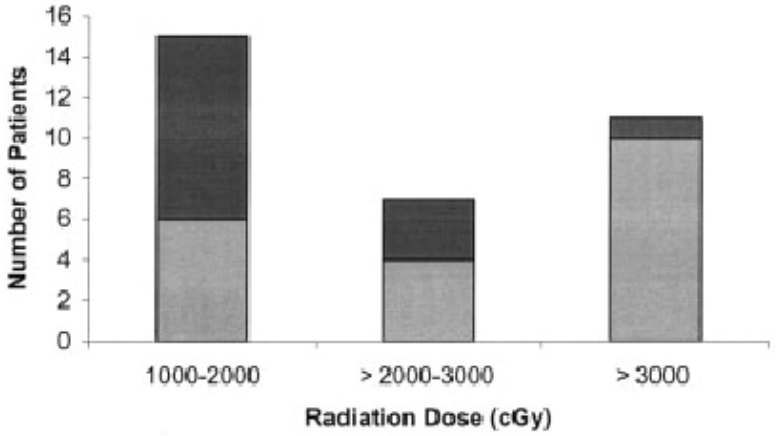
- ***Other Lesions***
- Thyroiditis
- Granulomatous disorders
- Infiltrative diseases
- Metastases
- Hyalinizing trabecular tumors

Risk Factors



Source: National Cancer Institute, U.S. National Institutes of Health. www.cancer.gov

Head and Neck Irradiation



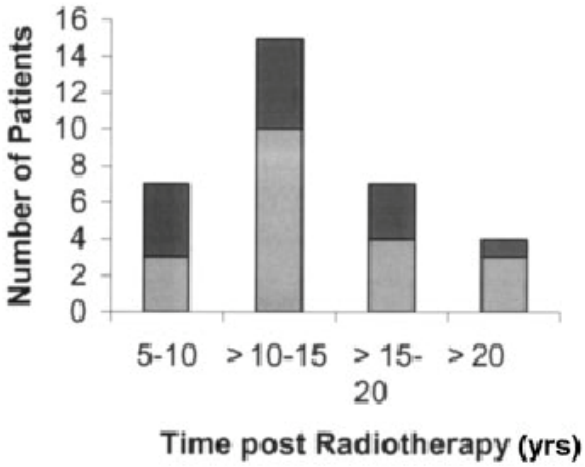


FIGURE 3. Distribution of thyroid neoplasms according to time since radiation. Light grey: benign; dark grey: malignant.

Suchitra a. et al. *Memorial Sloan Kettering Cancer Center, New York.* Cancer.2003;97:2397-2403.

The Chernobyl 1986 vs. the Fukushima, 2011 experience

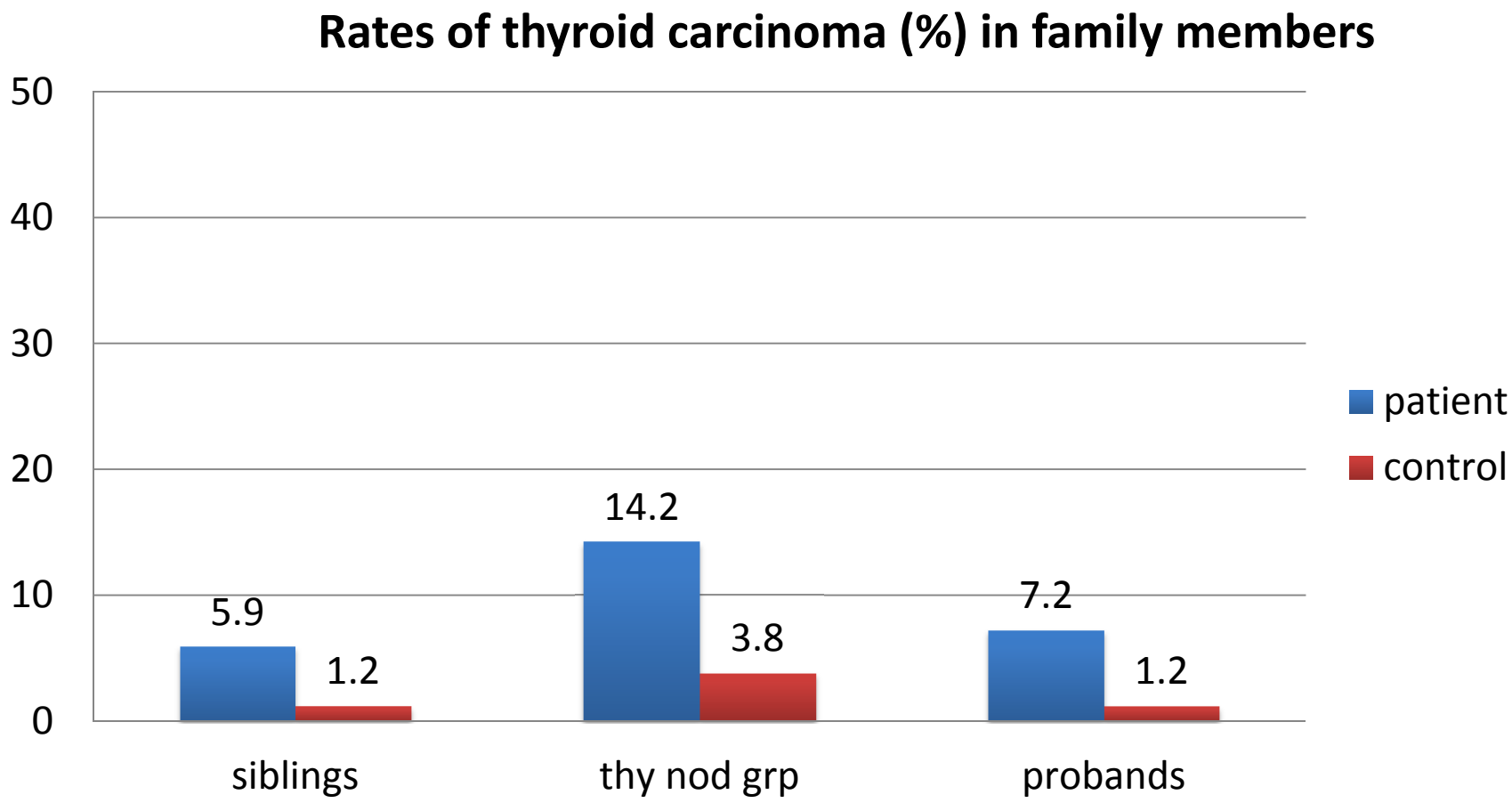
- Impact:
  - Over 40 million Currie of I-131 released into the atmosphere.
  - 5 million exposed (over 1 million children)
  - 5,000 cases of thyroid cancer reported among those exposed.
- Minimal latency to tumor development is 4 yrs.
- Younger children most susceptible.
- Most are PTC with a solid variant histology.
- Molecular mechanism involves predominantly intrachromosomal rearrangement more than point mutation in radiation-induced PTC.
- The nuclear architecture predisposes the thyroid follicular cells to intrachromosomal fusions.
- Decrease action of ATM and other DNA repair proteins may facilitate rearrangements and may confer genetic predisposition to radiation-induced cancer.
- ATM kinase inhibitor increased rate of RET/PTC rearrangement induction.

- 14megaCurie was released into the environment (as compared to 50megaCurie at Chernobyl) and the exposure was volatile and not particulate.

- Calculated cancer risk is estimated at <1% for all cancers and <5% for thyroid cancers for individuals exposed to >5 rem within 80 km limit.

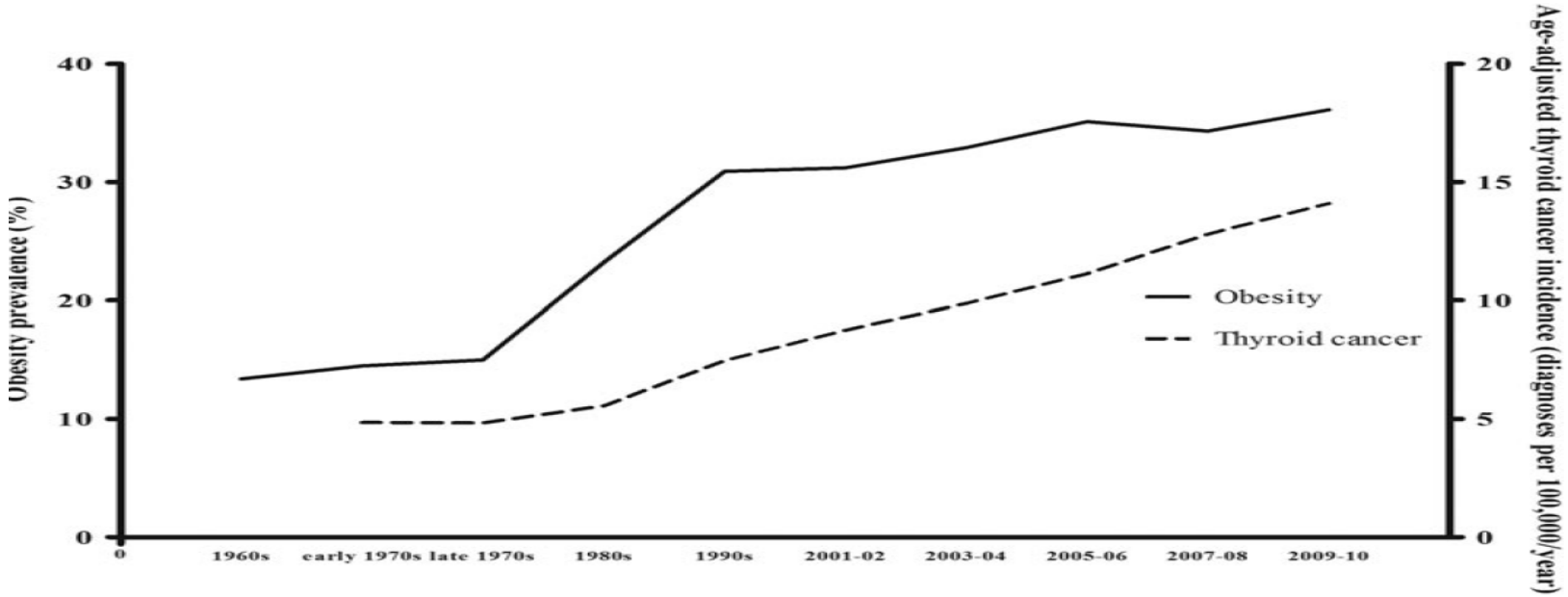
Yuri

Ultrasonographic screening for thyroid cancer in siblings of patients with .apparently sporadic papillary carcinoma



.Rosario PW, Mineiro Filho AF, Prates BS, Silva LC, Lacerda RX, Calsolari MR
.Thyroid. 2012 Aug;22(8):805-8. Epub 2012 Jul 12

Obesity and Thyroid Cancer: A Clinical Update



Theodora Pappa and Maria Alevizaki THYROID Volume 24, Number 2, 2014, 190-199

Mijovic´ T, How J, Pakdaman M, Rochon L, Gologan O, Hier MP, Black MJ, Young J, Tamilia M, Payne RJ 2009 .Body mass index in the evaluation of thyroid cancer risk. Thyroid 19:467–472

Poster 84

Clinical Poster Thursday Thyroid Cancer

OBESITY AS A RISK FACTOR FOR THYROID CANCER

J. HAN1, S. BAE2, H. KIM2, G. GONG3, S. HONG4, T. KIM1, Y. SHONG1, W. KIM1 1Internal Medicine, Asan Medical Center, Seoul, Republic of Korea; 2Health Screening & Promotion Center, Asan Medical Center, Seoul, Republic of Korea; 3Pathology, Asan Medical Center, Seoul, Republic of Korea; 4Surgery, Asan Medical Center, Seoul, Republic of Korea

Obesity has been associated with increased incidence of cancers of the esophagus, colon, kidney, breast, melanoma, rectum, and gall blad- der. There have been few studies on the relationship between obesity and thyroid cancer. We conducted this study to evaluate .the associ- ation between obesity and incidence of thyroid cancer

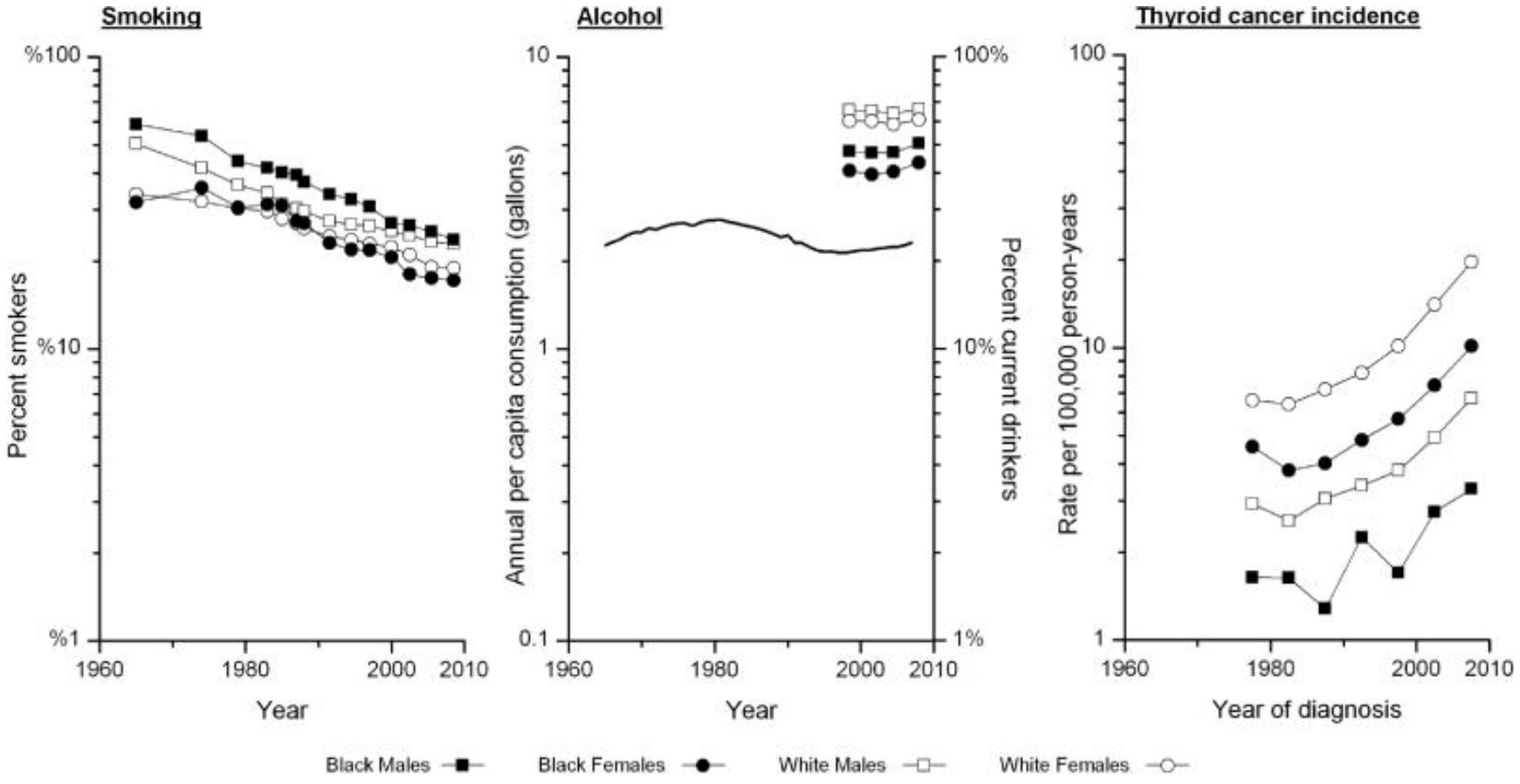
We recruited data of 16,481 (8,741 men and 7,740 women) subjects who were free of prior or family history of thyroid disease (thyroid dysfunction, nodule, cancer, and surgery), and who underwent thy- roid ultrasonography from 2007 to 2008 in the Health Screening and Promotion Center of Asan Medical Center, Seoul, Korea. We retro- spectively reviewed the medical records and analyzed risk .factors predicting presence of thyroid cancer separately in men and women

Of the 16,481 subjects, thyroid cancers were diagnosed in 227 (100 men and 127 women) patients, which were confirmed by surgery. In men, there was no significant association between the body–mass index (BMI) and incidence of thyroid cancer. In women, thyroid cancerincidence was significantly associated with BMI (per 5 kg/m2 increase) (OR = 1.63, 95% CI: 1.20–2.18, p = 0.001), after adjustment OR 0.29,)of age, smoking, TSH values. We also found that thyroid cancer was negatively associated with tobacco smoking in women .(CI: 0.07–0.78, p = 0.036 95%

Obesity was an independent risk factor for thyroid cancer in women when evaluated in a routine health check-up. Not only in- creased detection but also true increase of incidence caused by obesity might be responsible for the increasing incidence of thyroid cancer over .recent decades

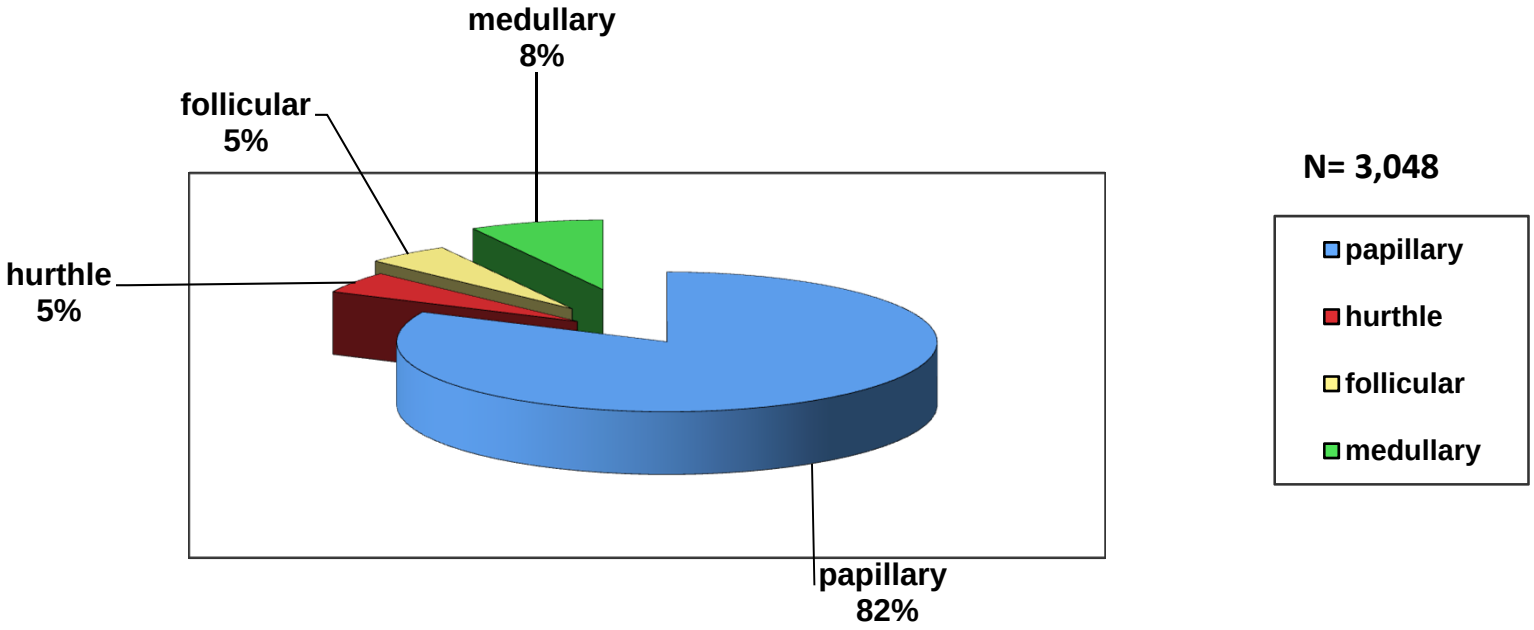
Michael Tamilia, 22/03/2014

Cigarette smoking, alcohol intake, and thyroid cancer risk: a .pooled analysis of five prospective studies in the United States



Kitahara CM, Linet MS, Beane Freeman LE, Check DP, Church TR, Park Y, Purdue MP, Schairer C, Berrington deGA 2012 Cigarette smoking, alcohol intake, and thyroid cancer risk: a pooled analysis of five prospective studies in the United States. Cancer Causes Control 23:1615–1624.

Differentiated thyroid cancer managed at Mayo Clinic 1940-2000. Histotype distribution.

