# McGill EPIB-671 Symposium - 2017

## Scientific Program, Friday, May 26

| Time | Presenter | Title |
|---|---|---|
| 13:00-13:15 | Host | Introduction to the symposium and instructions |
| 13:15-13:30 | Victor Brochu | Cell phone use and brain tumours |
| 13:30-13:45 | Melina Janelle | Formaldehyde: the risk behind pathology practice |
| 13:45-14:00 | Ben Royal-Preyra | Pros and cons of PSA screening |
| 14:00-14:15 | Sindy Magnan | Screening for anal cancer |
| 14:15-14:30 | Samar Kaifi | Vitamin D and cancer risk |
| 14:30-14:45 | Lojain Bassyoni | Precancerous lesions of the oral cavity |
| 14:45-15:00 | Gabriel Silva-Pinto | *Chlamydia trachomatis* as a co-factor in cervical cancer risk |
| 15:00-15:15 | ***Coffee Break*** | |
| 15:15-15:30 | Atuhani Burnett | Cancer: Is it just bad luck? |
| 15:30-15:45 | Baharak Khadang | Epidemiology of mesothelioma |
| 15:45-16:00 | Robin Luo | Depression and cancer risk |
| 16:00-16:15 | Ayesha Baig | Betel-quid and areca-nut chewing: the ugly truth! |
| 16:15-16:30 | Karena Volesky | Epidemiology of *H. pylori* and gastric cancer |
| 16:30-16:45 | Karyne Martel | Screening for genetic variants in breast cancer patients |
| 16:45-17:00 | Catch-up with content, exam, and end of course: Have a Happy Summer! | |

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

# Handheld 2b

(CELL PHONE USE AND BRAIN CANCER)

VICTOR BROCHU M.D., C.M.

EPIB-671 CANCER EPIDEMIOLOGY

MAY 26TH 2017

# Outline

Brain cancer overview

Cell phone overview

Epidemiology

- Important case control and cohort studies
- Meta-analyses

Conclusions

# Primary brain cancer

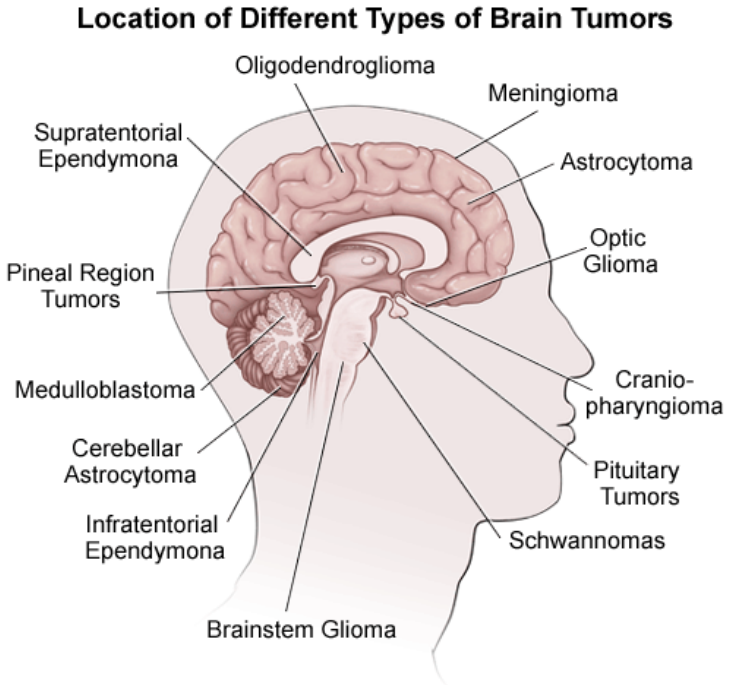
**Glioma**

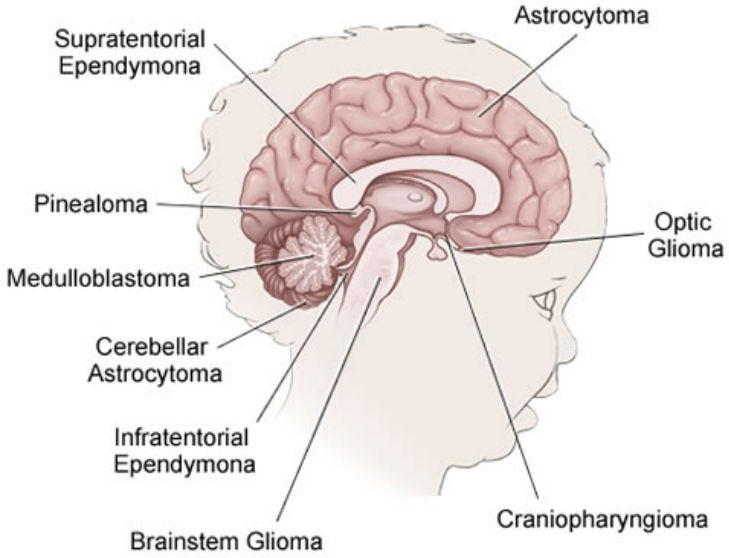
- Astrocytoma
  - Grade I: Pilocytic astrocytoma- SEGA
  - Grade II: Diffuse astrocytoma- PMA- PXA
  - Grade III: Anaplastic astrocytoma
  - **Grade IV: Glioblastoma**
- Oligodendroglioma
- Ependymoma

**Meningioma**

Acoustic neuroma

PNET/Medulloblastoma



# Primary brain cancer

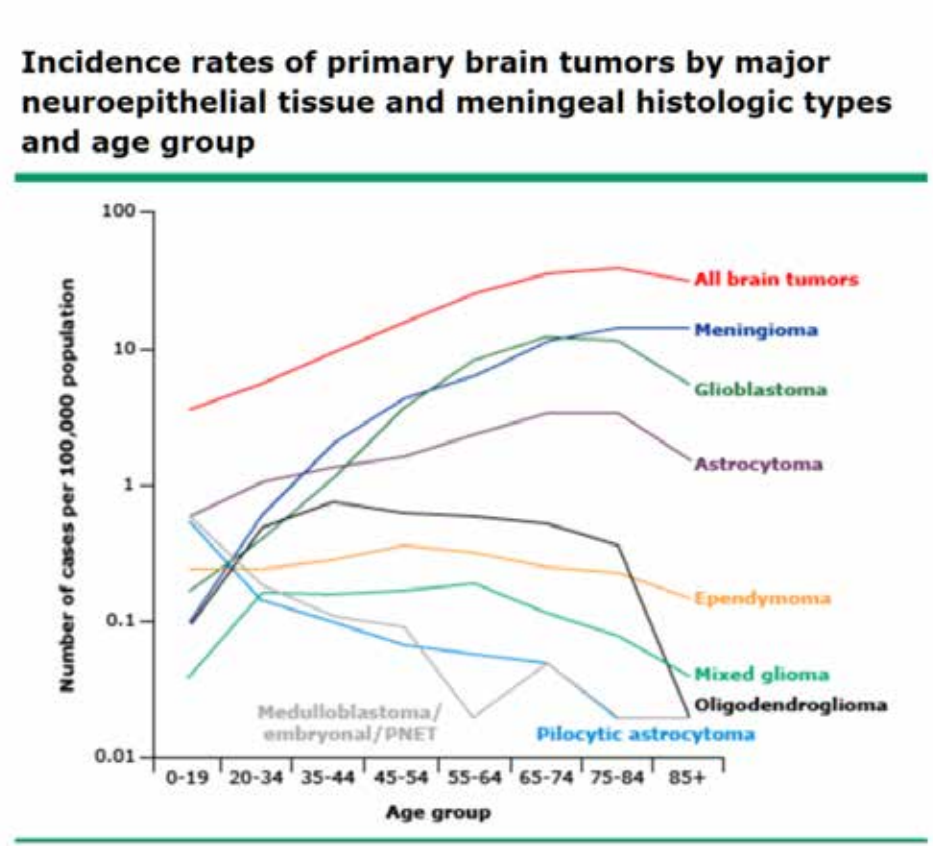
2% of all cancers, disproportionate mortality rate

- US incidence rate 28.6 per 100,000
- US annual age-adjusted mortality rate 5.8 per 100,000

5 year survival:

- Overall 34%
- Anaplastic astrocytoma 28 %
- Glioblastoma 5%

High morbidity associated to treatment



# Risk factors

Occupational?

Trauma?

Allergies (protective)?

Diet?

Tobacco?

Alcohol?

Infections?

**Genetics**

- Accounts for 10% of cases
- NF1/NF2, von Hippel-Lindau, Li-Fraumeni, FAP, Turcot, Gorlin, familial glioma

Radiation

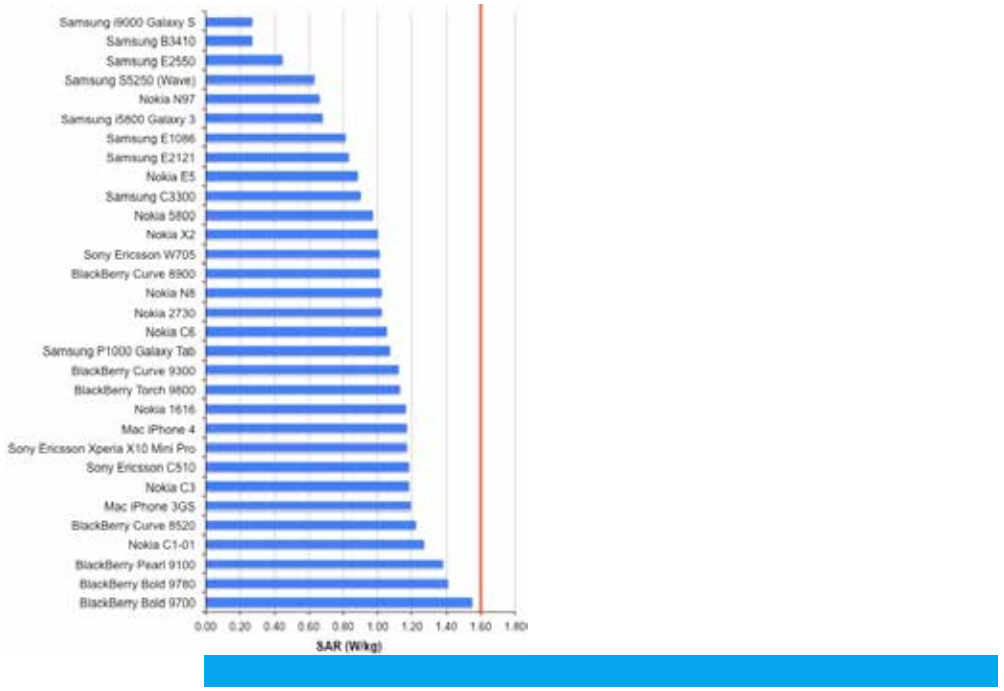
- **Ionizing**
- Electromagnetic?
- **Radiofrequency?**

# Why cellular phones

1993 on Larry King Live, CNN
- “the tumor was exactly in the pattern of the antenna”
- Urged NCI to conduct epidemiologic research

Rapid increase in cell phone use prevalence
- 327.5 million U.S. users (2014) from 110 million (2000)

“Radiofrequency radiation” exposure
- Length and frequency of use
- Distance to the head
- Distance of cell phone tower
- Cell phone traffic in direct area
- Phone specific absorption rate (SAR)
  - 1.6 W/kg upper limit (FCC)




Full body MRI : 4 W/kg

# Radiofrequency on the body

3 kHz – 300 GHz

- Non-ionising à Cannot break DNA

Heating?

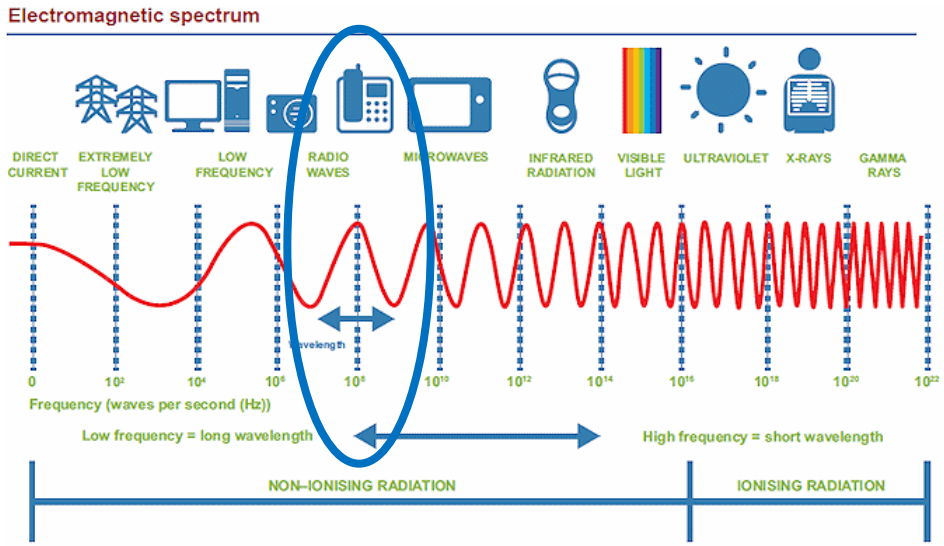
- Microwave known to heat via RF
- Cell phones no change in body temperature

Change brain glucose metabolism?

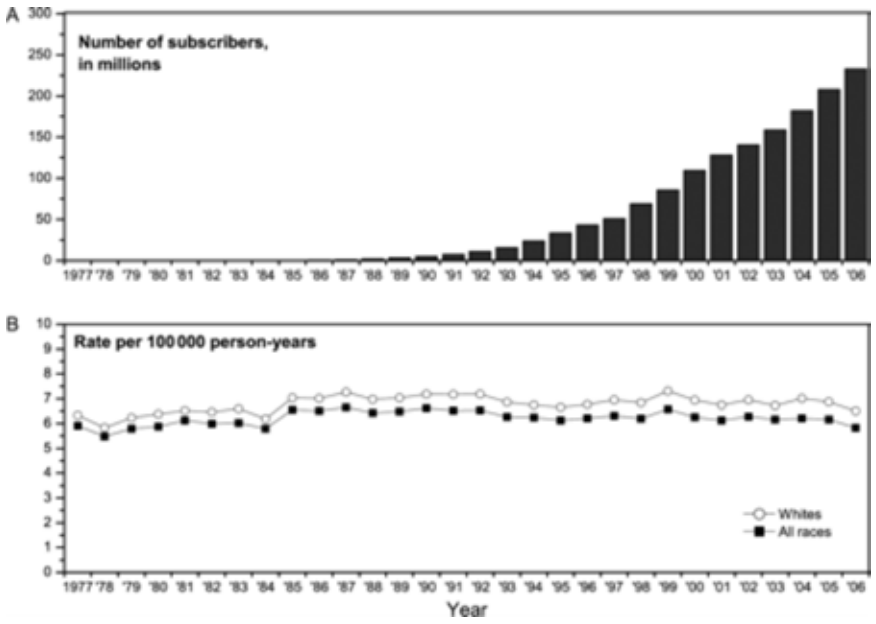
- Volkow ND et al. Effects of cell phone radiofrequency signal exposure on brain glucose metabolism. *JAMA* 2011; 305(8):808–813
- Kwon MS et al. GSM mobile phone radiation suppresses brain glucose metabolism. *Journal of Cerebral Blood Flow and Metabolism* 2011; 31(12):2293-301

Change in cerebral bloodflow?

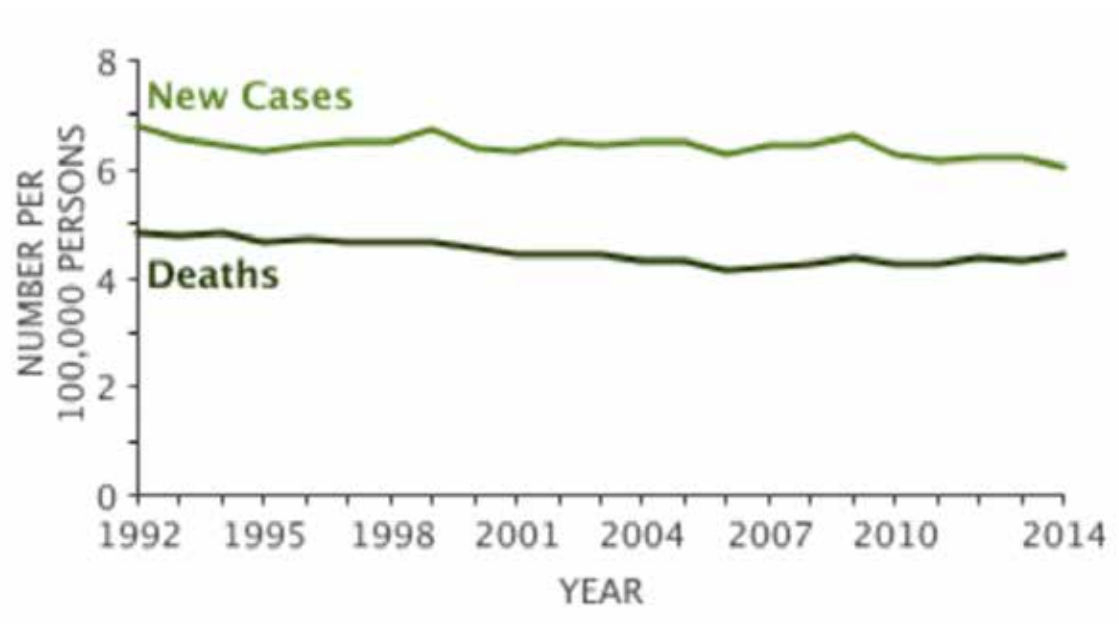
- Kwon MS et al. No effects of short-term GSM mobile phone radiation on cerebral blood flow measured using positron emission tomography.*Bioelectromagnetics* 2012; 33(3):247-56.



# Change in brain cancer incidence?




From: Brain cancer incidence trends in relation to cellular telephone use in the United States
Neuro Oncol. 2010;12(11):1147-1151.




https://seer.cancer.gov/statfacts/html/brain.html

# Danish study

## Method

- Retrospective cohort study in Denmark
- Billing information from all cell phone users from 1982 – 1995 (420 095 subscribers)
- All cancer incidence data from the Danish Cancer Registry

## Results

- No Statistically increased SIR

| | 2001 | 2006 | 2011 |
|---|---|---|---|
| Brain SIR | 0.95 (0.81 - 1.12) | 0.66 (0.44 to 0.95) | ♂ 1.03 (0.83 - 1.27)<br>♀ 0.91 (0.41 - 2.04) |

## Conclusion

- Does not support association of cell phone use and incidence of cancers, particularly brain cancers.


Johansen C, Boice J Jr, McLaughlin J, Olsen J. Cellular telephones and cancer: a nationwide cohort study in Denmark. Journal of the National Cancer Institute 2001; 93(3):203–207

Schüz J, Jacobsen R, Olsen JH, et al. Cellular telephone use and cancer risk: update of a nationwide Danish cohort. Journal of the National Cancer Institute 2006; 98(23):1707–1713.

Frei P, Poulsen AH, Johansen C, et al. Use of mobile phones and risk of brain tumours: update of Danish cohort study. British Medical Journal 2011; 343:d6387.

# The INTERPHONE Study Group

## Method

- Interview based case control studies pooled from 13 countries
- 2708 glioma and 2409 meningioma cases and matched controls

## Results

| | Ever user | 10+ years user | 10th decile cumulative call time (>1640 h) |
|---|---|---|---|
| Glioma | 0.81 (0.70-0.9) | 0.98 (0.76-1.26) | 1.40 (1.03-1.89) |
| Meningioma | 0.79 (0.68-0.91) | 0.83 (0.61-1.14) | 1.15 (0.81-1.62) |

## Conclusions

- No statistically significant increases in brain or central nervous system cancers related to higher amounts of cell phone use over 10 or more years
- Important participation/recall biases

The INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *International Journal of Epidemiology* 2010; 39(3):675–694

# Million Women Study

Method

- UK prospective cohort, self-reported via questionnaire
- 791,710 middle-aged women reporting cell phone use from 1999 to 2005, 7 years follow-up

Results

| | Ever user | 10+ years user |
|---|---|---|
| Glioma | 1.01 (0.90-1.14) | 0.78 (0.55-1.10) |
| Meningioma | | 1.10 (0.66-1.84) |
| Acoustic neuroma | | 2.46 (1.07-5.64)<br>*1.17 (0.60–2.27) |

Conclusion:

- Self-reported cell phone use not associated with an increased risk of glioma, meningioma, or non-central nervous system tumors

Benson VS, Pirie K, Schüz J, et al. Mobile phone use and risk of brain neoplasms and other cancers: Prospective study. *International Journal of Epidemiology* 2013; 42(3): 792-802.

Benson VS, Pirie K, Schüz J, et al. Authors' response to: the case of acoustic neuroma: comment on mobile phone use and risk of brain neoplasms and other cancers.International Journal of Epidemiology 2014; 43(1):275.

# Limitations

Recall bias
- Brain tumor patients might remember cell phone use differently

Inaccurate reporting
- Cell phone usage difficult to quantify

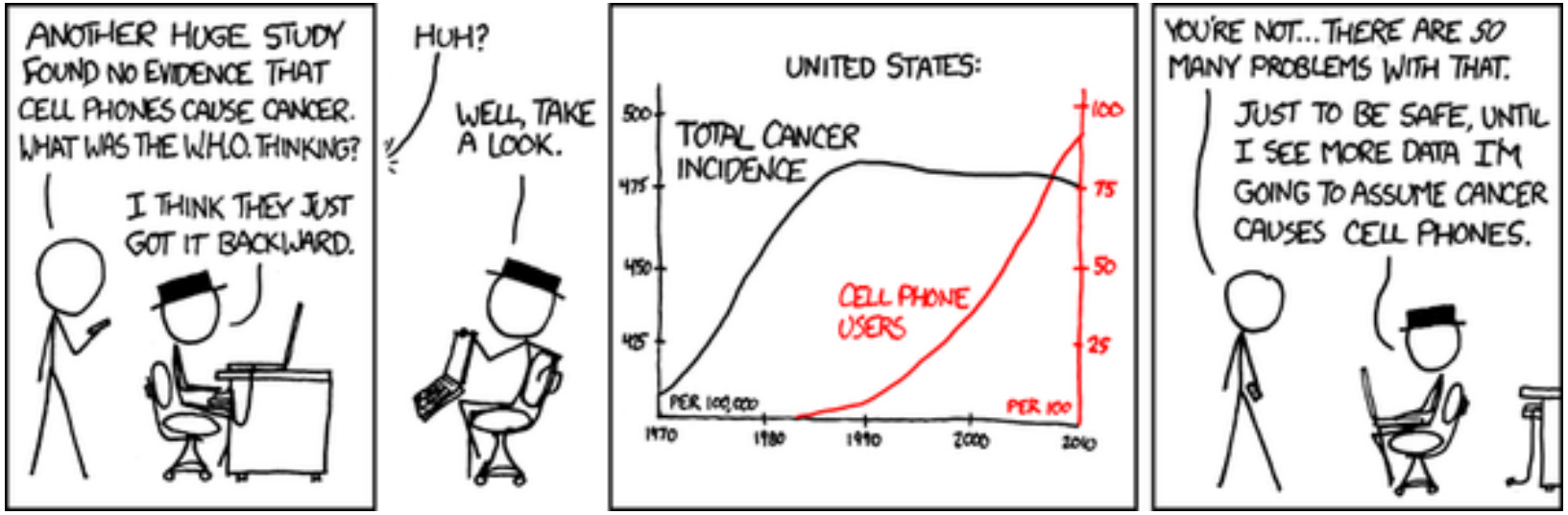
Morbidity and mortality
- Glioblastoma has a very short survival, treated patients become impaired

Participation bias
- Brain cancer patients really want to participate in research studies, compared to healthy individuals
- In control group, heavy users more likely to participate

Latency
- Only 10 years in most studies

Change in cell phone technology
- Analog vs digital cell phones, WiFi, 3G/4G/LTE, texting, Bluetooth headsets

# What now?


ANOTHER HUGE STUDY FOUND NO EVIDENCE THAT CELL PHONES CAUSE CANCER. WHAT WAS THE W.H.O. THINKING?
I THINK THEY JUST GOT IT BACKWARD.
HUH?
WELL, TAKE A LOOK.
UNITED STATES:
TOTAL CANCER INCIDENCE
CELL PHONE USERS
500
475
450
425
100
75
50
25
PER 100,000
PER 100
1970
1980
1990
2000
2010
YOU'RE NOT... THERE ARE SO MANY PROBLEMS WITH THAT.
JUST TO BE SAFE, UNTIL I SEE MORE DATA I'M GOING TO ASSUME CANCER CAUSES CELL PHONES.

# Systematic reviews

| Paper reference | Category | Cum. OR | 95% CI |
|---|---|---|---|
| Leng, L. The relationship between mobile phone use and risk of brain tumor: a systematic review and meta-analysis of trails in the last decade, *Chinese Neurosurgical* Journal, December 2016 2:38 | Ever user | 1.04 | 0.86 – 1.25 |
| Prasad, M. et al. Mobile phone use and risk of brain tumours: a systematic review of association between study quality, source of funding, and research outcomes, *Neurological Sciences*, May 2017, Volume 38, Issue 5, pp 797–810 | Ever user<br>10+ years user | 1.03<br>**1.33** | 0.92 – 1.14<br>1.07 – 1.66 |
| Repacholi, M. H. et al. Systematic review of wireless phone use and brain cancer and other head tumors, *Bio Electro Magnetics,* Volume 33, Issue 3, April 2012, Pages 187–206 | Ever user<br>1-6 years use<br>10+ years use | 1.07<br>1.03<br>1.40 | 0.89–1.29<br>0.86–1.24<br>0.84–2.31 |
| Yang M, Guo W, Yang C, Tang J, Huang Q, Feng S, Jiang A, Xu X, Jiang G. Mobile phone use and glioma risk: A systematic review and meta-analysis, *PLoS One*. 2017 May 4 ; 12(5). | Glioma 10+ years user<br>Low grade glioma | **1.44**<br>**2.22** | 1.08-1.91<br>1.69-2.92 |
| Bortkiewicz A, Gadzicka E, Szymczak W. Mobile phone use and risk for intracranial tumors and salivary gland tumors - A meta-analysis. *Int J Occup Med Environ Health*. 2017 Feb 21;30(1):27-43 | 10+ years users | **1.324** | 1.028-1.704 |
| M, Hardell L. Evaluation of Mobile Phone and Cordless Phone Use and Glioma Risk Using the Bradford Hill Viewpoints from 1965 on Association or Causation. Biomed Research International. 2017 | 10+ years users<br>20+ years users | **1.62**<br>**2.01** | 1.20-2.19<br>1.41-2.88 |

Very sparse and heterogeneous data in all case-control and cohort studies…

# Hills criteria

| Criteria | Results | Comment |
|---|---|---|
| Strength | OR 1.90 (1.31-2.76) with highest cumulative exposure (>1640h) | Recall bias? |
| Consistency | Cum. OR 1.62 (1.20-2.19) with 10+ years latency | |
| Specificity | Increased risk for glioma was in the temporal lobe | And ipsilateral side |
| Temporality | OR = 2.01 (1.41-2.88) with 20+ years latency | |
| Biological gradient | Cumulative use increases risk | Only in top 1 decile |
| Plausibility | Increased production of reactive oxygen species (ROS) from RF radiation in mice spermatocytes cell lines | |
| Coherence | Change in the natural history of glioma and increasing incidence | UK 2003-2013 very small increase |
| Experiment | Antioxidants reduced ROS production from RF radiation | |
| Analogy | Increased risk in subjects exposed to extremely low-frequency electromagnetic fields. | Classified Group 2b just like RF |

# Conclusions

IARC: Possibly carcinogenic to humans (Group 2B)

- Limited evidence on humans
  - Bias
  - Cannot rule out causal association
- Limited evidence on mice
- Inconsistent evidence on mechanistic studies

Recent trend of increased risk in meta-analyses?

Further studies…

# Future studies

Some existing cohorts are still followed

- Longer latency

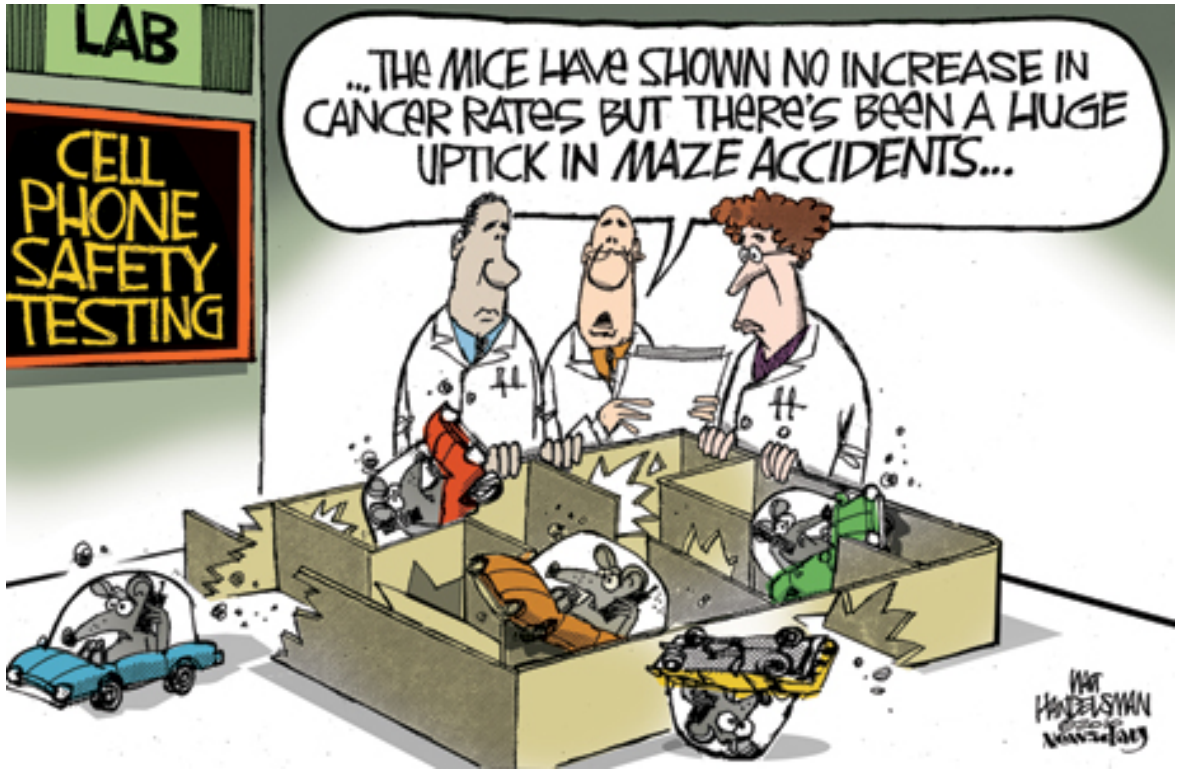
COSMOS: Large prospective cohort study

- Launched March 2010
- 290 000 European cell phone users aged 18+ followed for 20-30 years

National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation

- 1.5 W/kg to 6 W/kg of RF to mice
- 9 hours per day, 2 years
- Partial release of data June 2016
  - Males = low risk, Females no risk

# Thank you!


LAB
CELL PHONE SAFETY TESTING
...THE MICE HAVE SHOWN NO INCREASE IN CANCER RATES BUT THERE'S BEEN A HUGE UPTICK IN MAZE ACCIDENTS...

# References


M, Hardell L. Evaluation of Mobile Phone and Cordless Phone Use and Glioma Risk Using the Bradford Hill Viewpoints from 1965 on Association or Causation. Biomed Research International. 2017

Michaud, D. et al., Incidence of primary brain tumors; UptoDate; Last updated Nov 11 2015; accessed May 25th 2017

Michaud, D. et al., Risk factors for brain tumors; UptoDate; Last updated Aug 22 2016; accessed May 25th 2017

Linet, M.S. et al. Cellular (Mobile) Telephone Use and Cancer Risk, Rev Environ Health. 2010 Jan-Mar; 25(1): 51–55

Volkow ND et al. Effects of cell phone radiofrequency signal exposure on brain glucose metabolism. *JAMA* 2011; 305(8):808–813

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Cellular phones, American Cancer Society, Last updated August 4, 2016, accessed May 25th 2017

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Yang M, Guo W, Yang C, Tang J, Huang Q, Feng S, Jiang A, Xu X, Jiang G. Mobile phone use and glioma risk: A systematic review and meta-analysis, *PLoS One*. 2017 May 4 ; 12(5).