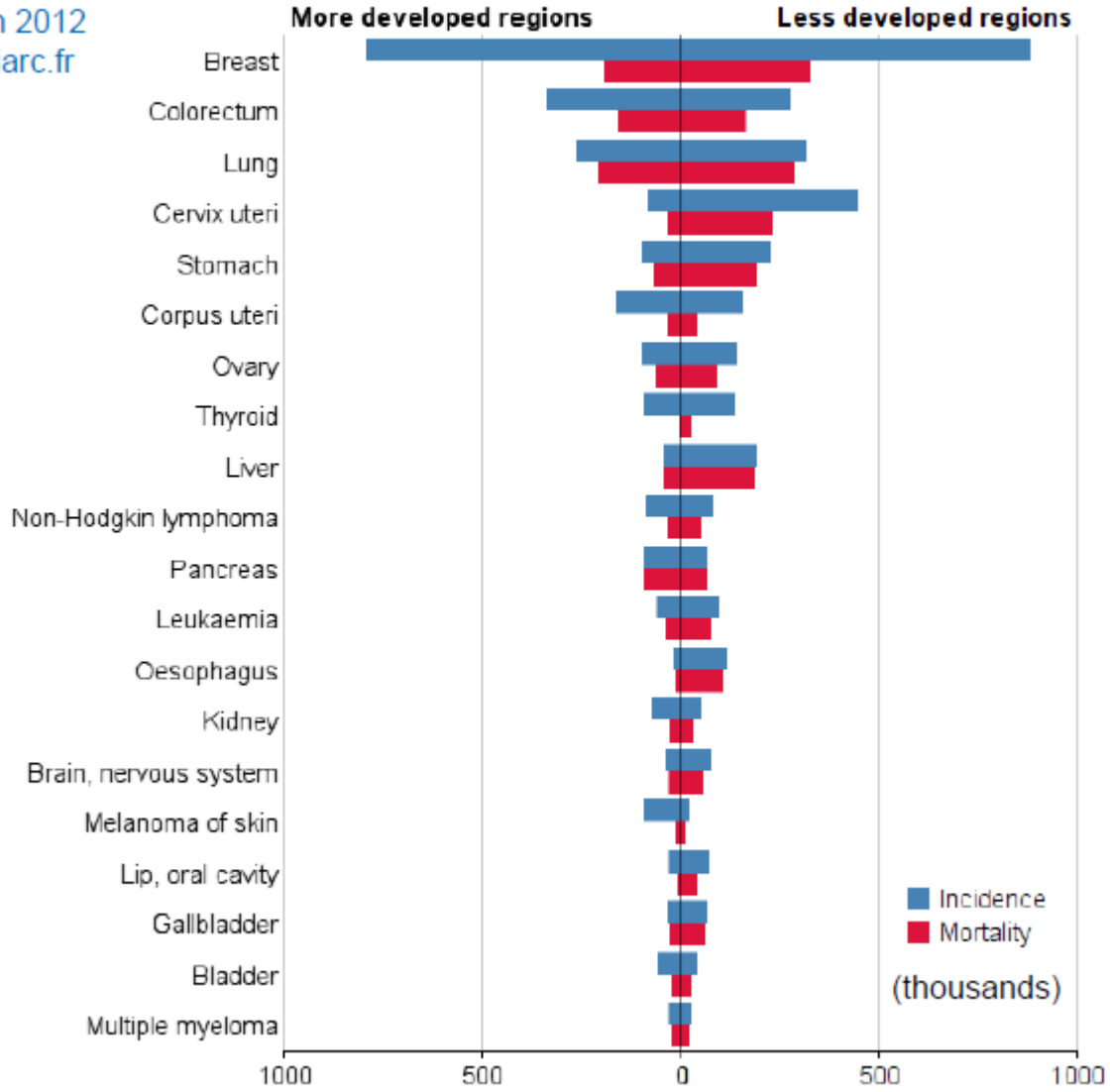


LiVolsi VA, Asa SL 1994 The demise of follicular carcinoma of the thyroid gland. Thyroid 4:233–236.

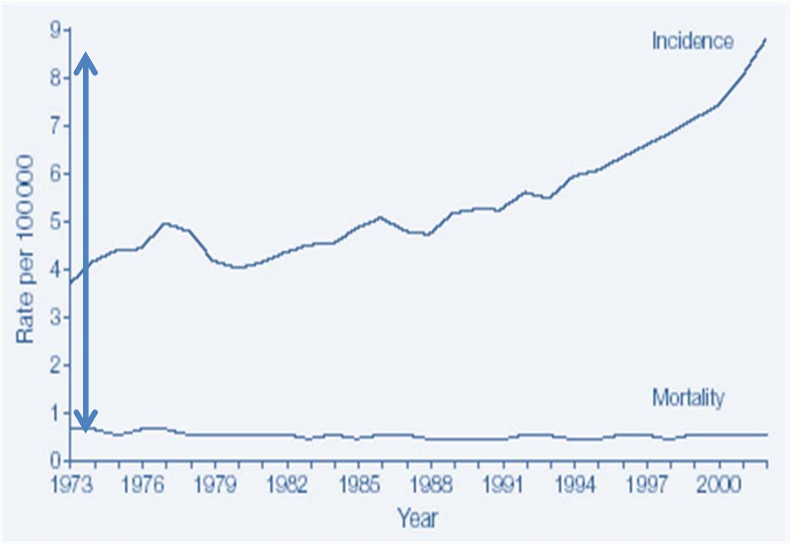
Estimated numbers of new cancer cases and deaths in 2012

IARC: Globocan 2012
http://globocan.iarc.fr

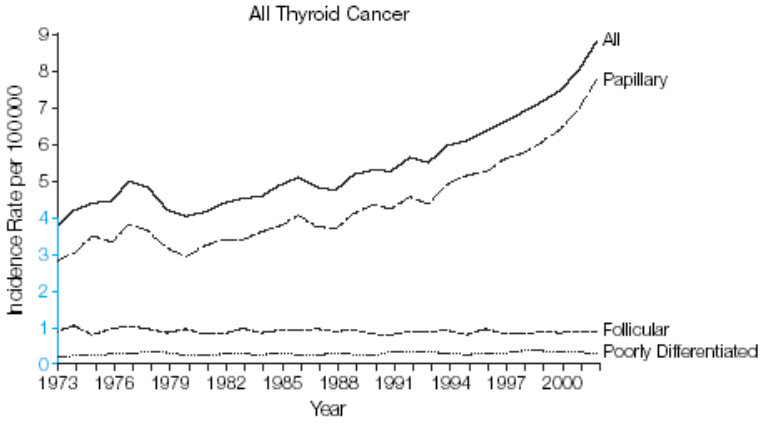
Female

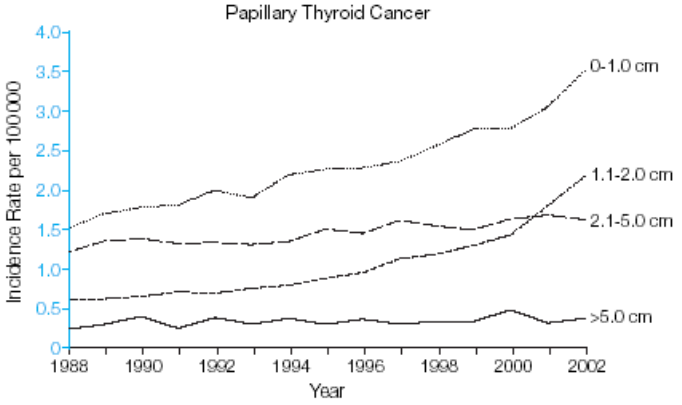


Thyroid cancer incidence and mortality



Thyroid Cancer Incidence and Mortality, 1973-2002





Davies L and Welch HG JAMA. 2006; 295(18): 2164-2167.

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The hypothesis of cancer overdiagnosis can be strongly (supported when 3 things are observed in a population: 1 incidence rates are rising, 2) mortality from the disease stays stable, and 3) the proportion of cancers diagnosed in the early stages increases.

Michael Tamilia, 13/10/2013

Geographic Differences in Changes in Thyroid Cancer Incidence Rates

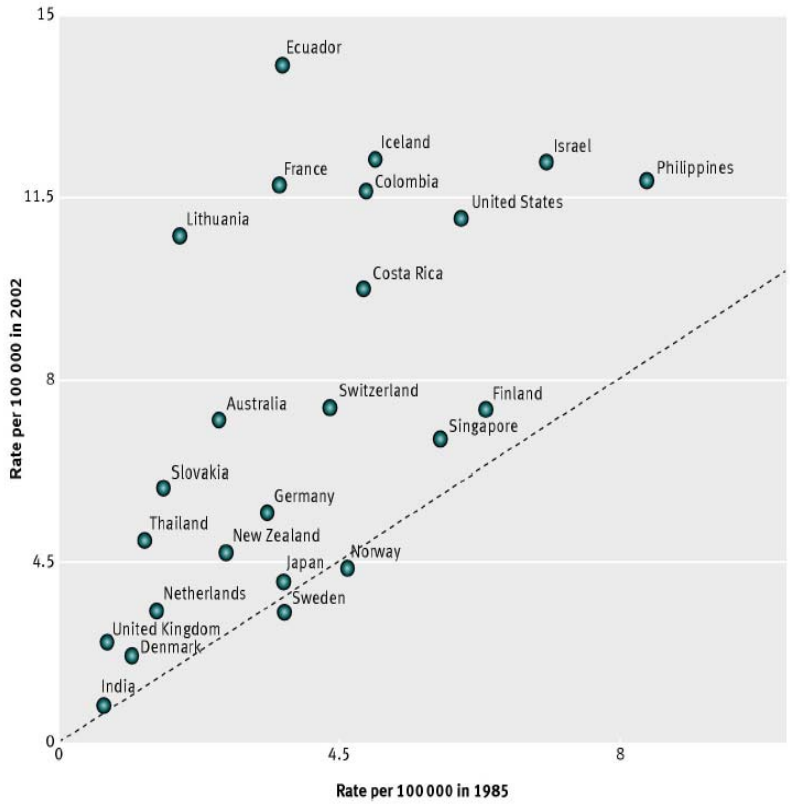

Fig 1 Incidence of thyroid cancer by country. Countries above the dotted line experienced a rise in incidence between 1985 and 2002

8

9

10

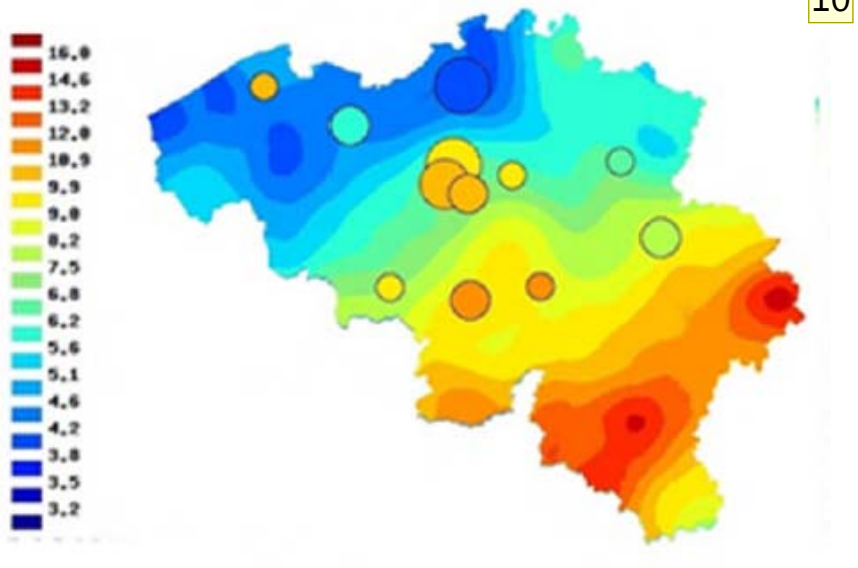

Figure 2. A, Map of Belgium and its regions. B, The incidence of thyroid cancer in females being higher in the southern region Wallonia as compared to the northern region Flanders. A lower aggregate incidence in the northern part (Flanders; 6 million inhabitants; 4.1/100 000 person years) compared to the southern part of the country (Wallonia; 4 million inhabitants; 8.3/100 000 person years).

8

.Thyroid cancer is the most common endocrine malignancy
Worldwide, its incidence has increased substantially over the
past 50 years. The Cancer Incidence in Five Continents report showed that the age standardised incidence of thyroid cancer in women
rose from 1.5 cases/100 000 population in 1953 to7.5 cases/100 000 in 2002, with a similar relative increase in men (fig 1⇓).2 Behind
,these averages hide important and surprising differences between and within countries. In the US
,the incidence of thyroid cancer has tripled in the past 30 years
increasing from 3.6 cases/100 000 in 1973 to 11.6 cases/100
.in 2009,3 making it one of the fastest growing diagnoses 000
By contrast, in Sweden, Japan, and China, the increase in
.incidence has been minimal

Michael Tamilia, 13/10/2013

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Geographic Variation in
care is a problem because it implies that care is being administered
differently in different areas, which means
,some people are probably getting too much healthcare
whereas others might not be getting enough. In the 40
years since Wennberg published his first study, researchers
at Dartmouth have cataloged wide variations in healthcare
spending (8), procedure rates (9), drug prescription
rates (10), and even average numbers of diagnoses per
person across the United States (11), to name just a few
.examples

Michael Tamilia, 13/10/2013

10

Regional Variation in Thyroid Cancer Incidence in
Belgium Is Associated With Variation in Thyroid
Imaging and Thyroid Disease Management

,Annick Van den Bruel,* Julie Francart,* Cecile Dubois, Marielle Adam
Joan Vlayen, Harlinde De Schutter, Sabine Stordeur, and Brigitte Decallonne
Division of Endocrinology (A.V.d.B.), Department of Internal Medicine, General Hospital Sint Jan, 8000
,Bruges, Belgium; Research Department (J.F., M.A., H.D.S.), Belgian Cancer Registry, 1210 Brussels
Belgium; Belgian Health Care Knowledge Centre (C.D., J.V., S.S.), 1000 Brussels, Belgium; and Division
of Endocrinology (B.D.), Department of Internal Medicine, University Hospitals Leuven, 3000 Leuven, Belgium

Context: Increased thyroid cancer incidence is at least partially attributed to increased detection
.and shows considerable regional variation
Objective: We investigated whether regional variation in cancer incidence was associated with

.variations in thyroid disease management

Design: We conducted a retrospective population-based cohort study that involved linking data from the Belgian Health Insurance database and the Belgian Cancer Registry to compare thyroidrelated .procedures between regions with high and low cancer incidence

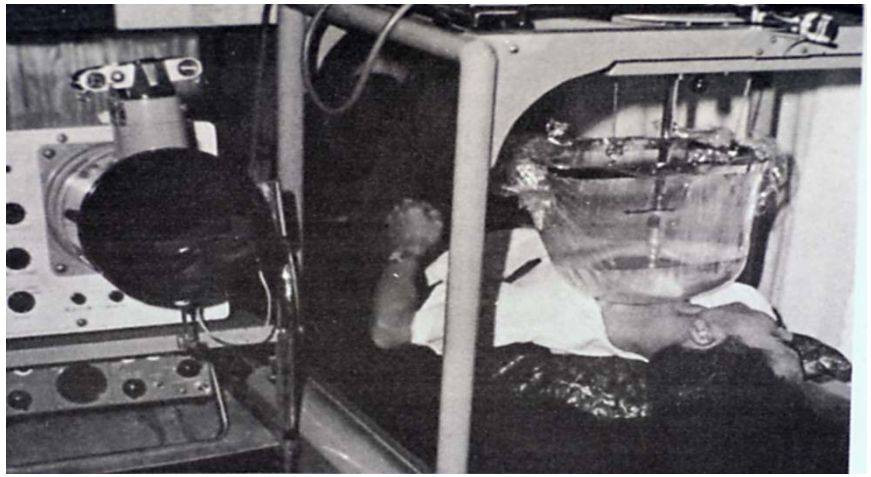
Main Outcome Measures: Primary outcome measures were rates of TSH testing, imaging, fineneedle aspiration cytology (FNAC), and thyroid surgery. Secondary study outcomes were proportions of subjects with thyrotoxicosis and nodular disease treated with surgery, of subjects treated with surgery preceded by FNAC or with synchronous lymph node dissection, and of thyroid cancer .diagnosis after surgery

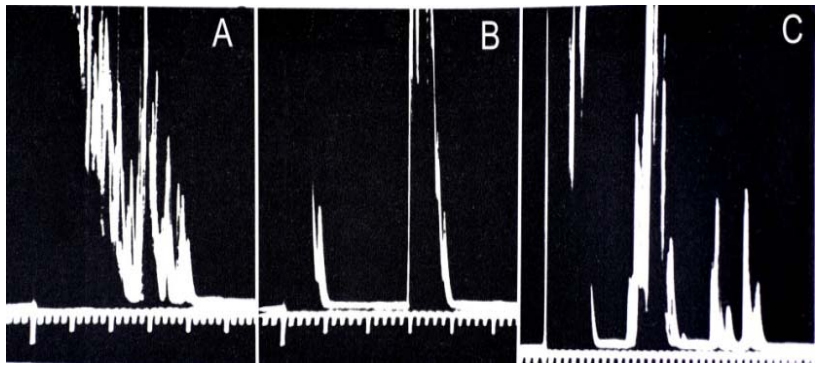
Results: The rate of TSH testing was similar, but the rate of imaging was lower in the low incidence region. The rate of FNAC was similar, whereas the rate of surgery was lower in the low incidence region (34 [95% CI 33; 35] vs 80 [95% CI 79; 81] per 100 000 person years in the high incidence region; P .05). In the low incidence region compared to the high incidence region, surgery represented a less chosen therapy for euthyroid nodular disease patients (47% [95% CI 46; 48] vs CI 68; 70]; P.05), proportionally more surgery was preceded by FNAC, more cancer was 95%] 69% diagnosed after total thyroidectomy,andthyroid cancer patientshadmorepreoperativeFNACand .synchronous lymph node dissection

Conclusion: Regional variation in thyroid cancer incidence, most marked for low-risk disease, is associated with different usage of thyroid imaging and surgery, supporting variable detection as a key determinant in geographic variation. (J Clin Endocrinol Metab 98: 4063–4071, 2013)The time for arguing that the entire increase in cancer ,incidence is due to a true rise in disease is over. This paper along with all the other accumulated data from studies of risk factor exposures and other healthcare systems make this clear. Because we are detecting a subclinical reservoir of disease, many patients are being diagnosed with thyroid .cancer and treated unnecessarily

Michael Tamilia, 13/10/2013

Thyroid Ultrasound





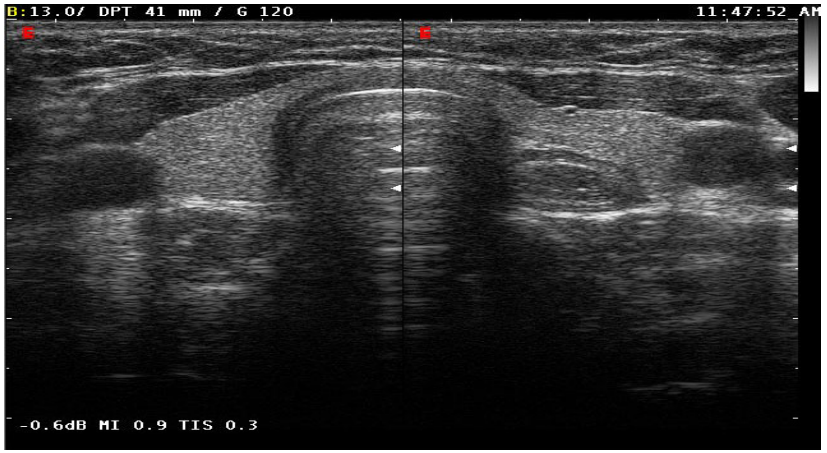
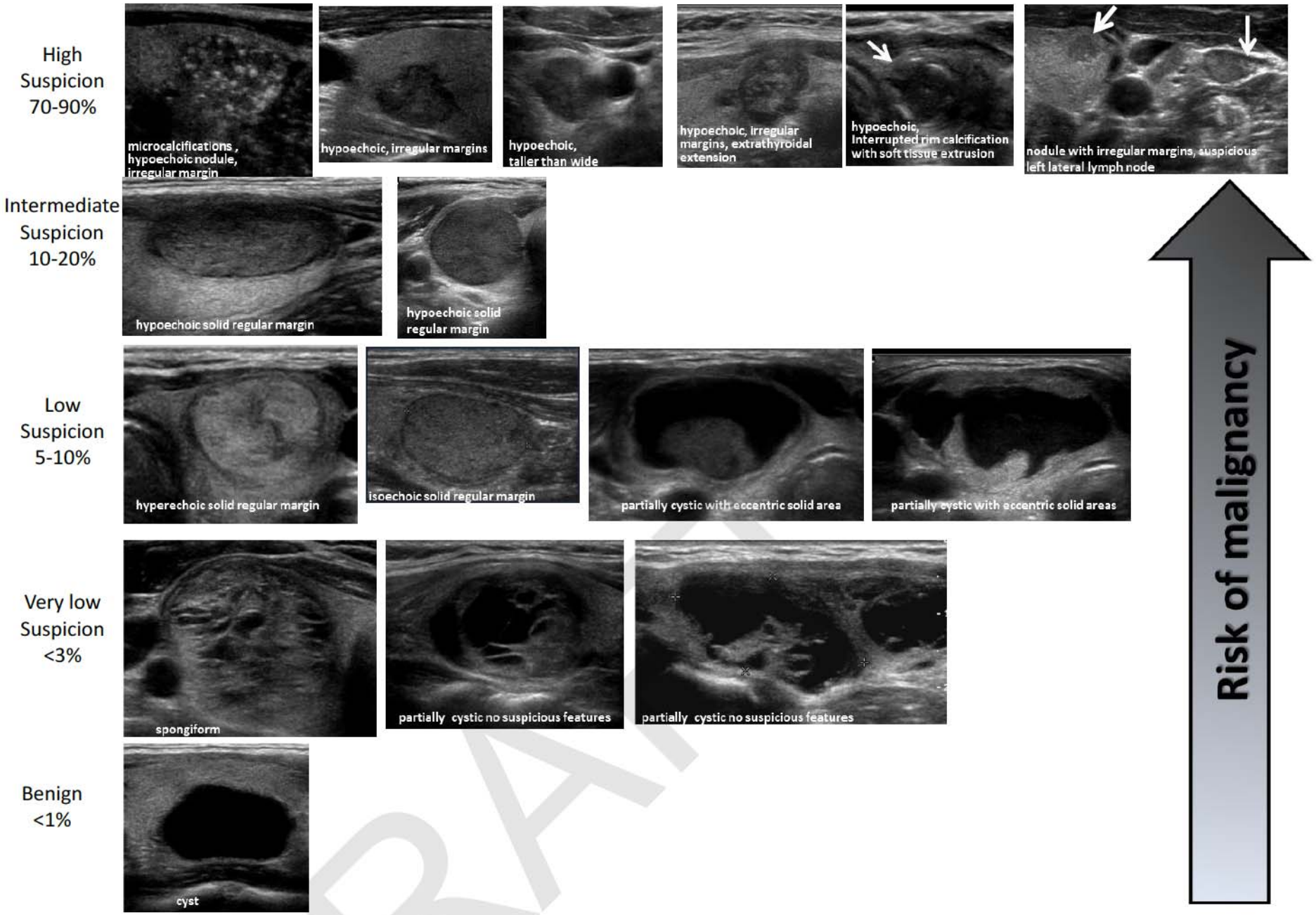
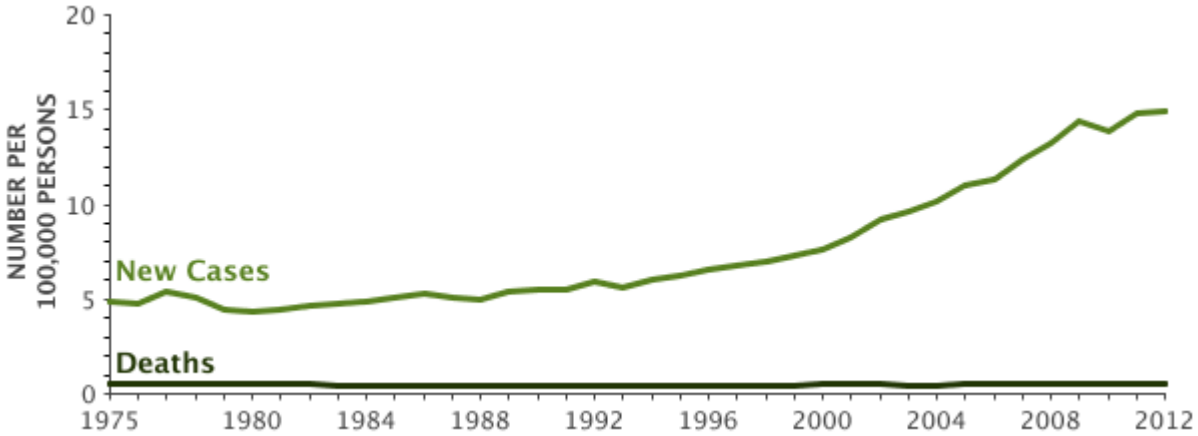