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M, Hardell L. Evaluation of Mobile Phone and Cordless Phone Use and Glioma Risk Using the Bradford Hill Viewpoints from 1965 on Association or Causation. Biomed Research International. 2017

Wyde, M et al. Report of Partial findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation in Hsd: Sprague Dawley® SD rats (Whole Body Exposure), BioRxiv beta, preprint June 23 2016

Illustrations:
https://www.saintlukeshealthsystem.org/health-library/brain-tumors-introduction
https://www.uptodate.com/contents/image?imageKey=ONC%2F72275&topicKey=NEURO%2F5216&source=outline_link
http://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/brain_tumor/center/pediatric/tumors/
https://www.niehs.nih.gov/news/newsroom/releases/2016/may27/cellphone_508.pdf
http://www.ict-pulse.com/2011/07/how-safe-is-your-mobile-phone/
https://xkcd.com/925/
http://smg.photobucket.com/user/voxman/media/GIF%20File%202/Political%20Cartoons/imageCAX51OKG.jpg.html
https://seer.cancer.gov/statfacts/html/brain.html

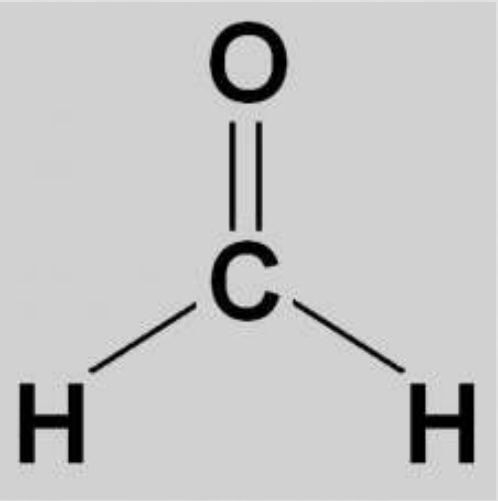
# FORMALDEHYDE: THE RISK OF CANCER ASSOCIATED WITH PATHOLOGY PRACTICE

MÉLINA JANELLE
PGY1 ANATOMICAL PATHOLOGY

MAY 26TH 2017

# FORMALDEHYDE

- Colorless gas with pungent odor
- $CH_2O$
- Formalin: aqueous solution 30-50% per weight
  - Formalin used in path: 10%
  - Dilution creates methylene glycol $CH_2(OH)_2$
- Methanol and other substances added as stabilizer
- Ubiquitant gaseous pollutant
  - Outdoor sources
  - Indoor sources
- Human carcinogen class 1 (IARC)
  - Nasopharyngeal cancer
  - Leukemia (myeloid)



# USE

## (NON EXHAUSTIVE LIST)

- Resins
  - Wood products
  - Surface coatings
  - Textile, leather, cement and rubber industry
  - Insulating material
  - Controlled-release nitrogen fertilizers
- Intermadiate chemical product
  - Plastics
  - Synthetic lubricating oils and plasticizers
  - Explosives
  - Polyurethane (foam)
  - Dye and tanning agents
  - Animal feeds
  - Perfumes
  - Vitamins, flavourings and drugs
  - Pesticides
- Disinfectant and preservative
  - Drugs
  - Embalm biological specimen
  - Cosmetic products
- Corrosion inhibitor
  - Mirror finishing
  - Electronics
  - Photographic film

# EXPOSURE

- Mainly inhaled, can be asborbed by the skin and GI tract
- Non occupational exposure
  - Normally present in outdoor and indoor air < 0.03ppm (US Consumer Product Safety Commission)
- Short-term exposure to high level (>3ppm) (IARC 2006)
  - Pathologists
  - Embalmers
  - Paper workers
- Highest continuous exposure (2-5ppm) (IARC 2006)
  - Varnishing of furnitures and wooden floors
  - Finishing of textiles
  - Garment industry
  - Treatment of fur
  - Manufactured board mills and foundries

# EXPOSURE

| Reference | Context | Mean level (ppm) | Range (ppm) |
|---|---|---|---|
| Rosén *et al.* (1984), Sweden | Pathology lab | 0.5 | NR |
| Triebig *et al.* (1989), Germany | Pathology lab | 0.5 | < 0.01–1.2 |
| Shaham *et al.* (2002), Israel | Histology lab | Assitant / technicians: 0.4<br>Physicians / orderlies: 2.2<br>Area samples: NR<br>Personal samples: NR | 0.04–0.7<br>0.7–5.6<br>1.4–1.6<br>2.8–3.1 |
| Skisak (1983), USA | Anatomy lab | NR | 0.3–2.6 |
| Akbar-Khanzadeh *et al* (1994), USA | Anatomy lab | Area samples: 1.7<br>Personal samples: 0.4 | 1.0–2.3<br>0.09–0.95 |
| Heikkilä *et al.* (1991), Finland | Varnishing<br>Resin plant<br>Furniture factories<br>Wood industry | 2.9<br>2.3<br>0.3<br>0.7 | 0.3–6.6<br>1.0–3.4<br>0.07–1.0<br>0.07–1.8 |

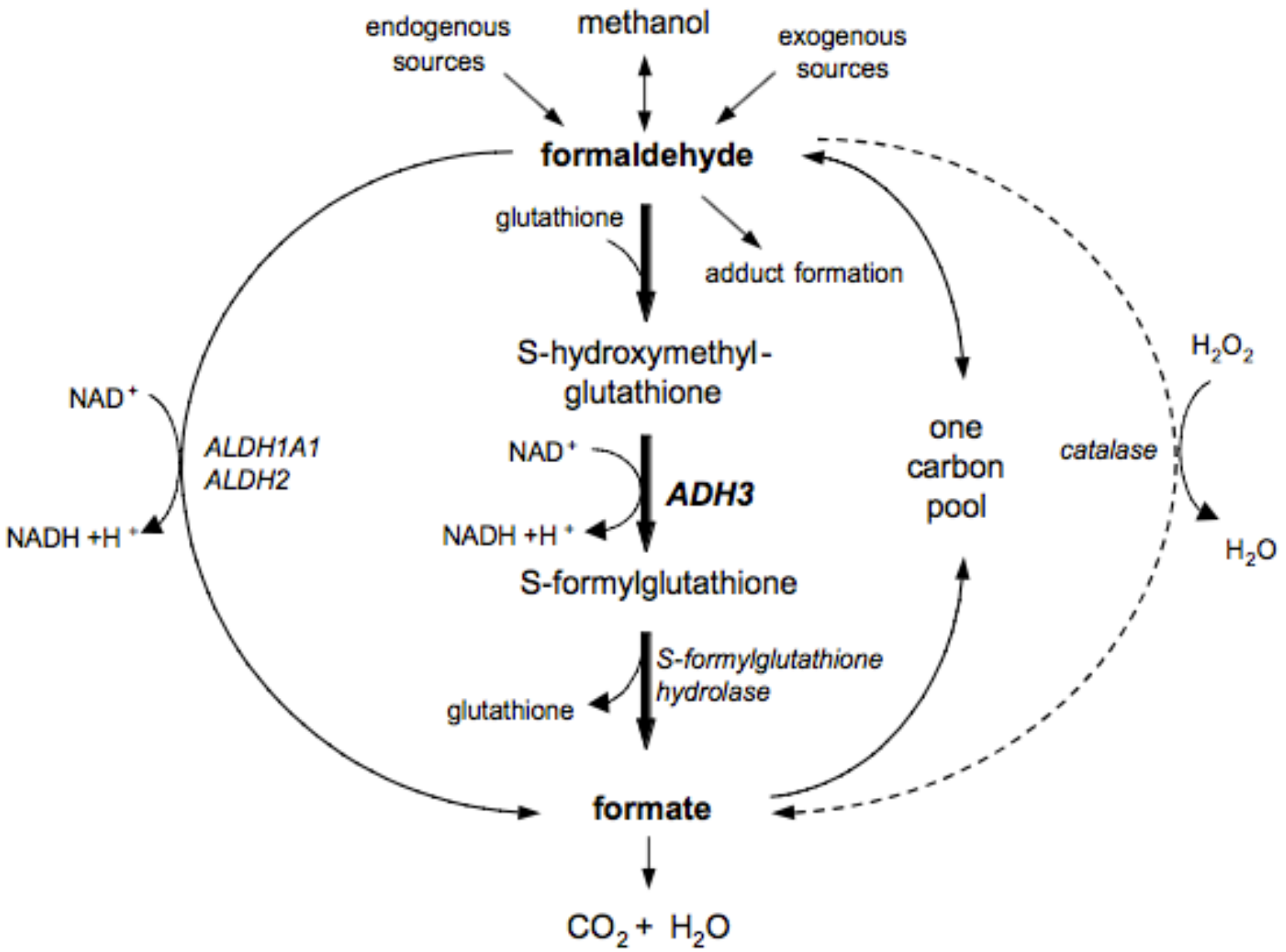
NR: not reported

Adapted from IARC formaldehyde monograph (2006)

# METABOLISM AND TOXICOKINETICS

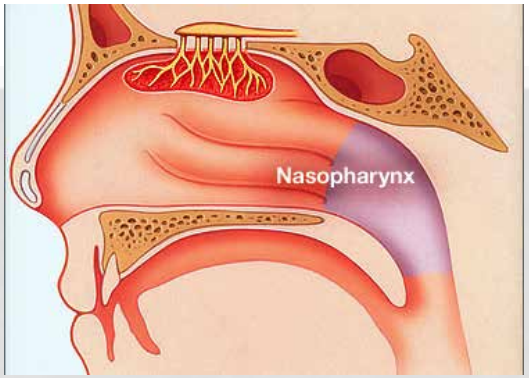
- Essential metabolic intermediate in all cells
  - Blood concentration: 2-3 mg/L
    - No significant change after 40min exposure to 1.9ppm inhalation (Heck *et al.*, 1985)
  - Formate in urines 12.5 mg/L (range, 2.4–28.4 mg/L)
    - No significant change after 3 week exposure to < 0.5ppm (Gottschling *et al.*, 1984)
- Half-life in rat plasma after intravenous injection: 1min (Rietbrock, 1965)
- >90% inhaled formaldehyde absorbed and removed by upper respiratory tract (Kimbell *et al.*, 2001a)
  - Oxidation è carbon dioxide
  - Incorporated in macromolecule
  - 22-42% removed by mucus flow (Schlosser, 1999)
- Toxic effects in human
  - Irritation eyes, nose, throat
  - Occupational asthma
  - Contact dermatitis

**Figure 2. Fate and metabolism of formaldehyde**




Adapted from Hedberg *et al.* (2002)

# NASOPHARYNGEAL CANCER




- Carcinogenesis (IARC 2012)
  - Local effects
  - Genotoxicity
  - Cell proliferation
    - increased in rat at concentration ≥6ppm (Monticello *et al.*, 1991)
- Elevated risk for overall formaldehyde exposure showed in different case-control studies (IARC 2006)

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Vaughan *et al.* (2000), USA (Connecticut, metropolitan Detroit, Iowa, Utah, Washington), 1987–93 | Epithelial nasopharyngeal carcinoma: epithelial NOS (801x–804x), undifferentiated or non-keratinizing (8020–1, 8072–3, 8082) and squamous-cell (805x–808x, except 8072–3) | 196 men and women [sex distribution not reported] from five cancer registries, aged 18–74 years | 244 population-based selected by random digit dialling; frequency-matched by sex, cancer registry and age (5-year groups) | Structured telephone interviews; occupational exposures assessed by a job–exposure matrix | Ever exposed | 1.3 (0.8–2.1) | Age, sex, race, centre, cigarette use, proxy status and education | Data presented for any potential exposure (possible, probable or definite); not influenced by a 10-year lag period or adding wood dust exposure to models |
| | | | | | *Max. exposure (ppm)* | | | |
| | | | | | < 0.1 | 1.4 (0.8–2.4) | | |
| | | | | | 0.1–0.5 | 0.9 (0.4–2.3) | | |
| | | | | | > 0.5 | 1.6 (0.3–7.1) | | |
| | | | | | *p* for trend | 0.57 | | |
| | | | | | *Duration (years)* | | | |
| | | | | | 1–5 | 0.8 (0.4–1.6) | | |
| | | | | | 6–17 | 1.6 (0.7–3.4) | | |
| | | | | | ≥ 18 | 2.1 (1.0–4.5) | | |
| | | | | | *p* for trend | 0.070 | | |
| | | | | | *Differentiated squamous-cell and epithelial NOS only* | | | |
| | | | | | Ever exposed | 1.6 (1.0–2.8) | | |
| | | | | | *Duration (years)* | | | |
| | | | | | 1–5 | 0.9 (0.4–2.1) | | |
| | | | | | 6–17 | 1.9 (0.9–4.4) | | |
| | | | | | ≥ 18 | 2.7 (1.2–6.0) | | |
| | | | | | *p* for trend | 0.014 | | |
| | | | | | *Cumulative exposure (ppm–years)* | | | |
| | | | | | 0.05–0.4 | 0.9 (0.4–2.0) | | |
| | | | | | > 0.4–1.10 | 1.8 (0.8–4.1) | | |
| | | | | | > 1.10 | 3.0 (1.3–6.6) | | |
| | | | | | *p* for trend | 0.033 | | |

Source: IARC formaldehyde monograph (2006)

# NASOPHARYNGEAL CANCER

| Reference | Cohort | Number of deaths | SMR (95% CI) |
|---|---|---|---|
| Hauptmann *et al*. (2003, 2004), USA | 25 619 workers; 22 493 men, 3126 women | 8 | 2.10 (1.05–4.21) statistically significant exposure–response relationships for peak and cumulative exposure |
| Hansen & Olsen (1995, 1996), Denmark | Workers, 2041 men, 1263 women diagnosed in 1970–84) | 4 | 1.3 (0.3–3.2) |
| Hayes *et al*. (1990), USA | Embalmers/funeral directors, 3649 white men, 397 non-white men | 3 (white)<br>1 (non white) | 1.89 (0.39–5.48)<br>4.00 (0.10–22.3) |

SMR: standardized mortality ratio,

Adapted from IARC formaldehyde monograph (2006)

# NASOPHARYNGEAL CANCER

- Meta-analysis

Adapted from IARC formaldehyde monograph (2012)

| Reference | mRR/SMR/OR (95% CI) |
|---|---|
| Collins *et al.*, 1997 | mRR 1.3 (1.2–1.5) |
| Bosetti *et al.* 2008 | SMR 1.33 ( 0.61–2.53) |
| Bachand *et al.*, 2010 | Case control studies OR 1.22 (1.00– 1.50)<br>Cohort studies OR 0.72 (0.40–1.29) |

mRR: meta relative risk SMR: standardized mortality ratio OR Odds ratio

- *Occupational exposure to formaldehyde causes nasopharyngeal cancer in humans.* (IARC 2012)

# LEUKEMIA

- Carcinogenesis not completely understood
- Statistically significant exposure-response relationship especially with myeloid leukemia (IARC 2006)

| Reference | Cohort | Number of deaths | SMR (95% IC) | Comment |
|---|---|---|---|---|
| Coggon *et al.* (2003), United Kingdom | Chemical workers, 14 014 men | Leukemia: 31 | 0.91 (0.47–1.59) | (Updated in 2014 with similar results and no elevation of mortality with higher exposure) |
| Hauptmann *et al.* (2003, 2004), USA | 25 619 workers; 22 493 men, 3126 women | 65 | 0.85 (0.67–1.09) | Statistically significant trend with peak exposure, particularly for myeloid leukaemia |
| Pinkerton *et al.* (2004), USA | Garment industry 11 039 workers; 2015 men, 9024 women | Leukemia: 24 Myeloid: 15 | 1.09 (0.70–1.62) 1.44 (0.80–2.37) | Statistically significant excess among workers with both ≥ 10 years of exposure and ≥ 20 years since first exposure (SMR, 2.43; 95% CI, 0.98–5.01 |

Adapted from IARC formaldehyde monograph (2006)

# LEUKEMIA

Adapted from IARC formaldehyde monograph (2006)

| Reference | Cohort | Number of deaths | SMR (95% IC) |
|---|---|---|---|
| Hall *et al*. (1991), United Kingdom | Pathologists, 4512 men and women | 4 | 1.52 (0.41–3.89) |
| Stroup *et al*. (1986), USA | Anatomists 2239 men | Leukemia: 10<br>Chronic myeloid: 3 | 1.5 (0.7–2.7)<br>8.8 (1.8–25.5) |
| Logue *et al*. (1986), USA | Pathologists, 5585 men | NR | 1.06 (NR) |
| Walrath & Fraumeni (1983), New York, USA, | Embalmers and funeral directors, 1132 white men | Leukemia: 12<br>Chronic myeloid: 6 | 1.19 (PCMR)<br>1.5 (PMR) |
| Walrath & Fraumeni (1984), California, USA, | Embalmers, 1007 white men | Leukemia: 12<br>Chronic myeloid: 6 | 1.40 (PCMR)<br>1.50 (PMR) |
| Hayes *et al*. (1990), USA | Embalmers/funeral directors, 3649 white men, 397 non-white men | Myeloid leukemia:<br>23 (white)<br>1 (non white) | 1.61 (1.02–2.41)<br>1.06 (0.02–5.93) |
| | | Other / unspecified leukemia:<br>17 (white)<br>3 (non white) | 2.08 (1.21–3.34)<br>4.92 (1.01–14.36) |

SMR: standardized mortality ratio, NR: not reported, PCMR: proportionate cancer mortality ratio, PMR: proportionate mortality ratio

# LEUKEMIA

- Meta-analysis

Adapted from IARC formaldehyde monograph (2012)

| Reference | Categories | mRR/SMR (95% CI) |
|---|---|---|
| Collins & Lineker, 2004 | Industrial workers<br>Embalmers<br>Pathologists and anatomists | mRR 0.9 (0.8-1.0)<br>mRR 1.6 (1.2-2.0)<br>mRR 1.1 (1.0-1.2) |
| Bosetti *et al.*, 2008 | Industrial workers<br>Professionals | SMR 0.9 (0.75–1.07)<br>SMR 1.39 (1.15-1.68) |
| Bachand *et al.*, 2010 | Leukemia overall<br>Myeloid leukemia<br>Lymphatic leukemia | mRR 1.05 (0.93–1.20)<br>mRR 1.09 (0.84– 1.40)<br>mRR 1.11 (0.81–1.52) |
| Zhang *et al.* (2009) | Leukemia<br>Myeloid leukemia | mRR 1.54 (1.18–2.00)<br>mRR 1.90 (1.31–2.76) |

mRR: meta relative risk SMR: standardized mortality ratio

- *Occupational exposure to formaldehyde causes leukaemia* (IARC 2012)

# OTHER CANCER SITES

- Sinonasal
  - IARC 2006: *limited epidemiological evidence that formaldehyde causes sinonasal cancer in humans*
- Oral cavity
- Oro and hypopharynx
- Pancreas
- Larynx
- Lung
- Brain

IARC 2006: no causal role for formaldehyde

# DISCUSSION

- Cancer associated with high and long exposure
  - Mean exposure in pathology lab 0.5ppm with short term exposure to high level >3ppm (IARC, 2006)
- Bias
  - Higher socioeconomic level
  - Data not adjusted for tabacco smoking
  - Non differential error in exposure assessment
- Exposure limits
  - US Occupational Safety and Health Administration (OSHA)
    - 0.75ppm on average over a 8h workday
    - Highest concentration 2ppm for 15min
  - Qc Commission des normes, de l'équité, de la santé et sécurité au travail (CNESST)
    - Ceiling value: 2ppm
    - Immediate danger for life and health: 20ppm
    - Exposure should be reduced to minimum
    - Recirculation prohibited

# CONCLUSION

- Exposure to formaldehyde is mainly by inhalation
- Exposure to formaldehyde increases the risk of nasopharyngeal cancers and leukemia (especially myeloid leukemia)
- Carcinogenesis includes local effect and genotoxicity (not completely understood)
- Overall low exposure to formaldehyde in pathology lab with peak of higher level

IN DOUBT, REDUCE YOUR EXPOSURE!!!

THANK YOU J

# REFERENCES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- CNESST, *Formaldehyde,* [online], page consulted May 25th 2017, http://www.csst.qc.ca/en/prevention/reptox/Pages/fiche-complete.aspx?langue=a&no_produit=1149
- Coggon *et al*. (2014) Upper airways cancer, myeloid leukaemia and other cancer in cohort of British chemical workers exposed to formaldehyde. *American Journal of epidemiology,* **179(11)**: 1301-1311
- Review of the Formaldehyde Assessment in the National Toxicology Program 12th Report on Carcinogens (2014),Washington (DC), *National Academy of Sciences.*

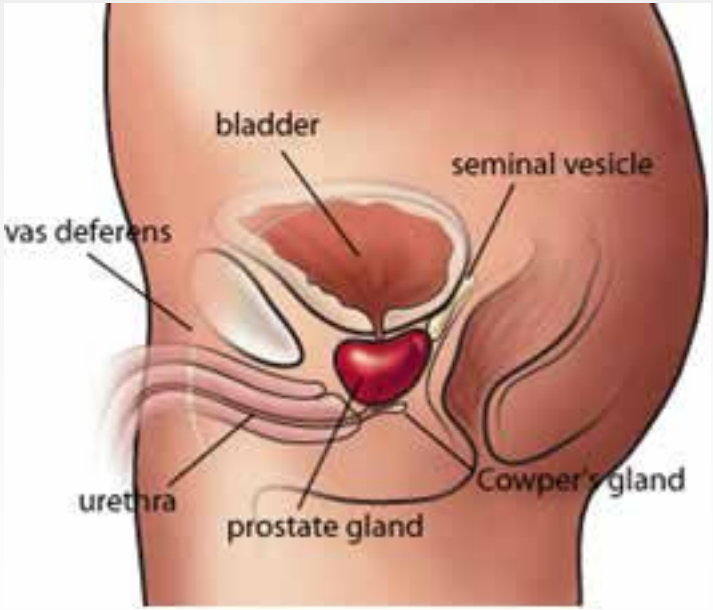
# Prostate Ca – Screening Pros and Cons

# Outline

- Background
- Screening methods
- Guidelines
- Methodology of the guidelines
- Results of studies
- Benefits of screening
- Harms of screening
- Key points
- Discussion

# Background

- Prostate Ca is most common cancer in men in Canada (1,2)
- Undiagnosed rate is high: >40% age 40-49yr and >70% 7-79 (1)
- High survival >95% 10 year survival (1,2)



# Background

- Peak in incidence in 90-93 and 2001 following introduction of PSA (1)
- Mortality declining 2.6%/yr since 1992 (1)
- Unlikely that decline in mortality due to screening (1)

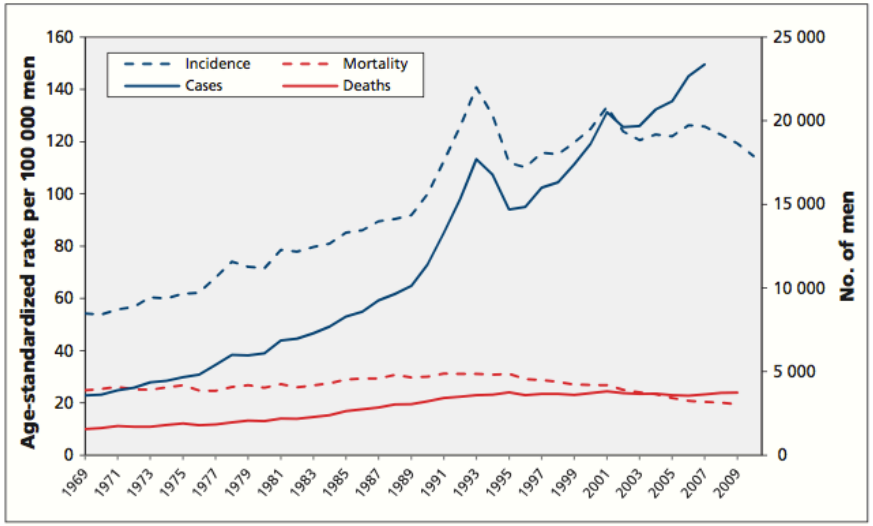
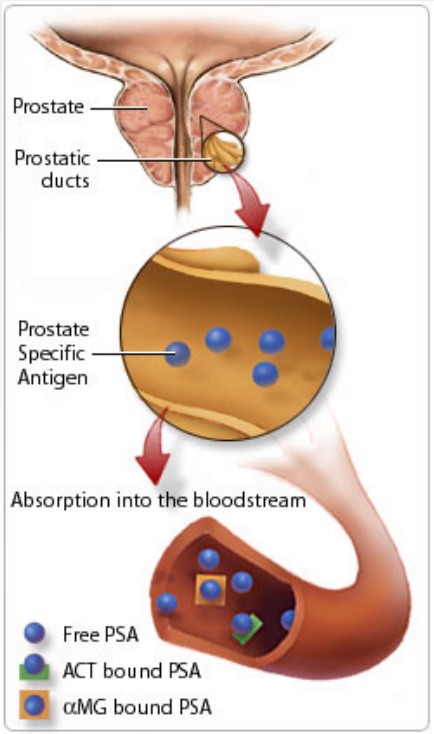



**Figure 1: Cases of and deaths from prostate cancer, with associated age-standardized incidence and mortality (per 100 000 men), among Canadian men aged 45 years and older. Age was standardized to the 1991 Canadian population. Incidence data were not available for Quebec from 2008 to 2010; therefore, the population denominator for age-standardized incidence was adjusted and case counts for 2008–2010 were omitted. Mortality data were available only to 2009.**

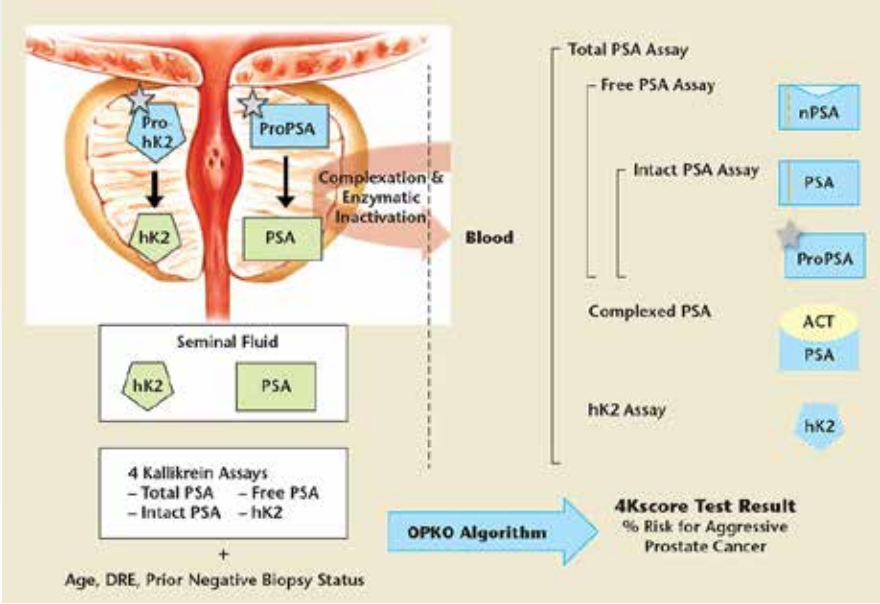
# Screening methods – Prostate Specific Antigen

- Prostate specific antigen: Glycoprotein produced by prostate epithelial cells (2)
- No single justifiable cut point to distinguish normal from pathological elevation (1,2)
  - <1ng/ml Pca unlikely
  - >4ng/ml Pca 20% sensitivity
- PSA can be elevated by many things (1,2)



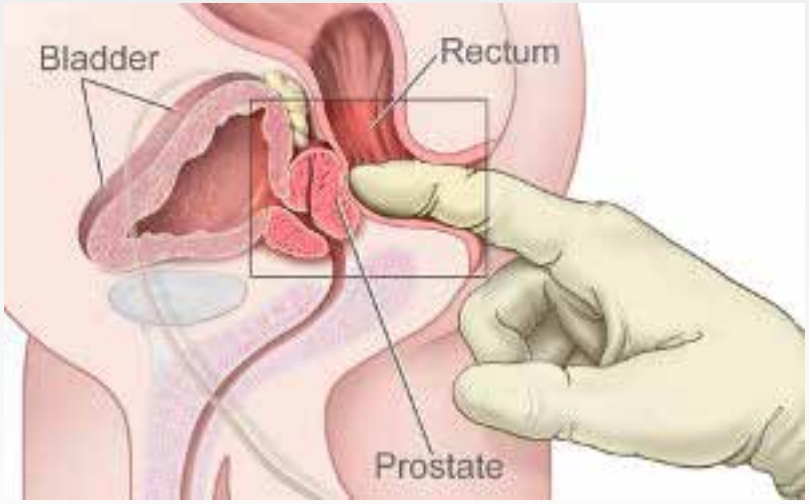
# Screening methods – Prostate Specific Antigen

- PSA velocity (2)
  - Not shown to be independent predictor over PSA alone
- PSA density (2)
  - Studies conflicting
- PSA isoforms (2)
  - Lower the ratio of free to total PSA the greater the risk of prostate ca



# Other Screening Methods

- Digital rectal exam
- PCA3 gene
- MRI



# Many guidelines (1) …

**Table 3:** Summary of recommendations for PSA screening for prostate cancer from Canada and elsewhere

| Organization | Age at initiation of PSA screening | Screening interval | Age at discontinuation of PSA screening |
|---|---|---|---|
| Canadian Task Force on Preventive Health Care (current) | Routine PSA screening not recommended | | |
| Canadian Task Force on the Periodic Health Examination (1994)[11] | Routine PSA screening not recommended as part of periodic health examination | | |
| US Preventive Services Task Force (2012)[8] | PSA screening not recommended; applies to men of all ages | | |
| Canadian Urological Association (2011)[54] | • Average risk: offer at age 50 yr to men with life expectancy ≥ 10 yr<br>• Increased risk (e.g., family history of prostate cancer, African descent): offer at 40 yr<br>• Offer baseline PSA test at age 40–49 yr to establish future risk of prostate cancer | Not specified | 75 yr |
| Canadian Cancer Society (2014)[55] | Men aged > 50 yr should talk with their doctor about whether they should be tested for prostate cancer | Not specified | Not specified |
| American Cancer Society (2012)[56] | Average risk: discussion at age 50 yr<br>Increased risk: discussion at age 40 or 45 yr, depending on extent of risk | PSA < 2.5 ng/mL: 2 yr<br>PSA ≥ 2.5 ng/mL: annual | Life expectancy < 10 yr |
| National Cancer Institute (2012)[22] | Insufficient evidence to determine whether screening with PSA or digital rectal examination reduces prostate cancer mortality | | |
| National Health Service (2013)[57] | No organized screening program; informed-choice program = men concerned about the risk of prostate cancer receive clear and balanced information about the advantages and disadvantages of PSA testing and cancer treatment | | |
| Prostate Cancer Canada (2013)[58] | • Offer baseline PSA test at age 40–49 yr<br>• Men aged > 40 yr should talk with their doctor about early detection<br>• Men at high risk should talk with their primary care provider before age 40 yr about prostate cancer | Not specified | ≥ 70 yr; decision should be based on individual factors (not specified) |
| American Urological Association (2013)[59] | • Routine screening not recommended for men aged 40–54 yr at average risk<br>• Shared decision-making recommended for men aged 55–69 yr; decision to proceed based on patient's values and preferences | ≥ 2 yr | ≥ 70 yr or life expectancy < 10–15 yr |
| American College of Physicians (2013)[60] | Men aged 50–69 yr: clinicians should discuss the limited benefits and substantial harms of screening for prostate cancer; they should not screen for prostate cancer with the PSA test in patients who do not express a clear preference for screening | Not specified | ≥ 70 yr or life expectancy < 10–15 yr |
| Cancer Council Australia, Australian Health Ministers' Advisory Council (2010)[61] | PSA test not suitable for population screening | | |

Note: PSA = prostate-specific antigen.

# Canadian Task Force on Preventive Health Care (CTFPHC) - 2014

## RECOMMENDATIONS

- For men aged less than 55 years, we recommend not screening for prostate cancer with the prostate-specific antigen test.

  (*Strong recommendation; low quality evidence*)

- For men aged 55–69 years, we recommend not screening for prostate cancer with the prostate-specific antigen test.

  (*Weak recommendation; moderate quality evidence*)

- For men 70 years of age and older, we recommend not screening for prostate cancer with the prostate-specific antigen test.

  (*Strong recommendation; low quality evidence*)

## ENDORSEMENT

This clinical practice guideline has been endorsed by the College of Family Physicians of Canada (CFPC).

# Methods of Guideline (CTFPHC)

- Development of guidelines: independent group of volunteer clinicians and methodologists
- Based on a systematic review of the literature that included 3 large RCTs
- Protocol, systematic review, and guideline underwent external peer review by academic and clinical experts

# Results

**Table 1:** Evidence of benefit of screening for prostate cancer with PSA testing

| Study (country) | Study characteristics | PSA threshold, ng/mL | Contamination (rate of screening in control group), % | Prostate cancer mortality, RR (95% CI) | All-cause mortality, RR (95% CI) | Absolute effect | GRADE quality of evidence* |
|---|---|---|---|---|---|---|---|
| PLCO[21] (United States) | RCT; 76 693 men aged 55–74 yr; annual PSA screening for 6 yr and digital rectal examination annually for 4 yr; 14-yr follow-up | 4 | 52 | 1.09 (0.87–1.36) | 0.96 (0.93–1.00) | No effect | Moderate |
| ERSPC[19] (Finland, Sweden, Italy, the Netherlands, Belgium, Spain and Switzerland) | RCT; 162 243 men aged 50–74 yr (core group 55–69 yr); PSA screening every 4 yr; 13-yr follow-up | 3.0 at most sites | 20 | Core group: 0.79 (0.69–0.91) All ages: 0.83 (0.73–0.94) | Core group: 1.00 (0.98–1.02) All ages: 1.00 (0.98–1.02) | 12.8 fewer deaths per 10 000 men screened | Moderate |

Note: CI = confidence interval, ERSPC = European Randomized Study of Screening for Prostate Cancer, PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, PSA = prostate-specific antigen, RCT = randomized controlled trial, RR = relative risk.
*GRADE (Grading of Recommendations, Assessment, Development and Evaluation)[13] rates the continuum of quality of evidence in 4 categories of high, moderate, low or very low; see evidence review for complete assessment of study quality.[13]

# Heterogeneity in ERSPC (2)

| Goteborg[55] |
|---|
| 1995-2008 |
| 20 000 |
| 50-64 |
| 1 city (Goteborg, Sweden) |
| PSA >2.5 ng/mL (From 2005 on) |
| PSA >2.9 ng/mL (From 1999-2004)<br>PSA >3.4 ng/mL (From 1995-98) |
| Every 2 years<br>78% had 14-year follow-up |
| 76% |
| 3% |
| Control Screened |
| 7.2% 11.4% |
| 78 44 |
| 44% ($p = 0.002$) |
| 1:293 |
| 1:12 |

# Benefits of Screening

- No all-cause mortality benefit (1,2)
- Small absolute risk reduction in Pca specific mortality in ERSPC only (1)

# Harms of Screening

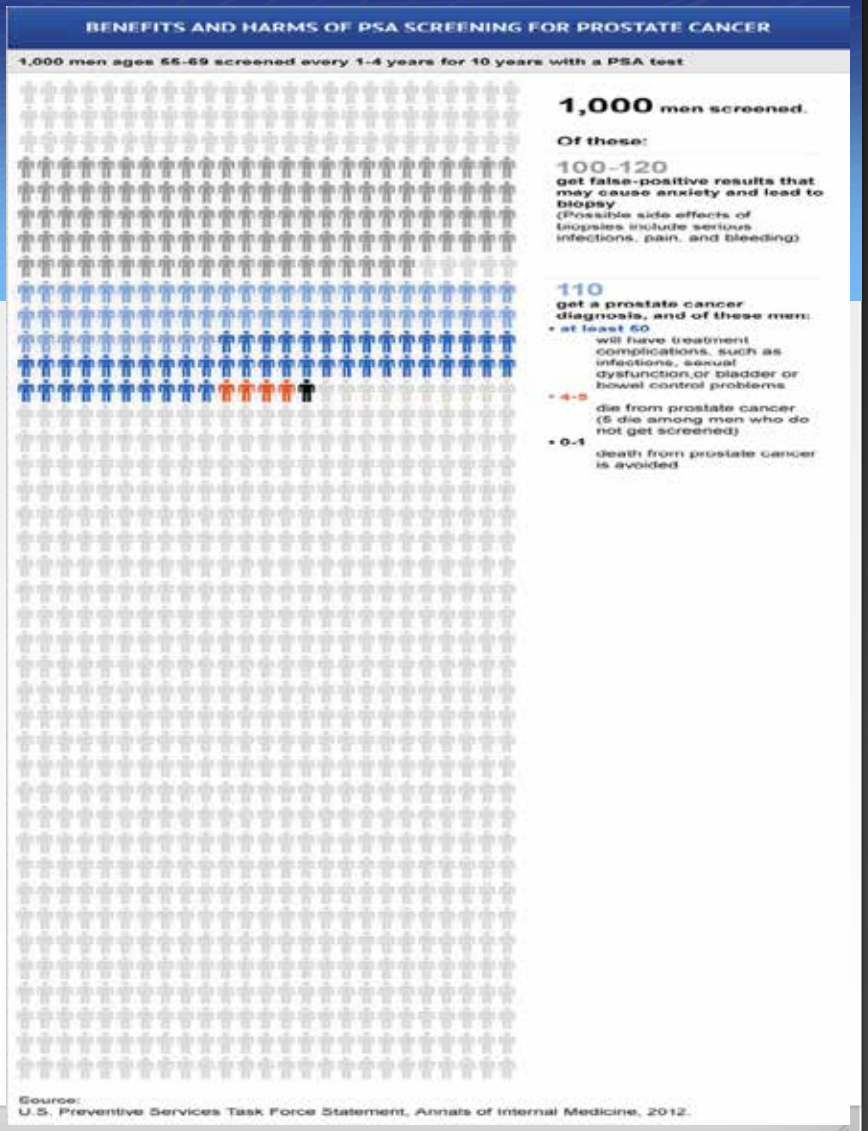
- 40-56% over diagnosis (1,2)
- 10-20% false positives (1,2)
- 1000 prostate biopsies: 9.4 infections, 21 hospital admissions, 1.7 deaths! (1,2)
- No evidence that DRE reduces mortality over PSA alone (1,2)

# Why Do Some Organizations Disagree?

- Some patients might value possible small mortality benefit over potential harms (4)
- Higher risk groups: family history, African (4)
- Vickers study (2013): baseline PSA at age 45-49 predicts future prostate Ca risk (4)

# Key Points

- Unclear benefits, substantial harms
- Does not justify population based screening
- Most patients aware of benefits but not harms



# Discussion


# Thanks

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- 2. CUA Guideline. Prostate cancer screening: guidelines 2011. CUAJ. August 2011.
- 3. Tudiver et al. What influences family physicians' cancer screening decisions when practice guidelines are unclear or conflicting? JFP online. September 2002.
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# References - IMAGES


- Slide 3: Retrieved from http://www.stampedetrial.org/patients/information_for_patients/about_prostate_cancer/
- Slide 5: Retrieved from https://www.menshormonalhealth.com/psa-test-results.html
- Slide 6: Retrieved from http://read.nxtbook.com/medreviews/urology/volume17no1/diagnosis_findingthewolf.html
- Slide 7: Retrieved from https://en.wikipedia.org/wiki/Rectal_examination
- Slide 13: Retrieved from https://blogs.scientificamerican.com/guest-blog/prostate-cancer-screening-the-pros-and-cons/
- Slide 14 Retrieved from https://www.pinterest.com/pin/129267451779148638/
- Slide 15: Retrieved from http://www.prostatecancer.ca
- Slide 16: Retrieved from https://www.cancer.gov/types/prostate/psa-fact-sheet
- All other images retrieved from above references

# Anal cancer screening

Sindy Magnan

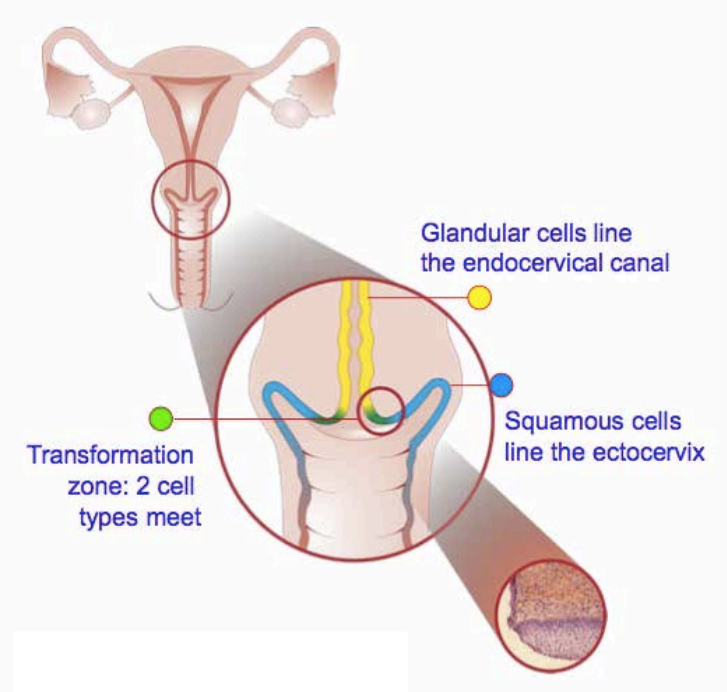
EPIB 671 – Cancer Epidemiology

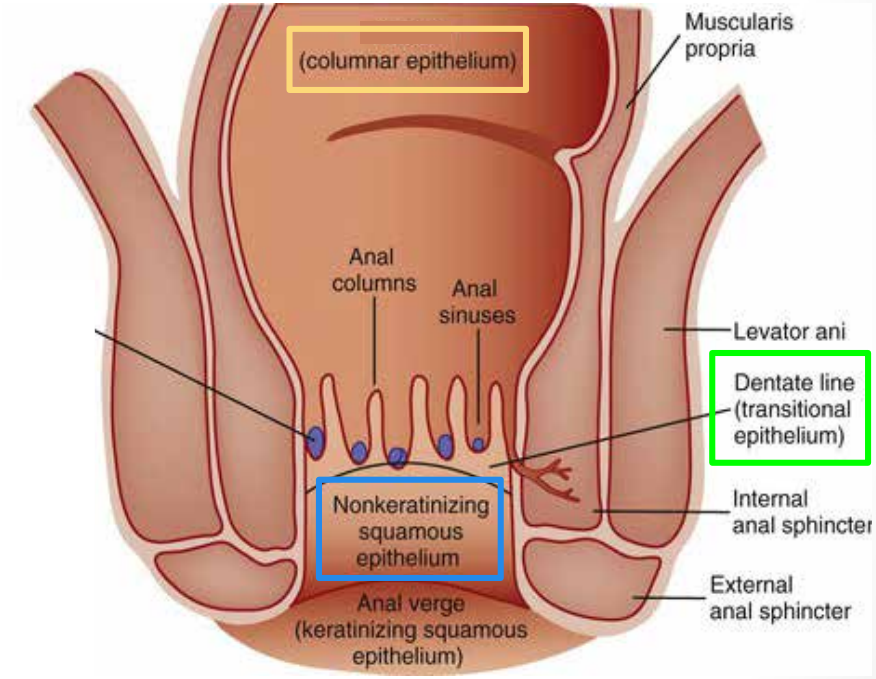
May 26, 2017

# Review - Screening criteria

- Target population
  - At significant risk of the disease
  - Likely to comply with subsequent advice/interventions
- Disease
  - Important health problem for the individual/community
  - Good understanding of the natural history (latent phase)
  - Treatment at an early stage more beneficial than at a later stage
  - There is an effective treatment or useful intervention
- Screening tool
  - Accurate: high sensitivity, specificity, predictive value
  - Feasible: acceptable and safe, cost-effective, facilities available, target population reachable
- Program
  - Scientific evidence of effectiveness
  - Overall benefits outweight the harm

# Similarities with cervical cancer



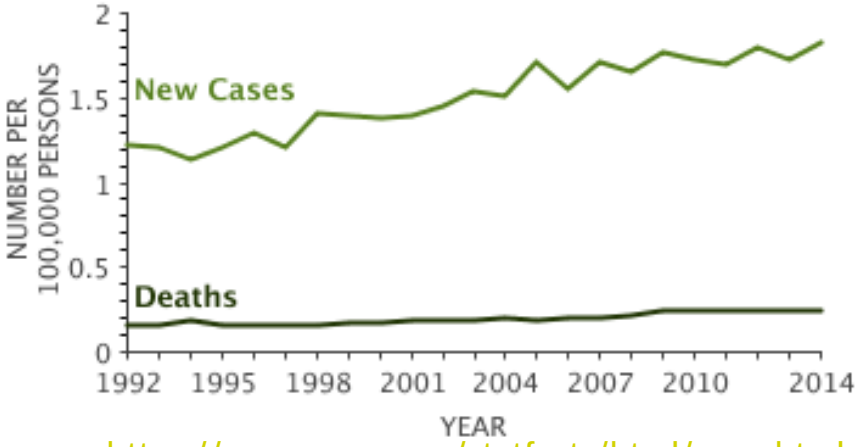



# Similarities with cervical cancer

- Risk factors
  - HPV infection à 90% of anal squamous cell carcinoma (SCC)
    - History of genital warts (RR 27-32.5)
    - History of cervical dysplasia (RR 2.3) or cancer (RR 4.6)
  - Sexual history
    - Multiple sexual partners (10 or more: RR 2.5-4.5)
    - Receptive anal intercourse (RR 30-33)
    - History of sexually transmitted disease (RR 4-17)
  - HIV infection
  - Chronic immunosuppression
    - Solid organ transplant recipients (RR 100), long term corticosteroids
  - Cigarette smoking (20 packs-year: RR 1.9; 50 packs-year: RR 5.2)

# Incidence

| | |
|---|---|
| Estimated New Cases in 2017 | 8,200 |
| % of All New Cancer Cases | 0.5% |
| Estimated Deaths in 2017 | 1,100 |
| % of All Cancer Deaths | 0.2% |




https://seer.cancer.gov/statfacts/html/anus.html

| Anal cancer rates among select populations, per 100000 person-years | |
|---|---|
| General population | 2[1] |
| General population, female | 0.55-2.4[13] |
| HIV positive women | 3.9-30[13] |
| HIV negative MSM | 5.1[12] |
| Solid organ transplant | 10-15[66] |
| Prior HPV related malignancy | 8-63.8[13] |
| HIV positive MSM | 49.5[12] |
| Colon cancer in general population | 41[2] |

Roberts, J. et al. World J. of Gastro. Oncol. 2017

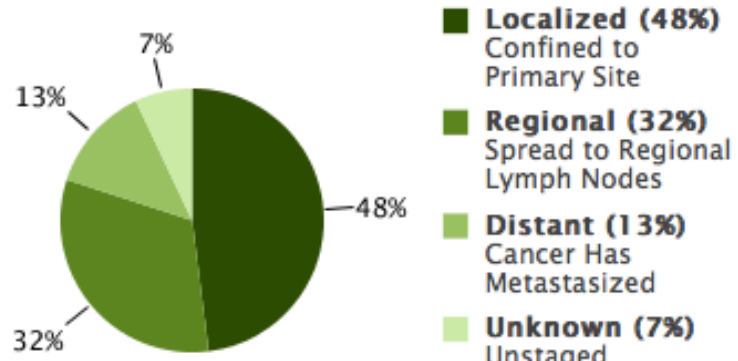
# Populations at increased risk

- HIV-positive men and women
- Men who have sex with men
- Iatrogenic immunosuppression
- Women with a history of high-grade cervical, vulvar, vaginal dysplasia or cancer

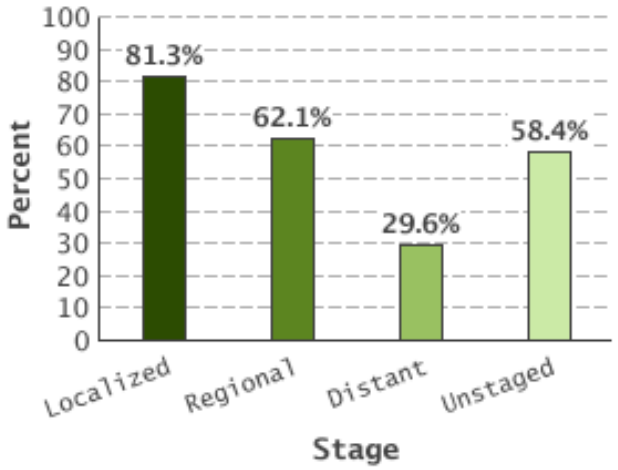
# Stage at presentation and survival

**Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Anal Cancer**

**Percent of Cases by Stage**




**5-Year Relative Survival**




SEER 18 2007-2013, All Races, Both Sexes by SEER Summary Stage 2000

https://seer.cancer.gov/statfacts/html/anus.html

# Primary treatment and outcomes

- Primary treatment for nonmetastatic anal carcinoma: concurent chemo-RT

| Stage | 5-year overall survival | 5-year locoregional failure | 3-year colostomy failure |
|---|---|---|---|
| T2N0 | 85% | 17% | 11% |
| T3N0 | 74% | 18% | 13% |
| T4N0 | 57% | 37% | 26% |
| T2N+ | 70% | 26% | 11% |
| T3N+ | 57% | 44% | 27% |
| T4N+ | 42% | 60% | 24% |

Gunderson LL et al. Int J Radiat Oncol Biol Phys. 2013

# Treatment toxicities

- Primary treatment for nonmetastatic anal carcinoma: concurent chemo-RT

| Acute toxicities | Late toxicities |
|---|---|
| **Mortality <2%** | **Serious 5-10%** |
| Neutropenia with sepsis | Anorectal/bladder dysfunction |
| Leukopenia | Rectal bleeding/hematuria |
| Thrombocytopenia | Ulcer, fistula, necrosis |
| Perineal dermatitis | Colostomy (10%) |
| Anoproctitis (diarrhea, mucus, pain, urgency, increased frequency, incontinence) | Dyspareunia |
| | Vaginal stenosis |
| | Impotence |
| Cystitis | Infertility |
| Fatigue | Chronic perineal dermatitis |
| | Pelvic fracture |
| | Secondary malignancies |

# Natural history

*International Journal of Gynecological Pathology*
**32**:76–115, Lippincott Williams & Wilkins, Baltimore

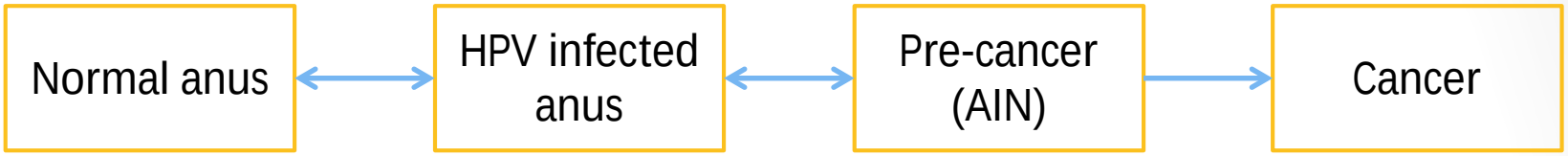

Original Article

## The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated Lesions: Background and Consensus Recommendations From the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology

Teresa M. Darragh, M.D., Terence J. Colgan, M.D., J. Thomas Cox, M.D., Debra S. Heller, M.D., Michael R. Henry, M.D., Ronald D. Luff, M.D., Timothy McCalmont, M.D., Ritu Nayar, M.D., Joel M. Palefsky, M.D., Mark H. Stoler, M.D., Edward J. Wilkinson, M.D., Richard J. Zaino, M.D., David C. Wilbur, M.D., and For Members of the LAST Project Work Groups

| LSIL | | | HSIL | |
|---|---|---|---|---|
| ASCUS | *IN 1 | *IN 2 p16- | *IN 2 p16+ | *IN 3 |

# Natural history




- In the cervix, regression/progression rates for each grade of cervical lesion have been characterized.
- Relatively little is known to date about the long-term natural history of anal SIL.
  - HSIL is a true precursor of invasive anal SCC
  - LSIL may spontaneously regress or progress to HSIL
  - HSIL is less likely to regress
  - Lesions containing HPV 16 are the least likely to regress

# Natural history

| Progression | No. patients | Rate of progression | Median or average progression time | Ref. |
|---|---|---|---|---|
| AIN II/III to SCC | 72 | 11% | 42 mo | [33] |
| AIN III to SCC | 35 | 8.6% | 53 mo | [34] |
| AIN I to AIN III | 199 | 12.6% (8.1/100 person-years) | 18 mo | [35] |
| ASCUS/AIN I to AIN II/III | 556 | 24.5% (10.5/100 person-years) | 36 mo | [36] |
| HSIL to SCC | 138 | 19.6% | 57 mo. w/prevalent HSIL; 64 mo. w/ incident HSIL | [37] |

Roberts, J. et al. World J. of Gastro. Oncol. 2017

# Screening tools

- Anal cytology
  - Water-moistened polyester fiber swab
  - Lateral position, swab inserted until it reaches rectal wall (proximal to transitional zone), withdrawn using spiral motion + lateral pressure to sample entire circumference
  - Sensitivity: 62-90%
  - Specificity: 64-85%
- High resolution anoscopy
  - 3-5% acetic acid + Lugol's iodine
  - +/- biopsy of visualized lesions
- HPV DNA ?

# Treatment of HSIL

- Topical therapy
  - Small lesions (<1cm$^2$)
  - Bichloroacetic/trichloroacetic acid
  - Regression to normal or LSIL ~80%

- Immune modulation
  - Widespread/multifocal disease
  - Imiquimod 3/week x 4 months
  - Regression to normal or LSIL ~35%
  - Recurrence ~40-70%

# Treatment of HSIL

- Radiofrequency ablation
  - Larger lesions (>1cm$^2$)
  - Regression to normal or LSIL ~60-65%
  - Recurence ~60% (ad 90% in HIV+ MSM) at 1.5 years
- Infrared coagulaton
  - Larger lesions (>1cm$^2$)
  - Regression to normal or LSIL ~70-80%
  - Recurence ~40-60% at 1.5 years
- Electrocautery
  - Larger lesions (>1cm$^2$)
  - Complete response ~1/3, partial response ~1/3, no response ~ 1/3
  - Recurence rate ~25% at 3 years

# Evidence for screening

- No data available from randomized prospective studies
- Ongoing study:

  Anal Cancer/HSIL Outcomes Research (ANCHOR) study (www.anchorstudy.org)
  - RCT supported by the National Cancer Institute and the National Institutes of Health Office of AIDS Research
  - HIV infected men and women
  - Screening for pre-cancerous anal lesions
  - If positive, randomized between:
    - Treatment
    - Monitoring every 6 months
  - Minimum follow-up of 5 years

# Actual recommendations

- No formal guidelines recommend screening for anal cancer

# Summary

- Rationnale for screening
  - Similarities between anal and cervical cancer
  - Success of cervical cancer screening program
  - High incidence of anal cancer in high risk populations
  - Availability of screening modalitites and treatments for HSIL
  - Significant morbidity and mortality associated with anal cancer
- Arguments against screening
  - Natural evolution of anal SIL still not well understood
  - Screening tools less accurate than for cervical cancer
  - High rate of recurrence after treatment for HSIL
  - Lack of scientific evidence of effectiveness
  - Cost-effectiveness?
  - Benefits outweight harms?

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# Vitamin D Epidemiology and Cancer Risk

Samar Kaifi MD, MAS

PGY1 Rad Onc

# What Is Vitamin D?

- Fat soluble prohormones
- Major role in bone strength by using the calcium and phosphorus
- The sources are UVB wave from sun exposure and some food
- The active form is Calcitriol produced by the kidney
- 25-hydroxyvitamin D to measure the vitamin D level in the blood

# Why Vitamin D?

- It is response element for almost 200 human genes that encode for proteins important in regulation of cell proliferation and differentiation. When vitamin D is deficient these activities are impaired [11]

- Accounts for various cellular responses to enhance the innate immunity [11]


- **11.The Role of Vitamin D in Cancer Prevention**Cedric F. Garland, DrPH, Frank C. Garland, PhD, Edward D. Gorham, PhD, MPH, Martin Lipkin, MD, Harold Newmark, ScD, Sharif B. Mohr, MPH, and Michael F. Holick, MD, PhD

# Vitamin D and Cancer

## Characteristics of Cancer Cells

- Independence of external growth signals
- Loss of sensitivity for growth inhibiting signals
- Unlimited growth potential
- Insensitivity for active cell death (= Apoptosis)
- Continuous neo-angiogenesis
- Tissue-invasion and growth in other organs

## Vitamin D Effects

- Inhibits cell proliferation
- Enhances cell differentiation
- Activates apoptosis
- Inhibits angiogenesis in tumors
- Decreases metastatic potential
- Activates the immune system

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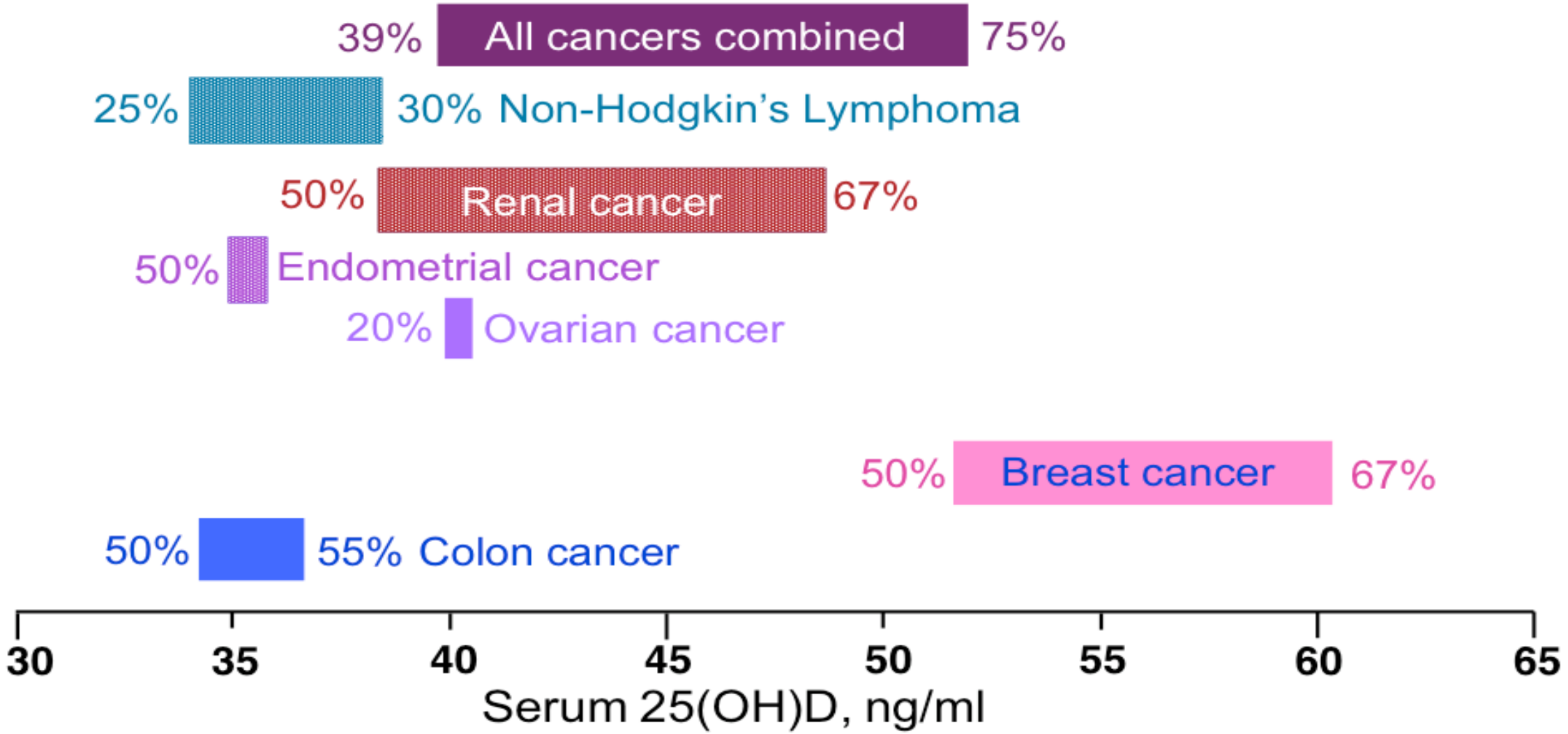
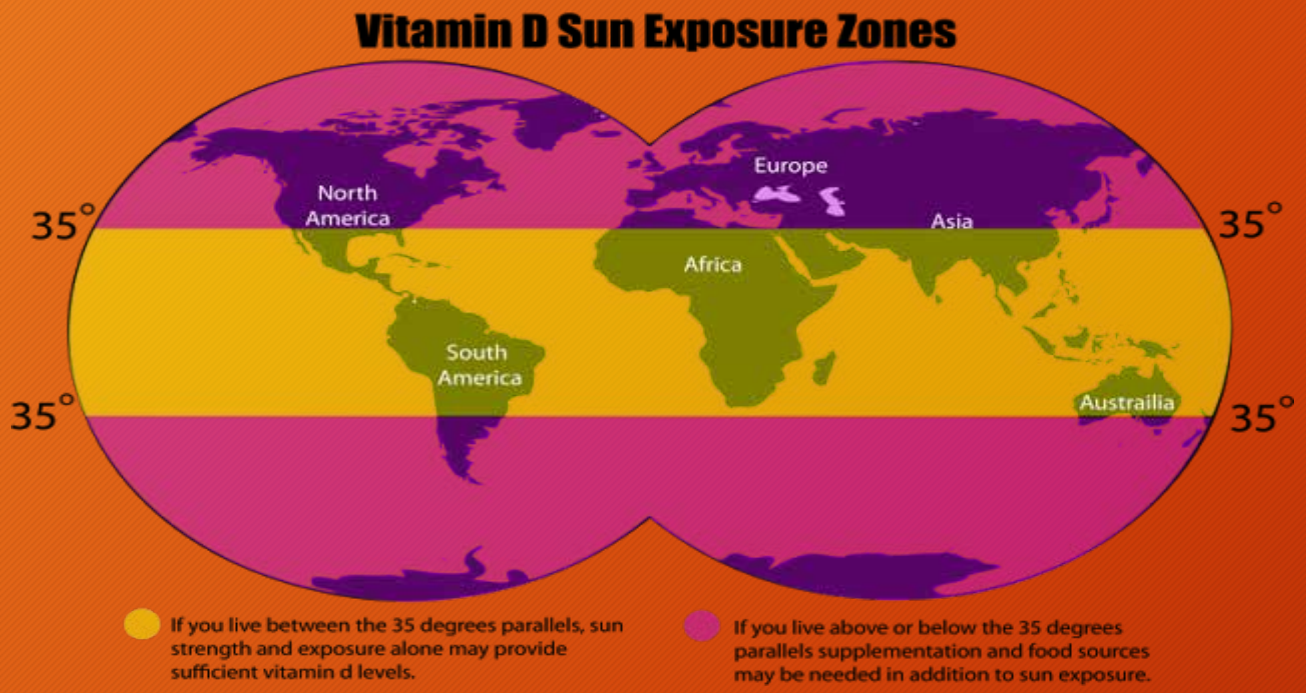
# Prevalence of Vitamin D Deficiency

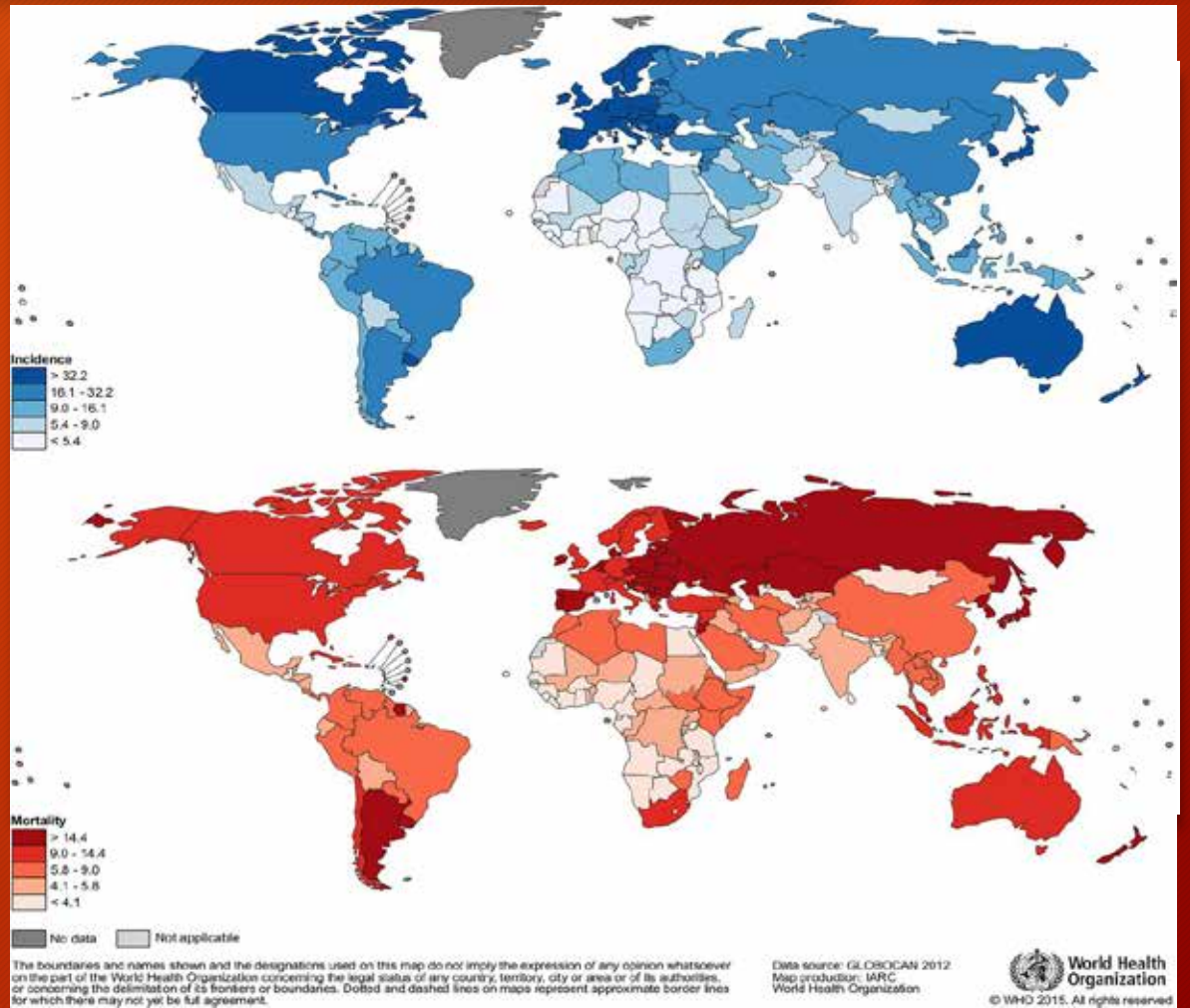
- Vitamin D half life is 3 weeks
- About 20% of adults are at high risk for Vitamin D deficiency
- Risk factors are :
  - Obese, pregnant
  - Dark skin, old age
  - Chronic illness, injury or surgery
  - Geographically located far from the equator, avoid the sun, wear sunscreen

# Estimated Proportion of Cancers Preventable by Serum 25(OH) D Range



# How Is vitamin D Affecting Colon Cancer




13.http://ajitvadakayil.blogspot.ca/2015/07/atapa-snana-bathing-home-and-workplace.html
14.Global patterns and trends in colorectal cancer incidence and mortalityMelina Arnold1, Mónica S Sierra1, Mathieu Laversanne1, Isabelle Soerjomataram1, Ahmedin Jemal2,Freddie Bray1

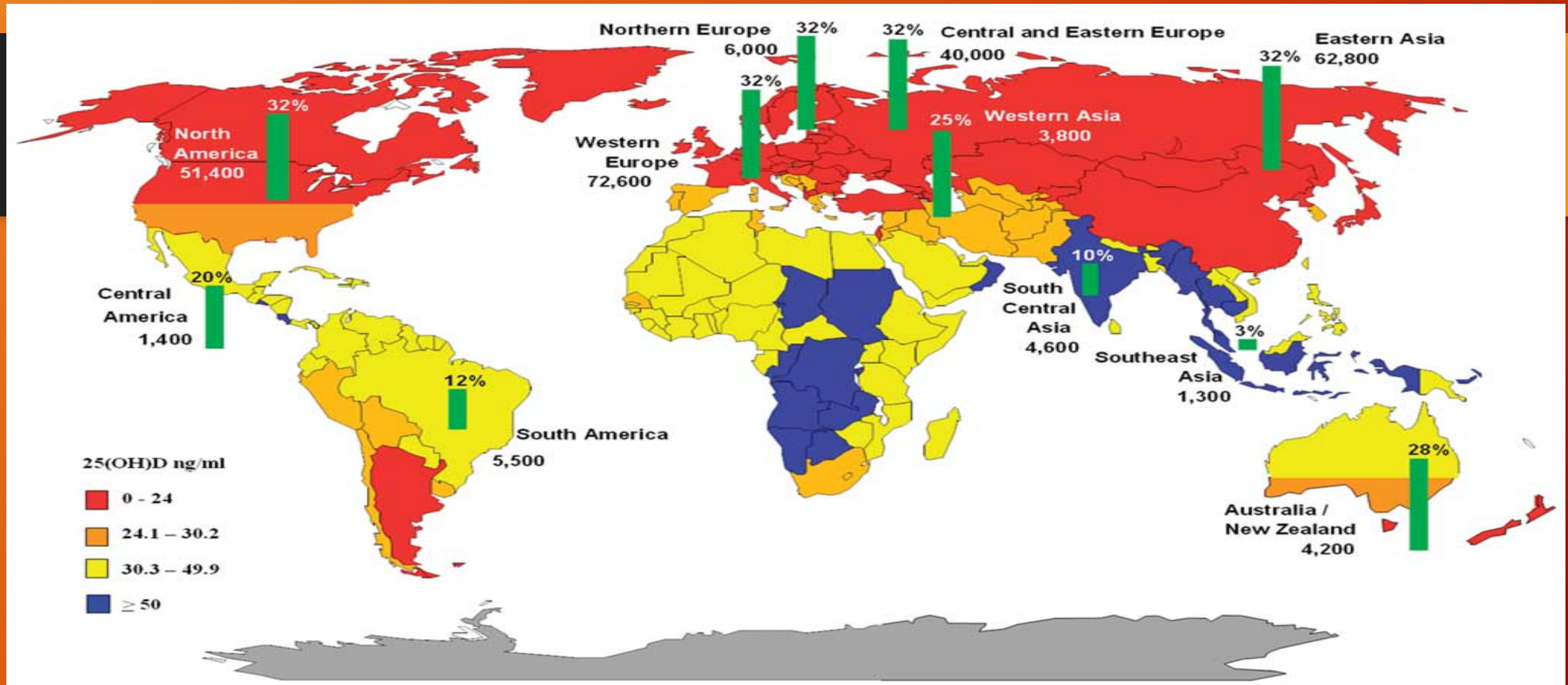
# Colorectal Cancer and Vitamin D

- Four meta analysis in 2011 showed inverse relation between vitD level and colorectal cancer risk.[1]
- Mixed-effects dose-response meta-analyses showed that each 10 ng/ml increase in blood 25-(OH)D concentration was associated with a 6% (95% CI, 3% to 9%) reduced risk for colon Ca.[1]
- Optimum vit D level help to maintain a normal Ca gradient in colon epithelium and reduces colonic epithelial proliferation.[11]
- Vit D < 30 ng/ml had twice the risk of colon Ca. [11]

| First Author, Year (Reference No.) | Study Design[a] | Sample Size[b] | Comparison/Outcome | Risk Estimate | 95% CI |
|---|---|---|---|---|---|
| | | *Circulating 25(OH)D* | | | |
| Colorectal | | | | | |
| Lee, 2011 (8) | Meta-analysis | 10 studies | Highest vs. lowest quantile | | |
| | Prospective only | | Colorectal | 0.66 | 0.54, 0.81 |
| | | | Colon | 0.77 | 0.56, 1.07 |
| | | | Rectum | 0.50 | 0.28, 0.88 |
| Gandini, 2011 (7) | Meta-analysis, retrospective ($n = 1$), and prospective | 9 studies | Per 25-nmol/L increase (colorectal) | 0.85 | 0.79, 0.91 |
| Ma, 2011 (9) | Meta-analysis | 9 studies | Highest vs. lowest quantile | | |
| | Prospective only | | Colorectal | 0.67 | 0.54, 0.80 |
| | | | Colon | 0.62 | 0.46, 0.81 |
| | | | Rectum | 0.61 | 0.43, 0.79 |
| Touvier, 2011 (10) | Meta-analysis, prospective only | 9 studies | Per-100 IU/L increase | | |
| | | | Colorectal | 0.96 | 0.94, 0.97 |
| | | | Colon | 0.95 | 0.92, 1.00 |
| | | | Rectum | 0.95 | 0.86, 1.05 |

1.Vitamin D and Cancer Risk and Mortality: State of the Science, Gaps,and Challenges Alison M. Mondul* , Stephanie J. Weinstein, Tracy M. Layne, and Demetrius Albanes

**11.The Role of Vitamin D in Cancer Prevention**Cedric F. Garland, **DrPH,** Frank C. Garland, **PhD,** Edward D. Gorham, **PhD, MPH,** Martin Lipkin, **MD,** Harold Newmark, **ScD,** Sharif B. Mohr, **MPH, and** Michael F. Holick, **MD, PhD.**




Estimated 25(OH)D serum levels (see legend) and projected percentage prevention of **colon cancer** cases (bars) with 2,000 IU/day of vitamin $D_3$ and 3-10 minutes daily of noon sunlight seasonally, when weather permits

# Breast Cancer and Vitamin D

- Two meta analysis showed inverse association with breast cancer was restricted to the retrospective studies only. (reverse causality bias?)
- No association in prospective studies.
- The finding of several studies suggest the relation between breast cancer and Vit D is complex and may differ by menopausal status and race.
- Several researches showed significant reduction in mortality.

| Breast | | | | | |
|---|---|---|---|---|---|
| Yin, 2010 (15) | Meta-analysis, retrospective ($n = 5$), and prospective | 9 studies | Per 50-nmol/L increase | | |
| | | | Overall | 0.73 | 0.60, 0.88 |
| | | | Retrospective | 0.59 | 0.48, 0.73 |
| | | | Prospective | 0.92 | 0.82, 1.04 |
| Gandini, 2011 (7) | Meta-analysis, retrospective ($n = 5$), and prospective | 10 studies | Per 25-nmol/L increase | | |
| | | | Overall | 0.89 | 0.81, 0.98 |
| | | | Prospective | 0.99 | 0.95, 1.03 |

1.Vitamin D and Cancer Risk and Mortality: State of the Science, Gaps,and Challenges Alison M. Mondul* , Stephanie J. Weinstein, Tracy M. Layne, and Demetrius Albanes

# Bladder Cancer and Vitamin D

- Two meta analysis conclude inverse association between high vit D level and bladder cancer risk
- Zhao et al concluded that only concentration of >30 ng/l considered protection.

| Bladder | | | | | |
|---|---|---|---|---|---|
| Zhang, 2015 (24) | Meta-analysis, retrospective ($n = 3$), and prospective | 7 studies | Highest vs. lowest quantile | 0.75[c,d] | |
| Zhao, 2016 (25) | Meta-analysis, retrospective ($n = 3$), and prospective | 7 studies | >75 vs. <25 nmol/L | 0.68 | 0.49, 0.86 |

1.Vitamin D and Cancer Risk and Mortality: State of the Science, Gaps,and Challenges Alison M. Mondul* , Stephanie J. Weinstein, Tracy M. Layne, and Demetrius Albanes