Figure 2


High Suspicion 70-90%
microcalcifications , hypoechoic nodule, irregular margin
hypoechoic, irregular margins
hypoechoic, taller than wide
hypoechoic, irregular margins, extrathyroidal extension
hypoechoic, Interrupted rim calcification with soft tissue extrusion
nodule with irregular margins, suspicious left lateral lymph node
Intermediate Suspicion 10-20%
hypoechoic solid regular margin
hypoechoic solid regular margin
Low Suspicion 5-10%
hyperechoic solid regular margin
isoechoic solid regular margin
partially cystic with eccentric solid area
partially cystic with eccentric solid areas
Very low Suspicion <3%
spongiform
partially cystic no suspicious features
partially cystic no suspicious features
Benign <1%
cyst
Risk of malignancy

Same Trends


NUMBER PER
100,000 PERSONS
20
15
10
5
0
New Cases
Deaths
1975
1980
1984
1988
1992
1996
2000
2004
2008
2012

Thank You

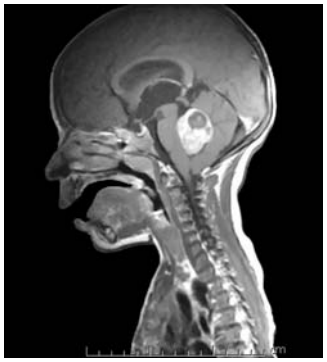
Epidemiology of medulloblastoma

Lukas Tamayo Orrego

Definition

- Medulloblastoma is a tumor of the posterior fossa

- First described by Harvey Cushing and Percival Bailey



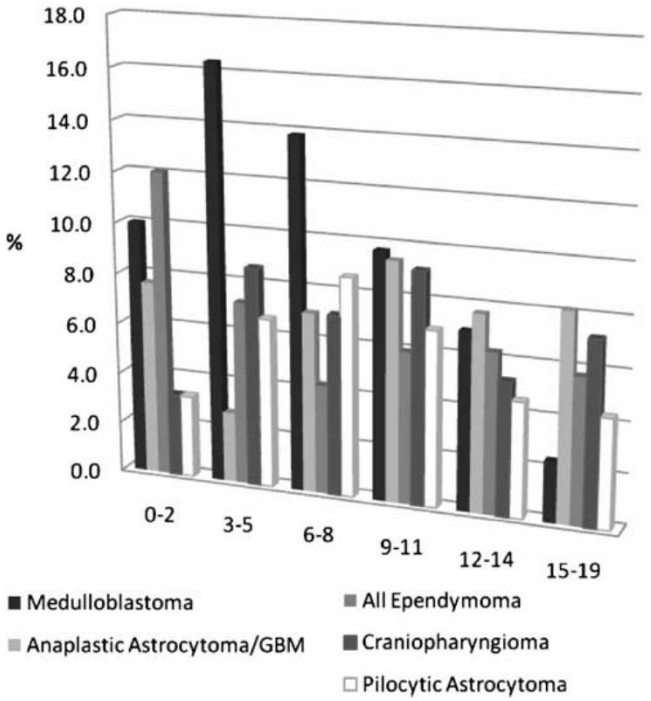


Fig. 3 Major histological tumours by age groups

Kaderali et al. Childs Nerv Syst (2009) 25:787–793

Epidemiology: incidence

Medulloblastoma is a pediatric cancer

Table I. Medulloblastoma/PNET Descriptive Factors

Age	
00–03	244 (32%)
04–09	315 (41%)
10–14	140 (18%)
15–19	69 (9%)
All ages	768
Gender	
Male(%)	487 (63%)
Female(%)	281 (37%)
Ethnicity	
White	626 (82%)
Black	70 (9%)
Other	72 (9%)

McNeil et al., Med Pediatr Oncol 2002;39:190–194

Table 1
Incidence rates and rate ratios of medulloblastomas

	Incidence rate per million (95% CI)	Incidence rate ratio
Overall	1.58 (1.50, 1.67)	–
Age group		
Infants*	4.56 (3.45, 5.91)	7.86
Children*	5.96 (5.52, 6.44)	10.28
Adolescents*	2.34 (2.08, 2.62)	4.03
Adults	0.58 (0.52, 0.64)	1.00
Sex		
Male (overall)*	1.93 (1.79, 2.06)	1.58
Infants	4.22 (2.78, 6.14)	0.86
Children*	7.59 (6.89, 8.35)	1.78
Adolescents	2.98 (2.57, 3.44)	1.78
Adults	0.65 (0.57, 0.75)	1.28
Female (overall)	1.22 (1.11, 1.33)	1.00
Infants	4.92 (3.32, 7.02)	1.00
Children	4.26 (3.73, 4.86)	1.00
Adolescents	1.67 (1.36, 2.02)	1.00
Adults	0.51 (0.43, 0.59)	1.00

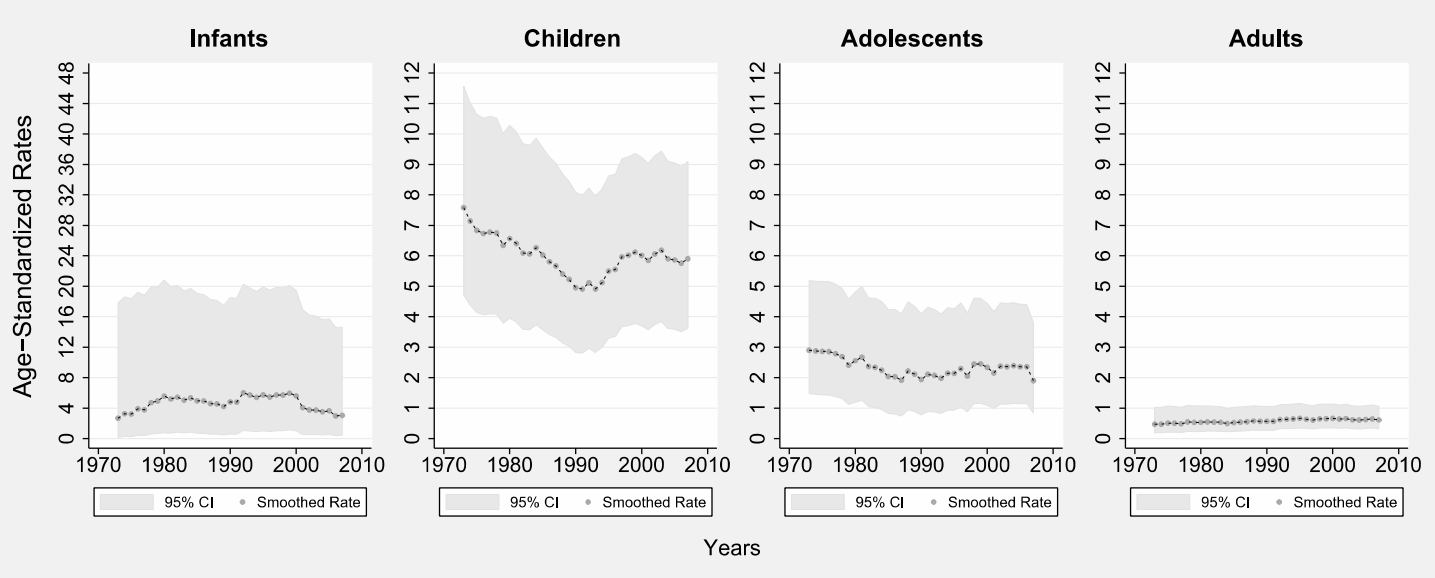


Fig. 1. Age-adjusted incidence rates and 95% confidence intervals (CI) according to year of diagnosis and by age group showing that the incidence of this tumour has neither increased nor decreased since 1973.

Birth characteristics

Prospective study performed in Norway with 1.5 million children

	All brain tumors			Medulloblastoma		
	Number of cases	IRR (95% CI)	*p* for trend	Number of cases	IRR (95% CI)	*p* for trend
Birth weight (g)			0.47			0.05
≤3,000	68	0.95 (0.71–1.26)		8	0.85 (0.37–1.93)	
3,001–3,500[2]	152	1.00		20	1.00	
3,501–4,000	145	0.90 (0.71–1.13)		27	1.26 (0.70–2.24)	
>4,000	70	0.89 (0.67–1.19)		18	1.71 (0.90–3.25)	
Length (cm)			0.24			0.30
≤49[2]	138	1.00		18	1.00	
50	89	0.93 (0.71–1.22)		11	0.88 (0.42–1.86)	
51	92	1.05 (0.81–1.37)		20	1.74 (0.92–3.29)	
52	69	0.97 (0.72–1.30)		18	1.91 (0.99–3.68)	
≥53	61	0.78 (0.57–1.06)		10	0.95 (0.44–2.09)	
Gestational age (weeks)			0.82			0.79
≤37	38	1.17 (0.81–1.70)		5	0.87 (0.32–2.35)	
38–39	131	1.27 (0.98–1.64)		21	1.16 (0.62–2.17)	
40[2]	103	1.00		18	1.00	
41–42	143	1.21 (0.94–1.56)		28	1.36 (0.75–2.46)	
≥43	20	1.18 (0.73–1.90)		1	0.34 (0.04–2.53)	
Season of birth			0.01[3]			0.26[3]
Spring[2] (Mar–May)	104	1.00		21	1.00	
Summer (June–Aug)	111	1.19 (0.91–1.55)		13	0.69 (0.34–1.37)	
Autumn (Sept–Nov)	107	1.23 (0.94–1.61)		20	1.14 (0.61–2.10)	
Winter (Dec–Feb)	137	1.52 (1.18–1.97)		24	1.32 (0.74–2.38)	

Birth weight positively correlates with medulloblastoma incidence

The season of birth correlates with risk of brain tumors

Heuch et al. *Int. J. Cancer:* **77,** 498–503 (1998)

Epidemiology: Risk factors

American Journal of Epidemiology
Vol. 168, No. 4
DOI: 10.1093/aje/kwn144
Advance Access publication June 25, 2008

Meta-Analysis

Birth Weight and Subsequent Risk of Childhood Primary Brain Tumors: A Meta-Analysis

Thomas Harder[1], Andreas Plagemann[1], and Anja Harder[2]

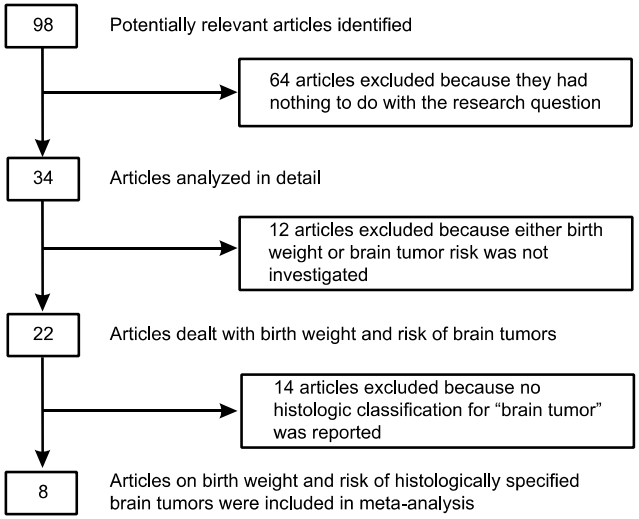
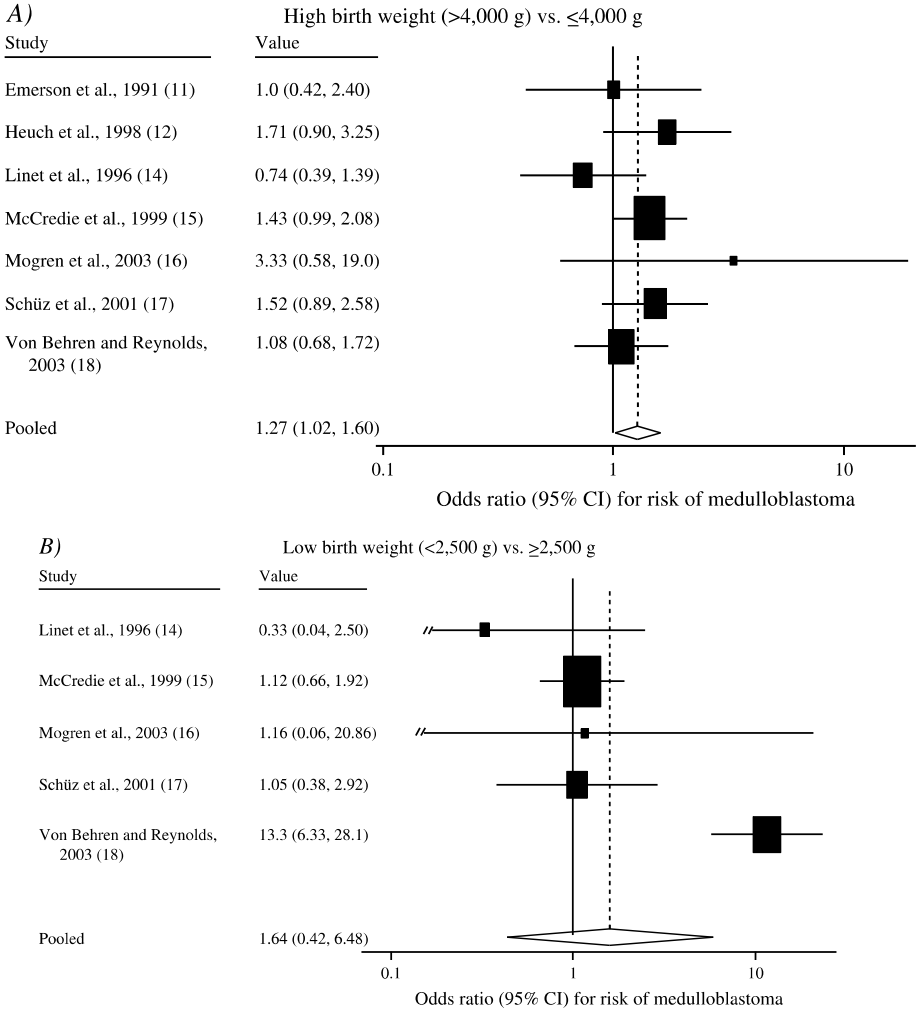


FIGURE 1. Course of a systematic literature review on birth weight and risk of childhood primary brain tumors, 1966–2007.



High and low birth weight are risk factors for medulloblastoma

Epidemiology: Risk factors. Environmental factors

Dietary consumption of N-nitroso compounds during pregnancy increases risk

				Cured meats	Vegetables, fruits and fruit juices	Vitamin supplements
Bunin *et al.* (1993) [68] US and Canada	Medulloblastoma /Primitive neuro-ectodermal brain tumors	Diagnosed during 1986–1989 0–6 years old	166 cases 166 controls	– OR = 1.1 (95% CI: 0.6–2.0; trend $p = 0.8$) for highest quartile of *total cured meats* intake (reference category: "lowest quartile of intake"). – OR = 1.7 (95% CI: 1.0–2.9) for consumption of *bacon* at least once per week ($p < 0.05$; reference category: "less than once per week").	– OR = 0.4 (95% CI: 0.2–0.7; trend $p = 0.005$) for highest quartile of frequency of *vegetable* intake (reference category: "lowest quartile of intake"). – OR = 0.3 (95% CI: 0.1–0.6; trend $p = 0.003$) for highest quartile of frequency of *fruit and fruit juice* intake (reference category: "lowest quartile of intake").	– OR = 0.6 for any consumption of *multivitamin supplements* during first 6 weeks of pregnancy ($p = 0.02$; reference category: "no consumption").