# Other Cancers

- Meta analysis showed 5% Lung cancer risk reduction with 2.5 ng/ml increase in vit D blood level.[1]
- Renal cancer showed inverse relation in two meta analysis with statistically significant results.[1]
- Ovarian cancer showed inverse relation but not statistically significant.[1]
- Pancreatic cancer unclear association.[1]
- Skin cancer (nonmelanoma) increase risk with high level of vit D.[1]

# Cochrane Systemic Review

- Recent review of 18 controlled trials tested vitamin D supplementation vs placebo or no intervention on overall cancer;
- RR = 1 95% CI : 0.94,1.06.[2]
- These findings do not support the hypothesis of VitD supplementation to impact cancer incidence but they point out that most of the trials had been conducted in elderly women and were originally designed to examine bone health outcomes.[1]
- Their recommendation is to conduct trials on young people, men and people with low vit D status with long trials.[2]
- Vit D supplements associated with reduced cancer mortality RR = 0.88 95%CI 0.78, 0.98 but concluded that the finding could be due to chance.[2]

# Conclusion

- Despite that there is no institutional recommendations regarding the use of vit D supplements, the use have increased substantially over the past decade.[1]
- over time, a daily usage of vitamin D supplements would decrease worldwide cases of breast and colorectal cancer by 450,000 cases a year.[4]
- The need for site specific organ research to determine the role of vit D supplementation for primary and secondary intervention.[1]
- US Preventive Services Task Force recommendation “I” for use of multivitamins to prevent cardiovascular disease or cancer.[3]
- The higher vit D level associated with improved survival.[1]

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- **11.The Role of Vitamin D in Cancer Prevention**Cedric F. Garland**, DrPH,** Frank C. Garland**, PhD,** Edward D. Gorham**, PhD, MPH,** Martin Lipkin**, MD,** Harold Newmark**, ScD,** Sharif B. Mohr**, MPH, and** Michael F. Holick**, MD, PhD.**
- **12. MORE CLUES TOWARD DETERMINING OPTIMUM VITAMIN D LEVELS.**
- 13.http://ajitvadakayil.blogspot.ca/2015/07/atapa-snana-bathing-home-and-workplace.html
- 14.Global patterns and trends in colorectal cancer incidence and mortalityMelina Arnold1, Mónica S Sierra1, Mathieu Laversanne1, Isabelle Soerjomataram1, Ahmedin Jemal2,Freddie Bray1
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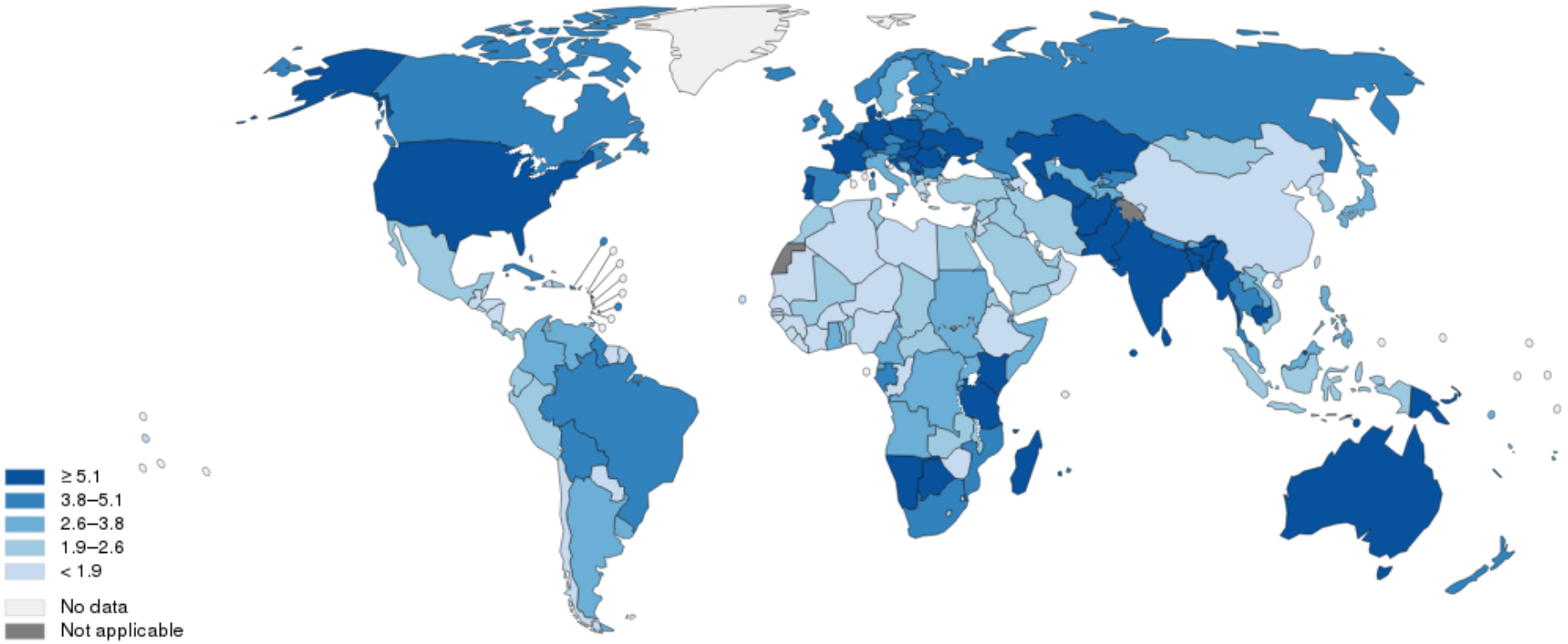
# Risk factors for malignant transformation of OPLs

Lojain Bassyoni BDS. FRCD(C)
Maxillofacial Surgeon
MSc. Candidate

Estimated age-standardized rates (World) of incident cases, both sexes, cancer of the lip and oral cavity, worldwide in 2012






Data source: GLOBOCAN 2012
Map production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization

**FIGURE 1.2** Percent distribution of estimated new cancer cases, by sex, Canada, 2016

**Males**
**102,900**
**New cases**

| | |
|---|---|
| Prostate | 21.0% |
| Colorectal | 14.1% |
| Lung and bronchus | 14.0% |
| Bladder | 6.4% |
| Non-Hodgkin lymphoma | 4.3% |
| Kidney and renal pelvis | 4.0% |
| Melanoma | 3.6% |
| Leukemia | 3.4% |
| Oral | 3.1% |
| Pancreas | 2.5% |
| Stomach | 2.1% |
| Esophagus | 1.7% |
| Liver | 1.7% |
| Brain/CNS | 1.7% |
| Multiple myeloma | 1.6% |
| Thyroid | 1.5% |
| Testis | 1.1% |
| Larynx | 0.9% |
| Hodgkin lymphoma | 0.5% |
| Breast | 0.2% |
| All other cancers | 10.7% |

**Females**
**99,500**
**New cases**

| | |
|---|---|
| Breast | 25.8% |
| Lung and bronchus | 14.1% |
| Colorectal | 11.7% |
| Body of uterus and uterus NOS | 6.6% |
| Thyroid | 5.3% |
| Non-Hodgkin lymphoma | 3.6% |
| Melanoma | 3.1% |
| Ovary | 2.8% |
| Pancreas | 2.6% |
| Leukemia | 2.4% |
| Kidney and renal pelvis | 2.3% |
| Bladder | 2.1% |
| Cervix | 1.5% |
| Oral | 1.5% |
| Stomach | 1.3% |
| Brain/CNS | 1.3% |
| Multiple myeloma | 1.2% |
| Liver | 0.6% |
| Esophagus | 0.5% |
| Hodgkin lymphoma | 0.5% |
| Larynx | 0.2% |
| All other cancers | 8.9% |

CNS=central nervous system, NOS=not otherwise specified

**Note:** The complete definition of the specific cancers listed here can be found in Table A8.

**Analysis by:** Surveillance and Epidemiology Division, CCDP, Public Health Agency of Canada
**Data sources:** Canadian Cancer Registry and National Cancer Incidence Reporting System databases at Statistics Canada

Canada, 2016:

- 9th most common in males
- 14th most common in females

**FIGURE 3.2** Percent distribution of estimated cancer deaths, by sex, Canada, 2016

**Males**
**41,700**
**Deaths**

| | |
|---|---|
| Lung and bronchus | 26.1% |
| Colorectal | 12.0% |
| Prostate | 9.6% |
| Pancreas | 5.8% |
| Bladder | 4.0% |
| Leukemia | 4.0% |
| Esophagus | 3.8% |
| Non-Hodgkin lymphoma | 3.6% |
| Brain/CNS | 3.1% |
| Stomach | 3.0% |
| Kidney and renal pelvis | 2.9% |
| Liver* | 2.2% |
| Oral | 2.0% |
| Multiple myeloma | 1.9% |
| Melanoma | 1.8% |
| Larynx | 0.8% |
| Thyroid | 0.2% |
| Hodgkin lymphoma | 0.2% |
| Breast | 0.1% |
| Testis | 0.1% |
| All other cancers | 12.7% |

**Females**
**37,100**
**Deaths**

| | |
|---|---|
| Lung and bronchus | 26.4% |
| Breast | 13.2% |
| Colorectal | 11.6% |
| Pancreas | 6.5% |
| Ovary | 4.7% |
| Leukemia | 3.2% |
| Non-hodgkin lymphoma | 3.2% |
| Body of uterus and uterus NOS | 3.0% |
| Brain/CNS | 2.7% |
| Stomach | 2.1% |
| Bladder | 1.8% |
| Kidney and renal pelvis | 1.8% |
| Multiple myeloma | 1.7% |
| Esophagus | 1.2% |
| Melanoma | 1.2% |
| Cervix | 1.1% |
| Oral | 1.1% |
| Liver* | 0.7% |
| Thyroid | 0.3% |
| Larynx | 0.2% |
| Hodgkin lymphoma | 0.1% |
| All other cancers | 12.1% |

CNS=central nervous system; NOS=not otherwise specified
* Liver cancer deaths are underestimated; see *Appendix II: Data and methods issues*.

**Note:** The complete definition of the specific cancers listed here can be found in Table A8.

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

- Ranked 13th and 17th cause of cancer death in men and women respectively in Canada, 2016.

# 5 years survival

| Stage Grouping | | Approximate 5-Year Survival Rate (%) |
|---|---|---|
| 0 | Tis, N0, N0 | 99% |
| I | T1, N0, M0 | 90%-92% |
| II | T2, N0, M0 | 75%-85% |
| III | T3, N0, M0 | |
| | T1, N1, M0 | |
| | T2, N1, M0 | 50% |
| | T3, N1, M0 | |
| IV | T4, N0, M0 | |
| | T4, N1, M0 | |
| | Any T, N2, M0 | 25%-35% |
| | Any T, N3, M0 | |
| | Any T, Any N, M1 | |

Adapted with permission from Beahrs OH, Henson DE, Hutter RVP, et al (eds): *Manual for Staging of Cancer*, 4th ed. Chicago, American Joint Committee on Cancer, 1992.

| Lip Stage | 5 years survival |
|---|---|
| I | 96% |
| II | 83% |
| III | 57% |
| IV | 48% |

| Tongue Stage | 5 years survival |
|---|---|
| I | 71% |
| II | 59% |
| III | 47% |
| IV | 37% |

| Floor of mouth Stage | 5 years survival |
|---|---|
| I | 73% |
| II | 60% |
| III | 36% |
| IV | 30% |

| Gum and other Stage | 5 years survival |
|---|---|
| I | 81% |
| II | 62% |
| III | 45% |
| IV | 40% |

Canadian Cancer Society

# Five years survival

**Lip**

| Stage | 5 yrs survival |
|---|---|
| Local | 93% |
| Regional | 48% |
| Distant | 52% |

**Floor of mouth**

| Stage | 5 yrs survival |
|---|---|
| Local | 75% |
| Regional | 38% |
| Distant | 20% |

**Tongue**

| Stage | 5 yrs survivla |
|---|---|
| Local | 78% |
| Regional | 63% |
| Distant | 36% |

# High risk population !!

- Patients with OPLs… leukoplakia, erythroleukoplakia, OSMF, LP.
- Which precancerous lesions will transform into cancer ??

Yardimci G *et al*. Premalignant oral lesions

**Table 1 Risk factors of malignant transformation**

| | |
|---|---|
| Female gender | |
| Long duration of leukoplakia | |
| Leukoplakia in non-smokers | |
| Location on the tongue and/or floor of the mouth | |
| Size > 200 $mm^2$ | |
| Non-homogenous type | (PVL, erythroluekoplakia ) |
| Presence of epithelial dysplasia | Gold standard |

# Dysplasia

- Gold standard.
- OPL risk of progression to oral cancer is associated with the presence of dysplasia, the grade of dysplasia and decreased significantly but not eliminated with excision. *Mehanna HM,et al. Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis. Head Neck 2009;31(12):1600–9.*
- In hospital-based study, lesions demonstrating mild epithelial dysplasia had malignant transformation rates similar to those with severe dysplasia. *Holmstrup P, et al. Long-term treatment outcome of oral premalignant lesions. Oral Oncol 2006;42:461-74.*
- Transformation rates based on grade of dysplasia are difficult to establish.
- Subjective… Multiple studies have demonstrated low-to-moderate interexaminer consensus for dysplasia grade among experienced oral pathologists.

# Genetic factors and Biomarkers

DNA methylation markers for oral pre-cancer progression: A critical review

Krithiga Shridhar[a,*,1], Gagandeep Kaur Walia[a,1], Aastha Aggarwal[a], Smriti Gulati[a], A.V. Geetha[a], Dorairaj Prabhakaran[a,b,c], Preet K. Dhillon[a], Preetha Rajaraman[d]

Vol. 123 No. 3 March 2017

**Individualized five-year risk assessment for oral premalignant lesion progression to cancer**

Jason T.K. Hwang, PhD,[a] Ying R. Gu, PhD, MBA,[a] Mi Shen, MSc,[a] Ranju Ralhan, PhD,[a,b,c,d] Paul G. Walfish, MD, CM, O.Ont, FRCPC, FCAHS,[a,b,c,d,e] Kenneth P.H. Pritzker, MD, FRCPC,[a,f,g] and David Mock, DDS, PhD, FRCD(C)[a,h]

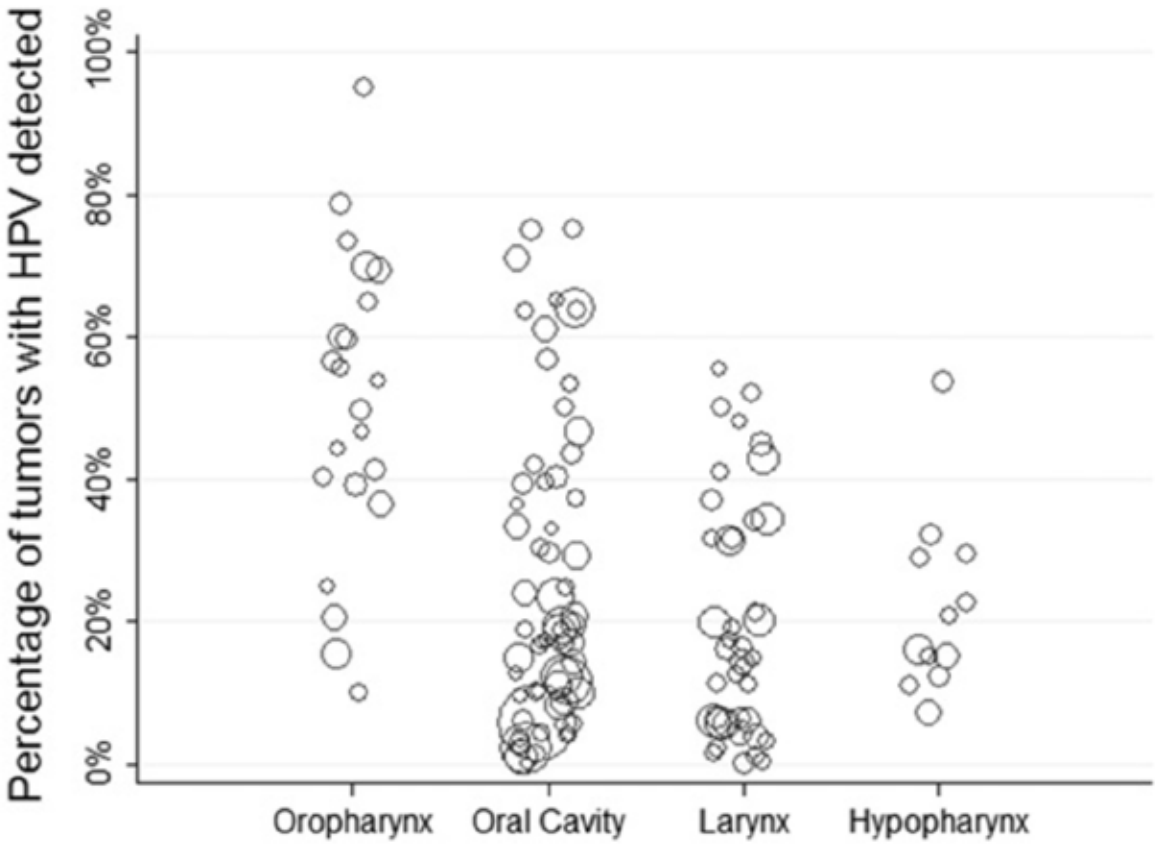
**Loss of Heterozygosity (LOH) Profiles—Validated Risk Predictors for Progression to Oral Cancer**

Lewei Zhang[4,5], Catherine F. Poh[1,2,4,5], Michele Williams[2,4], Denise M. Laronde[1,4], Ken Berean[5], Pamela J. Gardner[3], Huijun Jiang[1], Lang Wu[6], J. Jack Lee[8], and Miriam P. Rosin[1,7]

DNA content status using brush biopsy with image cytometry correlated with staging of oral leukoplakia: A preliminary study

Xuan Xiao[a,1], Linjun Shi[a,1], Hongquan Li[a], Yang Song[a], Wei Liu[b,*], Zengtong Zhou[a,*]

# HPV and oral cancer




*A. W. Joseph, G. D'Souza*
***Epidemiology of human papillomavirus-related head and neck cancer***
*Otolaryngol Clin North Am, 45 (2012), pp. 739–764*

# Viruses
# HPV

## Association of high-risk human papillomavirus infection with oral epithelial dysplasia

Christina McCord, DDS,[a] Jing Xu, PhD,[b] Wei Xu, PhD,[c] Xin Qiu, MMath,[c] Richard John McComb, BDS, MSc,[a] Bayardo Perez-Ordonez, MD,[d] and Grace Bradley, DDS, MSc[a,e]

## Detection of human papillomavirus–16 and HPV-18 DNA in normal, dysplastic, and malignant oral epithelium

Masaru Sugiyama, DDS, PhD,[a] Ujjal Kumar Bhawal, BDS, PhD,[b] Tamiko Dohmen, DDS, PhD,[c] Shigehiro Ono, DDS, PhD,[d] Miwa Miyauchi, DDS, PhD,[c] and Takenori Ishikawa, DDS, PhD,[e] Hiroshima, Japan
HIROSHIMA UNIVERSITY

## Comparison of the prevalence of human papilloma virus infection in histopathologically confirmed premalignant oral lesions and healthy oral mucosa by brush smear detection

Daniel Dalla Torre, MD, DMD,[a,b] Doris Burtscher, MD, DMD,[c] Michael Edlinger, MSc, PhD,[d] Elisabeth Sölder, MD,[e] Andreas Widschwendter, MD,[e] Michael Rasse, MD, DMD,[a] and Wolfgang Puelacher, MD, DMD[a]

## Detection and typing of Human Papillomaviruses (HPV) in malignant, dysplastic, nondysplastic and normal oral epithelium by nested Polymerase Chain Reaction, immunohistochemistry and transitional electron microscopy in patients of Northern Greece

E. Blioumi[a,*], D. Chatzidimitriou[b], Ch. Pantzartzi[c], Th. Katopodi[d], G. Tzimagiorgis[e], E.-N. Emmanouil-Nikoloussi[f], A. Markopoulos[a], C. Kalekou[a], N. Lazaridis[g], E. Diza[h], D. Antoniades[a]

Table II. Literature review of HPV prevalence in potentially malignant lesions.

| Molecular investigation techniques | Oral lesions | HPV+ | % | Studies |
|---|---|---|---|---|
| SB | Leucoplakia | 4/5 | 80 | Löning *et al*, 1985 (70) |
| SB | Dysplasia/hyperplasia/lichen planus | 16/21 | 28.6 | Maitland *et al*, 1987 (37) |
| ISH | Dysplasia | 21/202 | 10.4 | Gassenmaier and Hornstein, 1988 (62) |
| ISH | Dysplasia | 6/22 | 27.3 | Syrjanen *et al*, 1988 (19) |
| ISH | Leucoplakia | 0/10 | 0 | Shroyer and Greer, 1991 (72) |
| SB | Leucoplakia | 3/3 | 100 | Cox *et al*, 1993 (79) |
| ISH | Leucoplakia | 5/13 | 38.5 | Gonzàles-Moles *et al*, 1998 (83) |
| PCR | Leucoplakia | 5/5 | 100 | Balaram *et al*, 1995 (99) |
| PCR | Dysplasia | 0/3 | 0 | Fouret *et al*, 1995 (59) |
| PCR | Leucoplakia | 9/21 | 42.9 | Palefsky *et al*, 1995 (65) |
| PCR | Hyperplasia/dysplasia | 29/34 | 85.2 | Bouda *et al*, 2000 (60) |
| PCR | Dysplasia | 31/51 | 60.8 | Sugiyama *et al*, 2003 (42) |
| PCR | Leucoplakia/lichen planus | 26/139 | 18.7 | Campisi *et al*, 2004 (33) |

# HPV & EBV in PVL

- PVL is the form of OL thought to have the strongest relationship to HPV infection. However, a Multi-centre study in (Campisi et al.,2004) reported no Statistically significant difference, in terms of HPV-DNA detection and type of OL or the onset of PVL.

- In a preliminary study by Bagan et al, EBV was examined by nested PCR in 10 cases of PVL, five with OSCC, and five normal mucosa samples. EBV was detected in 60% of the PVL cases and in 40% of OSCC, but in none of the normal mucosa samples.

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# The role of *Chlamydia trachomatis* infection as a cofactor in the development of cervical cancer

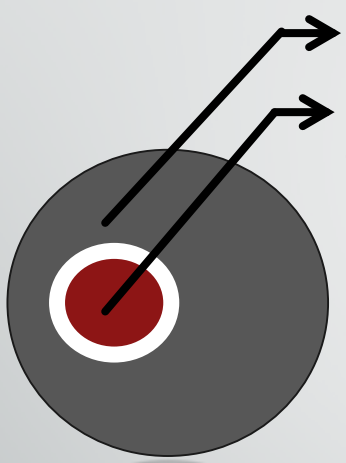
**Cancer Epidemiology and Prevention Course EPIB 671**

May 2017

Gabriel Pinto

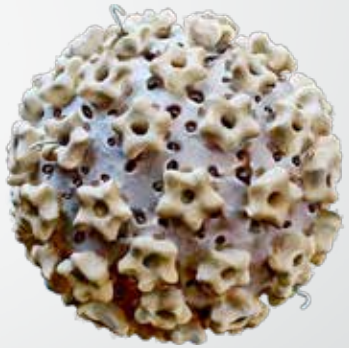
# HUMAN PAPILLOMAVIRUS (HPV)

- Genital HPV infection is a most common sexually transmitted infection among women
- The presence of HPV DNA is necessary for cervical cancer development



200 HPV genotypes

40 genotypes infect the genital tract



HPV - Oncogeneses

Low risk- Genital warts

6 11

High risk - Squamous intraepithelial cervical lesion and cervical cancer

16 18

HPV´s oncogenic potential is attributed mainly to two early viral proteins E6 and E7

Murphy et al., 1995; van Regenmortel et al., 2000; Neves et al., 2002

## Estimates of new cases of cancer- BRAZIL 2010
## incidence per 100.000 and the number of new cases of cancer

| | Casos | Taxa Bruta |
|---|---|---|
| Mama Feminina | 49.240 | 49,27 |
| Cervical cancer | 18.430 | 18,47 |
| Cólon e Reto | 14.800 | 14,80 |
| Traqueia, Brônquio e Pulmão | 9.830 | 9,82 |
| Estômago | 7.680 | 7,70 |
| Leucemias | 4.340 | 4,33 |
| Cavidade Oral | 3.790 | 3,76 |
| Pele Melanoma | 2.970 | 2,92 |
| Esôfago | 2.740 | 2,69 |
| Outras Localizações | 78.770 | 78,83 |
| **Subtotal** | **192.590** | **192,74** |
| Pele não Melanoma | 60.440 | 60,51 |
| **Todas as Neoplasias** | **253.030** | **253,23** |

*Números arredondados para 10 ou múltiplos de 10

# Incidence estimates of new cases of cancer
# BRAZIL 2016

| Localização Primária | Casos | % |
|---|---|---|
| Próstata | 61.200 | 28,6% |
| Traqueia, Brônquio e Pulmão | 17.330 | 8,1% |
| Cólon e Reto | 16.660 | 7,8% |
| Estômago | 12.920 | 6,0% |
| Cavidade Oral | 11.140 | 5,2% |
| Esôfago | 7.950 | 3,7% |
| Bexiga | 7.200 | 3,4% |
| Laringe | 6.360 | 3,0% |
| Leucemias | 5.540 | 2,6% |
| Sistema Nervoso Central | 5.440 | 2,5% |

**Homens**

**Mulheres**

| Localização Primária | Casos | % |
|---|---|---|
| Mama feminina | 57.960 | 28,1% |
| Cólon e Reto | 17.620 | 8,6% |
| Cervical cancer | 16.340 | 7,9% |
| Traqueia, Brônquio e Pulmão | 10.890 | 5,3% |
| Estômago | 7.600 | 3,7% |
| Corpo do útero | 6.950 | 3,4% |
| Ovário | 6.150 | 3,0% |
| Glândula Tireoide | 5.870 | 2,9% |
| Linfoma não Hodgkin | 5.030 | 2,4% |
| Sistema Nervoso Central | 4.830 | 2,3% |

*Números arredondados para múltiplos de 10.

# Incidence estimates of new cases of cancer
# In the north of BRAZIL 2016

| Localização Primária | Casos | % |
|---|---|---|
| Próstata | 2.470 | 28,6% |
| Estômago | 970 | 11,2% |
| Traqueia, Brônquio e Pulmão | 680 | 7,9% |
| Cólon e Reto | 440 | 5,1% |
| Bexiga | 370 | 4,3% |
| Leucemias | 310 | 3,6% |
| Cavidade Oral | 290 | 3,4% |
| Laringe | 250 | 2,9% |
| Linfoma não Hodgkin | 230 | 2,7% |
| Sistema Nervoso Central | 230 | 2,7% |

**Homens**

**Mulheres**

| Localização Primária | Casos | % |
|---|---|---|
| Cervical cancer | 1.970 | 23,1% |
| Mama Feminina | 1.810 | 21,2% |
| Cólon e Reto | 480 | 5,6% |
| Estômago | 480 | 5,6% |
| Traqueia, Brônquio e Pulmão | 410 | 4,8% |
| Glândula Tireoide | 270 | 3,2% |
| Leucemias | 250 | 2,9% |
| Ovário | 250 | 2,9% |
| Corpo do Útero | 230 | 2,7% |
| Sistema Nervoso Central | 190 | 2,2% |

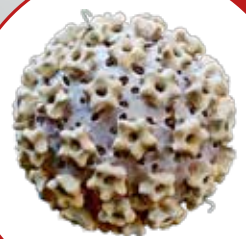
*Números arredondados para múltiplos de 10.

# Possible risk factors associated with persistent HR-HPV in the last two decades

- Only a small minority of HPV-exposed women actually develop cervical cancer
- Risk factors are involved not only in the infection point but also in the carcinogenic process

LIFESTYLE

- **Hormonal contraceptives**
- **Early sexual activity**
- **Multiple sex partiners**
- **Tobacco**
- **Parity**

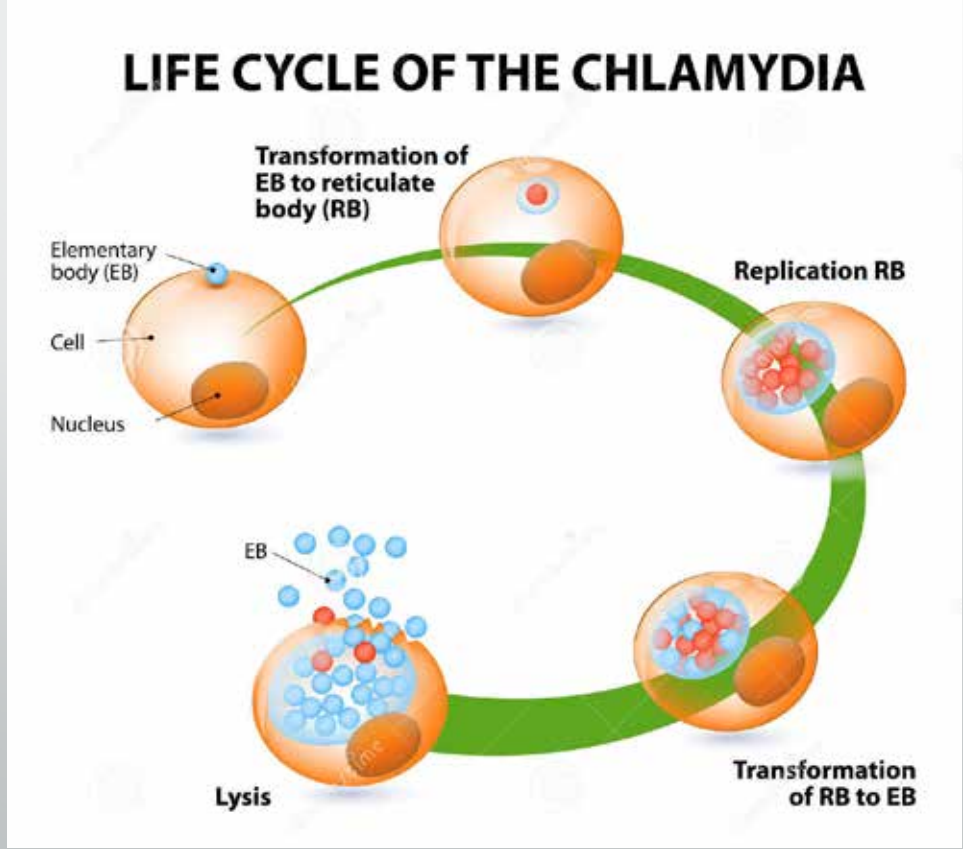


- **Intertype HPV variations**
- **Multi-infection with multiple HPV genotypes**
- **Coinfection with other agents**

Tota JE, Prev Med. 2011 , Moreno V, . Lancet. 2002

# *Chlamydia trachomatis* (CT)

- CT infections are the most commonly reported sexually transmitted bacterial infections in the US and globally
- Gram-negative bacteria
- Intracellular Life cycle: reticulate and elementary body
- Infects ocular, genital and respiratory tissues

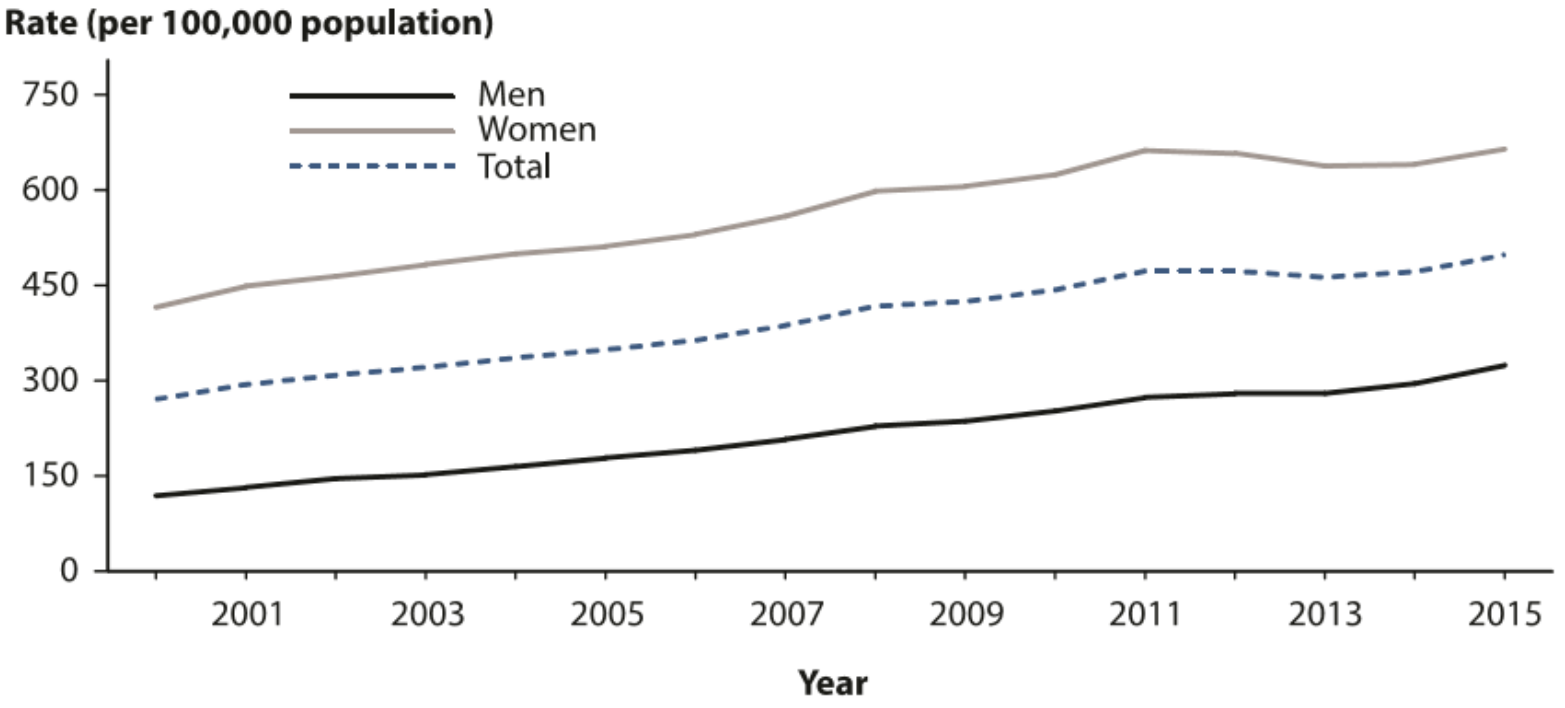



Wang SP et al., 1970
Bastidas et al., 2013.
O'Connell CM, Microb Cell. 2016

# *Chlamydia trachomatis* (CT)

- The World Health Organization estimated a global prevalence at 4.2%

**Figure 1. Chlamydia — Rates of Reported Cases by Sex, United States, 2000–2015**




**NOTE:** Data collection for chlamydia began in 1984 and chlamydia was made nationally notifiable in 1995; however, chlamydia was not reportable in all 50 states and the District of Columbia until 2000. Refer to the National Notifiable Disease Surveillance System (NNDSS) website for more information: https://wwwn.cdc.gov/nndss/conditions/chlamydia-trachomatis-infection/.

# CHLAMYDIA TRACHOMATIS – GENITAL TRACT PATHOGEN

- 20% of the women with lower genital tract CT infection will develop pelvic inflammatory disease (PID). **Prince MJ, et al, Am J Epidemiol. 2013.**

- 4% will develop chronic pelvic pain. The clinical spectrum of chlamydial PID ranges from subclinical endometritis to frank salpingitis, tubo-ovarian masses, pelvic peritonitis, periappendicitis and perihepatitis. However, the majority of genital chlamydial infections are asymptomatic. **Paavonen J et al, Hum Reprod Update. 1999**

- CT infection causes severe inflammation of the cervix associated with metaplastic atypia of the transformation zone of the cervix. **Kiviat NB, J Am Med Assoc 1985**

- A possible biological explanation for the increased risk of HPV infection among women with CT co-infection is that CT infection causes local inflammation leading to damage of the epithelial tissue which could make the woman more susceptible for HPV infection. **Paba P, et al Intervirology. 2008**

| Reference | Country | Type, n, sample type | Main findings |
|---|---|---|---|
| **Schmauz et al. 1989** | Uganda | - Case control study<br>- n = 34 cases/ 23 controls<br>- Tissue and serum | A linear trend in the rise of risk for cervical cancer was noted with increasing number of infections. |
| **Anttila et al. 2001** | Finland, Norway and Sweden | - Nested case-control<br>- n= 181 cases / 533 controls<br>- Serum | Increasing numbers of different CT serotypes, especially serotype G, increases risk of cervical cancer |
| **Paba et al. 2008** | Italy | - Clinical trial<br>- 149 samples<br>- Tissue | CT infection favors the entry and persistence of multiple HR-HPV types, which leads to viral integration, inhibition of apoptosis, overexpression of E6/E7 oncogenes and cell transformation. |
| **Abreu et al. 2016** | Brazil | - Cross-sectional<br>- n=838 samples<br>- Cervical samples | Coinfections of HR-HPV and CT exhibited a five times higher increased risk of HSIL |

# Evidence for *Chlamydia trachomatis* as a Human Papillomavirus Cofactor in the Etiology of Invasive Cervical Cancer in Brazil and the Philippines

Smith JS, et al. The Journal of Infectious Diseases 2002;185:324–31

**Table 4.** Odds ratios (ORs) of invasive squamous cervical cancer among human papillomavirus (HPV) DNA–positive study participants, by *Chlamydia trachomatis* and *C. pneumoniae* seropositivity.

| Parameter | HPV-positive patients/ HPV-positive control women | OR (95% CI) |
|---|---|---|
| *C. trachomatis* IgG | | |
| Brazil | | |
| Seronegative | 78/22 | 1[a] |
| Seropositive | 49/6 | 2.5[a] (0.9–6.9) |
| The Philippines | | |
| Seronegative | 147/23 | 1[a] |
| Seropositive | 156/10 | 1.6[a] (0.7–3.7) |
| Both countries combined[b] | | |
| Seronegative | 225/45 | 1[a] |
| Seropositive | 205/16 | 2.1[a] (1.1–4.0) |
| Seropositive titer | | |
| 8 | 56/7 | 1.4[a] (0.6–3.3) |
| 32 | 94/8 | 2.7[a] (1.2–5.9) |
| 128 | 55/1 | *P* for trend = .01 |
| *C. pneumoniae*, both countries combined[b] | | |
| Seronegative | 102/15 | 1[c] |
| Seropositive | 328/46 | 1.2[c] (0.6–2.3) |

NOTE. CI, confidence interval.

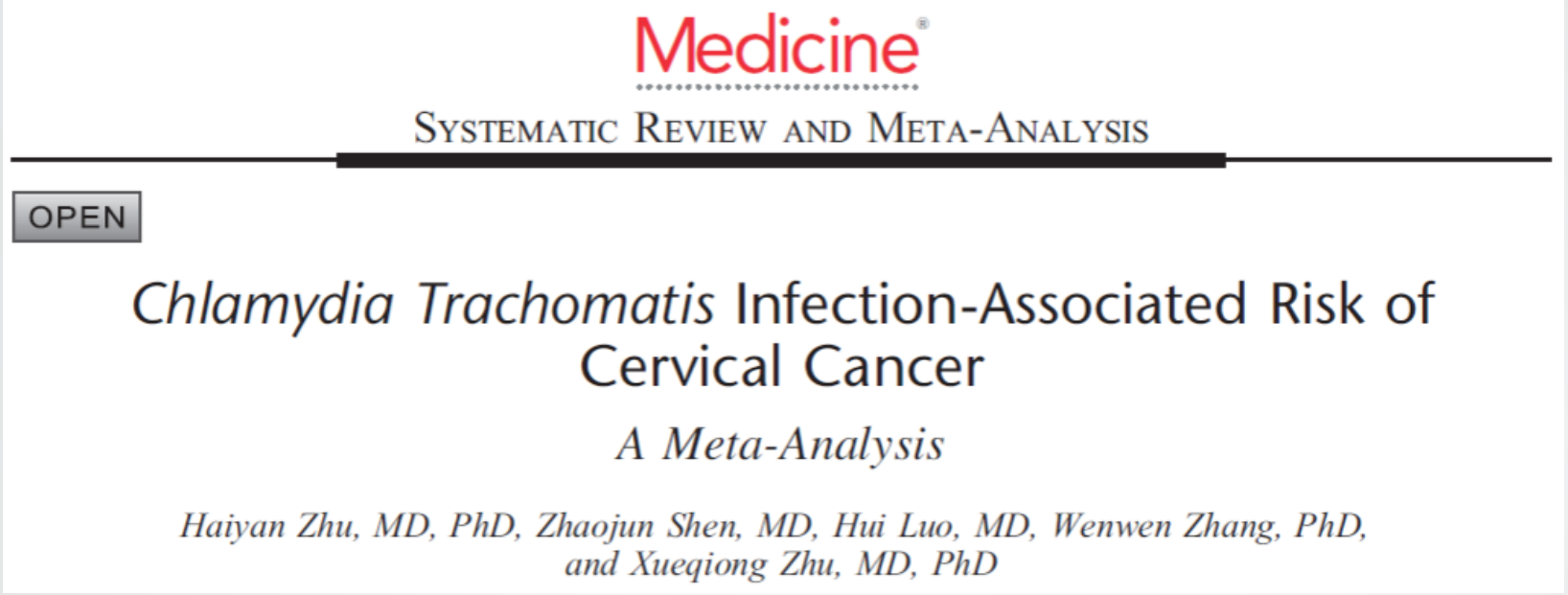
[a] OR adjusted for age, herpes simplex virus (HSV)–2 seropositivity, and husband's no. of sex partners during marital relationship.

[b] Combined country analyses were adjusted for country of residence.

[c] OR adjusted for age, HSV-2 seropositivity, husband's sex partners during marital relationship, and *C. trachomatis* seropositivity.

The increasing risk of squamous cervical cancer with increasing CT antibody titers gives further support to the results found.

- High antibody titers may be a marker of persistent CT infection, since women with long-term complications of CT infection, such as pelvic inflammatory disease or tubal infertility, have significantly higher levels of antibody than women with cervical CT infection.




- Assessed CT infection and cervical cancer prevalence
- 22 case control and cross sectional studies on CT and the risk of cervical cancer
- 1981 to 2014
- 31 countries

Medicine Volume 95, Number 13, April 2016

- The overall prevalence of CT infection in women with cervical cancer was 42% and in controls 26%

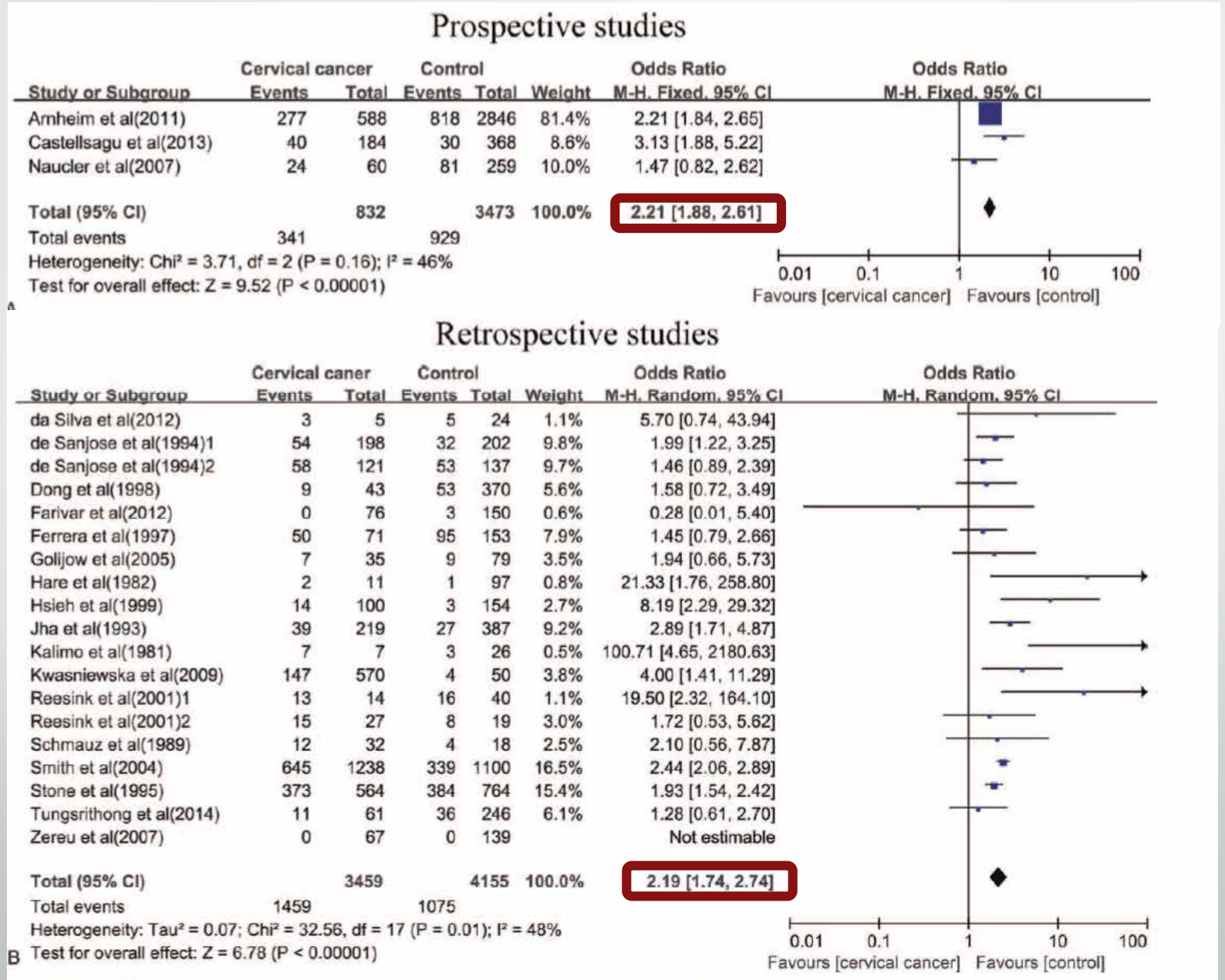
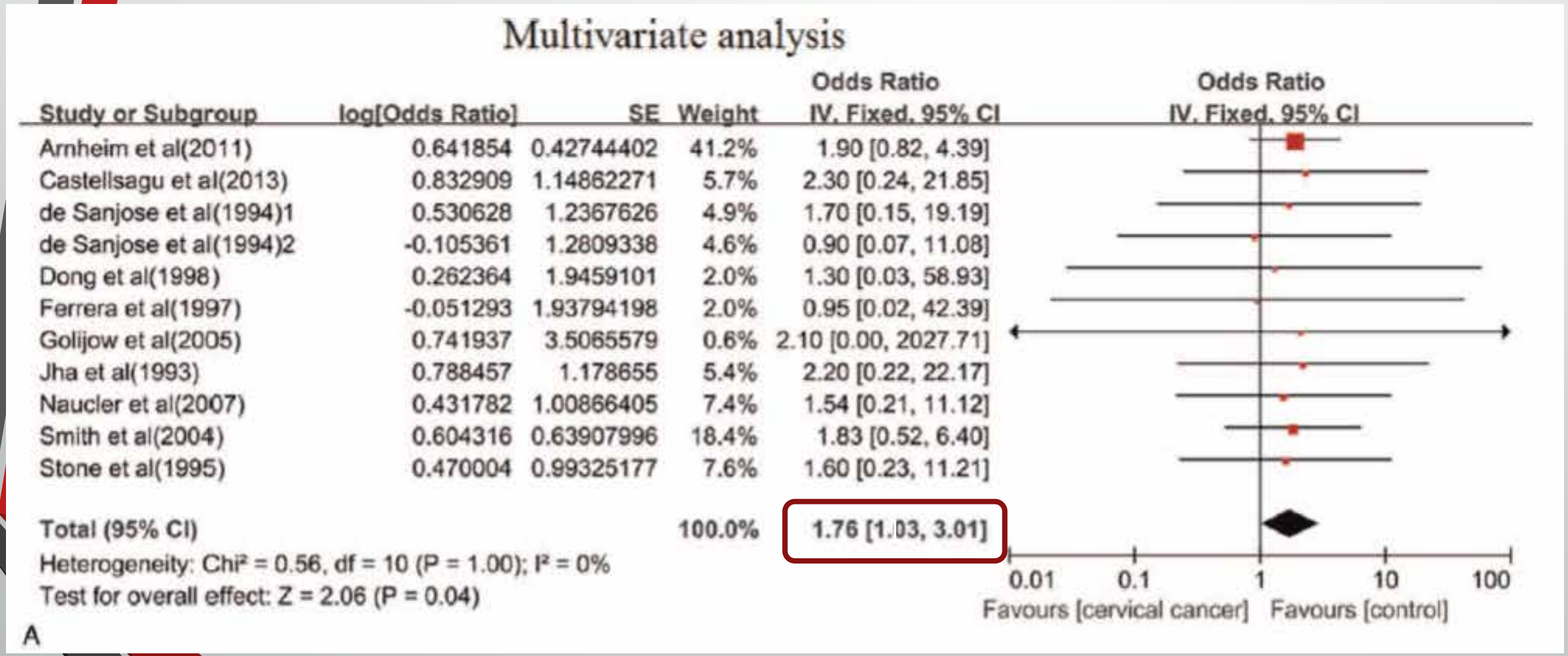



FIGURE 2. The association between *C. trachomatis* infection and the risk of cervical cancer in prospective studies and retrospective studies.

- CT infection was identified as an independent predictor of cervical cancer in 11 studies with adjustment for HPV infection and age.



- 6 studies evaluated the coinfection of HPV and CT and suggested that coinfection was related to a higher risk of cervix cancer: Adjusted for oral contraceptive, sexual status, number of full-term pregnancy and history of smoking

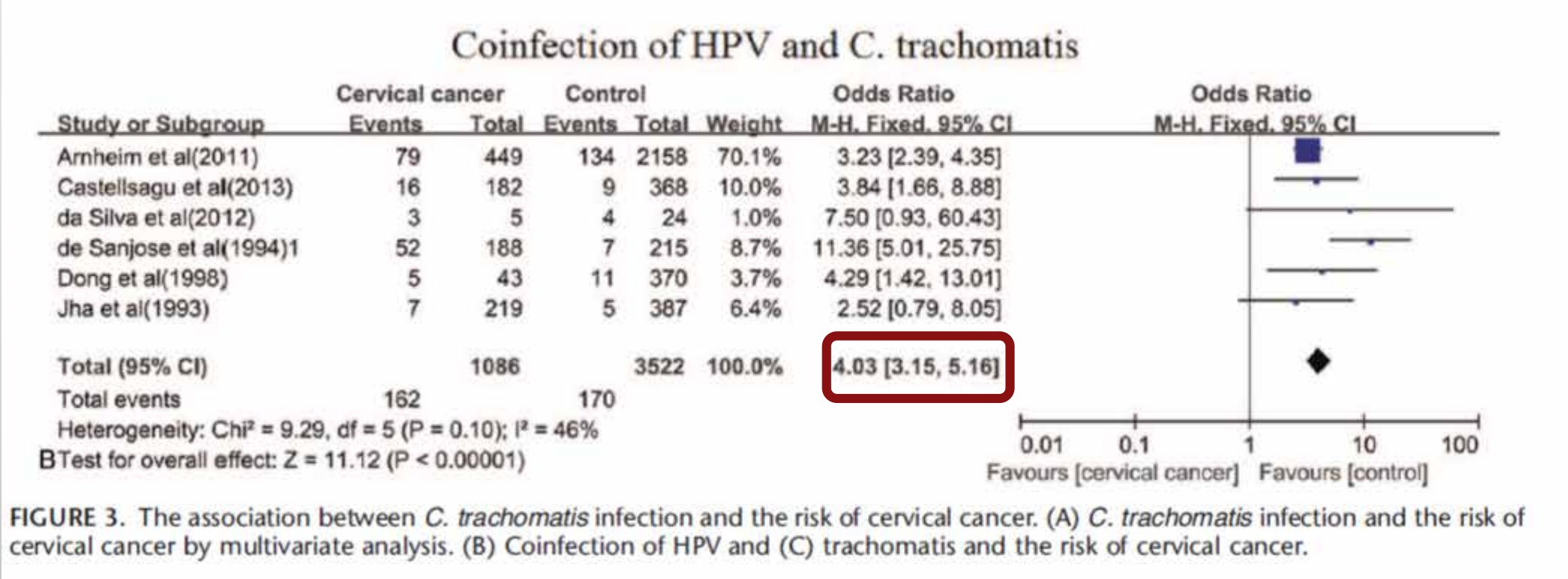



FIGURE 3. The association between *C. trachomatis* infection and the risk of cervical cancer. (A) *C. trachomatis* infection and the risk of cervical cancer by multivariate analysis. (B) Coinfection of HPV and (C) trachomatis and the risk of cervical cancer.

- A subgroup analysis found:
  - **SCC** (OR=2.21, 95% CI: 2.00–2.45)
  - **Adenocarcinoma** (OR=1.61, 95% CI: 1.21– 2.15)

# Summary

- HPV is necessary, but not sufficient, to cause SCC, which supports the influence of additional factors in carcinogenesis associated with persistence of HR-HPV.
- CT infection may increase the susceptibility to HPV via the production of micro-abrasions or alterations in epithelial cells, which facilitates the entry of virions – Vertano R, BMC Infect Dis. 2009
- CT infection can reduce host ability to resolve HPV infection: chronic cervical inflammation seems to influence the HPV persistence through a raised production of free radicals and a reduction of host cell-mediated - Vertano R, BMC Infect Dis. 2009
- CT infection induces a shift in the immune response, and the unresolved infections are associated with the humoral immune response, but the cellular (Th1) immune response is important for the clearance of HPV infection. Therefore, modulation of the cervical immune response by CT may Influence the clearance of HPV and contribute for persistent of HPV and progression of the lesions. - Samoff E, Am J Epidemiol. 2005
- Coinfections of HR-HPV and CT exhibited a five times higher increased risk of HSIL - de Abreu AL, Am J Cancer Res. 2016

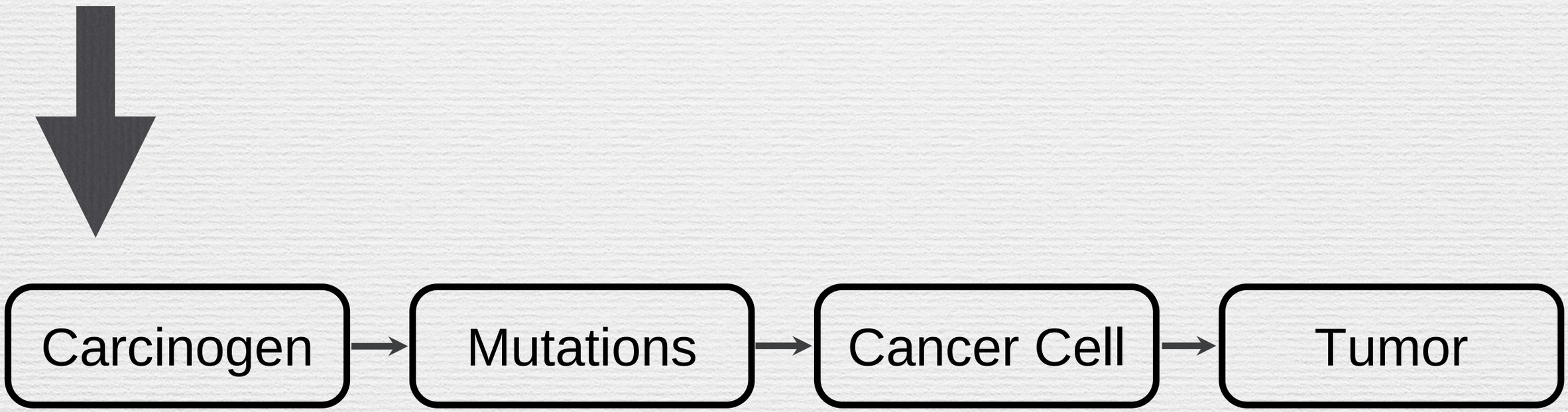
# Cancer, Is It Just Bad Luck?

Estimating the contribution of DNA replication mutations to carcinogenesis

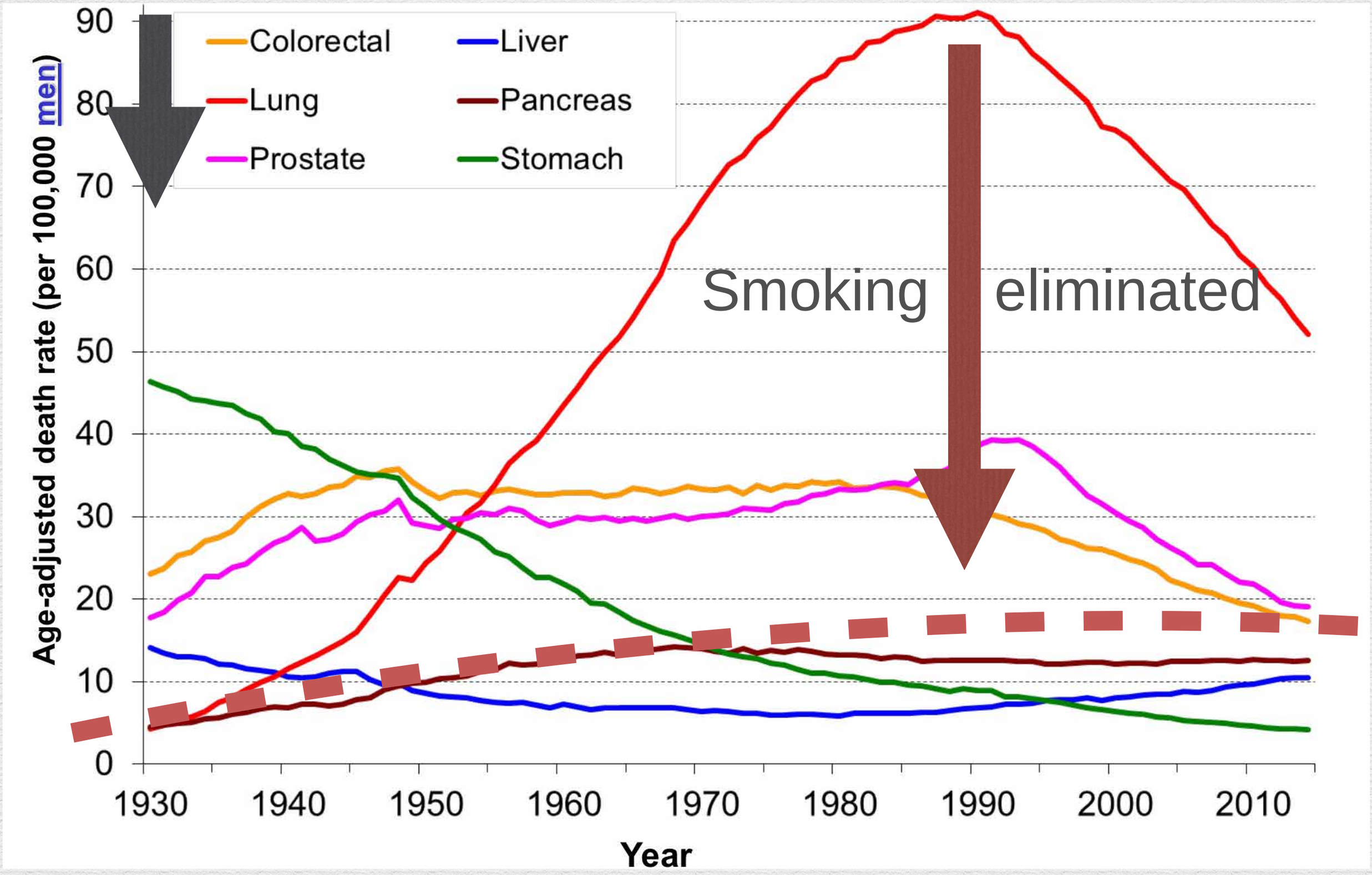
Atuhani Burnett, MD, PhD

# Standard Paradigm

Risk factor/
Initiating event → Latency → Disease



Risk factor/
Initiating event → Latency → Disease



# Consider this...

Every time genome is copied 100,000 errors are made

Most are fixed, leaving about 1 mutation per genome per replication cycle

# Human tissue accumulates 40 mutations per year in each adult stem cell

# By age 70 that amounts to 2800 accumulated mutations in each stem cell

Nature. 2016 Oct 13;538(7624):260-264. doi: 10.1038/nature19768. Epub 2016 Oct 3.

**Tissue-specific mutation accumulation in human adult stem cells during life.**

Blokzijl F[1,2], de Ligt J[1,2], Jager M[1,2], Sasselli V[2], Roerink S[3], Sasaki N[2], Huch M[2], Boymans S[1,2], Kuijk E[1,2], Prins P[2], Nijman IJ[2], Martincorena I[3], Mokry M[4], Wiegerinck CL[4], Middendorp S[4], Sato T[2], Schwank G[2], Nieuwenhuis EE[4], Verstegen MM[5], van der Laan LJ[5], de Jonge J[5], IJzermans JN[5], Vries RG[6], van de Wetering M[2], Stratton MR[3], Clevers H[2], Cuppen E[1,2], van Boxtel R[1,2].

# Could it be?

Cancers would develop anyway in the absence of any risk factors?

# Are some cancers caused by bad luck?

# Variation in cancer risk among tissues can be explained by the number of stem cell divisions

Cristian Tomasetti[1]* and Bert Vogelstein[2]*

Science. 2015 Jan 2;347(6217):78-81. doi: 10.1126/science.1260825.

**Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions.**

Tomasetti C1, Vogelstein B2.

# Study Design

- Population based observational study
- Correlation between molecular biology estimates of stem cell lifetime divisions (surrogate for #mutations) and US incidence of the cancer associated with that tissue
- Aim to prove that tissues with more cell divisions accumulate more mutations, which then give rise to more cancers, which explains differences in body site cancer incidence that known risk factors alone cannot explain

Science. 2015 Jan 2;347(6217):78-81. doi: 10.1126/science.1260825.
**Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions.**
Tomasetti C1, Vogelstein B2.

| Cancer type | Lifetime cancer incidence | Total number of normal cells* in tissue of origin | Number of normal stem cells* in tissue of origin (s) | Number of divisions of each stem cell per year | Number of divisions of each stem cell per lifetime (d) | Cumulative number of divisions of all stem cells per lifetime (lscd) |
|---|---|---|---|---|---|---|
| Colorectal adenocarcinoma | 0.048 | $3 \cdot 10^{10}$ | $2 \cdot 10^{8}$ | 73 | 5840 | $1.168 \cdot 10^{12}$ |
| Esophageal squamous cell carcinoma | 0.001938 | $3.24 \cdot 10^{9}$ | $8.64 \cdot 10^{5}$ | 17.4 | 1390 | $1.203 \cdot 10^{9}$ |
| Lung adenocarcinoma (nonsmokers) | 0.0045 | $4.34 \cdot 10^{11}$ | $1.22 \cdot 10^{9}$ | 0.07 | 5.6 | $9.272 \cdot 10^{9}$ |
| Lung adenocarcinoma (smokers) | 0.081 | $4.34 \cdot 10^{11}$ | $1.22 \cdot 10^{9}$ | 0.07 | 5.6 | $9.272 \cdot 10^{9}$ |

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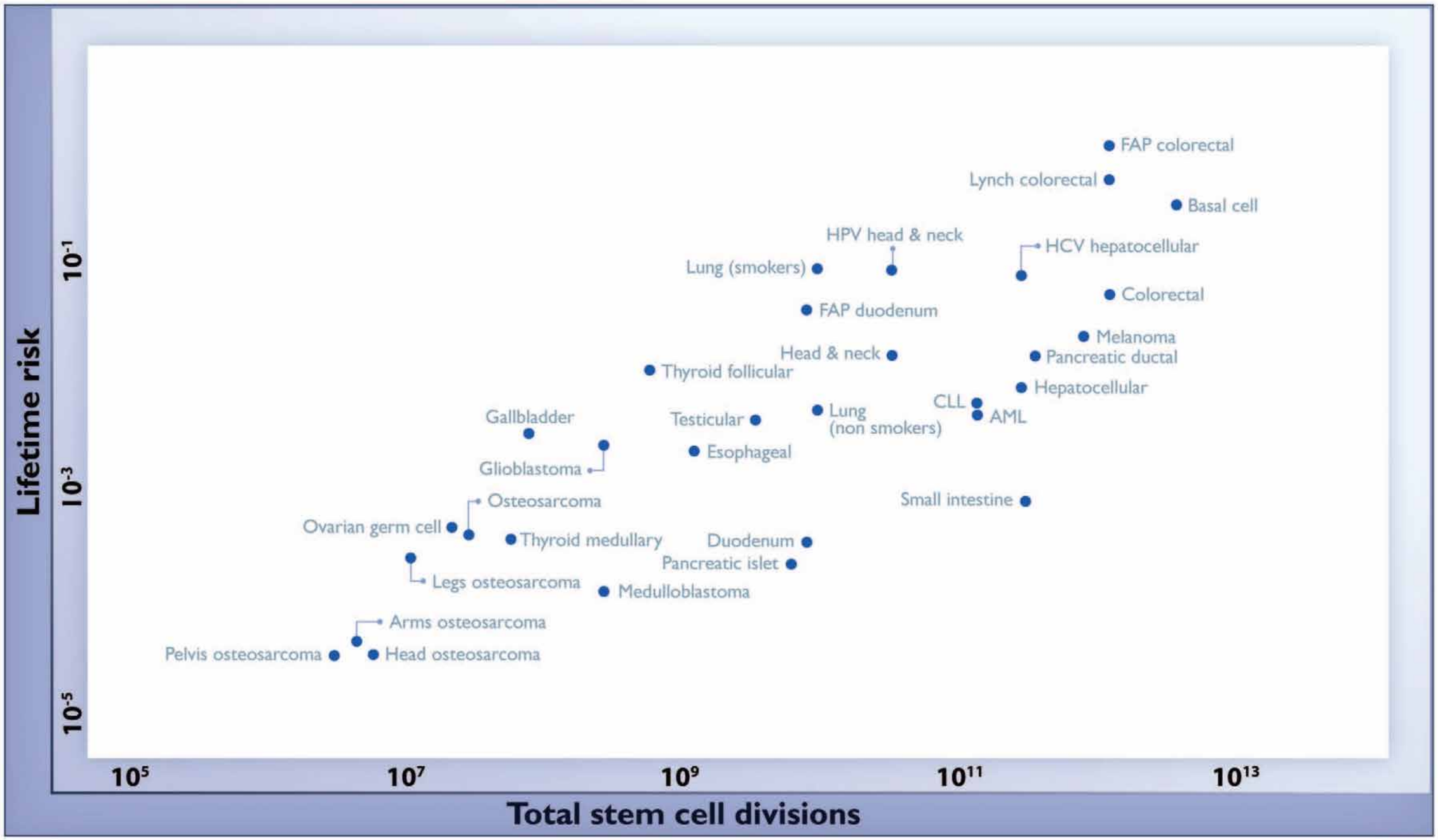


**Fig. 1. The relationship between the number of stem cell divisions in the lifetime of a given tissue and the lifetime risk of cancer in that tissue.**
Values are from table S1, the derivation of which is discussed in the supplementary materials.

Science. 2015 Jan 2;347(6217):78-81. doi: 10.1126/science.1260825.

# Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions.

Tomasetti C1, Vogelstein B2.

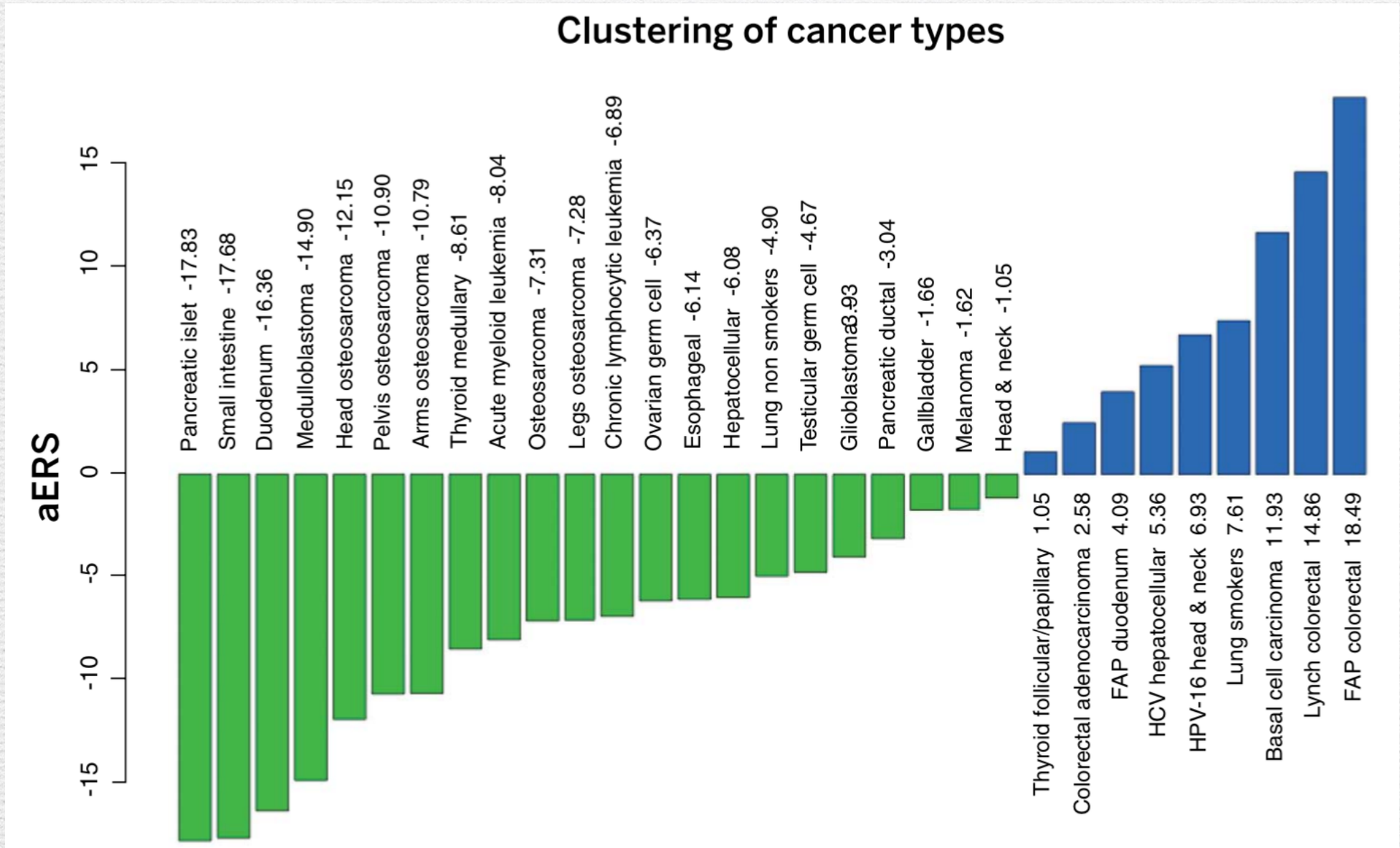


**Fig. 2. Stochastic (replicative) factors versus environmental and inherited factors: R-tumor versus D-tumor classification.** The adjusted ERS (aERS) is indicated next to the name of each cancer type. R-tumors (green) have negative aERS and appear to be mainly due to stochastic effects associated with DNA replication of the tissues' stem cells, whereas D-tumors (blue) have positive aERS. Importantly, although the aERS was calculated without any knowledge of the influence of environmental or inherited factors, tumors with high aERS proved to be precisely those known to be associated with these factors. For details of the derivation of aERS, see the supplementary materials.

Science. 2015 Jan 2;347(6217):78-81. doi: 10.1126/science.1260825.