Smoking during pregnancy increases medulloblastoma incidence

Medulloblastoma					
No	44	7,776,767	REF[e]		REF[e]
Yes	18	2,853,812	1.12	1.16	0.66–2.06
1–9 cigs	11	1,758,444	1.11	1.15	0.59–2.26
≥10 cigs	7	1,095,369	1.13	1.18	0.52–2.69

Use of pesticides (lawn care) during pregnancy: OR= 1.6 (CI: 1.0-2.5)

Brooks et al. Cancer Causes and Control 15: 997–1005, 2004

Epidemiology: Risk factors. Infections

Table 2 Risk of childhood brain tumors in relation to direct and indirect indicators of infection during pregnancy or childhood

	Case (n = 272) n (%)	Control (n = 272) n (%)	OR^{a}_{adj}	95% CI
Infection of mother during gestation				
Yes	13 (4.8)	11 (4.0)	1.2	0.5–2.6
No	259 (95.2)	261 (96.0)	1.0	
Use of antibiotics during gestation				
Yes	19 (7.0)	11 (4.0)	1.7	0.8–3.6
No	253 (93.0)	261 (96.0)	1.0	
Infection of neonate at birth				
Yes	4 (1.5)	1 (0.4)	4.1	0.5–37.0
No	268 (98.5)	271 (99.6)	1.0	
Use of antibiotics during childhood				
Yes	126 (46.3)	121 (44.5)	1.4	0.7–2.9
No	146 (53.7)	151 (55.5)	1.0	
Age at first antibiotic use				
Did not use antibiotics	146 (53.7)	151 (55.5)	1.0	
0–6 months	24 (8.8)	33 (12.1)	1.0	0.4–2.4
7–12 months	42 (15.4)	41 (15.1)	1.5	0.6–3.4
>12 months	60 (22.1)	47 (17.3)	1.9	0.8–4.3
Removal of child's tonsils, adenoids or appendix				
Yes	22 (8.1)	19 (7.0)	1.2	0.6–2.4
No	250 (91.9)	253 (93.0)	1.0	
Age at first removal[b]				
Did not remove	250 (91.9)	253 (93.4)	1.0	
0–24 months	15 (5.5)	7 (2.6)	2.3	0.9–6.0
>24 months	7 (2.6)	11 (4.1)	0.7	0.3–1.9
Breast fed				
Yes	141 (51.8)	149 (54.8)	0.8	0.6–1.2
No	131 (48.2)	123 (45.2)	1.0	
Duration of breast feeding				
None	131 (48.2)	123 (45.2)	1.0	
≤8 weeks	51 (18.8)	46 (16.9)	1.0	0.6–1.6
9–24 weeks	55 (20.2)	70 (25.7)	0.7	0.4–1.1
>24 weeks	35 (12.9)	33 (12.1)	0.9	0.5–1.6

Indicators of infection are associated with risk of brain tumors

Being the 2nd child born is a risk factor for medulloblastoma: OR: 2.3 (1.3-4.3)

Shaw et al. Cancer Causes Control (2006) 17:1267–1274

Epidemiology: Risk factors

Table 3 Childhood brain tumors associated with occupational paternal exposure

	Around time of conception			
	Cases	Controls	OR1[a]	95 % CI
Exposure to PAH				
Not exposed	1,241	5,076	1.00	Reference
Exposed	120	424	1.22	[0.98–1.52]
Low	110	388	1.22	[0.97–1.53]
High	10	36	1.20	[0.58–2.48]
Exposure to DME				
Not exposed	1,185	4,700	1.00	Reference
Exposed	176	800	0.89	[0.74–1.07]
Low	169	758	0.90	[0.75–1.08]
High	7	42	0.67	[0.29–1.52]
Exposure to asbestos				
Not exposed	1,117	4,710	1.00	Reference
Exposed	244	790	1.12	[0.95–1.32]
Low	221	722	1.10	[0.92–1.30]
High	23	68	1.42	[0.87–2.32]
Exposure to silica				
Not exposed	1,276	5,135	1.00	Reference
Exposed	85	365	0.96	[0.74–1.23]
Low	77	332	0.96	[0.74–1.25]
High	8	33	0.92	[0.41–2.03]
Exposure to metals				
Not exposed	1,232	5,074	1.00	Reference
Exposed	129	426	1.18	[0.96–1.46]
Low	114	372	1.22	[0.97–1.53]
High	15	54	0.96	[0.53–1.74]

[a] OR1 is adjusted for the matching variables: age, sex, and country

Table 4 Childhood brain tumors associated with occupational maternal exposure

	During pregnancy			
	Cases	Controls	OR1[a]	95 % CI
Exposure to PAH				
No	1,329	5,367	1.00	Reference
Yes	32	133	0.91	[0.61–1.35]
Exposure to DME				
No	1,343	5,382	1.00	Reference
Yes	18	118	0.81	[0.49–1.35]
Exposure to asbestos				
No	1,337	5,398	1.00	Reference
Yes	24	102	1.03	[0.65–1.63]
Exposure to silica				
No	1,353	5,445	1.00	Reference
Yes	8	55	0.69	[0.33–1.47]
Exposure to metals				
No	1,356	5,485	1.00	Reference
Yes	5	15	1.32	[0.47–3.75]

[a] OR1 is adjusted for the matching variables: age, sex, and country

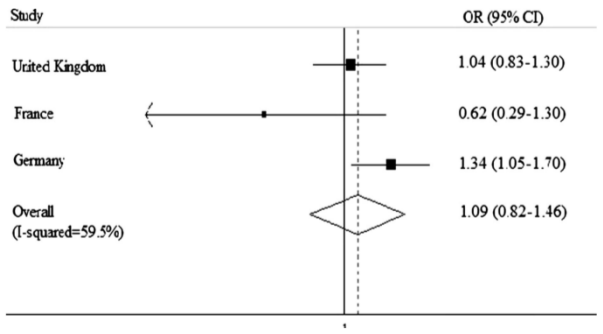


Fig. 1 Forest plot for paternal occupational exposure to asbestos, by country

Huoi et al. Cancer Causes Control (2014) 25:1603–1613

Epidemiology: Risk factors

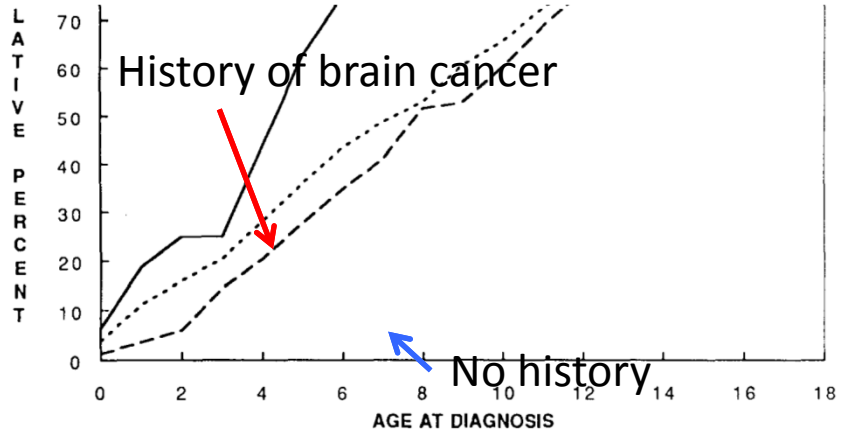


Figure 1. Cumulative percent by age at brain tumor diagnosis, plotted separately for children with a grandparent or great-grandparent who had a brain neoplasm (uninterrupted line), a grandparent or great-grandparent who had another type of neoplasm (dotted line), and for children who had no such family history of neoplasm (dashed line).

age (years) of brain tumor presentation in
l without family tumor histories. The numbers
epresent the number of children for whom a
as available. The total number for each row
ause information was lacking for a few relatives

Table 2. The mean age at brain tumor presentat
classified by the number of grandparent
grandparents who had a tumor

Presentation at younger age is associated with a family history of cancer

Sussman et al., 2002

Head injury or X-rays are not associated with increased risk of medulloblastoma

Table 2 Odds ratios for head injury and X-rays with exposure to the head from a case–control study of medulloblastoma/PNET with 299 case–control pairs

Risk factor	Number cases exposed/controls exposed	OR[a]	95% CI	*p* value
Head injury	33/36	0.78	0.40–1.5	0.47
Head X-ray due to head injury	8/10	0.62	0.21–1.9	0.40
Head X-ray not due to head injury	24/12	2.3	0.91–5.7	0.08
1 X-ray	17/9	2.5	0.83–7.5	0.11
2 or more X-rays	6/3	1.7	0.31–9.2	0.55
Head X-ray not due to head injury[b]	15/12	1.3	0.49–3.7	0.57
1 X-ray	13/9	1.9	0.56–6.1	0.31
2 or more X-rays	2/3	0.50	0.06–3.9	0.51
Head X-ray any reason	32/20	1.7	0.82–3.4	0.16
Head X-ray any reason[b]	23/20	1.2	0.54–2.5	0.69
Any X-ray before age 1	35/23	1.3	0.68–2.61	0.40
Dental X-ray	16/18	0.85	0.37–1.9	0.70
Any type of X-ray[c]	75/55	1.4	0.83–2.3	0.22
Any type of X-ray[b,c]	69/55	1.2	0.71–2.0	0.51

The number of matched case–control sets ranged from 294 to 299 due to missing data

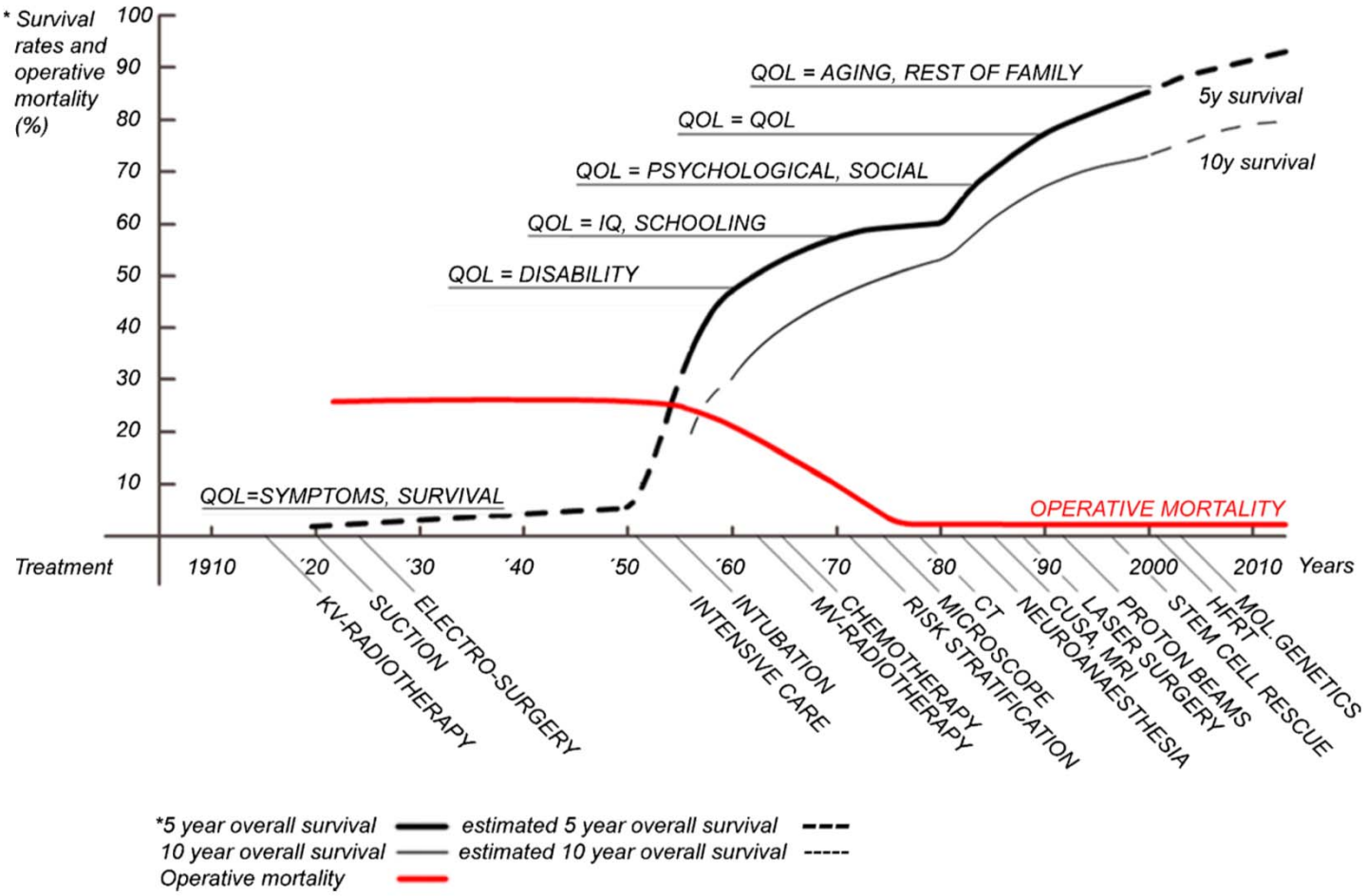
[a] Adjusted for annual household income >$50,000, mother's education (less than high school, high school, some post high school, and college/grad/professional), and age of child at interview

[b] Subjects were considered "unexposed" if the reason for X-ray was possibly tumor related

[c] Includes head X-ray for any reason, other X-ray before 1, and dental X-ray

Khan et al., 2010

Treatment



Childs Nerv Syst (2014) 30:979–990

5 and 10 year OS for medulloblastoma is 85%

Permanent side-effects from treatments (radiation therapy) are still very important

Slides for questions

Table 1 | Established prognostic variables accepted by the North American Children's Oncology Group (COG) and the SIOP (International Society of Pediatric Oncology) Group.

Risk classification	Characteristics
Standard-risk tumor	$\geq$3 years of age without evidence of metastatic spread and having $\leq$1.5 cm^2 (maximum cross-sectional area) of residual disease after surgery
High-risk tumor	$\geq$3 years of age with evidence of CSF spread (M1–M3) and/or those with less complete resection ($\geq$1.5 cm^2) or $<$3 years of age at diagnosis

Treatment: specific therapies

BRIEF REPORT

Treatment of Medulloblastoma with Hedgehog Pathway Inhibitor GDC-0449

Charles M. Rudin, M.D., Ph.D., Christine L. Hann, M.D., Ph.D., John Laterra, M.D., Ph.D., Robert L. Yauch, Ph.D., Christopher A. Callahan, M.D., Ph.D., Ling Fu, M.D., Thomas Holcomb, M.S., Jeremy Stinson, B.S., Stephen E. Gould, Ph.D., Barbara Coleman, R.N., C.C.R.P., Patricia M. LoRusso, D.O., Daniel D. Von Hoff, M.D., Frederic J. de Sauvage, Ph.D., and Jennifer A. Low, M.D., Ph.D.

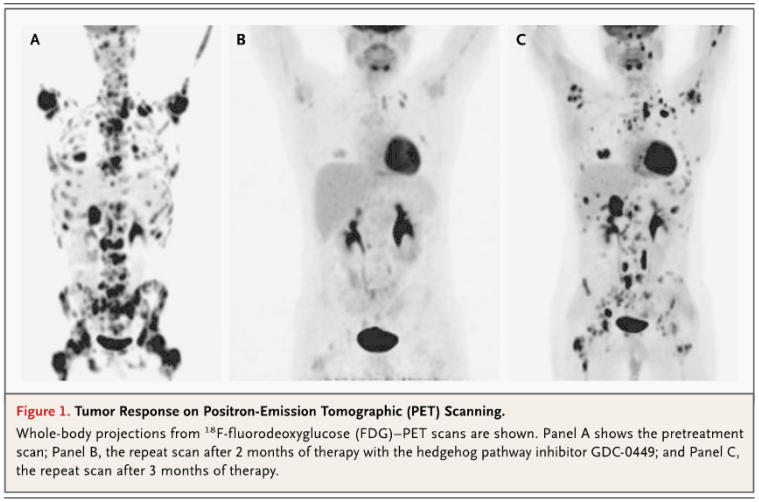


Figure 1. Tumor Response on Positron-Emission Tomographic (PET) Scanning.
Whole-body projections from ^{18}F-fluorodeoxyglucose (FDG)–PET scans are shown. Panel A shows the pretreatment scan; Panel B, the repeat scan after 2 months of therapy with the hedgehog pathway inhibitor GDC-0449; and Panel C, the repeat scan after 3 months of therapy.

Table 1 Multivariate overall survival analyses

Prognostic factor	RR	CI low	CI high	*P value*
All patients ($n = 204$)				
Subgroup				0.036
SHH vs. WNT	1.9	0.4	8.9	0.4
Group 3 vs. WNT	4.1	0.9	18.2	0.065
Group 4 vs. WNT	1.9	0.4	8.7	0.4
MYC(N) amplification yes vs. no	3.4	1.7	6.5	<0.001
17p loss yes vs. no	2.4	1.4	4.3	0.002
SHH medulloblastomas ($n = 54$)				
Histology				0.001
Desmoplastic vs. Classic	0.3	0.1	1.1	0.071
LCA vs. Classic	8.9	2.0	40.6	0.005
3q gain yes vs. no	4.5	1.5	13.9	0.008
Group 3 medulloblastomas ($n = 44$)				
17q gain yes vs. no	2.6	1.0	6.6	0.049
Group 4 medulloblastomas ($n = 79$)				
17p loss yes vs. no	3.6	1.2	10.8	0.020

Hh pathway inhibitors are effective against Medulloblastoma but tumors become resistant

treatment

Table 2
Studies with adjuvant chemotherapy on adult patients.

Study	No. patients	Treatment	5-yr OS
Bloom 1990 [86]	47	RT RT → CT (in 1971–1981)	1952–1963: 38% 1964–1981: 59% 1971–1981: 76%
Prados 1995 [85]	47	RT → CT (in 32pts)	AR: 81% HR: 54%
Frost 1995 [8]	48	RT (only 1 pt treated with CT)	62%
Chan 2000 [11]	32	RT → CT (in 24 pts)	83%
Louis 2002	24	RT → CT (in 6 pts)	82%
Padovani 2007 [42]	253	RT → CT (in 143 pts)	AR: 77% HR: 65%
Brandes 2003 & 2007 [12]	10 AR 26 HR	RT CT → RT → CT	AR: 80% HR: 73%
Friedrich 2012 [51]	70 (non metastatic)	RT → CT	4 yr OS: 89%

Abbreviations: RT, radiotherapy; CT, chemotherapy; DEC, cisplatin, etoposide, cyclophosphamide; CDDP, cisplatin; CCNU, lomustine; PFS, progression-free survival; OS, overall survival; EFS, event-free serviva; AR, average risk; HR, high risk.

Cancer risk following the 1986 Chernobyl disaster

Pylyp Zolotarov PGY-1 Pathology

Introduction

- 26 April 1986 at the Chornobyl Nuclear Power Plant in Ukraine (part of Soviet Union at that time)
  - reactor 4 suffered a catastrophic power increase, leading to explosions in its core
  - dispersal of large quantities of radioactive fuel and core materials into the atmosphere
- Worst nuclear power plant accident in history in terms of cost and casualties

https://en.wikipedia.org/wiki/Chernobyl_disaster

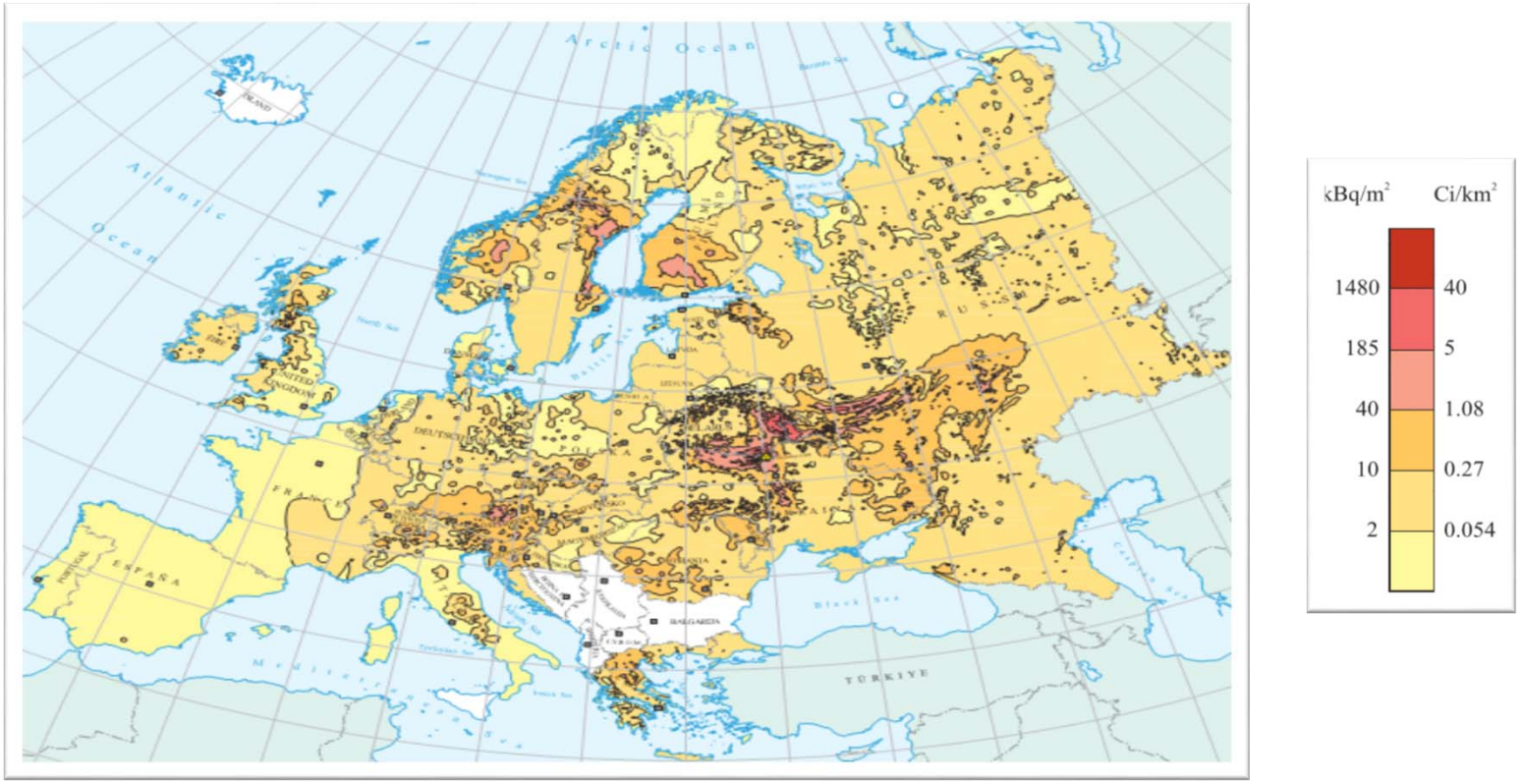
Introduction

- 400 times more radioactive material was released from Chernobyl than by the atomic bombing of Hiroshima
- Approximately 100,000 km² of land significantly contaminated with fallout
  - worst hit regions being in Belarus, Ukraine and Russia
  - slighter levels of contamination were detected over all of Europe except for the Iberian Peninsula

https://en.wikipedia.org/wiki/Chernobyl_disaster

Introduction

Surface ground deposition of caesium-137 released in Europe after the Chernobyl accident



UNSCEAR Health effects due to radiation from the Chernobyl accident, 2008

Introduction

Total average effective doses accumulated over 20 years by the highest Chernobyl exposed populations