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3,200 - 25,000 mut / tumor genome

2,900 - 40,000 mut / tumor genome

840 - 1260 mut / tumor genome

7,000 - 26,000 mut / tumor genome

Cell. 2012 Sep 14;150(6):1121-34. Govindan R et al

**Genomic landscape of non-small cell lung cancer in smokers and never-smokers.**

Gastroenterology. 2016 May;150(5):1171-82. Epub 2016 Feb 10. Sawada G et al

**Genomic Landscape of Esophageal Squamous Cell Carcinoma in a Japanese Population.**

Nature. 2012 Jul 18;487(7407):330-7. Cancer Genome Atlas Network.

**Comprehensive molecular characterization of human colon and rectal cancer.**

Science. 2015 Jan 2;347(6217):78-81. doi: 10.1126/science.1260825.

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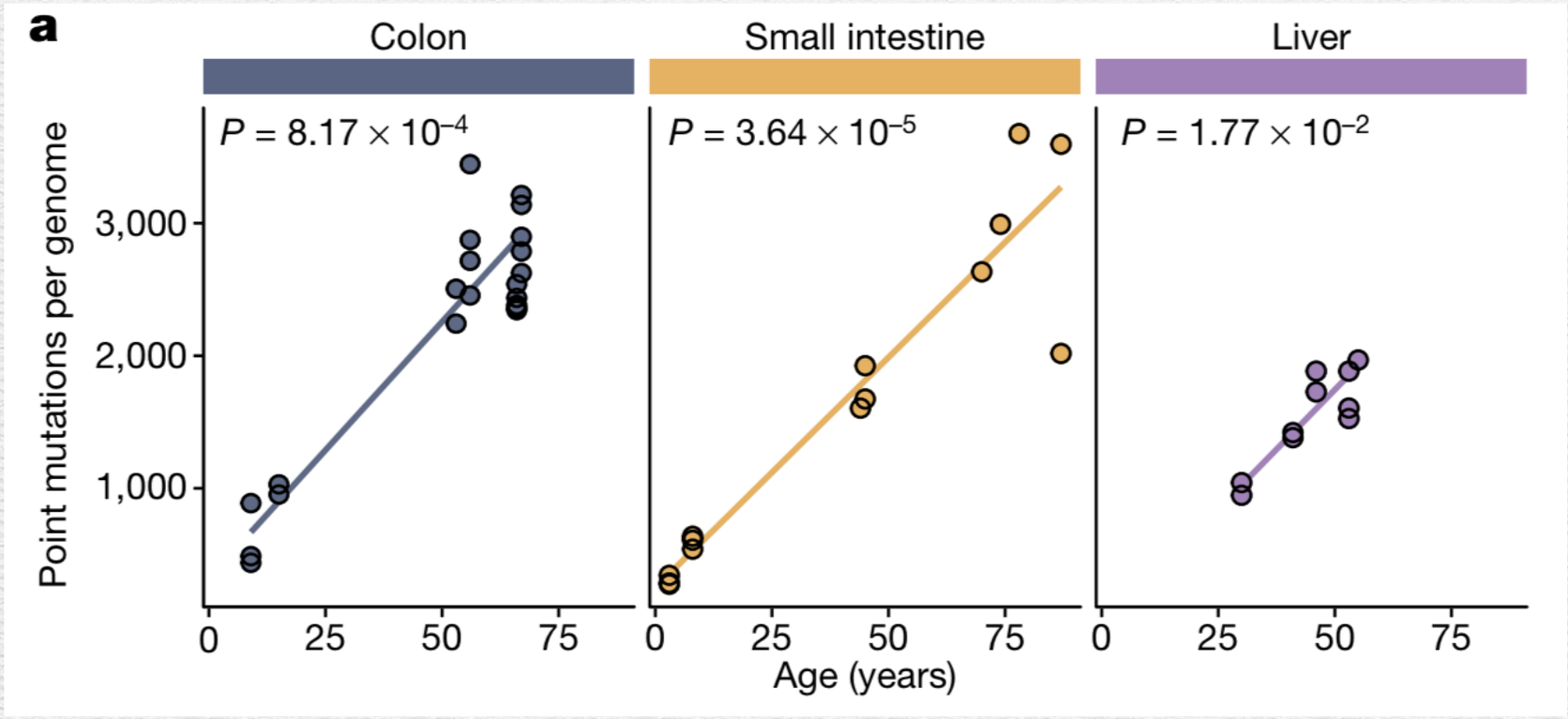
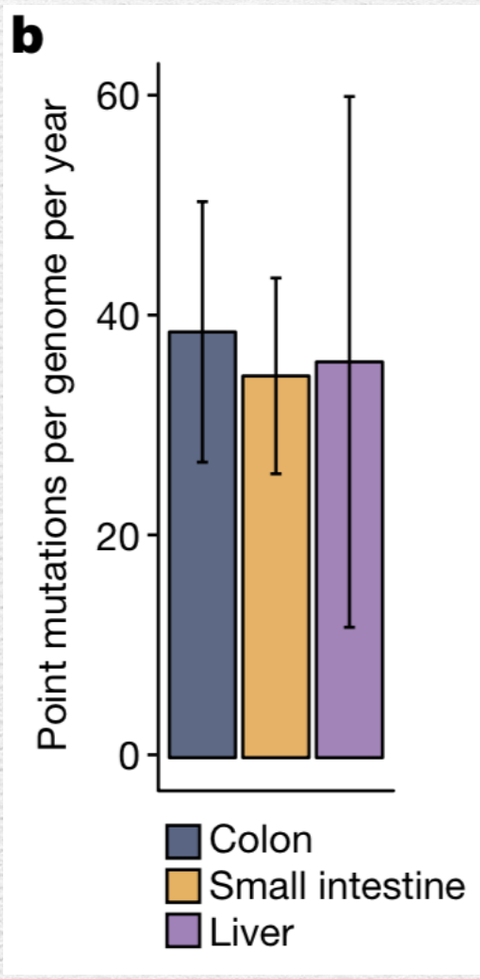
Tomasetti C1, Vogelstein B2.

# How many mutations do stem cells really accumulate in a year?

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# How many mutations do you really need to create a cancer?

**Only three driver gene mutations are required for the development of lung and colorectal cancers**

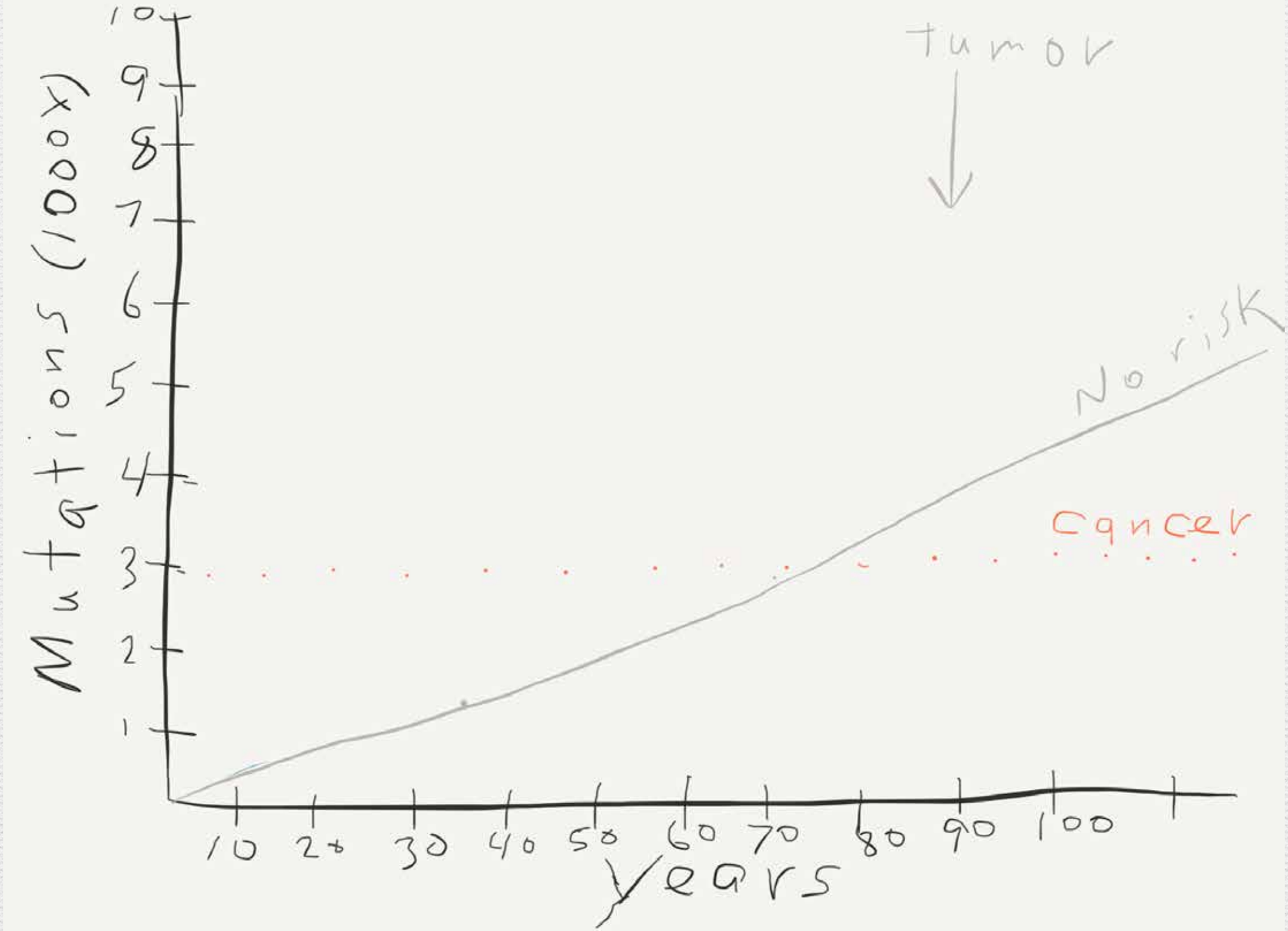
**Cristian Tomasetti[a,b,1], Luigi Marchionni[c], Martin A. Nowak[d], Giovanni Parmigiani[e], and Bert Vogelstein[f,g,1]**

[a]Division of Biostatistics and Bioinformatics, Department of Oncology, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, and [b]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205; [c]Cancer Biology Program, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD 21205; [d]Program for Evolutionary Dynamics, Department of Mathematics, Harvard University, Cambridge, MA 02138; [e]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute and Harvard School of Public Health, Boston, MA 02215; and [f]Ludwig Center for Cancer Genetics and Therapeutics and [g]Howard Hughes Medical Institute, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD 21205

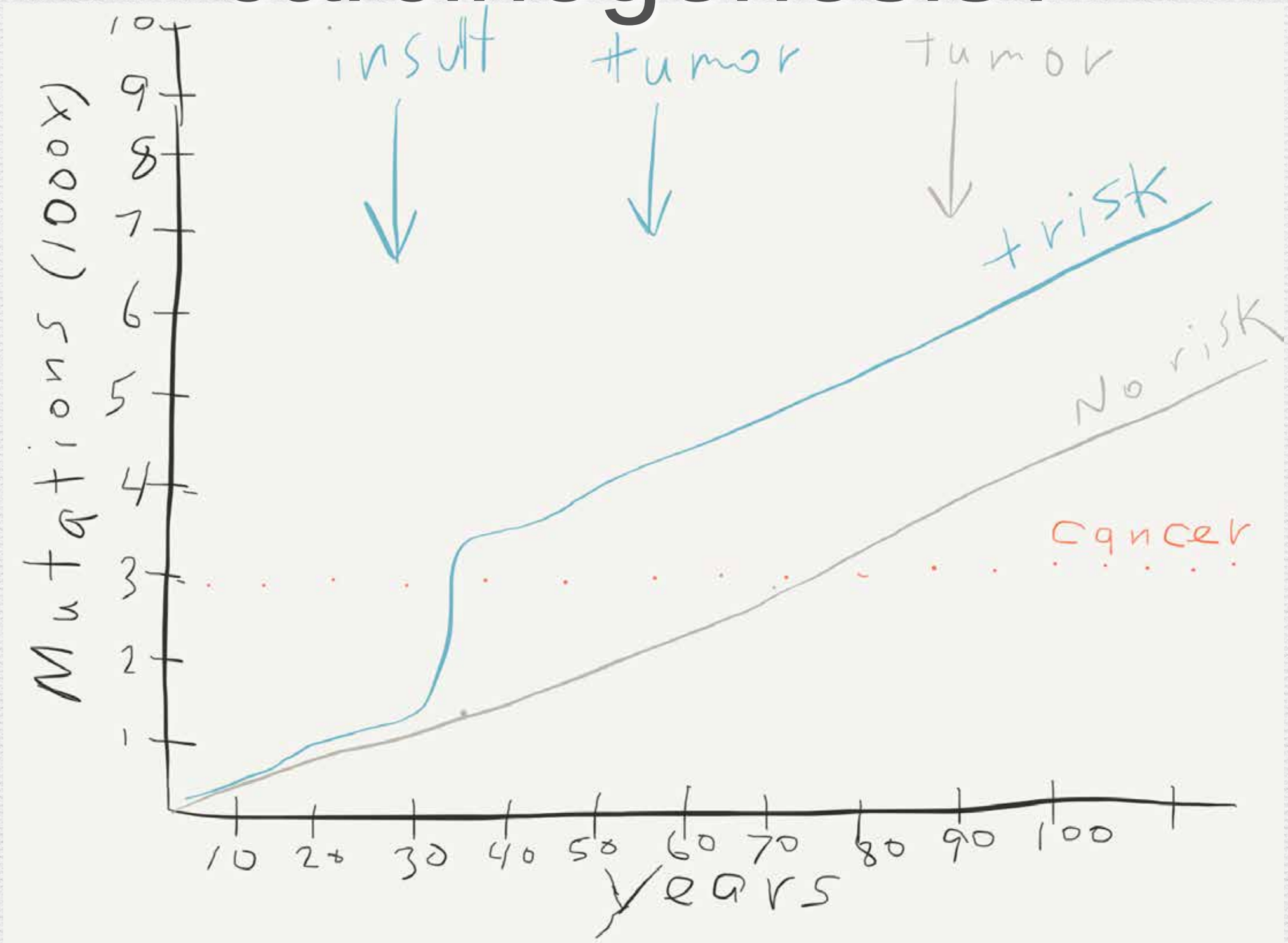
# Other criticisms of the study

- May overestimate the importance of replicative mutations (2/3) and underestimate the importance of risk factors
- Doesn't help explain differences in incidence across countries
- Important tumors like stomach, breast, prostate, are missing

# New model for carcinogenesis?



# New model for carcinogenesis?



# Conclusions

- Pairing molecular biology and genetic data with epidemiology provides more powerful and precise tools to probe smaller effects
- Potentially paradigm shifting ability to detect underlying replicative mutation rate and its contribution to carcinogenesis was discovered using this combination
- This leads us to ask the question: given the underlying replicative mutation rate, we should be aware that there may come a point when further population based risk reduction of a particular cancer may become less relevant while early detection becomes more relevant

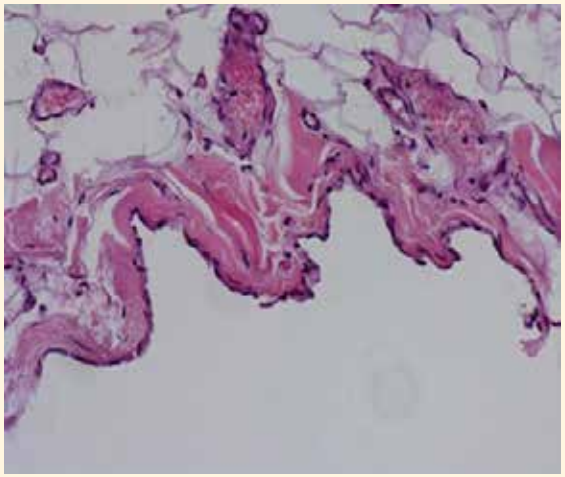
# EPIDEMIOLOGY OF MESOTHELIOMA

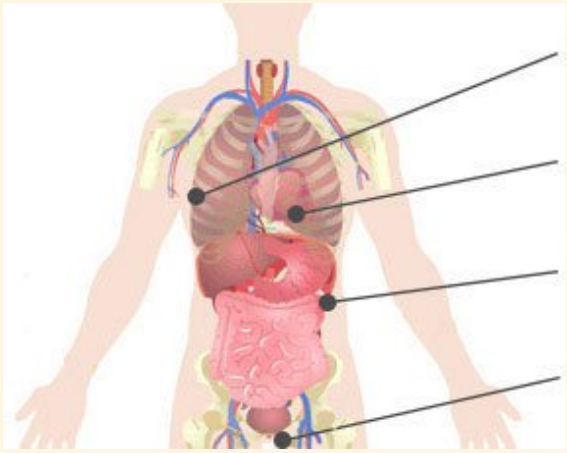
*Baharak Khadang, PGY-1 Pathology*

EPIB 671
May 2017

# Introduction

- **Mesothelioma is a highly aggressive and a relatively rare cancer (1% of all cancers) which originates from the mesothelial cells.**





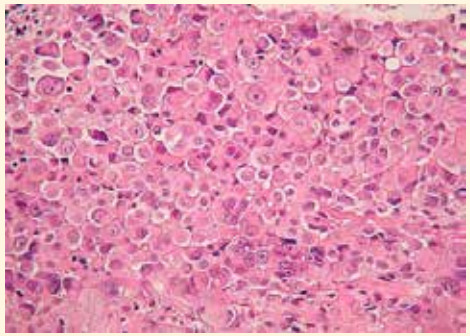
Pleural **75%**

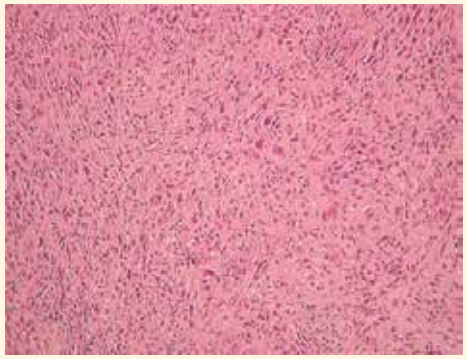
Pericardial **1%**

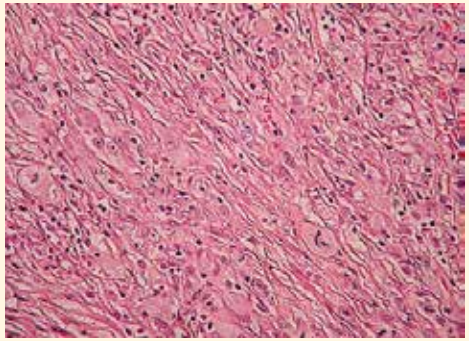
Peritoneal **10-20%**

Testicular **< 1%**

# Histology







**Three main histotypes:**

**1-Epithelioid (with a tubulopapillary or trabecular pattern)**

**Flattened or cuboidal cells with monotonous nuclei line the papilla or tubules. Mitotic figures are uncommon**

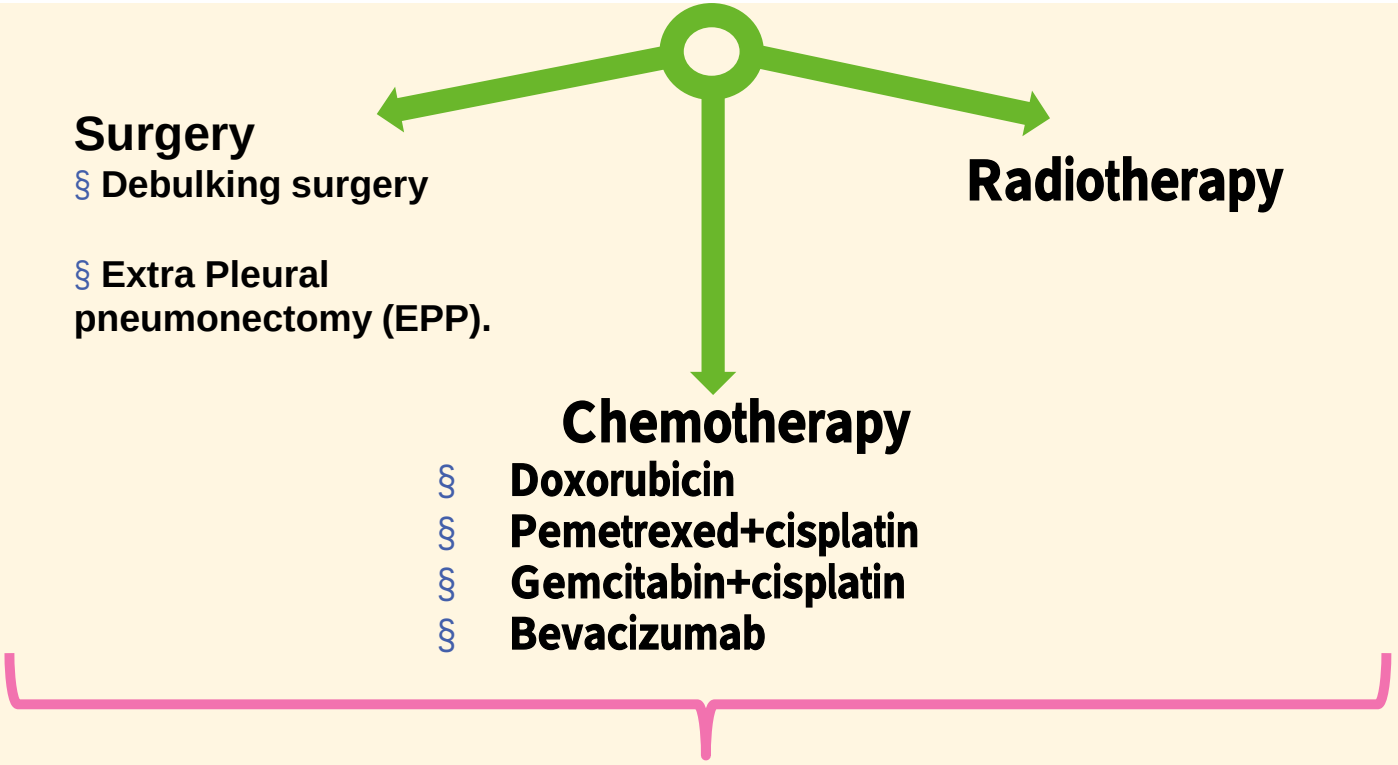
**2- Sarcomatoid**

- **Worse prognosis in all sites**
- **Less common in the peritoneum than pleura**
- **Tightly packed spindle cells. Malignant osteoid, chondroid, or muscular elements may be present**

**3- Biphasic**

**consisting of both epithelial and spindle-shaped phenotypes mixed together.**

# Therapeutic Strategies




## Multimodality Therapy

- No curative modality
- Long-term survival is rare even with aggressive multimodal therapy
- Median survival: 10-17 months

# Epidemiology

- The first case report was in 1947.
- In 1960, Wagner et al. reported a mesothelioma epidemic among asbestos miners in south Africa and first demonstrated a relationship between asbestos exposure and mesothelioma (2).
- The incidence is expected to peak between 2015 and 2025 despite restrictions on the use of asbestos, due to the long latency period for the development of disease after asbestos exposure (3).
- About 3300 new cases of mesothelioma in the United States each year (4).
- 90% of cases are among whites.
- The global mesothelioma burden is unclear. Driscoll et al. estimated that as many as 43 000 people worldwide die from the disease each year (5).
- It has also been estimated that there are around 10 000 mesothelioma cases annually in Australia, Japan, North America and western Europe combined (6).
- Based on World Health Organization reports, mesothelioma is more common in some countries that still use asbestos including Brazil, China, India, and Thailand (7).

- In the Surveillance, Epidemiology, and End Results database, Mesothelioma peaked in the 1980s to 1990s and is now plateauing.
- In men, the incidence has been stable at 1.8 cases per 100,000 for the past 10 years, with peak values in the early 1990s (2.3 cases per 100,000), whereas in women, the rate has been 0.4 cases per 100,000 and has not changed substantially over time(8,9).

Mesothelioma

Age-Adjusted SEER Cancer Incidence Rates[a], 1980-2014

By Race, Sex and Year of Diagnosis

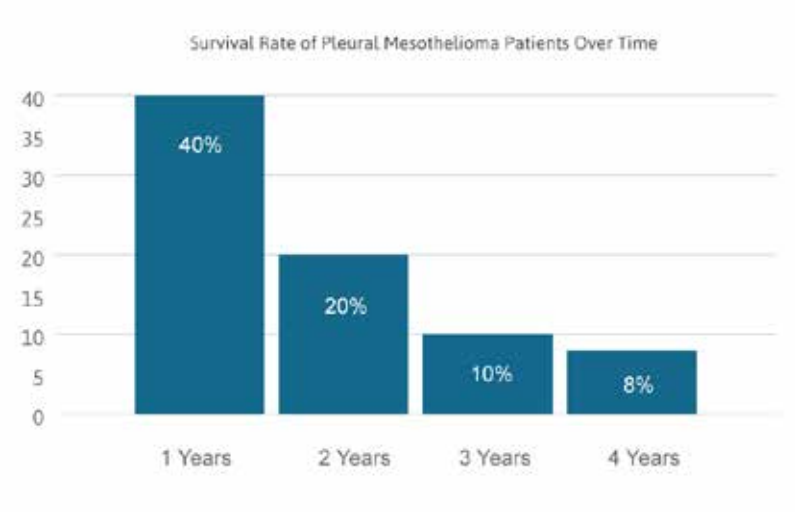
| | Year of Diagnosis | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Race/Sex | 1980-1981 | 1982-1983 | 1984-1985 | 1986-1987 | 1988-1989 | 1990-1991 | 1992-1993 | 1994-1995 | 1996-1997 | 1998-1999 | 2000-2001 | 2002-2003 | 2004-2005 | 2006-2007 | 2008-2009 | 2010-2011 | 2012-2014 |
| All Races | | | | | | | | | | | | | | | | | |
| Both Sexes | 0.9 | 0.9 | 1.0 | 1.0 | 1.1 | 1.1 | 1.1 | 1.2 | 1.1 | 1.1 | 1.1 | 1.0 | 1.1 | 1.0 | 1.0 | 1.0 | 0.9 |
| Males | | | | | | | | | | | | | | | | | |
| All Ages | 1.6 | 1.6 | 1.9 | 1.7 | 2.0 | 2.1 | 2.3 | 2.2 | 2.0 | 2.1 | 2.0 | 1.8 | 2.0 | 1.7 | 1.8 | 1.8 | 1.6 |
| Ages 0-54 | 0.3 | 0.3 | 0.3 | 0.2 | 0.3 | 0.2 | 0.2 | 0.3 | 0.2 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Ages 55-64 | 3.7 | 3.7 | 4.5 | 3.5 | 3.1 | 4.4 | 3.7 | 3.3 | 4.2 | 3.7 | 2.6 | 3.0 | 2.8 | 2.4 | 2.4 | 2.1 | 1.2 |
| Ages 65-74 | 8.2 | 7.2 | 8.6 | 8.3 | 11.9 | 9.5 | 10.7 | 10.3 | 9.0 | 9.8 | 9.3 | 7.8 | 8.7 | 8.0 | 7.3 | 6.1 | 6.8 |
| Ages 75-84 | 10.0 | 11.7 | 12.0 | 12.6 | 12.7 | 17.2 | 16.1 | 17.9 | 15.2 | 16.8 | 19.5 | 17.2 | 17.8 | 14.4 | 15.3 | 19.2 | 14.7 |
| Ages 85+ | - | - | - | - | 12.8 | 12.0 | 20.5 | 12.4 | 15.8 | 15.9 | 14.4 | 13.5 | 19.8 | 15.6 | 22.8 | 15.7 | 19.1 |
| Females | | | | | | | | | | | | | | | | | |
| All Ages | 0.3 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| Ages 0-54 | - | 0.1 | - | 0.1 | 0.1 | 0.1 | - | 0.1 | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Ages 55-64 | 0.9 | 1.0 | 0.8 | 1.0 | - | 0.9 | 0.9 | 1.1 | 0.8 | - | - | 0.9 | 0.8 | 0.6 | 0.7 | 0.6 | 0.6 |
| Ages 65-74 | - | 2.1 | 1.4 | 1.4 | 1.7 | 1.4 | 1.3 | 1.6 | 1.5 | 1.6 | 1.2 | 1.5 | 1.5 | 1.8 | 1.4 | 1.8 | 1.4 |
| Ages 75-84 | - | 2.0 | 3.1 | 2.3 | 1.7 | 3.0 | 2.8 | 2.6 | 2.3 | 2.0 | 2.8 | 2.7 | 3.2 | 3.8 | 2.4 | 3.0 | 2.7 |
| Ages 85+ | - | - | - | - | - | - | - | - | - | - | 2.9 | - | - | - | 3.1 | 2.9 | 3.0 |

**Mesothelioma deaths in the mortality database of the World Health Organization, worldwide, 1994–2008**

| Characteristic | Deaths | | No. of countries reporting deaths | Age at death (years) | | AAMR (per million) | M:F ratio |
|---|---|---|---|---|---|---|---|
| | No. | % | | Mean | SD | | |
| **Total** | 92 253 | 100.0 | 83 | 70.0 | 11.6 | 4.9 | 3.6:1 |
| **Sex** | | | | | | | |
| **Male** | 72 000 | 78.0 | 81 | 69.9 | 11.2 | 9.0 | NA |
| **Female** | 20 252 | 22.0 | 73 | 70.2 | 13.1 | 1.9 | NA |
| ***Anatomical disease site*** | | | | | | | |
| **Pleura** | 38 121 | 41.3 | 58 | 70.1 | 11.0 | 2.3 | 3.7:1 |
| **Peritoneum** | 4 116 | 4.5 | 43 | 66.0 | 12.6 | 0.3 | 1.6:1 |
| **Pericardium** | 298 | 0.3 | 30 | 61.1 | 15.6 | 0.03 | 1.8:1 |
| **Other sites** | 6 184 | 6.7 | 53 | 70.7 | 12.4 | 0.4 | 3.2:1 |
| **Unspecified** | 39 726 | 43.1 | 65 | 70.9 | 11.5 | 2.3 | 4.0:1 |
| **Site not reported** | 3 808 | 4.1 | 16 | 63.6 | 12.8 | 2.6 | 2.6:1 |
| ***Continent*** | | | | | | | |
| **Africa** | 2 333 | 2.5 | 4 | 63.4 | 12.7 | 4.8 | 3.3:1 |
| **Americas** | 23 869 | 25.9 | 36 | 70.5 | 12.7 | 3.6 | 3.3:1 |
| **Asia** | 12 012 | 13.0 | 11 | 69.5 | 12.2 | 2.6 | 3.2:1 |
| **Europe** | 49 779 | 54.0 | 30 | 70.1 | 10.9 | 7.2 | 3.7:1 |
| **Oceania** | 4 260 | 4.6 | 2 | 71.3 | 10.6 | 16.0 | 5.6:1 |
| ***10 countries reporting the highest number of deaths*** | | | | | | | |
| **United States of America (7)** | 17 062 | 18.5 | NA | 72.8 | 11.1 | 5.0 | 4.2:1 |
| **United Kingdom of Great Britain and Northern Ireland (9)** | 13 517 | 14.6 | NA | 71.3 | 9.9 | 17.8 | 5.7:1 |
| **Japan (14)** | 11 212 | 12.1 | NA | 70.0 | 11.9 | 3.2 | 3.3:1 |
| **Germany (9)** | 9 569 | 10.4 | NA | 70.3 | 10.6 | 6.8 | 3.2:1 |
| **France (8)** | 6 608 | 7.2 | NA | 71.8 | 10.5 | 7.6 | 3.4:1 |
| **Netherlands (13)** | 5 141 | 5.6 | NA | 70.0 | 10.2 | 6.4 | 4.0:1 |
| **Australia (8)** | 3 747 | 4.1 | NA | 71.3 | 10.7 | 16.5 | 5.4:1 |
| **Italy (3)** | 3 706 | 4.0 | NA | 71.2 | 10.6 | 10.3 | 2.4:1 |
| **South Africa (12)** | 2 322 | 2.5 | NA | 63.4 | 12.7 | 6.7 | 3.3:1 |
| **Spain (7)** | 1 840 | 2.0 | NA | 67.8 | 12.2 | 3.9 | 2.9:1 |

# Survival

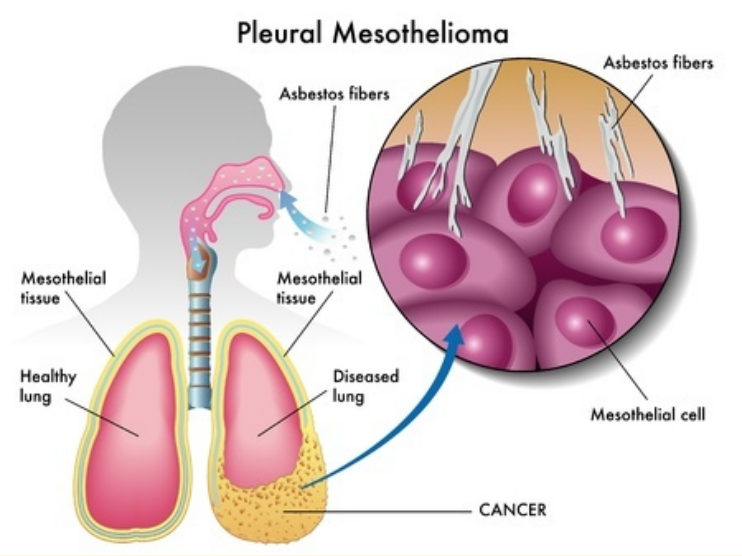
- On average, 40 percent of pleural mesothelioma patients survive at least one year after starting treatment. By year four, survival drops to 8 percent.
- Women experience nearly three-fold better survival than men (10).
- National Cancer Institute data shows that five-year survival among whites is 7.6 percent, compared to 12.3 percent for blacks.



# Etiology And Risk Factors

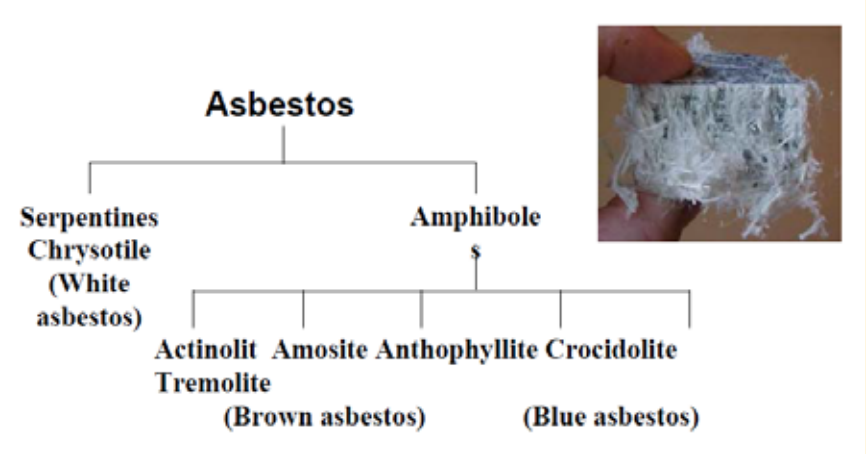
## *1- Asbestos*

- Asbestos exposure is the most important risk factor.



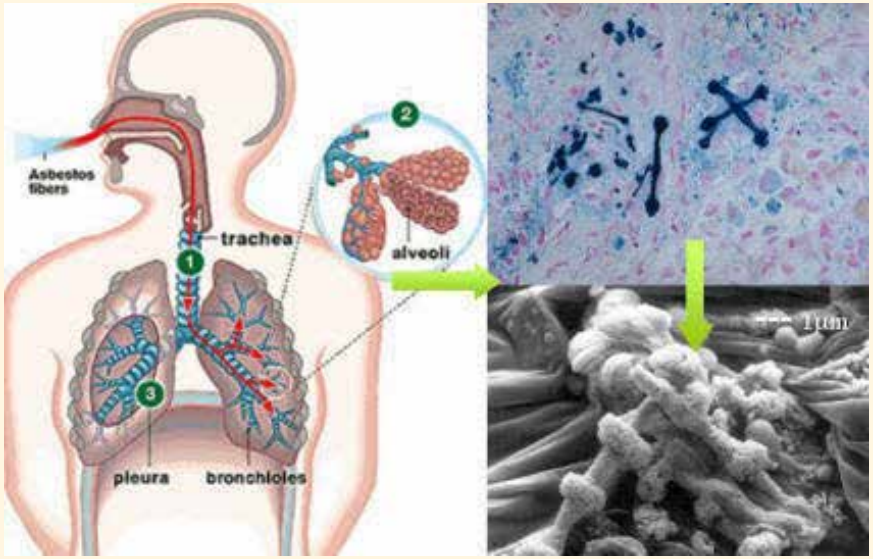

- In March 2011, the International Agency for Research on Cancer (IARC) presented an update on the link between asbestos and cancer at a World Health Organization conference in Spain
- The National Institutes of Health (NIH) estimates that 11 million people were exposed to asbestos between 1940 and 1978 (11).
- Asbestos exposure can be either occupational ( e.g industrial, shipyard or construction workers) and non- occupational (living near areas of large deposits or secondary exposure in family of workers)

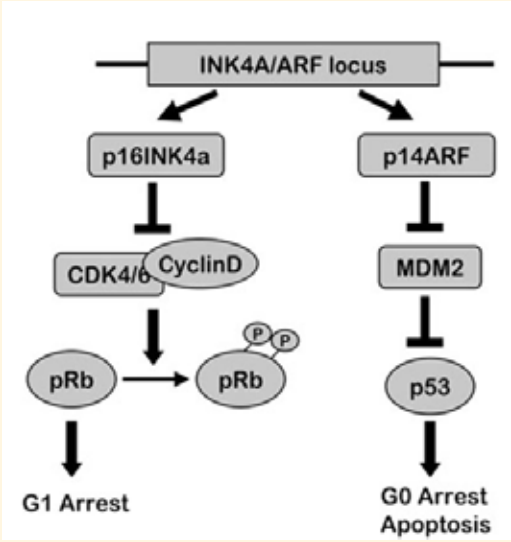
- Asbestos is the commercial name for a group of hydrated magnesium silicate fibrous minerals.
- It exists in soil and rock as long fibers.
- There are two major types: serpentine and amphibole.
- About 95 percent of the asbestos produced and used worldwide is chrysotile, which is a serpentine fiber that is reportedly less carcinogenic. However, even chrysotile asbestos has been linked to the development of pleural mesothelioma
- There are still current controversies about potency differences in carcinogenesis (i.e. chrysotile versus amphiboles) and sizes(i.e. long and thin fibers), however, epidemiologic evidence indicates that all forms and sizes of commercial asbestos fibers are carcinogenic to humans (12).



# Alterations

- The fibers can be inhaled, ingested and enter the pleural space and cause various cycles of damage and local inflammation. They can lead to scarring (plaques) or interfere with mitosis spindle, causing aneuploidy or other chromosomal damage and cancer.
- Asbestos exposure induces the activation of several signal transduction pathways in mesothelial cells, such as EGFpathway or causing deletion in genes such as INK4a/ARF locus interfering with P53 and Rb tumor suppressor pathways (13).



***2- Radiation*** — Ionizing radiation to supradiaphragmatic fields may be a risk factor for the subsequent development of mesothelioma

- Two large studies from the Surveillance, Epidemiology, and End Results (SEER) database found that survivors of Hodgkin lymphoma and non-Hodgkin lymphoma who had received radiation treatment were at increased risk for mesothelioma (14).
- A population-based series of over 40,000 men treated for testicular cancer between 1943 and 2001 and followed long-term found 10 excess cases of pleural mesothelioma (relative risk 4) for men treated with radiation therapy alone (15).

## *3- Simian virus 40 (SV40)*

- SV40 is a polyoma virus with oncogenic potential in humans.
- It was first revealed that between 1955 and 1963 around 90% of children and 60% of adults in USA were inoculated with SV40-contaminated polio vaccines.
- Its actions in mesothelioma are thought to be due to interaction with p53 pathway, which forms a complex that promotes transformation (16).
- Several studies identified SV40 nucleic acids in a large proportion of mesothelioma cases (some of which did not have obvious asbestos exposure) (17). However, a number of epidemiologic studies have failed to confirm these observations (18).

## *4- Genetic factors*

- Familial clustering of pleural mesothelioma has been noted ( e.g in Cappadoccia, Turkey)
- A genetic predisposition for mesothelioma has been identified (mutation in the gene BAP1) that has been associated with other cancers, especially ocular melanoma (19).

# Best treatment: Prevention

**Asbestos exposure, the almost-singular cause of this disease, could have been (and can be) banned by more diligent regulation of the asbestos industry and by more moral and ethical corporate leadership.**

**Globally, there are more than 70 activist organizations that spread awareness about the dangers of asbestos**

- *Asbestos Disease Awareness Organization*
- *Asbestos Diseases Foundation of Australia (ADFA)*
- *Asian Ban Asbestos Network (A-BAN)*
- *Asociación Argentina de Expuestos al Amianto (ASAREA)*
- *Associacão Brasileira dos Expostos ao Amianto (ABREA)*
- *Association Belge des Victimes de l'Amiante (ABEVA)*
- *Associazione Famigliari e Vittime dell'Amianto (AFEVA)*
- *Ban Asbestos Canada*
- *Ban Asbestos France*
- *Ban Asbestos Network Japan (BANJAN)*
- *Ban Asbestos Network of India (BANI)*
- *Ban Asbestos Philippines*
- *Right on Canada*

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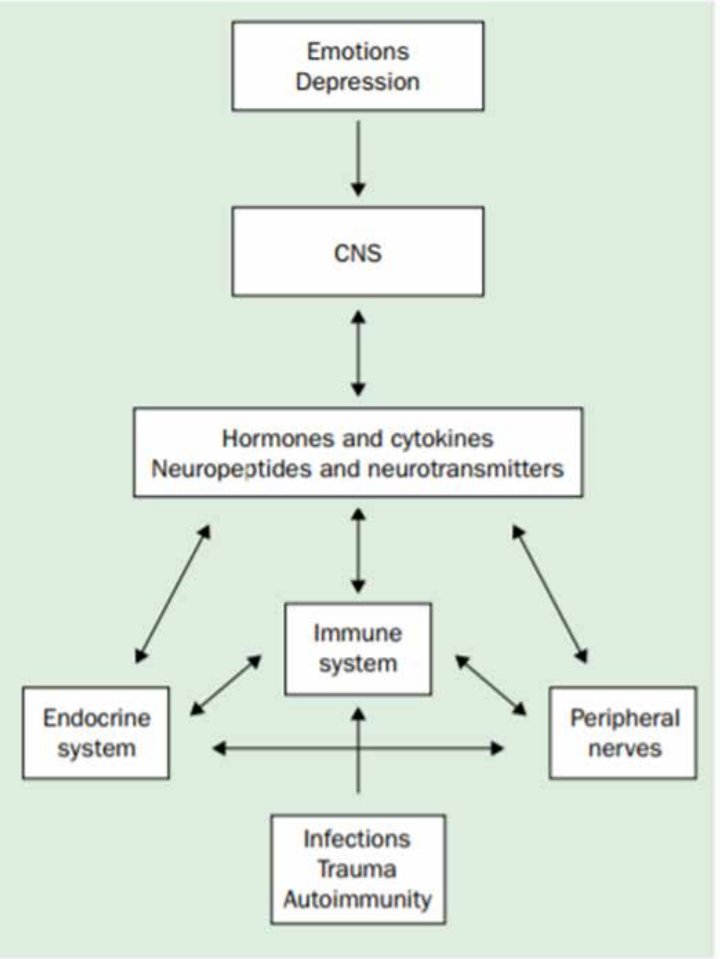
# Depression as a Cancer Risk Factor

EPIB – 671

Robin Luo

# Laboratory Evidence Suggests Link Exists

- Animals studies:
  - Rats unable to escape from electric shock had earlier tumour appearance, enlarged tumours, and decreased survival time
  - Stressful conditions suppress the immune response of lymphocytes, including NK cell activity, and production of interleukin 2 and interferon
- Human studies:
  - depressed patients had mild reduction in absolute NK-cell counts, reduced mitogen-stimulated lymphocyte proliferation and neutrophil phagocytosis, moderate decreases in T-cell and NK-cell functions




Reiche et al., 2004

# Taiwan Cross-section Study

- 1160 Taiwanese women completed surveys about anxiety and depression levels before completing a mammography screening. Then OR for breast cancer diagnoses was calculated

Crude OR and 95% CI for psychological factors ($n$ = 1160)

| Variable | OR | 95% CI | *P* |
|---|---|---|---|
| Anxiety | | | |
| Borderline anxiety vs. no anxiety | 3.099 | 1.685-5.698 | 0.001 |
| Anxiety vs. no anxiety | 2.173 | 1.009-4.684 | 0.043 |
| Depression | | | |
| Borderline depression vs. no depression | 1.840 | 0.897-3.772 | 0.092 |
| Depression vs. no depression | 4.497 | 1.643-12.303 | 0.001 |
| Stress | 1.124 | 1.062-1.190 | <0.001 |

OR: Odds ratio, CI: Confidence interval

Lee and Yeh, 2015

# Denmark Cohort Study

- 89,491 Danish adults who were admitted to hospital for affective disorder between 1969 and 1993
- 9,922 cases of cancer were diagnosed in the cohort, with 9,434.6 having been expected (adjusted for sex, age, and calendar time)

| Site of cancer | Bipolar or unipolar psychosis | | | Reactive depression or dysthymia | | |
|---|---|---|---|---|---|---|
| | Obs | SIR | 95% CI | Obs | SIR | 95% CI |
| **Total** | 5,210 | 0.98 | 0.95, 1.01 | 4,058 | 1.14 | 1.10, 1.17 |
| **Tobacco-related cancers (buccal cavity, esophagus, pancreas, larynx, lung, kidney, bladder)** | 1,342 | 1.02 | 0.96, 1.07 | 1,289 | 1.47 | 1.39, 1.55 |
| **Non-tobacco-related cancers** | 3,868 | 0.97 | 0.94, 1.00 | 2,769 | 1.03 | 0.99, 1.07 |

Dalton et al., 2004

# US Older Adults Cohort Study

- 4825 adults >71 yo followed for 3.8 years (Connecticut, Iowa, Massachusetts)

**Table 4.** Adjusted hazard ratios* (95% confidence interval) of cancer incidence, by cigarette smoking and chronically depressed mood status

| | Hazard ratio (95% confidence interval) | |
|---|---|---|
| | No chronically depressed mood | Chronically depressed mood |
| Nonsmoker | 1.0 (referent) | 2.34 (1.26–4.35) |
| Ex-smoker | 1.65 (1.29–2.10) | 2.17 (0.68–6.88) |
| Current smoker | 1.96 (1.16–3.34)† | 2.80 (0.65–11.94)† |

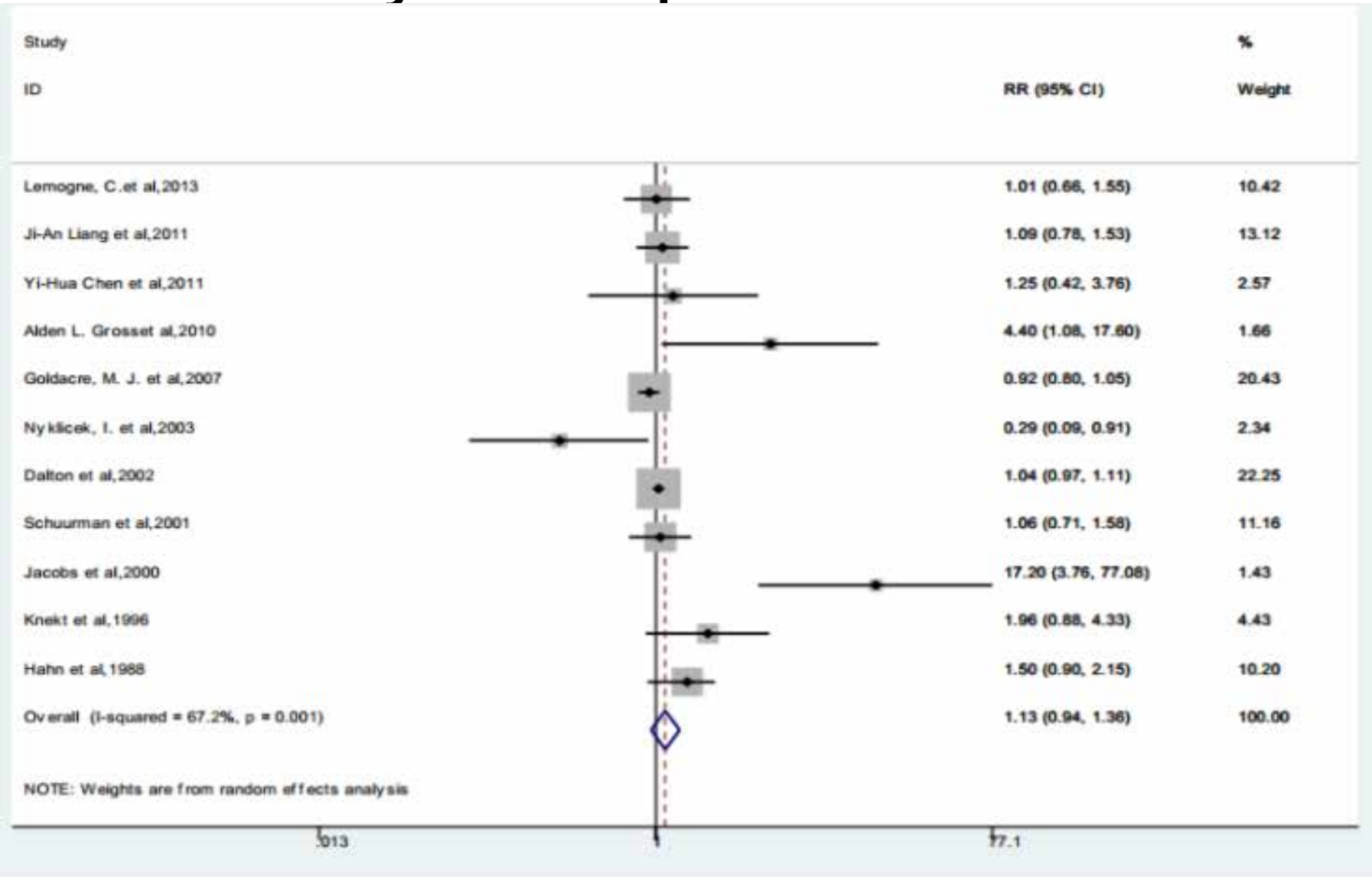
*Adjusted for age, sex, ethnic origin, physical disability, number of hospital admissions during follow-up, and alcohol intake: community-stratified summary.

†Also adjusted for number of cigarettes smoked per day.

- No significant interaction between chronic depression and smoking
- Chronically depressed patients had excess cancers predominantly at sites not related to tobacco
- Chronically depressed patients have adjusted cancer mortality risk of 2.22 (95% CI = 1.19–4.16).

Penninx et al., 1998

# Meta-analysis: Depression and Breast Cancer




Sun et al., 2015

# Reasons for Contradicting Results

- Different populations studied: culture, lifestyle, wide age-range
- Breast cancer: depression could delay age of first childbirth
- Antidepressant medications
- Depression: decreased physical activity and social activity
- What is the latency period between depression and cancer?
  - studies using a longer time frame found a stronger association than studies using a shorter time frame

# Conclusion

- Depression seems to be associated weakly with cancer incidence
- Depression is linked to behaviors (eg. smoking) that have large effects on cancer risk
- More studies needed to confirm or reject the association
- Important issue, because depression also associates with cancer mortality

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# BETEL-QUID AND ARECA-NUT CHEWING: An Ugly truth!

A presentation by Ayesha Baig,
R1 Anatomical Pathology

# Different Forms

FIG.1: *ARECA CATECHU:*


Mohammadet al., IJP 2015 & IARC 2004

- Globally, areca nut is among the most common addictions following tobacco, alcohol and caffeine - **10% of the world's population**
- Prevalent in Asia and in Asian-migrant communities

- Habits starts as a kid – easily accessible
- While males switched to tobacco smoking - females could not
- Rural communities consume more betel nut than urban communities
- Betel nut usage is also highly associated with the chewing of tobacco

World Health Organization, 2012

**Various forms and Names but one culprit**

Arabic: Fufal, Fofal
English: Betel Nut
Hindi: Supari
Persian: Popal
Sanskrit: Ghonta, Kramuka, Gubak
Unani: Fufal, Chhalia, Supari
Urdu: Chalia, Supari

*ALTAF QADRI/ASSOCIATED PRESS* A shop sold chewing tobacco in New Delhi, June 11.

# Why is it used?

- Used in Chinese and Unani medicine
- Symbol of royalty, habit of rich and famous
- Offered as a mark of respect and auspicious beginnings
- Popular - used by film icons in famous songs (E.g **Amitabh Bachchan in Don**)

https://www.youtube.com/watch?v=1PWYmHJhsME

- Glamorization as a mouth freshener in advertisements
- Many people are unaware of health effects
- The “attraction” - psycho-stimulating and euphoria-inducing effect (5min – 2 hrs), helpful for the digestive system
- Not a stigma, Discrete
- Affordable
- No gender bias
- Betel quid with smokeless tobacco leaves (BQSTL) – organic tobacco


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# Table 1: Summary of the systemic effects of areca nut

| Site | Effect of areca nut | Pathway/mediators |
|---|---|---|
| Nervous system | Euphoria and dependency syndrome | GABA inhibition by arecoline |
| | Increased skin temperature | Arecoline effecting the ANS |
| | Salivation | |
| | Palpitation | |
| | Heightened alertness | Increased α and β activity |
| | Anti-migraine effect | Inhibition of iNOS |
| | Neurotoxicity | Suppression of anti-oxidative mechanisms |
| Cardiovascular system | Tachycardia and increased systolic BP | Central sympathetic response |
| | Decreased diastolic BP | Peripheral cholinergic effect |
| | Increased atherogenesis | Blocking of HDL receptors and inhibition of LDL uptake by the liver |
| | Coronary artery spasm | Parasympathomimetic effect of arecoline |
| | Increased risk of CAD | Atherogenesis and coronary artery spasm |
| Gastrointestinal system | Type II DM, hyperlipidemia, hypertriglyeridemia and metabolic syndrome | Arecoline inhibits adipocyte differentiation and insulin-promoted glucose uptake |
| | Hepatotoxicity | Go-G1 cell cycle arrest and DNA damage |
| | Laxative and sialogogue effect | Action of arecoline on M3 receptors and AChE action |
| | Decreased growth in weight and BMI | Arecoline |
| Endocrine system and reproductive health | Thyroid | Arecoline |
| | Acute effect - increased $T_3$, $T_4$ and decreased TSH | |
| | Chronic effect - hypothyroidism | |
| | Prostate hyperplasia | Increased expression of androgen receptors |
| | Infertility | Changes in sperm count, motility and morphology |
| | Fetus | |
| | Low birth weight and length, preterm labour | |
| | Increased exposure to teratogens and carcinogens | Arecoline |
| | Arrest of endothelial cell differentiation | |
| | Vitamin D deficiency | Increased expression of 25(OH)ase |
| Blood and its components | Increased fibrogenesis | Increased platelet aggregation, Ca++ and $TXA_2$ release |
| | Decreased production of IL-2 and IFN-γ | Cytotoxic to splenocytes |
| | Suppresses T-cells and cytokine Th-1 | Oxidative stress |
| | Cytotoxic to RBCs | Damages the RBC membrane |
| Leukotrines and arachidonic pathway | Analgesic at high doses | Central and peripheral pathways |
| | Anti-inflammatory | Decreased release of leukotrines, prostaglandins and histamines |
| | Carcinogenic and mutagenic effect | Stimulation of gingival keratinocytes |
| | | Increased peroxyl radicals |
| | | Increased malonaldehyde |
| Respiratory system | Aggravation of asthma Decreased $FEV_1$ | Arecoline |
| Acute toxicity of areca | Dyspnea, tachycardia, palpitations, chest tightness, | Arecoline and other alkaloids |

Boucher et al., Addict. Biol.2002

**Table 18. Prevalence of tobacco and areca-nut habits among permanent residents of Mumbai, India, of lower socioeconomic status**

| Habit | Men | | Women | | All | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| No current habit[a] | [12 280] | [30.7] | [25 268] | [42.5] | [37 548] | [37.7] |
| Smokeless tobacco | 18 322 | 45.7 | 34 019 | 57.1 | 52 341 | 52.5 |
| Smoking | 5 494 | 13.7 | 146 | 0.2 | 5 640 | 5.7 |
| Smokeless tobacco and smoking | 3 975 | 9.9 | 94 | 0.2 | 4 069 | 4.1 |
| Total | 40 071 | 100.0 | 59 527 | 100.0 | 99 598 | 100.0 |
| *Use of smokeless tobacco* | | | | | | |
| *Mishri* | [4 140] | 10.3 | 15 740 | 26.5 | 19 880 | 20.0 |
| *Mishri* + betel quid with tobacco | 4 976 | 12.4 | 10 687 | 18.0 | 15 663 | 15.7 |
| Betel quid with tobacco | 5 871 | 14.7 | 3 527 | 5.9 | 9 398 | 9.4 |
| Tobacco + slaked lime | 2 997 | 7.5 | 640 | 1.1 | 3 637 | 3.7 |
| Others with tobacco | 1 144 | 2.9 | 1 200 | 2.0 | 2 344 | 2.4 |
| Multiple practices | 2 993 | 7.4 | 2 013 | 3.3 | 5 006 | 5.0 |
| Areca nut[b] | 176 | 0.4 | 306 | 0.5 | 482 | 0.5 |
| No smokeless tobacco use (no habit + smoking only) | 17 774 | 44.4 | 25 414 | 42.7 | 43 188 | 43.4 |
| Total | 40 071 | 100.0 | 59 527 | 100.0 | 99 598 | 100.0 |

From Gupta (1996)

[a] Includes about [14%] of men and [5%] of women who were former users of tobacco, mostly in the form of smokeless tobacco.

[b] Areca-nut chewing, most often as betel quid without tobacco

**Table 37. Chewing and smoking habits and oral cancer in two cohort studies, India**

| Habit | Ahmedabad[a] | | | Ernakulam[b] | | |
|---|---|---|---|---|---|---|
| | Number re-examined[c] | New oral cancers | Incidence per 100 000 | Person–years | New oral cancers | Age-adjusted incidence per 100 000 |
| Chewing | 3 266 | 1 | 31 | 23 416 | 9 | 23 |
| Chewing and smoking | 16 881 | 6 | 36 | 8 476 | 4 | 32 |
| Smoking | 15 378 | 6 | 39 | 20 222 | 0 | 0 |
| None | 7 065 | 0 | 0 | 30 962 | 0 | 0 |

[a] Industrial workers aged 35 years and over; data from Bhargava *et al.* (1975)

[b] House-to-house survey of individuals aged 15 years and over; data from Gupta *et al.* (1980)

[c] Approximately 2 years after the first examination

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS
Volume 85 (2004)

**The Insight for Initiation and Maintenance of Areca nut chewing Habit and its Effects on Oral Health Status among School Age Population in Western Rajasthan, India**

- 2846 subjects were surveyed - rural government schools – age 4 to 8 years
- A systemic oral examination was done to access current oral health status in these users

**RESULTS:**

- Total 34.5% children in Group 1 (4-10 y) and 72.8% in Group 2 (11-18y), were indulged with the habit of chewing areca nut

- Social environment and secondarily stimulating effect of areca nut have association with initiation and maintenance of habits

- 55 subjects were diagnosed at various clinical stages of Oral Submucous Fibrosis (OSMF)


Singhvi et al., J Clin Diag. Res. 2016

**The challenge of betel nut consumption to economic development: a case of Honiara, Solomon Islands - Asia-Pacific Development Journal**

The median yearly expenditure per betel nut consumer was SI$9,100

## Table 1. Prevalence of betel nut consumption (per cent)

| | Gender | | | Province | | | Education level | |
|---|---|---|---|---|---|---|---|---|
| | Total | Male | Female | Guadacanal | Malaita | Other provinces | Tertiary | Below tertiary |
| Yes | 81.0 | 84.5 | 76.9 | 66.1 | 86.4* | 82.6 | 69.6 | 89.7* |
| No | 19.0 | 15.5 | 23.1 | 33.9 | 13.6 | 17.4 | 30.4 | 10.3 |

*Source:* Author's calculations.

*Note:* * indicates 5 per cent significance level from adjacent column.

## Table 2. Motivations for chewing betel nut

| Reason | Percentage |
|---|---|
| Makes you feel good | 69.3 |
| Makes your breath smell nice | 63.8 |
| Is good to pass the time | 42.9 |
| Makes me less tired | 35.3 |
| Makes me less hungry | 33.8 |
| Makes your lips look attractive | 32.8 |
| Helps you to digest your food | 30.7 |
| Increases my mental sharpness | 27.8 |
| Increase my ability for physical exercise | 22.5 |
| Increases my sex drive | 3.4 |
| Other reasons | 14.1 |

*Source:* Author's calculations.

Stephen Pratt, APDJ 2014

# Overall evaluation

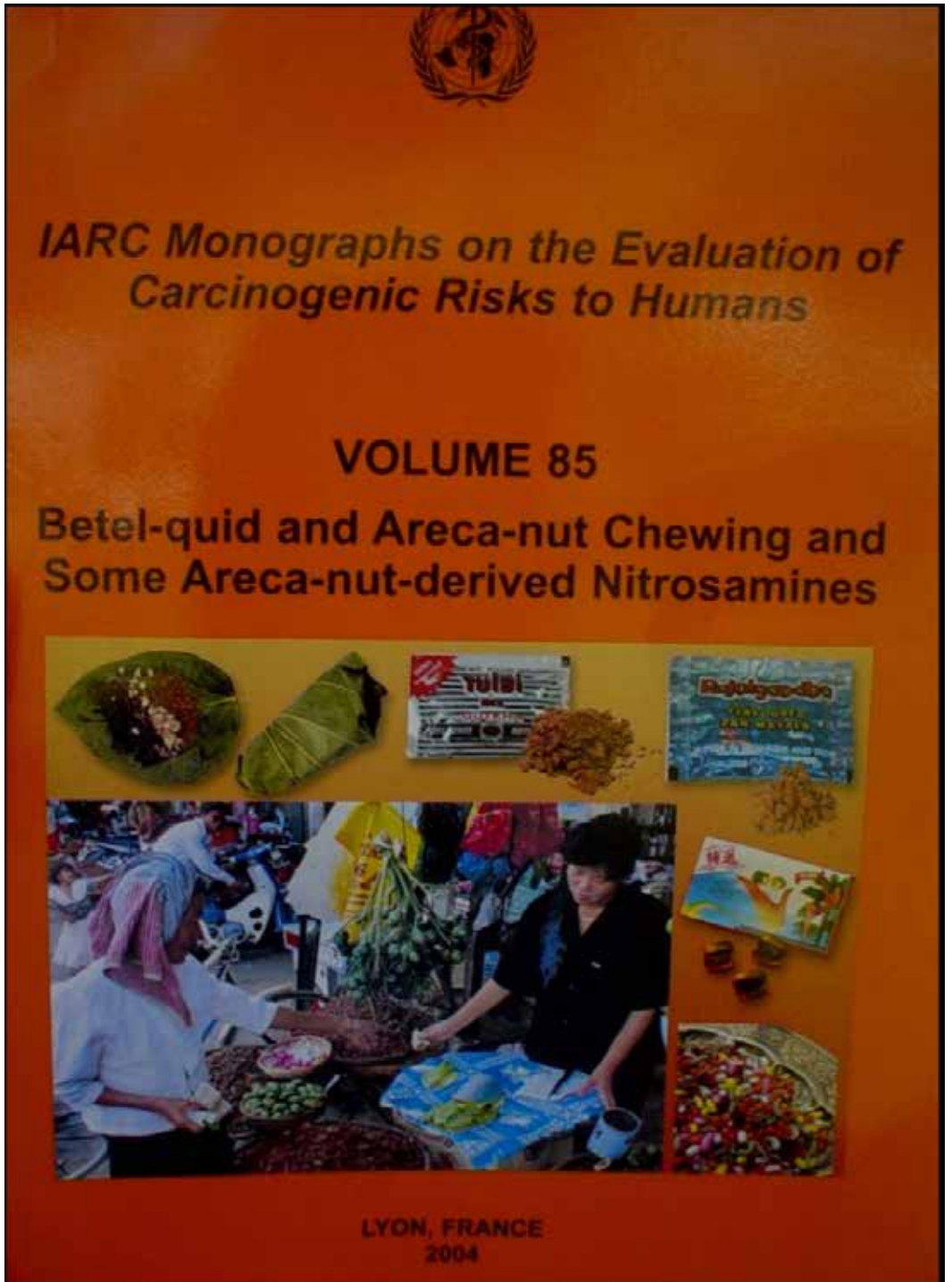
**Betel quid with tobacco is carcinogenic to humans (Group 1)**
**Betel quid without tobacco is carcinogenic to humans (Group 1)**
**Areca nut is carcinogenic to humans (Group 1)**

There is limited evidence in experimental animals for the carcinogenicity of arecoline

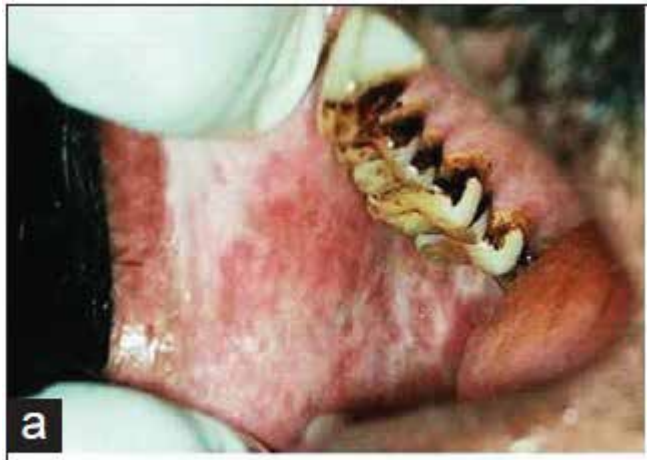
There is inadequate evidence in experimental animals for the carcinogenicity of arecaidine

<u>There is evidence suggesting lack of carcinogenicicy in experimental animals for betel leaf</u>

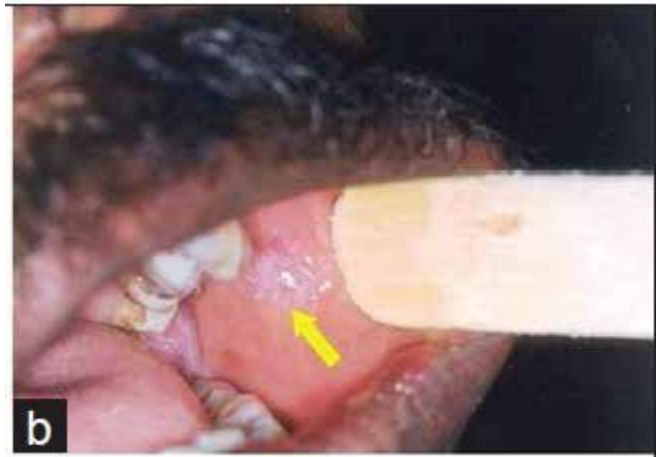
There is evidence suggesting lack of carcinogenicicy in experimental animals for slaked lime



# Betel nut chewing and its deleterious effects on oral cavity



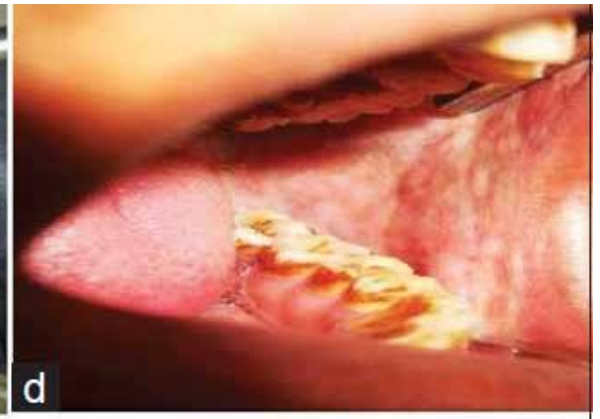

(a) Betel Chewers Mucosa



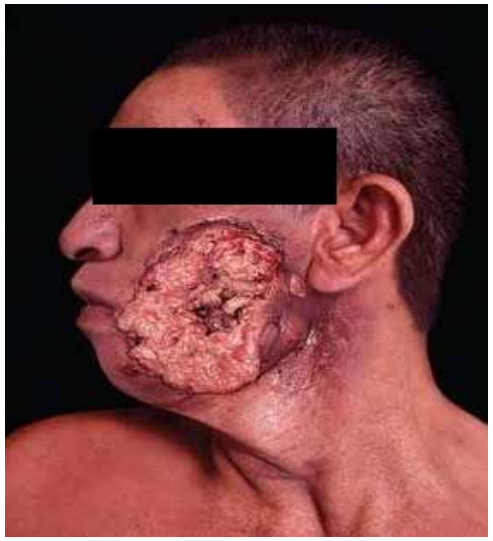

(b) Betel-quid lichenoid lesion

Areca nut → Oral submucous fibrosis → Oral cancer


(c) Oral Leukoplakia




(d) Oral Submucous Fibrosis



Areca nut + Tobacco → leukoplakia → Oral cancer

Anand et al., J. of Cancer Research and Therapeutics 2014

# Global epidemiology of oral cancer

- Oral cancer is number one cancer in South Asia (SA) - chew betel quid & smokeless tobacco
- Chewing habits cause cheek & gum cancer – SA
- Western countries smoking - floor of mouth cancer

Auluck et al., BC Cancer Agency 2010

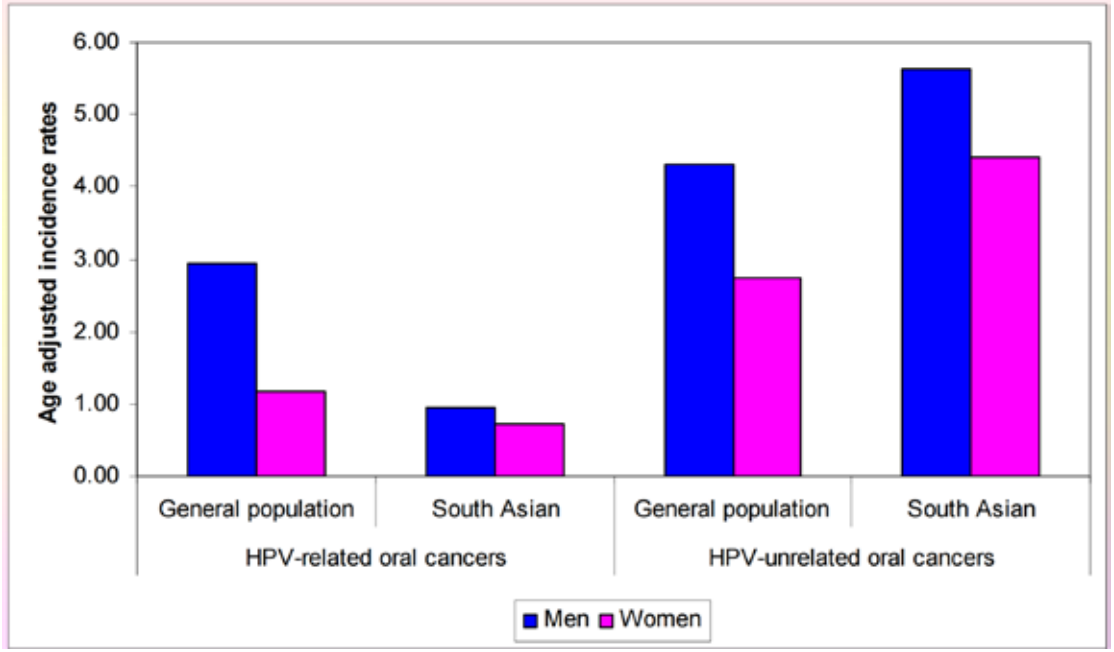
Review of cases with oral precancerous lesions among South Asian immigrants[3,4,6,7,15,25,26–35]

| Country [reference number] | Year of study | Ethnic group of patients |
|---|---|---|
| Canada [26–28] | 1985, 1987 | Indian |
| United Kingdom [6, 7, 15, 25, 29–31] | 2007, 2006, 1999, 2000, 1984, 2001, 2002 | Bangladeshi, Indian, Pakistani |
| Germany [32] | 2006 | Indian |
| Australia [33] | 1992 | Indian |
| France [34] | 1986 | Indian |
| South Africa [35] | 1984 | Indian |
| USA [3,4] | 2005, 2006 | Bangladeshi |