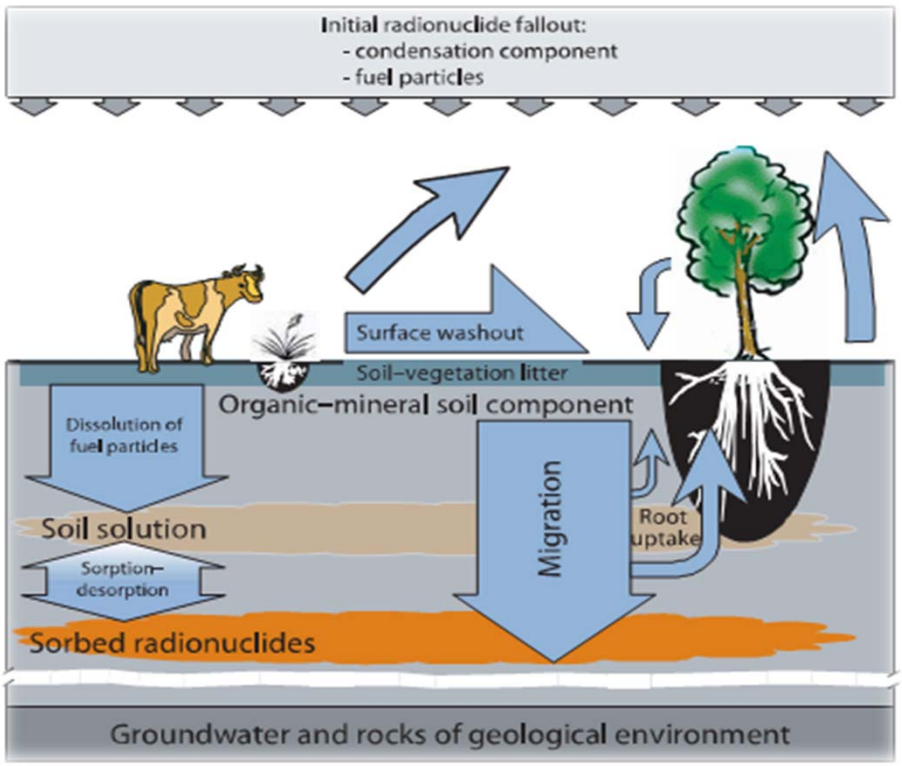
Population (years exposed)	Number	Average total in 20 years (mSv)[1]
Liquidators (1986–1987) (high exposed)	240 000	>100
Evacuees (1986)	116 000	>33
Residents SCZs (>555 kBq/m2) (1986–2005)	270 000	>50
Residents low contam. (37 kBq/m2) (1986–2005)	5 000 000	10–20
Natural background	2.4 mSv/year (typical range 1–10, max >20)	48
Approximate typical doses from medical x-ray exposures per procedure:		
Whole body CT scan	12 mSv	
Mammogram	0.13 mSv	
Chest x-ray	0.08 mSv	

[1] These doses are additional to those from natural background radiation.

http://www.who.int/ionizing_radiation/chernobyl/backgrounder/en/

Introduction

The main transfer pathways of radionuclides in the terrestrial environment



UNSCEAR Health effects due to radiation from the Chernobyl accident, 2008

Most harmful radionuclides spread from Chernobyl:

- I-131 (half-life 8.02 days)
- Cs-137 (half-life 30.2 years)
- Sr-90 (half-life 28.8 years)

Thyroid cancer

- Dramatic increase in the incidence in persons exposed as young people
- 1986 to 2002, nearly 4,000 cases diagnosed and treated (Belarus, Ukraine and 4 most contaminated regions of Russia)
- This incidence could be at least in part attributable to a screening bias
  - majority of these cases are aggressive (extracapsular invasion and distant metastases)
  - they would have been likely to be diagnosed even in the absence of screening
- Risk estimates from the large case-control and cohort study (Belarus, Ukraine) are very close and similar
- There is some evidence that iodine deficiency at the time of exposure may have increased the risk of developing thyroid cancer among persons exposed to I -131 as children
  - prolonged stable iodine supplementation in the years after exposure may have reduced this risk
  - further studies are needed to replicate these findings
- The effect of exposure on adults remains unclear

Thyroid cancer

Figure D-VIII. Thyroid cancer incidence rates for different age groups (age at diagnosis) of the total Belarusian female population

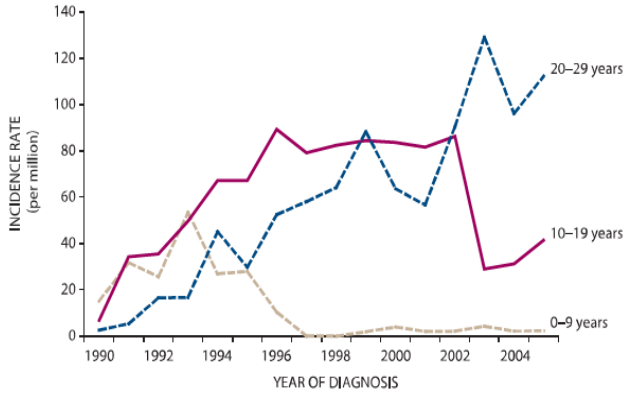


Figure D-X. Thyroid cancer incidence rates for different age groups (age at diagnosis) of the total Ukrainian female population

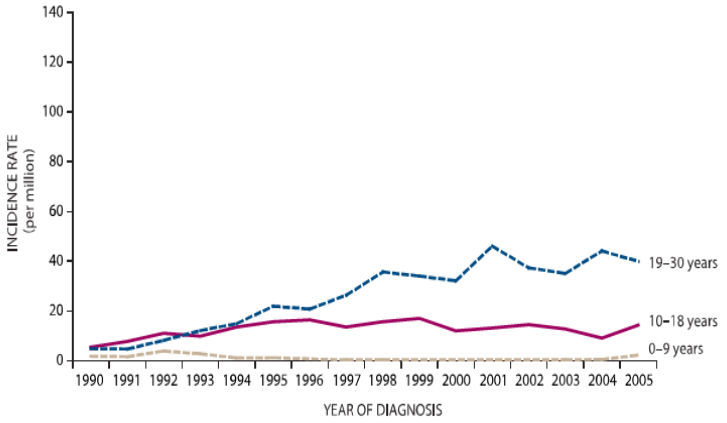


Figure D-XI. Thyroid cancer incidence rates for different age groups (age at diagnosis) of the total Belarusian male population

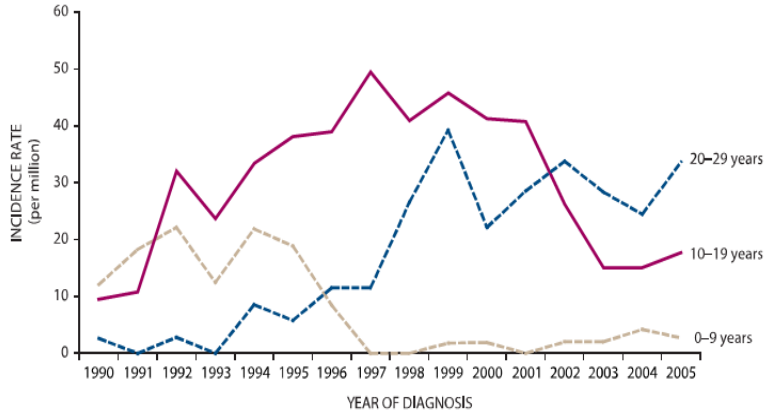
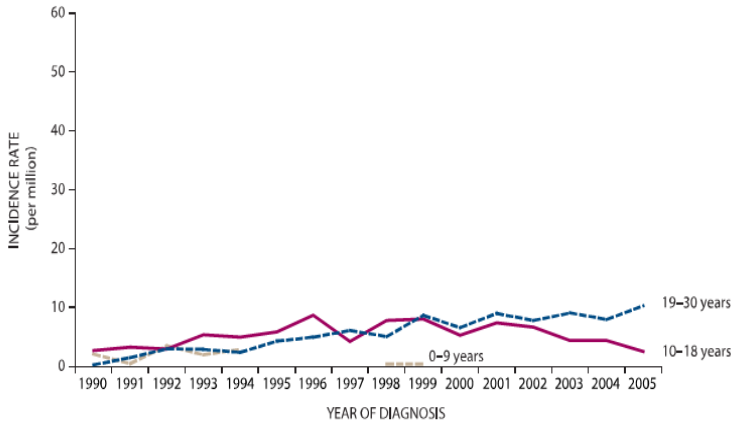


Figure D-XIII. Thyroid cancer incidence rates for different age groups (age at diagnosis) of the total Ukrainian male population



UNSCEAR Health effects due to radiation from the Chernobyl accident, 2008

Thyroid cancer

Study	Observed cases	Controls/ study population	Median dose (Gy)	Excess relative risk at 1 Sv
Case-control studies				
Belarus (*10*)	107	214	0.106	OR ≥1 Gy vs. <0.3Gy: 5.04 (1.5-16.7) to 5.84 (1.96-17.3)
Belarus and Russian Federation (*11*)	276	1 300	0.365 (Belarus) 0.040 (Russia)	4.5 (2.1-8.5) to 7.4 (3.1-16.3)
Russian Federation – Bryansk (*63*)	66	132	0.020	49.7 (5.8 to 1152)
Cohort study				
Ukraine (*13*)	45	13 127	0.78 (mean)	5.25 (95% CI 1.70, 27.5)
Ecological study				
Belarus and Ukraine (*12*)	1,089	623 000	0.002-0.5 (mean) depending on region	18.9 (11.1-26.7)

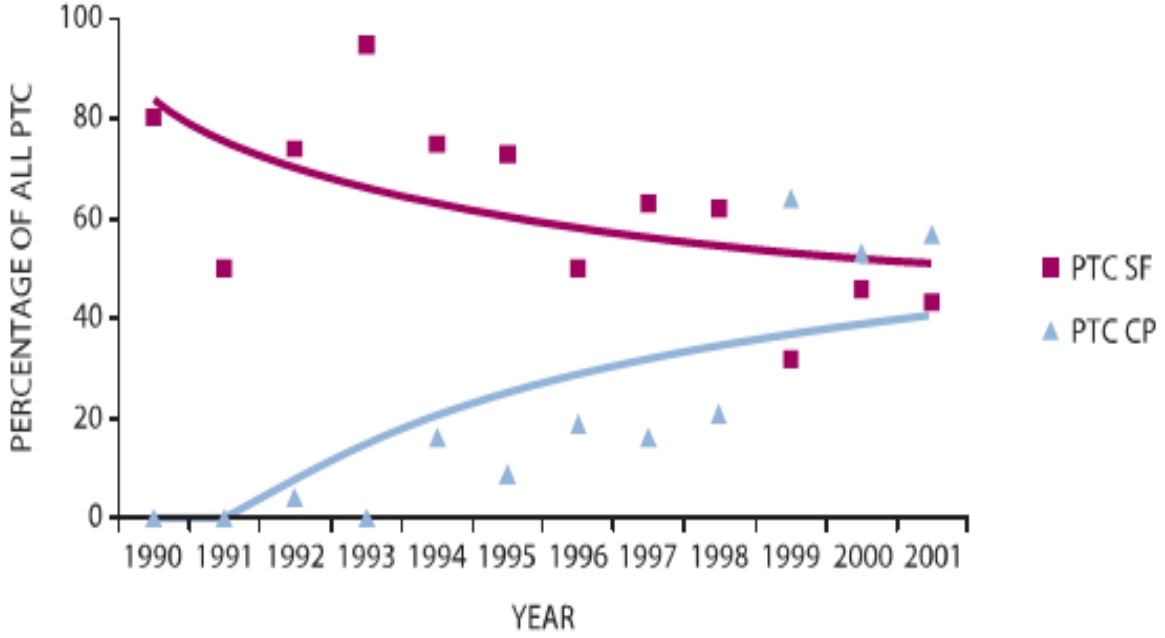
Elisabeth Cardis, Geoffrey Howe, Elaine Ron Cancer consequences of the Chernobyl accident: 20 years on, J. Radiol. Prot. 26 (2006) 127–140

Thyroid cancer

- The biology of radiation-induced thyroid cancer is not fundamentally different from that seen in non-irradiated populations
- Chernobyl related thyroid carcinomas have been almost all papillary carcinomas
- The majority of these carcinomas show either a BRAF point mutation or a RET-PTC rearrangement
- In post Chernobyl thyroid carcinomas BRAF mutations have been less common than in unexposed populations
- BRAF is linked to a more aggressive tumour than RET-PTC
- BRAF tumours are liable to undergo the rare transition to an anaplastic carcinoma but not RET-PTC

Thyroid cancer

Figure D-XIV. Change in the proportion of papillary carcinoma subtypes with time after the accident
PTC SF = Solid/follicular subtype (Ukraine); PTC CP = Subtype composed mainly of papillae



UNSCEAR Health effects due to radiation from the Chernobyl accident, 2008

Leukaemia

- Leukaemia (except CLL) has been associated with exposure to ionising radiation
  - atomic bomb survivors
  - patients treated with radiotherapy
  - populations exposed occupationally in medicine and the nuclear industry
- Chronic myeloid leukaemia, acute lymphoblastic leukaemia, and acute myeloid leukaemia have all been linked to ionizing radiation exposure and specific rearrangements
- Increases in leukaemia risk appear within 2 to 5 years after exposure
- ERR per unit of dose (particularly in children) is one of the highest among all radiation-induced cancers

Leukaemia

- Study results do not provide unequivocal evidence about increased risk of leukaemia in those exposed *in utero* due to the Chernobyl accident
  - several studies have demonstrated a possible association but not a clear trend with regard to radionuclide contamination levels
  - major limitations are lack of individual dose estimates and very small number of cases
- European Childhood Leukaemia Lymphoma Study found no evidence of a radiation-related increase in incidence of leukaemia in Europe in the first 5 years after the accident
- Only 2 case–control studies of childhood leukaemia have been published to date
  - significant association between leukaemia risk and radiation dose to the bone marrow was found in Ukraine but results are difficult to interpret (problems in the selection and comparability of controls)
  - No significant increase was seen in Belarus or Russia
- There is lack of evidence of increased leukaemia risk in adults
  - questionable studies (large uncertainties in officially recorded doses and unknown case verification procedures)
  - due to low power to detect (leukaemia is a relatively rare event) exposure effects
  - due to absence of exposure effect on leukaemia incidence in adults

Non-thyroid solid cancers

- Ionising radiation has been shown to increase the risk of cancers at many sites
- Data from Chernobyl on this matter are very sparse
- No significant increase in the incidence of solid cancers was seen in a cohort of over 55 000 Russian liquidators
- Several reviews concluded that there is no clearly demonstrated increase in incidence of solid cancers related to the Chernobyl radiation
- Increases in the incidence of cancers and other diseases have been reported in Belarus, Russia and Ukraine
  - much of the increase appears to be due to other factors, including improvements in diagnosis, reporting and registration
- Assessment of solid cancer incidence in Ukraine 20 years after the Chernobyl accident showed a continuous increase for cancers of oropharyngeal cavity, rectum, female breast, prostate, urinary bladder, kidney and thyroid
  - all studies were ecological
  - large variability in dose within the geographical study area
  - absence of control for important confounding factors
- Analyses of rates of breast cancer among subjects included in the Ukrainian Chernobyl registry and Mogilev region of Belarus indicated a significantly increased incidence compared to the general population
  - these reports are difficult to interpret, no information about radiation dose level available

Non-thyroid solid cancers

Table D19. Incidence of all solid cancers combined for exposed population groups in Russia and Ukraine (thyroid cancer excluded)

Standardized incidence ratios, by country and calendar year period

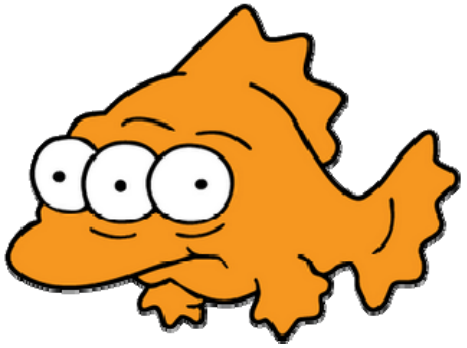
Country/exposed group	*Calendar year periods*			
Russian Federation [I25, I26]	1991–1995	1996–2000	2001–2005	1991–2005
Population of seven contaminated districts (raions) of the Bryansk oblast	1.03 (n = 4 701)	0.99 (n = 4 751)	0.97 (n = 5 018)	1.00 (n = 14 470)
(95% CI)	(1.00, 1.06)	(0.96, 1.02)	(0.95, 1.00)	(0.98, 1.02)
Ukraine [P16, S18]	1990–2004			
Evacuees from 30-km zone (males and females)	0.84 (n = 2 182)			
(95% CI)	(0.80, 0.88)			
Adult residents of contaminated areas (males and females)	0.85 (n = 11 221)			
(95% CI)	(0.83, 0.86)			

UNSCEAR Health effects due to radiation from the Chernobyl accident, 2008

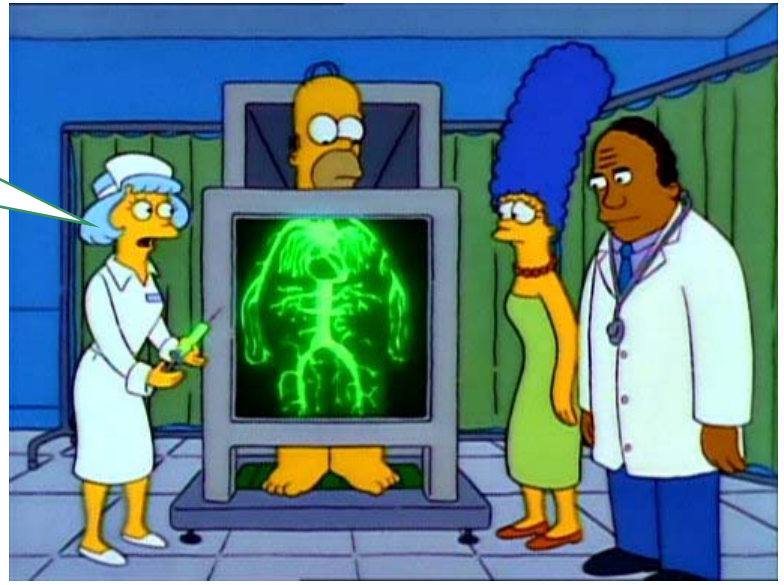
Conclusion

- It is expected that Chernobyl-related thyroid cancers will continue to occur for many more years
  - the long-term magnitude of risk cannot yet be quantified
- Further epidemiological survey is necessary for elucidation of the association between the haematological malignancies in children following the Chernobyl accident
- There is lack of evidence of increased leukaemia risk in adults
- No clearly demonstrated increase in the incidence of other cancers can be attributed to radiation exposure from the accident
- Studies of cancer risk other than thyroid are few and most have methodological limitations:
  - doses to most organs outside the thyroid tended to be low
  - studies lacked statistical power
  - latent period is likely to be longer than for leukaemia or thyroid cancer (10–15 years or more)
- Studies of external radiation indicate that risks of solid cancers remain elevated throughout life and it is too early to evaluate the full radiological impact of the Chernobyl accident

THANK YOU



QUESTIONS ?



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Brominated Flame retardants and breast cancer risk

Lidija Latifovic

EPIB-671 Cancer Epidemiology & Prevention

June 17, 2015

Descriptive Epidemiology of Breast Cancer

- Most common cancer in women worldwide
- Approximately 1.7 million new cases diagnosed in 2012
  - 12% of all new cancer cases
  - 25% of all cancers in women
- Hormonally related
- Risk factors for premenopausal and postmenopausal breast cancer differ

World Cancer Research Fund. Breast Cancer 2010 Report. http://www.wcrf.org/sites/default/files/Breast-Cancer-2010-Report.pdf

Established and Probable Risk factors for Breast cancer

FOOD, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER (PREMENOPAUSE) 2010

	DECREASES RISK	INCREASES RISK
Convincing	**Lactation**	**Alcoholic drinks**
Probable	**Body fatness**	**Adult attained height[1]** **Greater birth weight**
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).

FOOD, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER (POSTMENOPAUSE) 2010

	DECREASES RISK	INCREASES RISK
Convincing	**Lactation**	**Alcoholic drinks** **Body fatness** **Adult attained height[1]**
Probable	**Physical activity[2]**	**Abdominal fatness** **Adult weight gain**
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).

2 Physical activity of all types: occupational, household, transport and recreational.

World Cancer Research Fund. Breast Cancer 2010 Report.
http://www.wcrf.org/sites/default/files/Breast-Cancer-2010-Report.pdf

Established and Probable Risk Factors for Breast Cancer

Factor	Relative risk	High risk group
Age	>10	Elderly
Geographical location	5	Developed country
Age at menarche	3	Menarche before age 11
Age at menopause	2	Menopause after age 54
Age at first full pregnancy	3	First child in early 40s
Family history	⩾2	Breast cancer in first degree relative when young
Previous benign disease	4-5	Atypical hyperplasia
Cancer in other breast	>4	
Socioeconomic group	2	Groups I and II
Diet	1.5	High intake of saturated fat
Body weight:		
Premenopausal	0.7	Body mass index >35
Postmenopausal	2	Body mass index >35
Alcohol consumption	1.3	Excessive intake
Exposure to ionising radiation	3	Abnormal exposure in young females after age 10
Taking exogenous hormones:		
Oral contraceptives	1.24	Current use
Hormone replacement therapy	1.35	Use for ⩾10 years
Diethylstilbestrol	2	Use during pregnancy

McPherson K, Steel CM & Dixon JM. Breast cancer – epidemiology, risk factors and genetics. BMJ. 2000; 321:624-628.

Breast Cancer and the Environment

- Highest incidence in North America and Oceania
- Lowest incidence in Asia and Africa
- Observed rates increase with industrialization and urbanization
- Rates change with migration

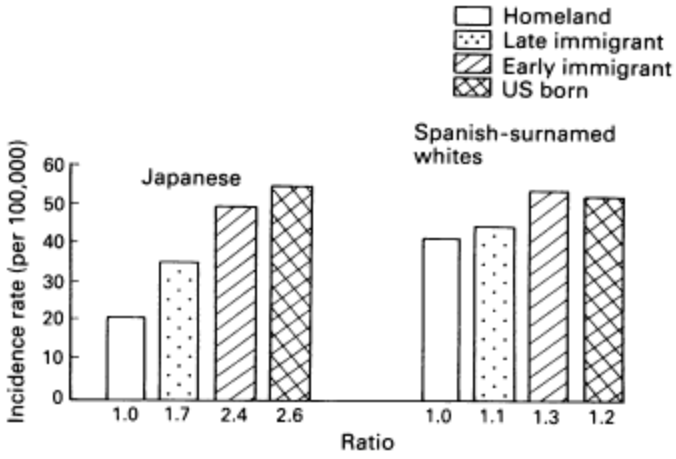


Figure 2 Age-adjusted incidence rates for female breast cancer by birthplace and age at immigration for Los Angeles County residents (1972–85) and in homelands* for Spanish-surnamed whites and Japanese. *Cali, Colombia (1972–82) for Spanish-surnamed whites and Miyagi, Japan (1973–81) for Japanese.

Shimizu *et al.*, 1991

World Cancer Research Fund. Breast Cancer 2010 Report.
http://www.wcrf.org/sites/default/files/Breast-Cancer-2010-Report.pdf

Flame Retardants

- Added to consumer products such as furniture, textiles, electronics, motor vehicles and building materials to increase fire resistance

- Three characteristics that make them hazardous
  - Stable in the environment (persistent)
  - Fat soluble
  - Potential to act as endocrine disruptors

- Increasing focus placed on a class of brominated flame retardants - polybrominated diphenyl ethers (PBDEs)

Production of Brominated Flame Retardants

Table 3
Global production of BFRs between 1989 and 1999

	1989[a]	1994[b]	1999[c]
Europe	28.0	32.5	30.9
Asia	28.7	38.5	113.9
United States	50.0	65	58.7
Total	106.7	136	203.5

All values in 1000 metric tonnes.

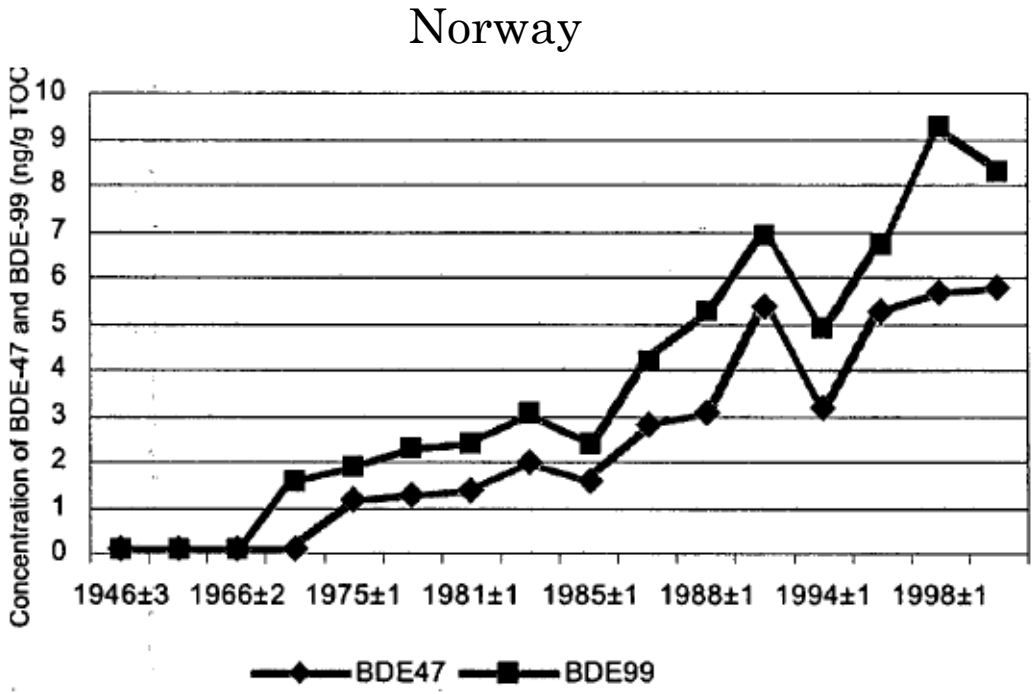
[a] From Flame Retardants Specialty Updated program 1990.

[b] Estimated values from Pettigrew (1994).

[c] From BSEF (2000).

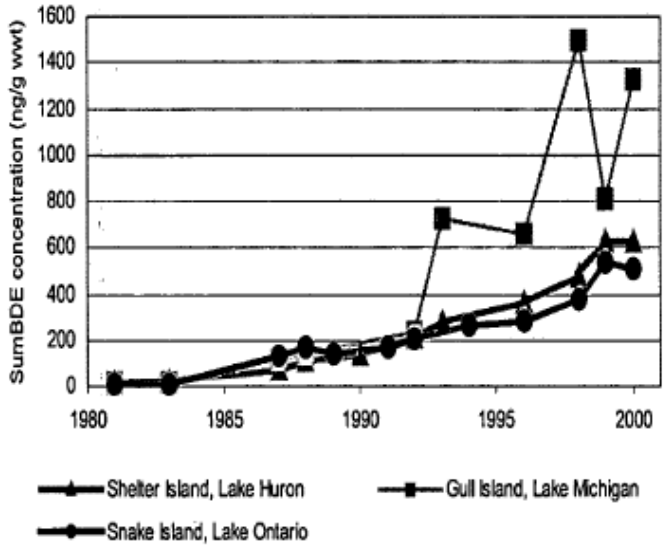
Alaee et al. An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release. 2003; 29: 683-689

Temporal Trends of PBDEs in the Environment



Zegers *et al*. Levels of PBDE flame retardants in sediment cores from Western Europe. Environ Sci Technol. 2003; 37:3803-3807

Temporal Trends of PBDEs in Wildlife



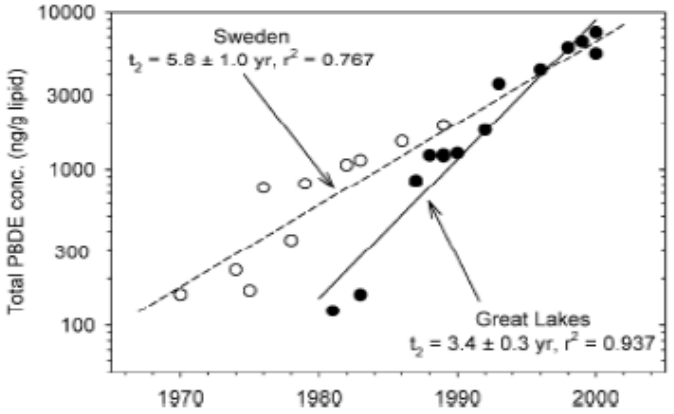
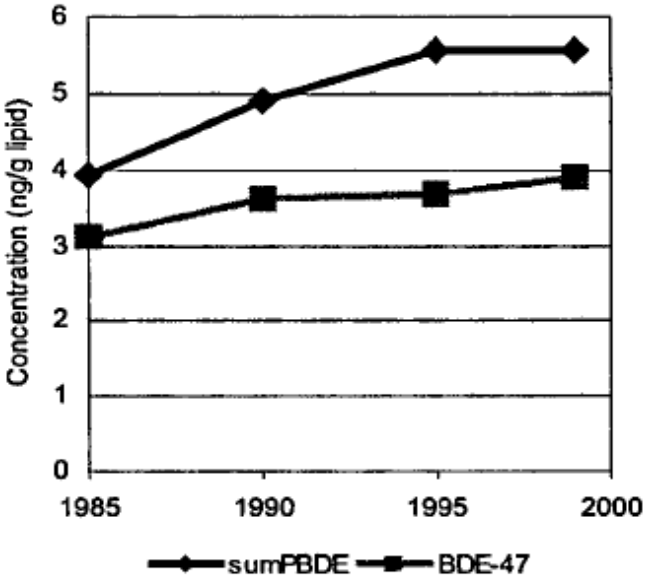


FIGURE 5. ∑PBDE concentrations in birds' eggs (in ng/g lipid) shown as a function of the year in which the samples were collected; see Table 6. The bottom line with filled symbols represents samples of herring gull eggs from the U.S. and Canadian Great Lakes (*16*), and the top line with open symbols is for guillemot eggs from Sweden (*17*). The regressions for the two data sets are shown separately; the doubling times of the two types of samples are significantly different.

Norstrom et al. Geographical distribution (2000) and temporal trends (1981-2000) of PBDE in Great Lakes herring gull eggs. Eniron Sci Tech. 2002; 36:4783-4789.

Hites RA. PBDE in the environment and in people: a meta-analysis of concentrations. Environ Sci Tech. 2004;38:945-956.

Temporal Trends of PBDEs in Human Tissue



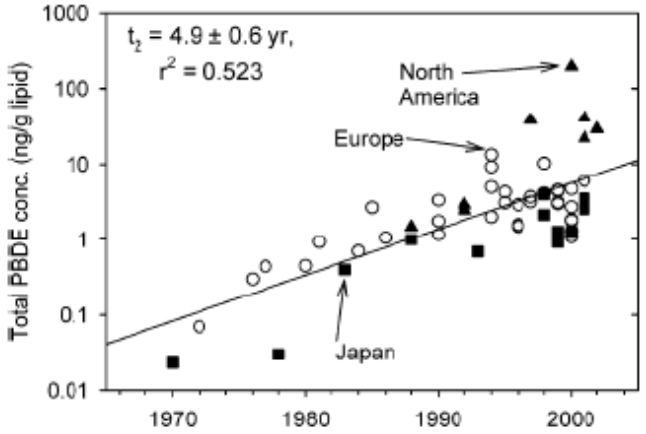


FIGURE 1. Total PBDE concentrations (∑PBDE) in human blood, milk, and tissue (in ng/g lipid) shown as a function of the year in which the samples were taken; see Table 2. The three symbol types indicate the location from which the samples were collected. The overall regression is shown.

Germany, 1985-1999

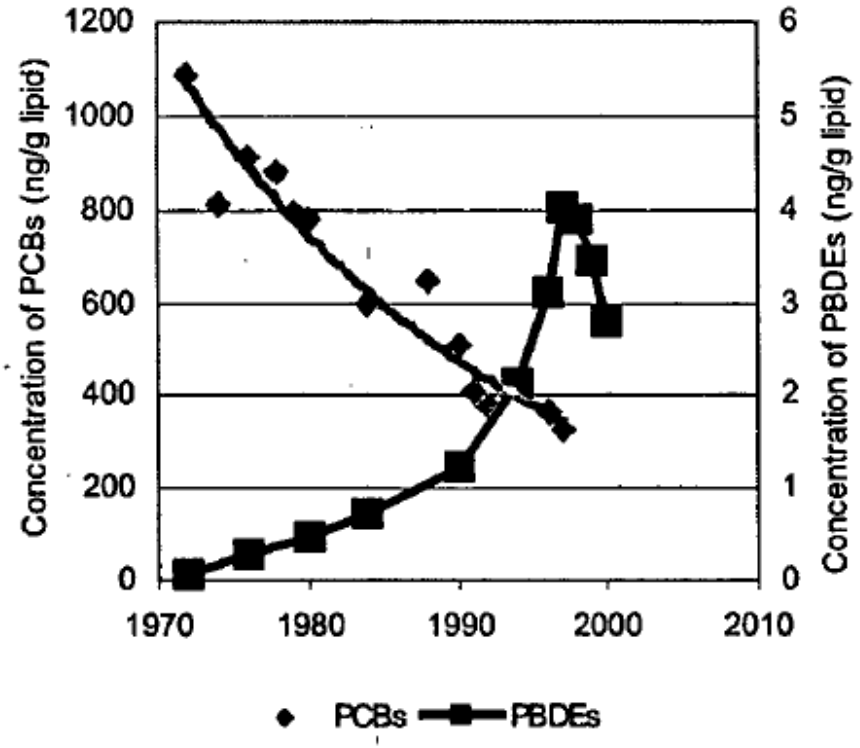
Europe & North America

Schröter-Kermani et al. German environmental specimen bank: application in trend monitoring of PBDE in human blood. Organohalogen. 2000; 47: 49-52

Hites RA. PBDE in the environment and in people: a meta-analysis of concentrations. Environ Sci Tech. 2004;38:945-956.

Temporal Trends of PBDEs in Human Tissue

Sweden



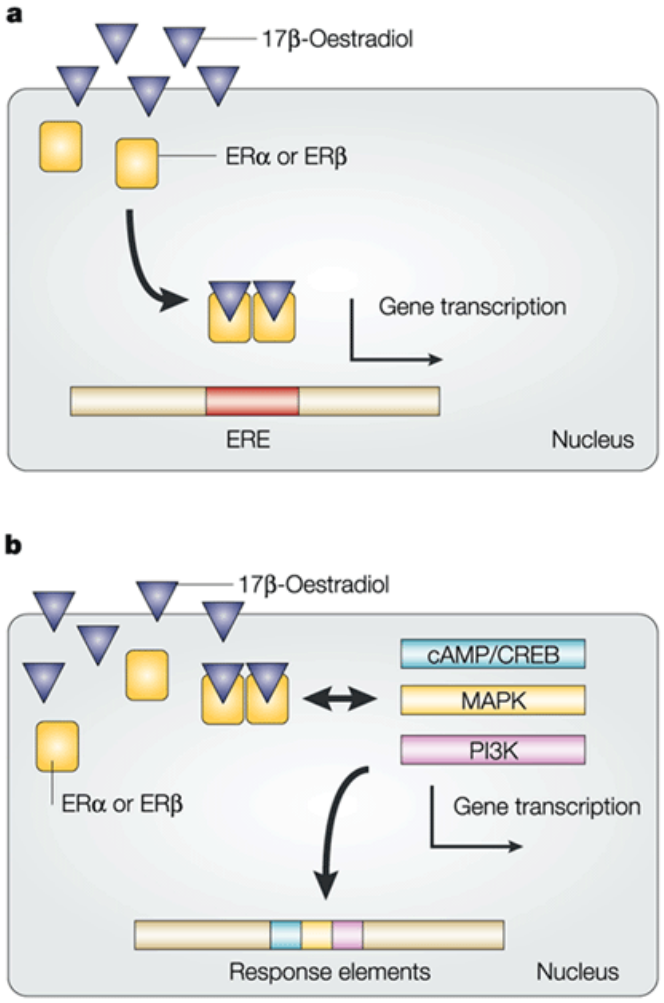
Noren & Meironyte. Certain organochlorine and organobromine contaminats in Swedish human milk in perspective of past 20-30 years. Chemosphere. 2000. 40:1111-1123.

Sources of Human Exposure to Flame Retardants

- Indoor air and dust
- Direct contact with treated products
- Contaminated food – fish, poultry, beef, dairy and eggs

Fromme *et al*. Human exposure to PBDEs, as evidenced by data from a duplicate diet study, indoor air house dust, and biomonitoring in Germany. Environ Int. 20009; 35:1125-1135

Proposed Mechanism with Breast Cancer



Nature Reviews | Neuroscience

Behl C. Oestrogen as a neuroprotective hormone. Nature Reviews Neuroscience. 2002; 3:433-442

Epidemiological Evidence to Date

Study	Country	Results	Details
McElroy et al. 2004	USA	Premenopausal - 70% increased risk (RR: 1.70, 1.16-2.50) Postmenopausal - No association	• Consumption of sport-caught fished used as a proxy for exposure
Hurley et al. 2011	USA	No association	• Small sample size • (78 cases, 56 controls) • More representative control series needed
Brophy et al. 2012	Canada	Overall - Increased risk (OR: 2.68, 1.47-4.88) Premenopausal OR: 4.76, 1.58-14.4	• Occupation in automotive plastics manufacturing as proxy for exposure

Significance

- High prevalence of exposure so even small risk increase may have significant effect at the population level

- Influence policy to inform regulation and improve risk mitigation

Chemoprevention of prostate cancer

EPIB 671 Cancer Epidemiology and Prevention
Student Symposium 2015

Joice Rocha Cury

Prostate Cancer Facts

- Prostate cancer is the most prevalent cancer in males in North America

- 2nd leading cause of cancer mortality in USA males and 3rd in Canadian men

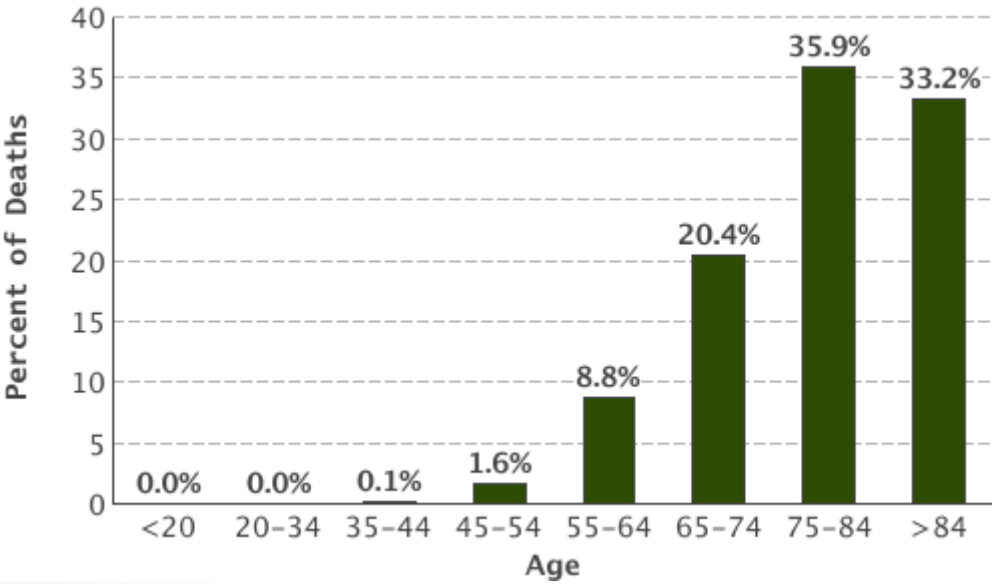
	USA[1]	Canada[2]
New cases/100,000*	137.9	99.3
Deaths/100,000*	21.4	17.4
Estimated number of men living with prostate cancer in 2015	2,795,592	176,365

*These rates are age-adjusted and based on 2008-2012 (USA) and 2008-2010 (Canada) cases and deaths.

1. SEER Stat Fact Sheets: Prostate Cancer, National Cancer Institute at the National Institute of Health http://seer.cancer.gov/statfacts/

2.Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2015.Toronto, ON: Canadian Cancer Society; 2015.

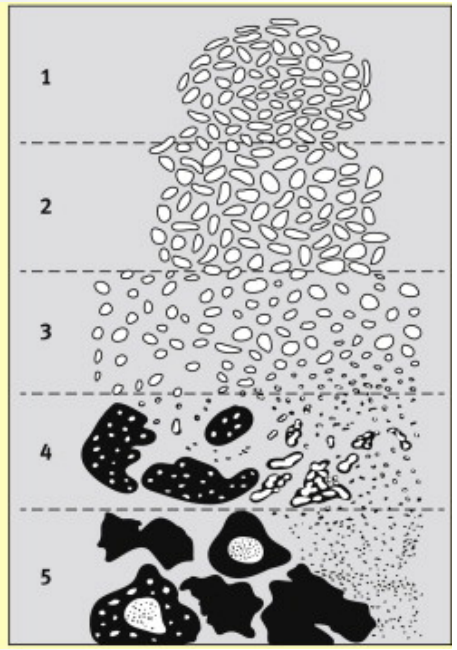
Percent of New Cases by Age Group: Prostate Cancer



Median Age At Diagnosis **66**

SEER 18 2008-2012, All Races, Males

Prostate Cancer grading



- **Gleason Grading**: 1-5 from well differentiated to least differentiated
- **Gleason score (GS):** 2 most common patterns (2-10)

PSA cut-off >4ng/ml (2.5 ng/ml)

- **Low risk**: one lobe of the prostate, GS ≤ 6 and PSA ≤10
- **Intermediated risk**:1-2 prostate lobes, GS ≤ 7 and/or a PSA ≤ 20 not of low risk
- **High risk:** extra capsular, Gleason 8-10 or PSA > 20

Epstein JI. 2005 Am J Surg Pathol. 29:1228-41

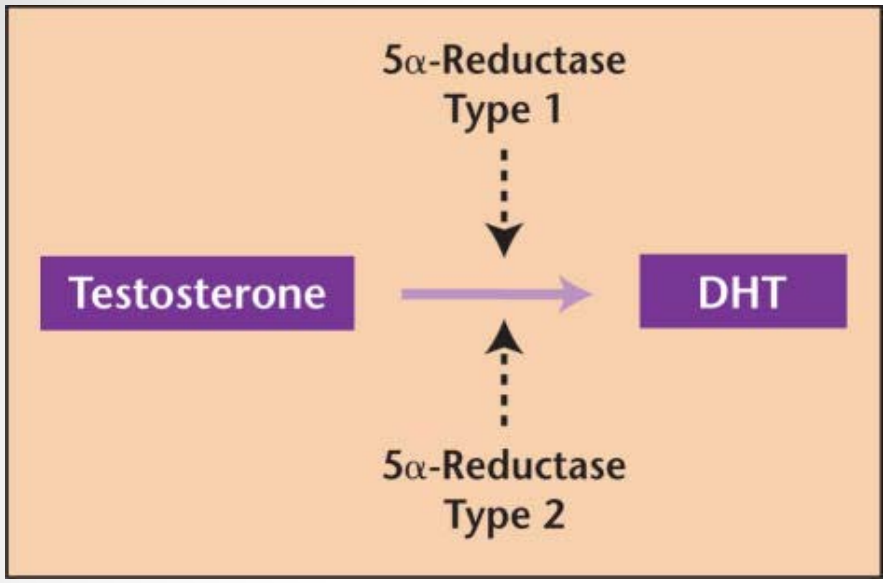
Prostate cancer chemoprevention

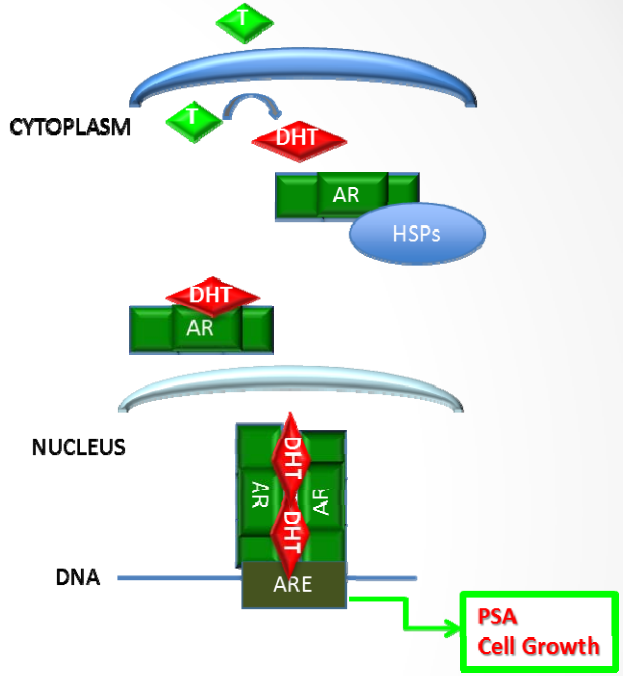
Table 1. Status of Putative Agents for Prevention of Prostate Cancer

	Presumed Mechanisms of Action	Findings to Date	Status
		Chemoprevention	
Finasteride	• Inhibits 5 α reductase	• 25% reduction in total prostate cancer risk after 7 years • 1.3% increased rate of high-grade tumors in the finasteride arm during the first year	Phase III trial completed
Dutasteride	• Inhibits 5 α reductase	• Have recruited ~ 8,000 men; results awaited	Phase III trial ongoing
Statins	• Inhibition of mevalonate CoA metabolism • Modulate cell cycle intermediates • Anti-inflammatory	• Conflicting observational evidence • Synergistic action with other chemopreventive agents • Concomitant benefit of the reduction of cardiovascular events	Epidemiological and experimental evidence
Selective estrogen receptor modulators	• Block estrogen-induced cell proliferation	• 48% reduction in risk seen in phase II trial • Fewer side effects than androgen inhibitors	Phase II trial completed Phase III trial ongoing

- Jayachandran and Freedland, American Journal of Men's Health 2008

5-alpha reductase inhibitors (ARI)





- 5-ARI reduced DHT (dihydrotestosterone) the major intra-prostatic androgen
- Shrinks the prostate gland, reducing lower urinary tract symptoms(LUTS)

Marks. Rev Urol. 2004;
Rocha Cury, 2013

5-ARI

- Finasteride – **Type1** 5-ARI (Proscar 5mg ,Propecia 1mg)
- Dutasteride – **Type 1 and 2** 5-ARI(Avodart) and in combination with tamsulosin (Jalyn)
- Proscar, Avodart and Jalyn are approved to **improve symptoms of benign prostatic hyperplasia** or BPH and reduce the risk of urinary retention
- Propecia is approved to treat **male pattern hair loss**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 15, 2013 VOL. 369 NO. 7

Long-Term Survival of Participants in the Prostate Cancer Prevention Trial

Ian M. Thompson, Jr., M.D., Phyllis J. Goodman, M.S., Catherine M. Tangen, Dr.P.H., Howard L. Parnes, M.D., Lori M. Minasian, M.D., Paul A. Godley, M.D., Ph.D., M. Scott Lucia, M.D., and Leslie G. Ford, M.D.

PCPT

- Randomized, double-blind, placebo-controlled, multicenter trial
- 18,882 men age 55 or older, with normal DRE and PSA levels ≤3.
- Evaluated the impact of daily use of Finasteride 5mg (n=9423) *versus* placebo (n=9459) in the reduction of prostate risk
- 7 years or until diagnosis of prostate cancer, initiation of BPH treatment with a 5-ARI or unacceptable side effects
- US guided biopsy was performed at the end of study or before if PSA>4 or abnormal DRE.
- Follow-up 18-years

Prostate cancer risk and survival outcomes

Table 1. Relative Risk of Prostate Cancer in the Finasteride Group, as Compared with the Placebo Group, According to Cancer Grade.*

Prostate-Cancer Grade	Primary 2003 Report†		Current Study‡	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Any grade	0.75 (0.69–0.81)	<0.001	0.70 (0.65–0.76)	<0.001
Low grade	0.62 (0.56–0.68)	<0.001	0.57 (0.52–0.63)	<0.001
High grade	1.27 (1.07–1.50)	0.005	1.17 (1.00–1.37)	0.05

* Low-grade cancers had a Gleason score of 2 to 6; high-grade cancers had a Gleason score of 7 to 10.

† Included in this analysis were men who had undergone end-point assessment, according to the protocol-specified window of inclusion. When all men who had undergone randomization were included, the relative risk in the finasteride group was 0.70 for any grade of prostate cancer (P<0.001), 0.58 for low-grade cancer (P<0.001), and 1.19 for high-grade cancer (P=0.05).

‡ Included in this analysis were eligible men who had undergone randomization and all prostate cancers detected during the follow-up period that extended through June 2004.

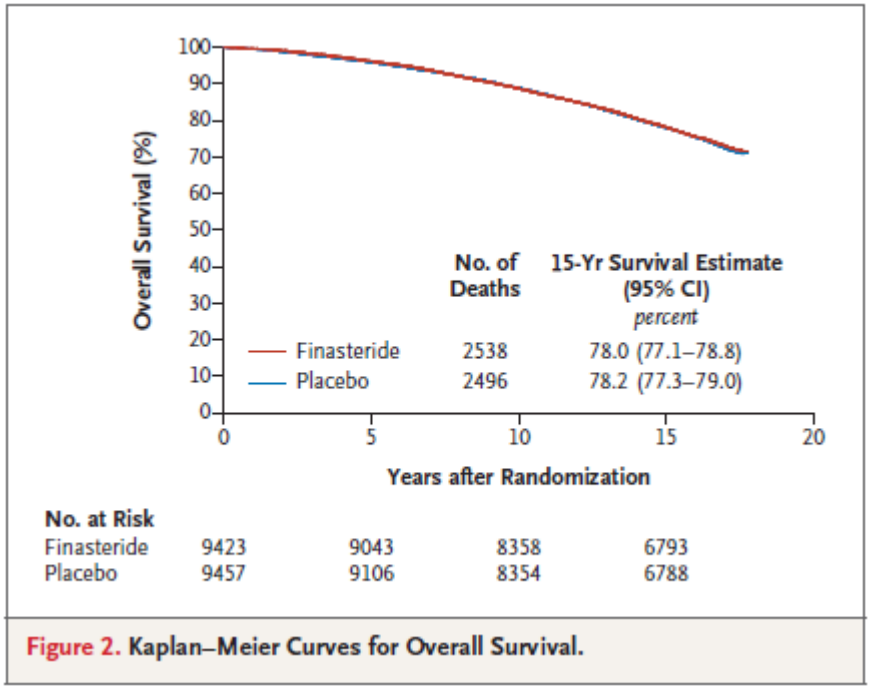


Figure 2. Kaplan–Meier Curves for Overall Survival.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Dutasteride on the Risk of Prostate Cancer

Gerald L. Andriole, M.D., David G. Bostwick, M.D., Otis W. Brawley, M.D., Leonard G. Gomella, M.D., Michael Marberger, M.D., Francesco Montorsi, M.D., Curtis A. Pettaway, M.D., Teuvo L. Tammela, M.D., Claudio Teloken, M.D., Ph.D., Donald J. Tindall, Ph.D., Matthew C. Somerville, M.S., Timothy H. Wilson, M.S., Ivy L. Fowler, B.S.N., and Roger S. Rittmaster, M.D., for the REDUCE Study Group*

Reduce

- Randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of dutasteride (once daily) in reducing the risk of biopsy-detectable prostate cancer
- 8231 men age 50-75 years (considered to be at risk for prostate cancer)
- PSA 2.5-10ng/ml and a negative biopsy
- Dutasteride 0.5mg (n=4105) versus placebo (n=4126)
- Duration 4 years; biopsies were performed at 2 and 4 years.

Prostate cancer risk reduction

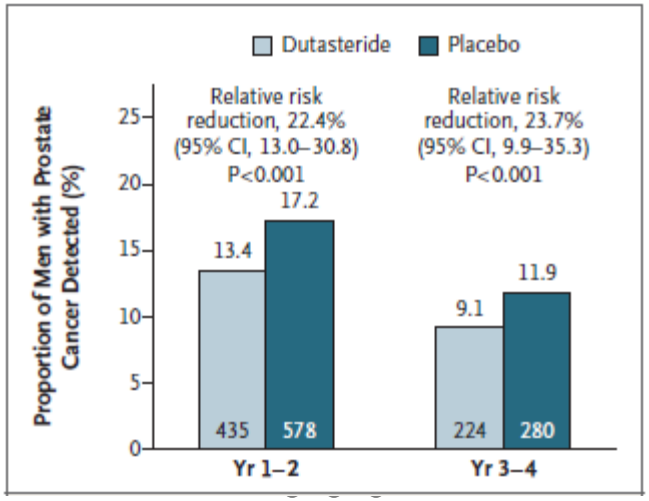


Figure 2. Proportions of Men with a Positive Biopsy for Prostate Cancer, According to Treatment Period and Group.

Data are shown for the efficacy population (i.e., all randomly assigned subjects with a baseline prostate biopsy that had been reviewed centrally and determined to be negative and who received at least one dose of study medication). Restricted crude rates of prostate cancer are shown (i.e., from analysis that included men who underwent at least one biopsy after baseline). The P value is for the comparison of dutasteride with placebo, with the use of the Mantel–Cox test. The numbers in the bars are numbers of men.

Detection of Prostate Cancer according to GS

Table 3. Detection of Prostate Cancer on Biopsy, According to Gleason Score, Treatment Period, and Treatment Group.*

Gleason Grade and Score	Years 1 and 2			Years 3 and 4			Years 1 through 4		
	Dutasteride (N=3239)	Placebo (N=3346)	P Value†	Dutasteride (N=2447)	Placebo (N=2343)	P Value†	Dutasteride (N=3299)	Placebo (N=3407)	P Value†
	no. (%)			*no. (%)*			*no. (%)*		
All tumors	434 (13.4)	576 (17.2)		223 (9.1)	274 (11.7)		657 (19.9)	850 (24.9)	
Grade 5 or 6	290 (9.0)	401 (12.0)	<0.001	147 (6.0)	216 (9.2)	<0.001	437 (13.2)	617 (18.1)	<0.001
5	1 (<0.1)	3 (0.1)		0	1 (<0.1)		1 (<0.1)	4 (0.1)	
6	289 (8.9)	398 (11.9)		147 (6.0)	215 (9.2)		436 (13.2)	613 (18.0)	
Grades 7–10	144 (4.4)	175 (5.2)	0.15	76 (3.1)	58 (2.5)	0.19	220 (6.7)	233 (6.8)	0.81
7‡	127 (3.9)	157 (4.7)		64 (2.6)	57 (2.4)		191 (5.8)	214 (6.3)	
3+4	99 (3.1)	125 (3.7)		47 (1.9)	51 (2.2)		146 (4.4)	176 (5.2)	
4+3	28 (0.9)	32 (1.0)		17 (0.7)	6 (0.3)		45 (1.4)	38 (1.1)	
8–10	17 (0.5)	18 (0.5)	1.00	12 (0.5)	1 (<0.1)	0.003	29 (0.9)	19 (0.6)	0.15
8	7 (0.2)	11 (0.3)		5 (0.2)	0		12 (0.4)	11 (0.3)	
9	10 (0.3)	7 (0.2)		6 (0.2)	1 (<0.1)		16 (0.5)	8 (0.2)	
10	0	0		1 (<0.1)	0		1 (<0.1)	0	

* The Gleason score is the sum of the two most common histologic patterns or grades in a prostate tumor, each of which is graded on a scale of 1 to 5, with 5 being the most cytologically aggressive.
† P values were calculated with the use of Fisher's exact test (unstratified analysis).
‡ Prostate cancers that comprise both Gleason pattern 3 and Gleason pattern 4 are classified as 3+4 if pattern 3 predominates and 4+3 if pattern 4 predominates.

Risk reduction of LUTS

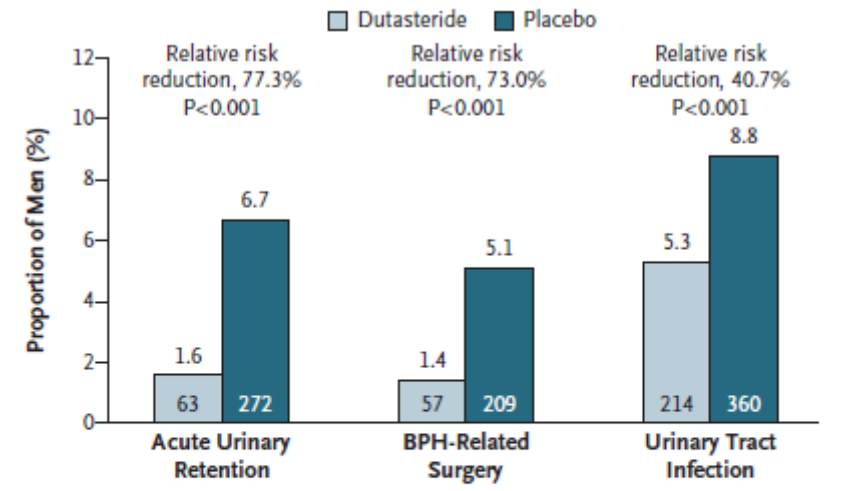


Figure 3. Proportions of Men Who Had an Episode of Acute Urinary Retention, Who Underwent Surgery Related to Benign Prostatic Hyperplasia (BPH), or Who Had a Urinary Tract Infection over the Course of the 4-Year Study Period.

The P values are for the comparison of dutasteride with placebo, with the use of the log-rank test. The numbers in the bars are numbers of men.

Discussion

- 5ARI reduces 23-25% overall prostate cancer risk (mostly low grade disease)

High grade disease real or artifact

- Sampling density bias - due to the reduction of gland volume
- PSA sensitivity
- High grade disease reduction of PSA was initially less increasing indication of biopsies and tumor detection

Number need to treat and harm

	PCPT	REDUCE*
NNT (to prevent 1 case of any GS CaP)	17	19-20
NNH (to cause 1 GS 7-10 CaP)	77	NA
NNT (to prevent 1 case of GS 7-10 CaP)	NA	250-1000
NNH (to cause 1 GS 8-10 CaP)	100	200-333

NNT = number needed to treat; NNH = number needed to harm; NA = not applicable (because incidence of GS ≥7 CaP in PCPT is higher and in REDUCE is lower in the treatment group vs the placebo group).
* Using both the classic (mentioned first) and the modified GS systems.

- Reviewed in Dunn *et al* JNCI 2015; Azzzouni and Mohler, Urology 2015

Recommendations

- Not approved for prostate cancer prevention by the FDA

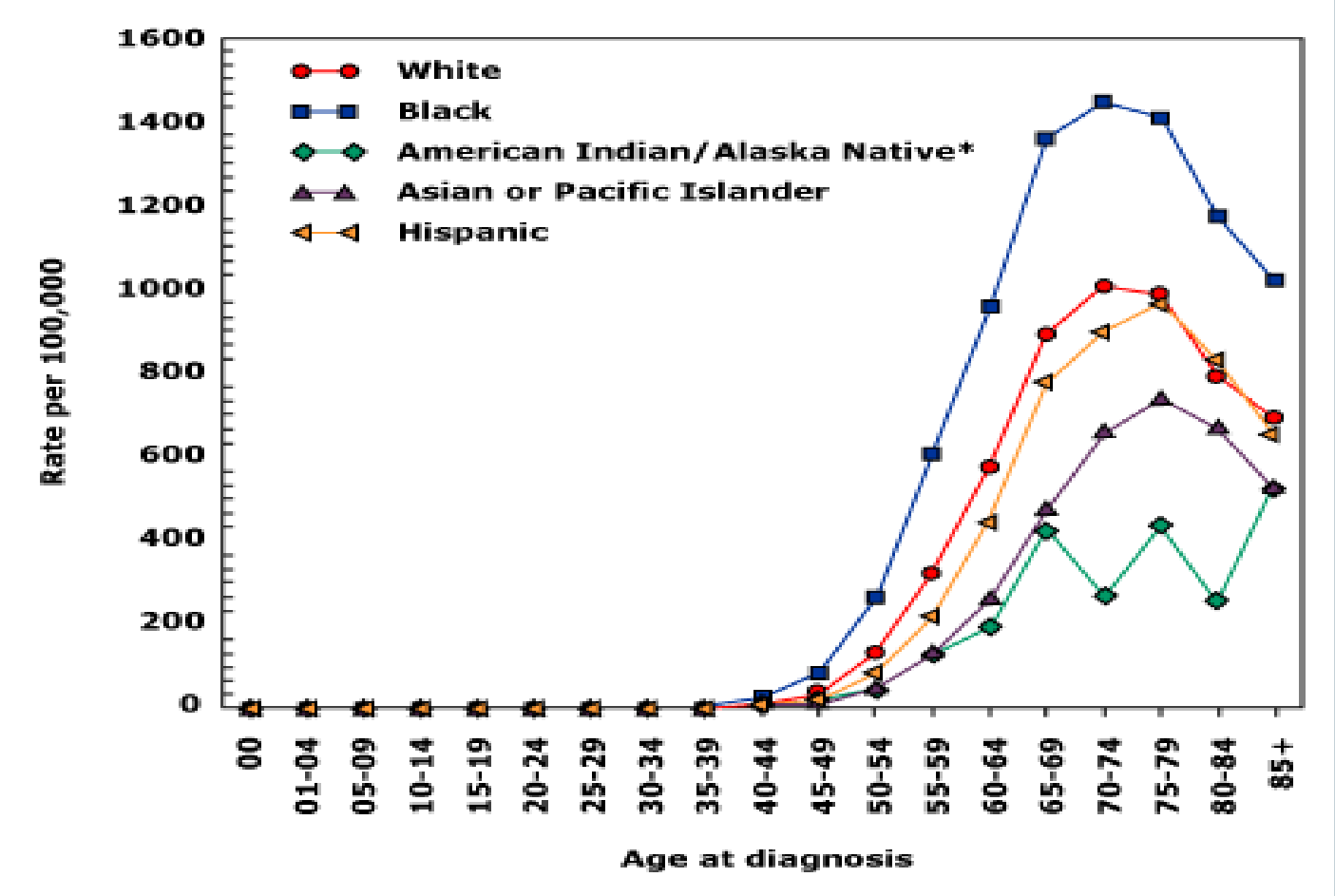
- AUA/ASCO- Asymptomatic men with a prostate-specific antigen (PSA) ≤3.0 ng/mL who are regularly screened with PSA **may benefit from a discussion of** both the **benefits of 5-ARIs for 7 years** for the prevention of prostate cancer and the **potential risks of high grade disease**

PSA Testing for Prostate Cancer Screening

HUDA ALTOUKHI
RADIATION ONCOLOGY
JUNE, 2015

- Prostate cancer is the 2nd most common cancer in men worldwide
- The 2nd leading cause of male cancer death
- The current lifetime risk of prostate cancer for in the US is estimated to be 16%
- The risk of dying of prostate cancer is only 2.9%

Age specific incidence rate



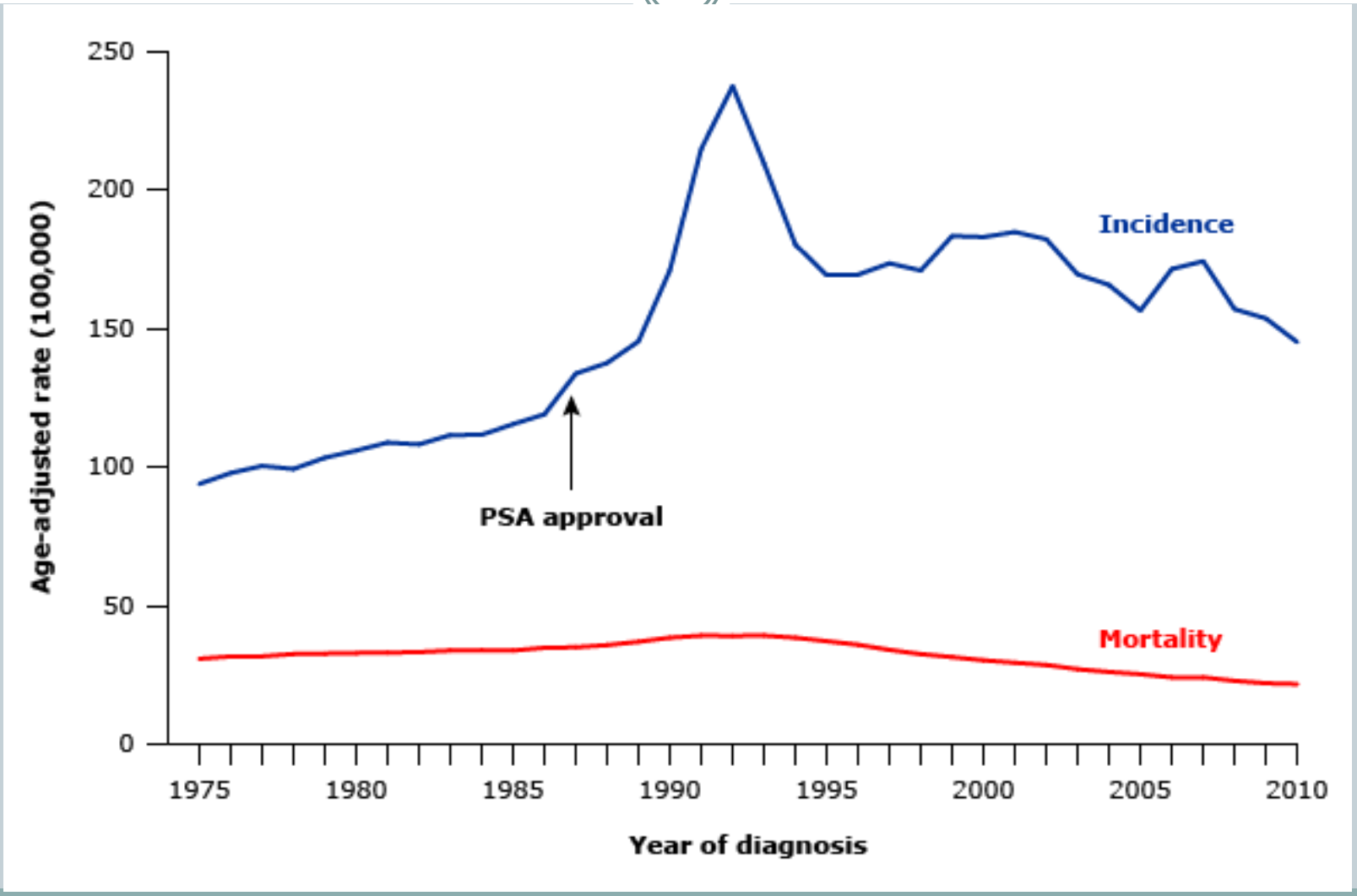
Surveillance, Epidemiology, and End Results (SEER) Program

PSA Screening

- Originally introduced as a tumor marker to detect cancer recurrence or disease progression following treatment.
- The use of PSA as a screening tool has increased in the US since 1988 -> led to a dramatic increase in the incidence of prostate cancer, peaking in 1992
- After an initial peak, incidence rates fell, but they have persisted at a rate nearly twice that recorded in the pre-PSA era
- Countries that do not utilize PSA testing typically have a much lower rate of prostate cancer compared to those that do.

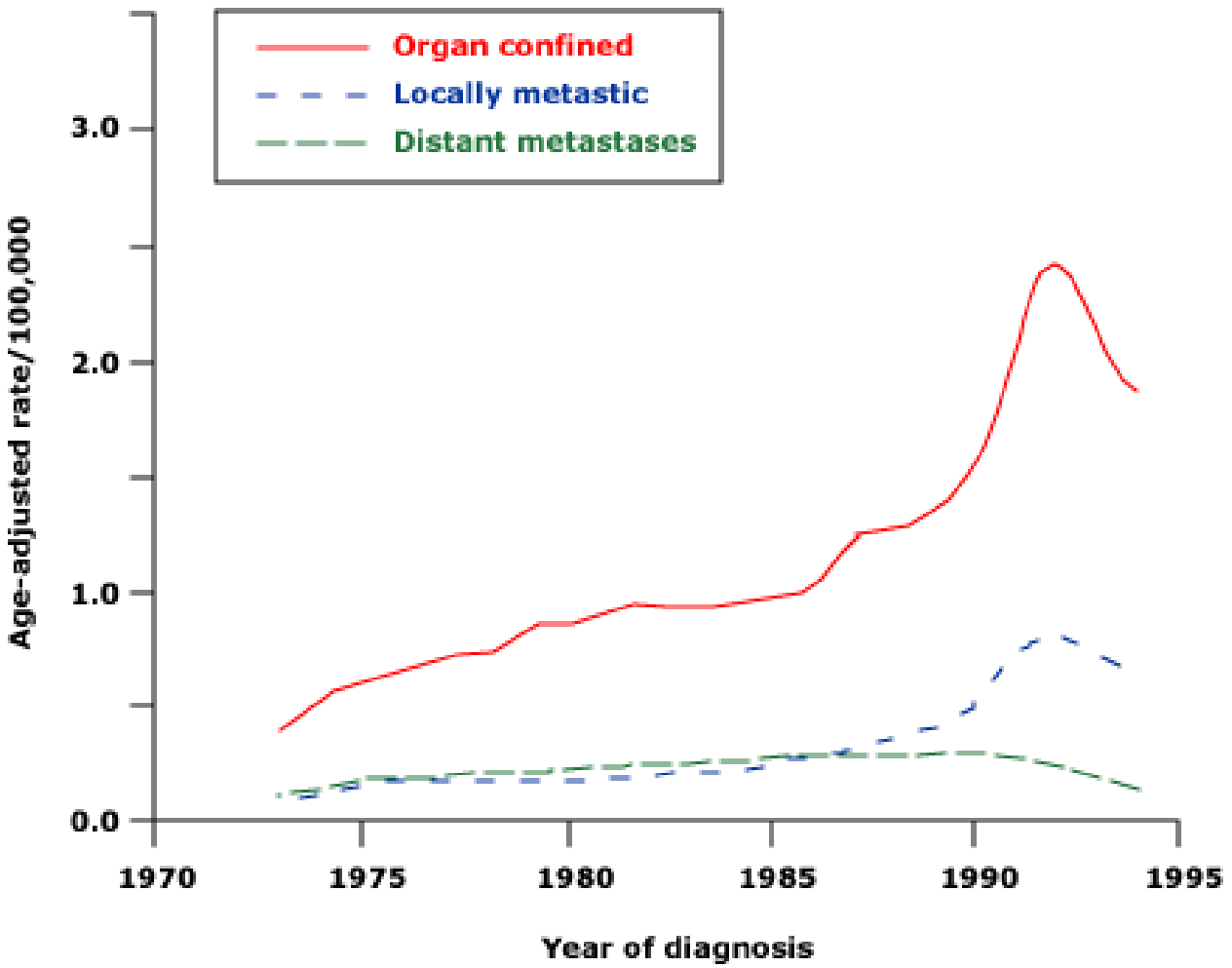
JAMA 1995;273:548-52

Prostate Cancer Incidence



Data from: Surveillance Epidemiology and End Results program

Rate of prostate cancer



Data from Farkas, A, Schneider, D, Perrotti, M, et al, Urology

PLCO Project Team

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.,

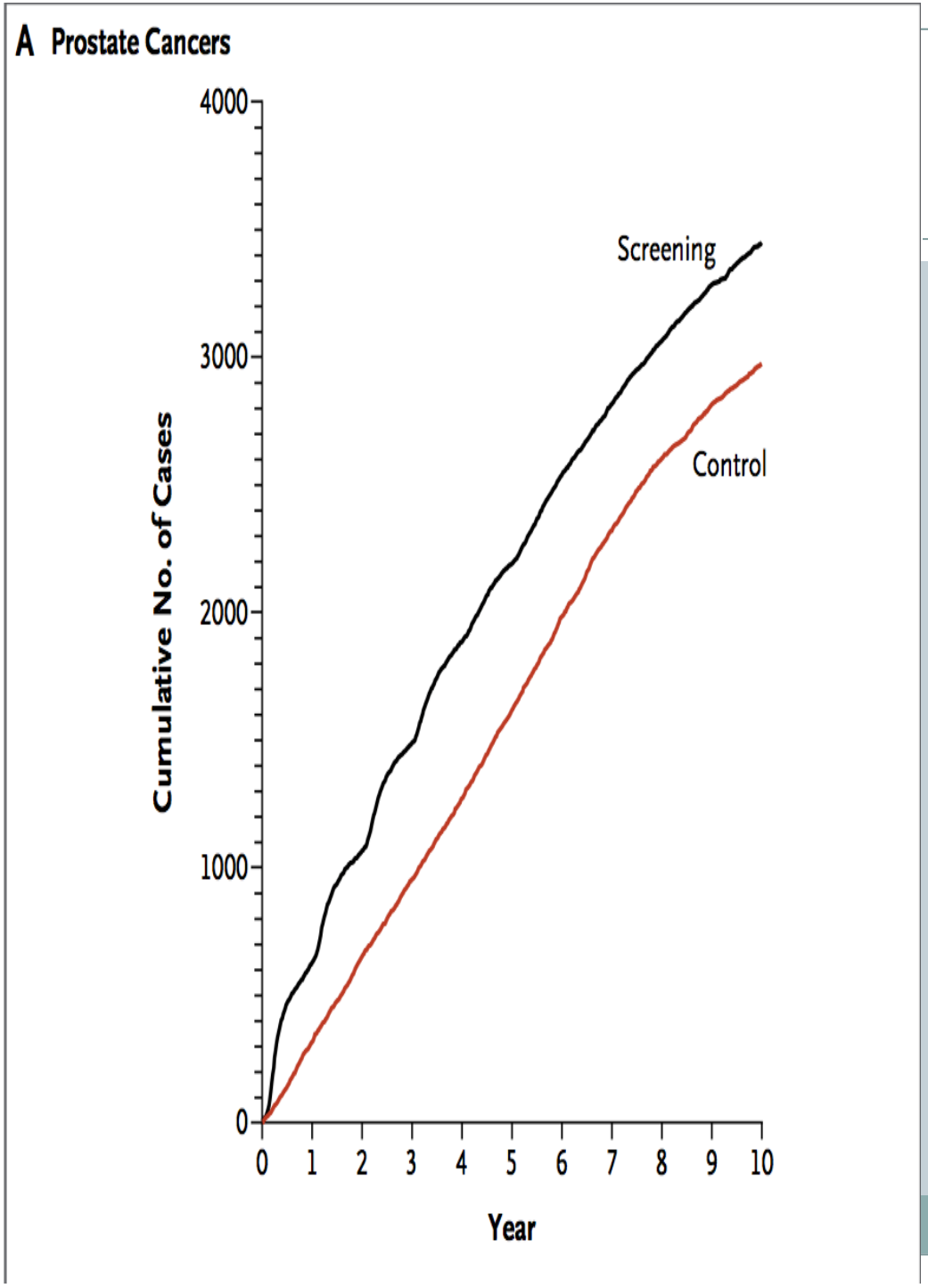
Objective: to determine the effect of screening with PSA testing and DRE on the rate of death from prostate cancer.

Intervention: 76,693 men randomly assigned 55-74 years from 1993-2001
Screening group: Annual PSA for 6 years and DRE for 4 years

*A serum PSA level of more than 4.0 ng/ml was considered to be positive for prostate cancer.

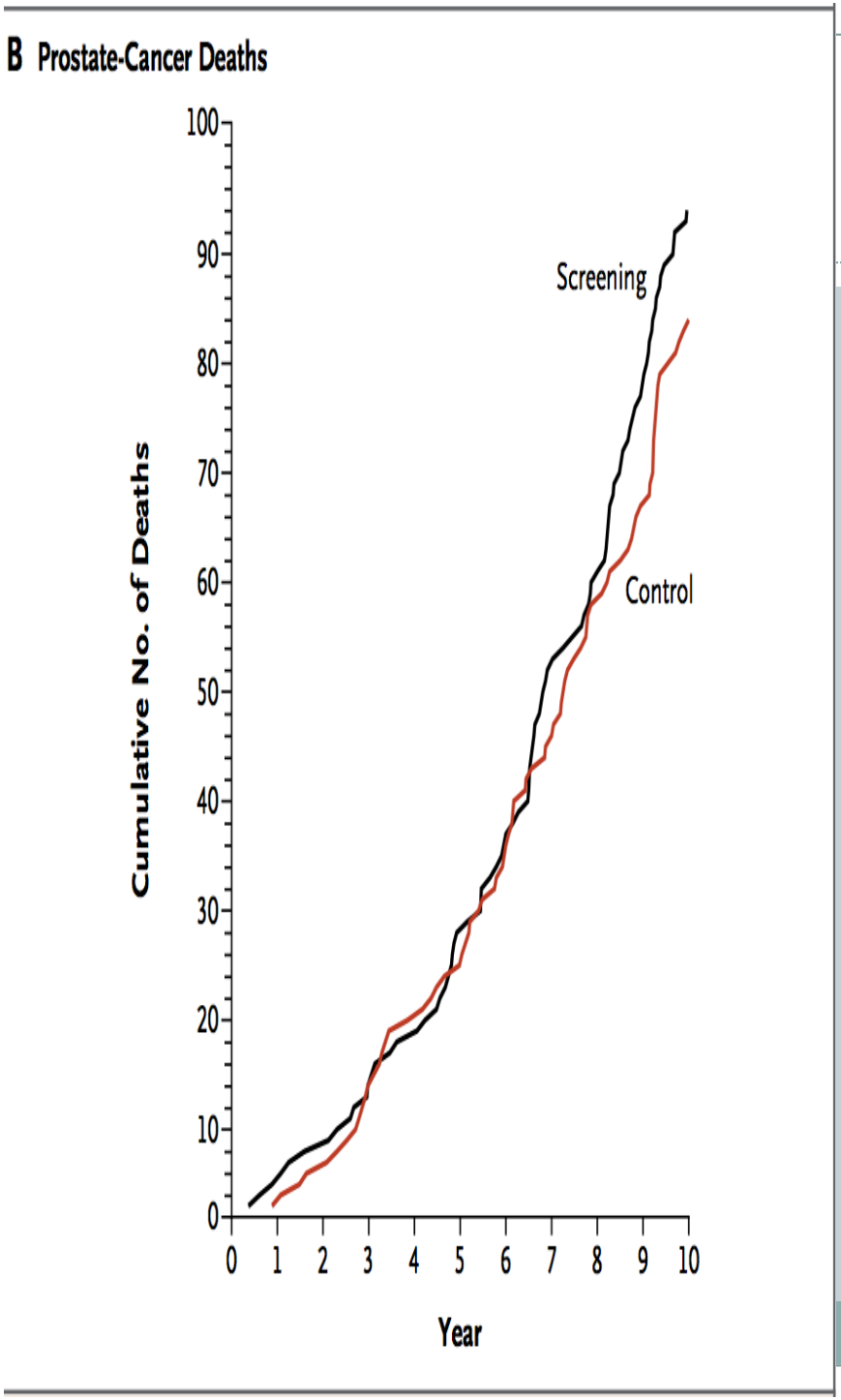
Exclusion criteria: history of a PLCO cancer, current cancer treatment, and having had more than one PSA blood test in the previous 3 years

End point: cause specific mortality



Results: after 7-10 years follow up the incidence of prostate cancer per 10,000 person-years was 116 in the screening group and 95 in the control group

At 10 years (rate ratio, 1.17; 95% CI, 1.11 to 1.22)



Results: The incidence of death per 10,000 person-years was 2.0 in the screening group and 1.7 in the control group

At 10 years, there were 83 deaths in the screening
group and 75 in the control group (rate ratio, 1.09; 95% CI, 0.80 to 1.50)

Conclusion: After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups.

ERSPC (European Randomized Study of Screening for Prostate Cancer)

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.,

Objective: to evaluate the effect of screening with PSA on death rates from prostate cancer

Intervention: 182,000 men between the ages of 50 and 74 years in seven European countries

Screening group: PSA screening once every 2- 4 years

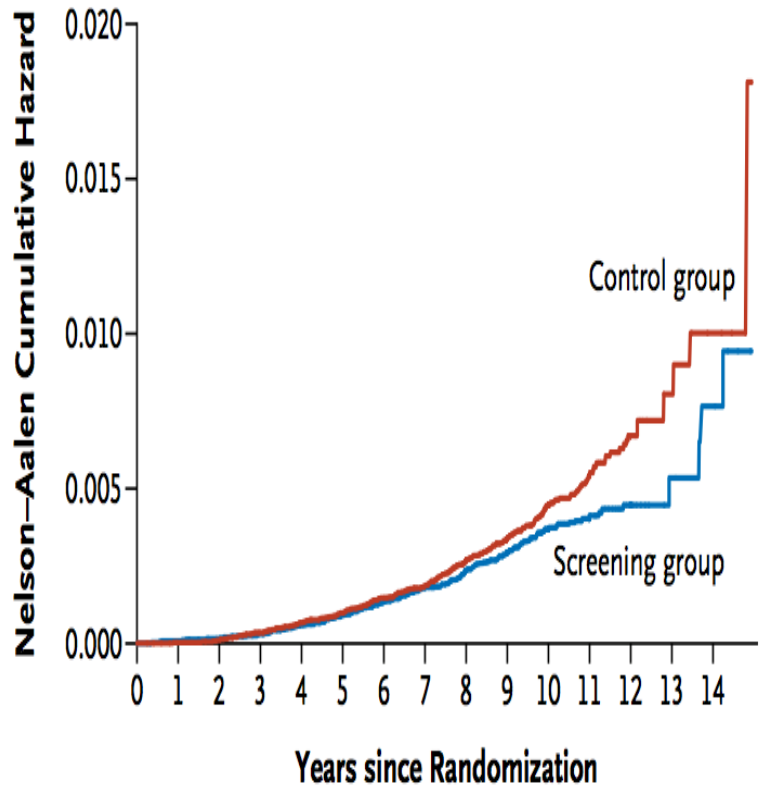
Control group: no screening offered

*PSA cutoff value of 3.0 ng/ml as an indication for biopsy.

Median follow up: 9 years (initiated in the early 90s, ended in December 31, 2006)

End point: 5990 prostate cancers in the screening group and 4307 in the control group -> cumulative incidence of 8.2% and 4.8%

ERSPC Results



No. at Risk			
Screening group	65,078	58,902	20,288
Control group	80,101	73,534	23,758

- Average follow up 8.8 years
- 214 prostate-cancer deaths in the screening group and 326 in the control group.
- The adjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95% CI, 0.65 to 0.98; P=0.04)

- n engl j med 360;13

Cumulative Risk of Death from Prostate Cancer

ERSPC Results/ Follow Up

After 11 years, PSA-based screening reduced the rate of death from prostate cancer by 20%
The rate of overdiagnosis was estimated to be as high as 50% in the screening group.

After 13 years, a 21% relative reduction in prostate cancer was found in intention to screen analyses.
-> 781 men needed to be screened and 27 to be diagnosed with prostate cancer to avert one death from the disease

Conclusion: Despite showing a clear prostate cancer mortality reduction, the findings are not sufficient to justify population-based screening

U.S. Preventive Services
TASK FORCE

Population	Recommendation	Grade (What's This?)
Men, Screening with PSA	The U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA)-based screening for prostate cancer.	D

Insufficient evidence in men under the age of 75 years to assess the balance between benefits and side effects associated with screening, and the panel recommended against screening men over the age of 75 years

Canadian Task Force
on Preventive Health Care

Screening Recommendations differ

- **The American Urological Association** and **The American Cancer Society** recommend offering annual PSA testing and DRE beginning at the age of 50 years to men with a normal risk of prostate cancer and beginning at an earlier age to men at high risk.

- **Prostate Cancer Canada** disagrees with the recommendations and has launched this Support PSA Tests campaign to remind Canadians that the benefits of PSA screening far outweigh the negatives.

What are the benefits and harms of screening 1000 men aged 55–69 y† with a PSA test every 1–4 y for 10 y?	
Possible benefit of screening	**Men, *n***
Reduced 10 y risk for dying of prostate cancer	
Die of prostate cancer with no screening	5 in 1000
Die of prostate cancer with screening	4–5 in 1000
Do not die of prostate cancer because of screening	0–1 in 1000

The benefits of PSA-based screening for prostate cancer do not outweigh the harms.

The harms of screening: pain, fever, bleeding, infection, and transient urinary difficulties associated with prostate biopsy, psychological harm of false-positive test results, and overdiagnosis

Harms of treatment: erectile dysfunction, urinary incontinence, bowel dysfunction, and a small risk for premature death. many men are being subjected to the harms of treatment for prostate cancer that will never become symptomatic.

Thank You

Refrences:

- Draisma G, Boer R, Ot to SJ, et a l. Lead 30.times and overdetection due to prostate specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003;95:868-78http://
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