Auluck et al., Rural Remote Health 2009

| Oral cancer cases from the British Columbia (BC) Cancer Registry from 1980 to 2006 | | | |
|---|---|---|---|
| South Asian men | General male population | South Asian women | General male population |
| 5.63 (95% CI; 2.02–9.63) | 4.32 (95% CI; 3.86–4.78) | 4.41 (95% CI; 1.17–7.79) | 2.73 (95% CI; 2.37–3.08) |
| RR 1.33 | | RR 1.66 | |

## Results - adjusted incidence rates of HPV-related & HPV- unrelated oral cancers by gender & ethnicity




Auluck et al., Rural Remote Health 2009

Auluck et al., BC Cancer Agency 2010

# So what to do?

- There is an urgent need to **recognize** areca nut as a harmful food substance by the policy makers
- Prohibit sale as a mouth freshener
- **Strict laws** are necessary to regulate the production of commercial preparations of areca nut

- **Banning advertisements**, legal actions, awareness by posters

- **“Yogi spots stained walls, bans paan-gutka in govt offices”** - Uttar Pradesh bans chewing paan, paan masala in offices, March 2017

- Seeking **medical help** earlier, earlier stage of oral lesion

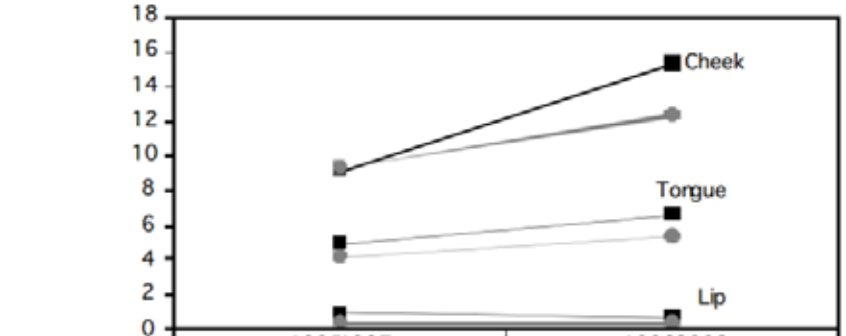
# Kolkata's landmark Howrah bridge corroded by pedestrians' paan-chewing habit

The Howrah bridge is being eroded by the acids in paan, the mixture of betel leaf, areca nut and slaked lime chewed by millions of Indians. Photograph: Alvaro Ybarra Zavala/Getty Images

www.theguardian.com/world/2010
www.abc.net.au/news/2011

# First results from Karachi Cancer Registry 2000, Pakistan

- A recent survey indicates that 36% of males and 44% females in Karachi chew pan or pan with tobacco
- Studies conducted in Pakistan and India have established the high risk of oral cancer associated with all forms of tobacco habits (Jafarey *et al.*, **1977**; Khan *et al.*, **1995**)




| | 1995-1997 | 1998-2002 |
|---|---|---|
| Lip - m | 0.9 | 0.7 |
| Tongue - m | 4.2 | 5.3 |
| Cheek - m | 9.1 | 15.3 |
| Lip - f | 0.4 | 0.4 |
| Tongue - f | 4.9 | 6.6 |
| Cheek - f | 9.3 | 12.3 |

**Figure 1. Trends in Subcategories of Oral Cancer 1996-1997; 1998-2002**



Bhurgri et al., Int. J. Cancer 2000
Department of Pathology, Dow Medical College, Karachi, Pakistan

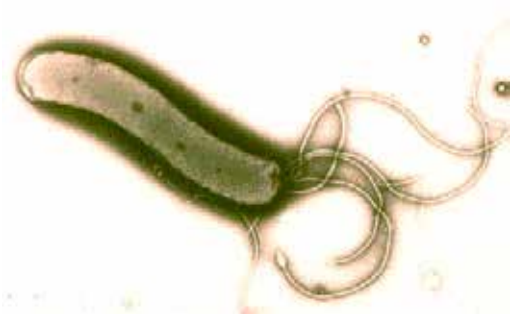
# The epidemiology of *helicobacter pylori* and gastric cancer

Karena Volesky

Cancer Epidemiology

May 26, 2017

# *Helicobacter pylori*

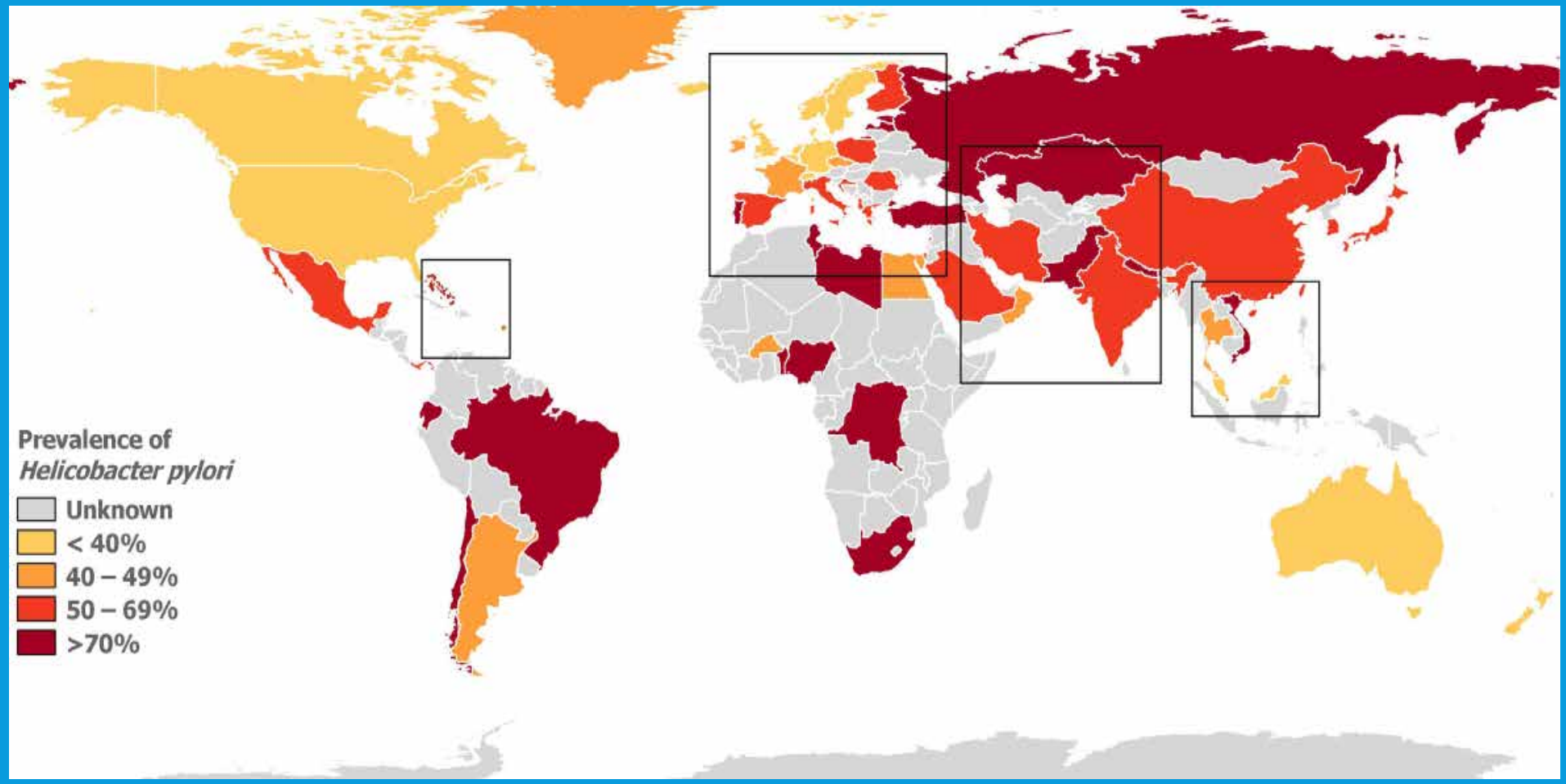


- Spiral shaped bacteria
- Low socioeconomic status is a key risk factor in its acquisition*
  - Bed sharing
  - Larger families
  - Crowding
- Acts indirectly through chronic inflammation
- Can be eradicated through combination antibiotic therapy, although antibiotic resistance is a concern

Image from: http://www.steadyhealth.com/articles/helicobacter-pylori-the-bacteria-that-cause-ulcers

*International Agency for Research on Cancer. Biological Agents. 2012 Monograph

# Global prevalence of *h. pylori**




*Hooi et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-analysis. Accepted by Gastroenterology Apr 2017

# Brief history of the epidemiology of *h. pylori*

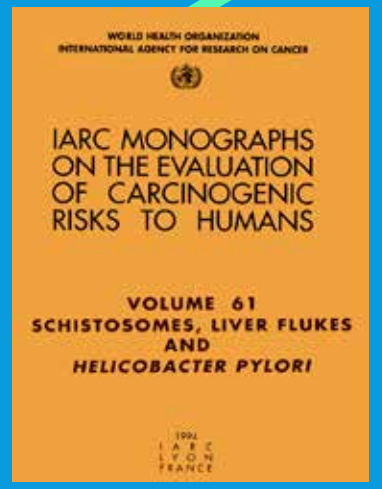
**1913:** 1st identified in gastric mucosa[1]

**1983:** Letter in *Lancet* describing bacteria in gastric biopsies[2]

**1991-3:** Prospective studies showing ~3 times the risk[3,4]

**1994:** Classified as group 1 carcinogen

**2015:** Attributable risk of *h. pylori* in NCGC increases[5]





[1] Pel P. 1913 [2] Warren JR & Marshall BJ. Letter to the Editor, Lancet, 1983. [3] Forman D et al. BMJ, 1991. [4] Parsonnet et al. NEJM, 1991 [5] Plummer M et al. IJC, 2015.

# Attributable risk*

Prevalence of *h. pylori* in the population

Relative risk of *h. pylori* with NGGC

$$AR = \frac{p\,(R - 1)}{1 + p\,(R - 1)}$$

*Formula from de Martel et al. Lancet Oncol, 2012

# Methods and materials

1. Obtained prevalence data from the National Health and Nutrition Examination Survey (NHANES)
2. Identified individual prospective studies
3. Corrected individual studies and prevalence for measurement error
4. Pooled corrected studies
5. Calculated PAR
6. Applied PAR estimates to non-cardia gastric cancer incidence in Canada
   - Adults (aged 18 or older)
   - Year 2012

# *H. pylori* population prevalence from NHANES data

**Positive:**

29.2% overall
30.0% men
29.2% women

**Positive (corrected):**

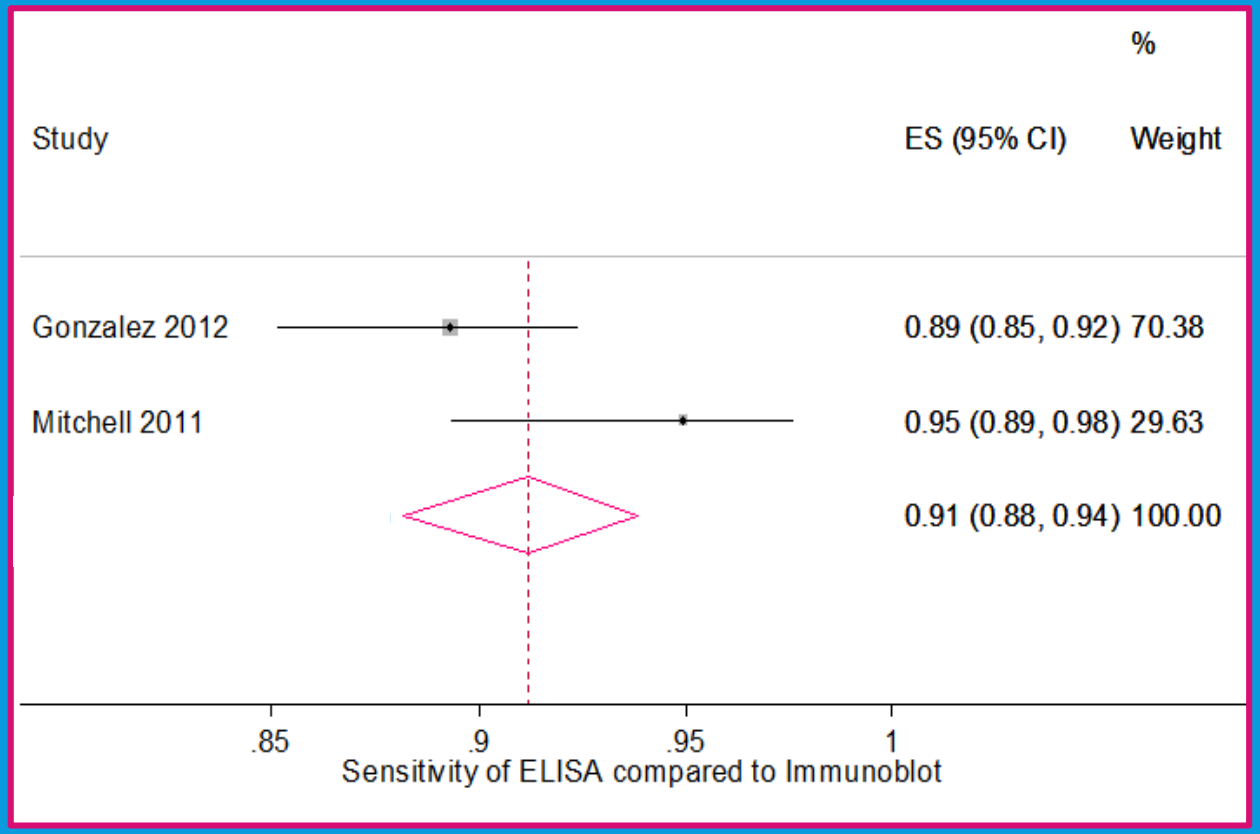
25.2% overall
25.6% men
24.7% women

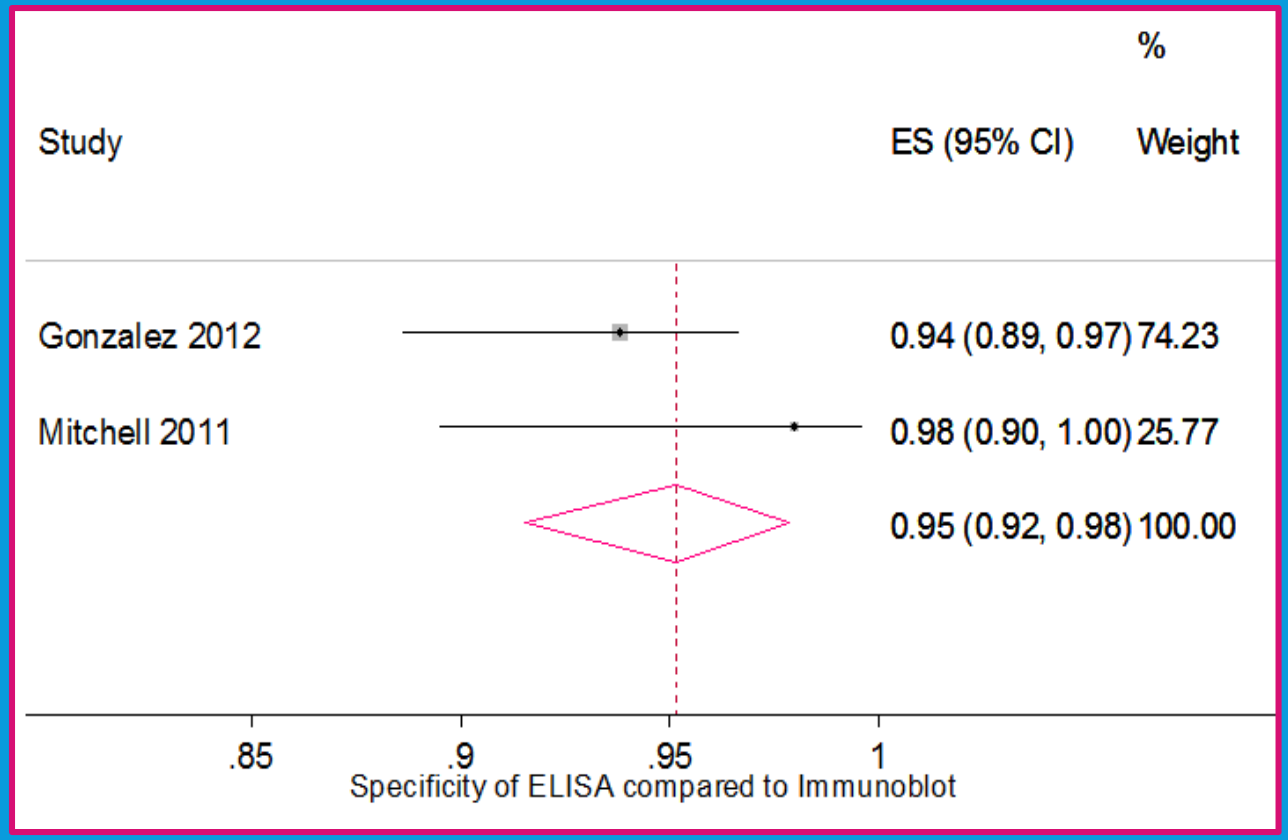
$$\text{Corrected prev}^{*} = \frac{(\text{uncorrected prev} + \text{spec} - 1)}{(\text{sens} + \text{spec} - 1)}$$

* Franco EL. Measurement errors in epidemiological studies of human papillomavirus and cervical cancer. IARC Sci Publ. 1992.

# Pooled sensitivity and specificity

## Sensitivity 91% and specificity 95%



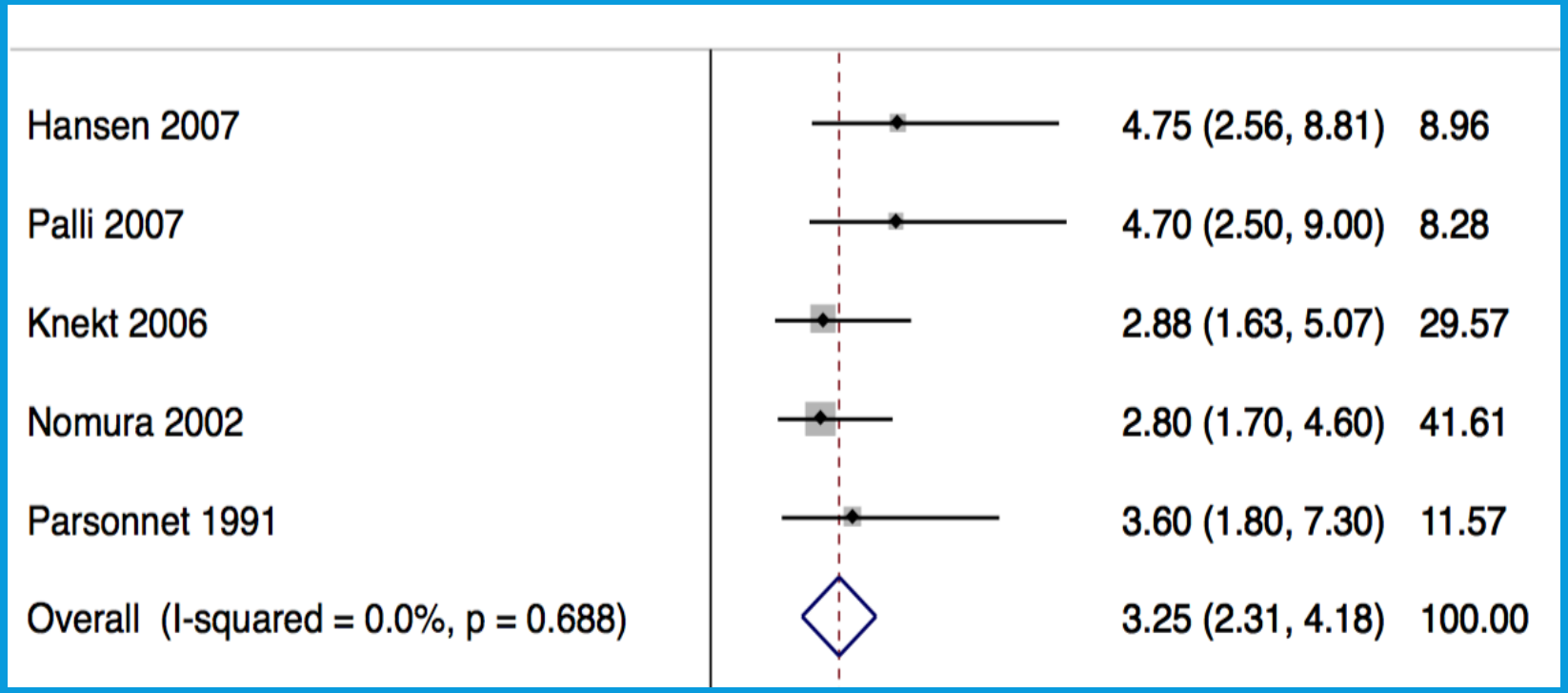



# Measurement error

| Study | Country | Follow-up yrs (mean/median) | Detection | Uncorrected OR | Corrected |
|---|---|---|---|---|---|
| Parsonnet 1991 | USA | 14.2 | ELISA | 3.6 (1.8–7.3) | 6.4 (3.0–13.3) |
| Nomura 2002 | USA | 12.7 | ELISA | 2.8 (1.7–4.6) | 7.4 (3.5–15.6) |
| Knekt 2006 | Finland | 24 | ELISA | 2.9 (1.6–5.1) | 97.6 (3.5–2,766) |
| Palli 2007 | Europe | 6.1 | ELISA | 4.7 (2.5–9.0) | 38.3 (6.2–237.3) |
| Hansen 2007 | Norway | 11.9 | ELISA | 4.8 (2.6–8.8) | 28.9 (6.3–97.9) |
| Siman 2007 | Sweden | 9.2–12.6 | Immunoblot | 17.8 (4.2–74.8) | … |
| Mitchell 2008 | Australia | 11.6 | Immunoblot | 10.6 (2.4–47.4) | … |
| Gonzalez 2012 | Europe | 10.7 | Immunoblot | 21.4 (7.1–64.4) | … |

# Pooled studies

Uncorrected studies, pooled odds ratio = 3.25




After correcting:

Odds ratio = 7.5

CI = 3.7–11.3

$I^2$ = 0.0

# Limitations

Relied on USA and European data

PAR analysis has strong assumptions

Misclassification parameters based on 2 studies

CI for sensitivity and specificity not accounted for

# Population attributable risk and potential no. of avoidable cases

**No correction**

PAR = 39.6%

Of the 2,375 NCGC cancer diagnosed in 2012, **941** cases could be avoided if *h. pylori* were eliminated

**Corrected**

PAR = 62.1%

Of the 2,375 NCGC cancer diagnosed in 2012, **1,475** cases could be avoided if *h. pylori* were eliminated

# References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# *Doctor is it genetic?*

## Screening for inherited predisposition to breast cancer

Karyne Martel MD FRCSC
Surgical Oncology Fellow

*“But the seeming straightforwardness of Jolie's case masks a much murkier reality, one that involves science, policy and probabilities, not to mention Americans (…) tendency to observe what the famous do and then conclude that we should do the same”*

# Do celebrity endorsements matter? Observational study of BRCA gene testing and mastectomy rates after Angelina Jolie's New York Times editorial

Sunita Desai,[1] Anupam B Jena[1,2,3]

the bmj | BMJ 2016;355:i6357 | doi:10.1136/bmj.i6357

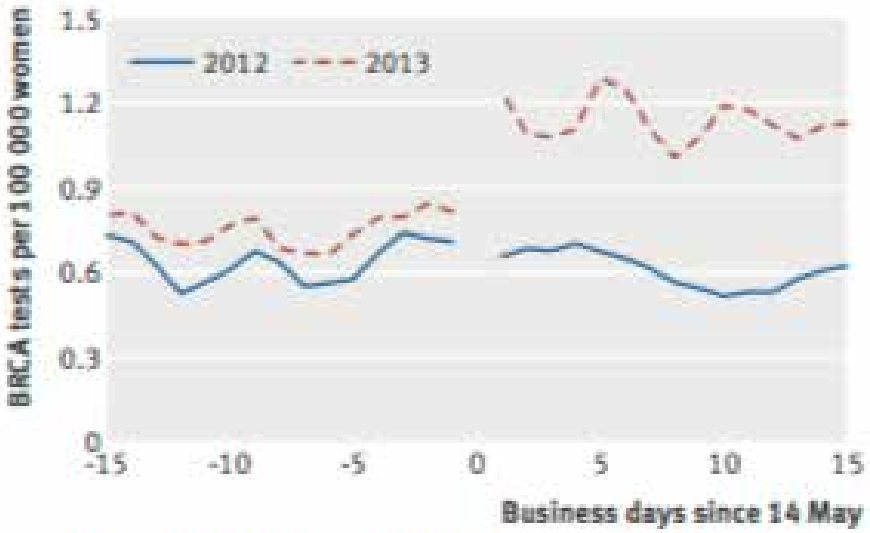



Fig 1 | Daily BRCA test rates in 15 business days before and after 14 May 2013 Jolie editorial versus control period in 2012. BRCA tests were identified with Current Procedural Terminology codes 81211-81217. Figure shows three day moving average of testing rate. Rates in 2012 are shown as control to account for seasonal trends


Fig 4 | 60, 90, and 180 day monthly mastectomy rates among women who had BRCA test before and after May 2013 Jolie editorial. For each data point, denominator is number of women who had BRCA gene test during month and numerator is number of women who had mastectomy in 60 (or 90 or 180) days after BRCA gene test. Rates for 2012 are not shown because coding changes implemented in early 2012 limit ability to accurately identify rates of BRCA gene testing in first three months of 2012

National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2017
## Breast and/or Ovarian Cancer Genetic Assessment

NCCN Guidelines Index
Table of Contents
Discussion

### CRITERIA FOR FURTHER GENETIC RISK EVALUATION[a]

- An individual with an ovarian[e] cancer
- An individual with a breast cancer diagnosis meeting any of the following:
  - A known mutation in a cancer susceptibility gene within the family
  - Early-age-onset breast cancer[b]
  - Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 y
  - Two breast cancer primaries[c] in a single individual
  - Breast cancer at any age, and
    - ≥1 close blood relative[d] with breast cancer ≤50 y, or
    - ≥1 close blood relative[d] with invasive ovarian[e] cancer at any age, or
    - ≥2 close blood relatives[d] with breast cancer and/or pancreatic cancer at any age, or
    - Pancreatic cancer at any age, or
    - From a population at increased risk[f]
  - Male breast cancer
- An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age
- An individual with a personal and/or family history of three or more of the following (especially if early onset[b] and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer[i], colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations[g,h] and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract[h]
- An individual with no personal history of cancer but with
  - A close relative with any of the following:[d,f]
    - A known mutation in a cancer susceptibility gene within the family
    - ≥2 breast cancer primaries in a single individual
    - ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y
    - Ovarian[e] cancer
    - Male breast cancer
  - First- or second-degree relative with breast cancer ≤45 y
  - Family history of three or more of the following (especially if early onset[b] and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer[i], colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations[g,h] and/or macrocephaly, hamartomatous polyps of GI tract[h]

→ Consider referral to cancer genetics professional[j] → See Assessment (BR/OV-2)

- who has the highest probability of testing + for a known actionable mutation?
- What are you gonna do about it?
  - increase  routine imaging
  - Risk-reducing stategies (medication, preventive mastectomy)

Annals of Internal Medicine

U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

# RISK ASSESSMENT, GENETIC COUNSELING, AND GENETIC TESTING FOR BRCA-RELATED CANCER IN WOMEN CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

| | | |
|---|---|---|
| **Population** | Women who have not been diagnosed with BRCA-related cancer and who have no signs or symptoms of the disease | |
| **Recommendation** | Screen women whose family history may be associated with an increased risk for potentially harmful BRCA mutations. Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing.<br>Grade: B | Do not routinely recommend genetic counseling or BRCA testing to women whose family history is not associated with an increased risk for potentially harmful BRCA mutations.<br>Grade: D |

| | | |
|---|---|---|
| **Risk Assessment** | Family history factors associated with increased likelihood of potentially harmful BRCA mutations include breast cancer diagnosis before age 50 years, bilateral breast cancer, family history of breast and ovarian cancer, presence of breast cancer in ≥1 male family member, multiple cases of breast cancer in the family, ≥1 family member with 2 primary types of BRCA-related cancer, and Ashkenazi Jewish ethnicity.<br>Several familial risk stratification tools are available to determine the need for in-depth genetic counseling, such as the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7. | |
| **Screening Tests** | Genetic risk assessment and BRCA mutation testing are generally multistep processes involving identification of women who may be at increased risk for potentially harmful mutations, followed by genetic counseling by suitably trained health care providers and genetic testing of selected high-risk women when indicated.<br>Tests for BRCA mutations are highly sensitive and specific for known mutations, but interpretation of results is complex and generally requires posttest counseling. | |
| **Treatment** | Interventions in women who are BRCA mutation carriers include earlier, more frequent, or intensive cancer screening; risk-reducing medications (e.g., tamoxifen or raloxifene); and risk-reducing surgery (e.g., mastectomy or salpingo-oophorectomy). | |
| **Balance of Benefits and Harms** | In women whose family history is associated with an increased risk for potentially harmful BRCA mutations, the net benefit of genetic testing and early intervention is moderate. | In women whose family history is not associated with an increased risk for potentially harmful BRCA mutations, the net benefit of genetic testing and early intervention ranges from minimal to potentially harmful. |
| **Other Relevant USPSTF Recommendations** | The USPSTF has made recommendations on medications for the reduction of breast cancer risk and screening for ovarian cancer. These recommendations are available at www.uspreventiveservicestaskforce.org. | |

# *Doctor is it genetic…?*

- Most breast cancer (BC) are sporadic
- 5-10% of unselected women wt BC have an hereditary form
  - Majority have a mutation in BRCA 1, BRCA2

# Prevalence of BRCA 1/2

- Prevalence of disease-related mutation
  - 1 in 300 in BRCA 1
  - 1 in 800 in BRCA2
- Prevalence of BRCA mutations varies according to
  - type of cancer, age
  - Ancestry
    - Ashkenazi Jews, unselected, risk is 1:40

# Meta-Analysis of *BRCA1* and *BRCA2* Penetrance

*Sining Chen and Giovanni Parmigiani*

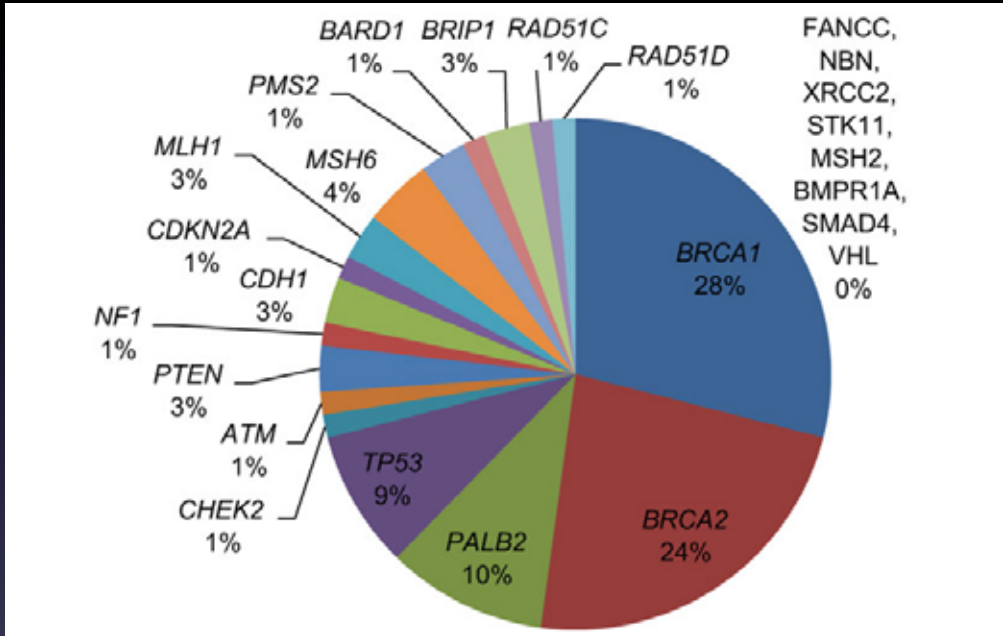
**Table 2.** Predicted Mean Cancer Risk to Currently Unaffected *BRCA1/2* Mutation Carriers

| | Risk (%) of Developing Cancer by Age | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 30 Years | | 40 Years | | 50 Years | | 60 Years | | 70 Years | |
| Current Age | Mean | 95% CI | Mean | 95% CI | Mean | 95% CI | Mean | 95% CI | Mean | 95% CI |
| Breast cancer: *BRCA1* | | | | | | | | | | |
| 20 years | 1.8 | 1.4 to 2.2 | 12 | 9.5 to 14 | 29 | 24 to 35 | 44 | 37 to 52 | 54 | 46 to 63 |
| 30 years | — | | 10 | 8.2 to 13 | 28 | 23 to 34 | 44 | 36 to 52 | 54 | 45 to 63 |
| 40 years | — | | — | | 20 | 16 to 25 | 38 | 31 to 45 | 49 | 41 to 58 |
| 50 years | — | | — | | — | | 22 | 18 to 27 | 37 | 30 to 44 |
| 60 years | — | | — | | — | | — | | 19 | 15 to 24 |
| Breast cancer: *BRCA2* | | | | | | | | | | |
| 20 years | 1 | 0.78 to 1.4 | 7.5 | 5.8 to 9.8 | 21 | 17 to 26 | 35 | 28 to 42 | 45 | 38 to 53 |
| 30 years | — | | 6.6 | 5.1 to 8.6 | 20 | 16 to 26 | 35 | 28 to 42 | 45 | 38 to 53 |
| 40 years | — | | — | | 15 | 12 to 19 | 30 | 24 to 36 | 42 | 34 to 49 |
| 50 years | — | | — | | — | | 18 | 15 to 22 | 32 | 26 to 38 |
| 60 years | — | | — | | — | | — | | 17 | 14 to 20 |
| Ovarian cancer: *BRCA1* | | | | | | | | | | |
| 20 years | 1 | 0.68 to 1.8 | 3.2 | 2.3 to 5.1 | 9.5 | 7.3 to 13 | 23 | 18 to 28 | 39 | 34 to 44 |
| 30 years | — | | 2.2 | 1.6 to 3.4 | 8.7 | 6.7 to 12 | 22 | 18 to 27 | 39 | 34 to 43 |
| 40 years | — | | — | | 6.7 | 5.2 to 8.9 | 20 | 17 to 24 | 38 | 33 to 41 |
| 50 years | — | | — | | — | | 15 | 12 to 17 | 34 | 29 to 36 |
| 60 years | — | | — | | — | | — | | 22 | 20 to 23 |
| Ovarian cancer: *BRCA2* | | | | | | | | | | |
| 20 years | 0.19 | 0.09 to 0.47 | 0.7 | 0.37 to 1.5 | 2.6 | 1.5 to 4.5 | 7.5 | 5.1 to 11 | 16 | 12 to 20 |
| 30 years | — | | 0.52 | 0.28 to 1 | 2.4 | 1.5 to 4.2 | 7.4 | 5.1 to 11 | 16 | 12 to 20 |
| 40 years | — | | — | | 1.9 | 1.2 to 3.2 | 7 | 4.8 to 10 | 16 | 12 to 20 |
| 50 years | — | | — | | — | | 5.2 | 3.7 to 7.2 | 14 | 11 to 17 |
| 60 years | — | | — | | — | | — | | 9.8 | 7.8 to 11 |

NOTE. The CI is provided for the mean risk, not the risk itself.

# GENES ASSOCIATED WITH HIGH BREAST CANCER RISK

- *Li-Fraumeni* (TP 53)
  - risk of BC close to 100%
- *Peutz-Jeghers* (STK11)
  - Risk BC 55%
- *Cowden* (PTEN)
  - risk BC: 85%
- Hereditary diffuse gastric cancer syndrome (CDH1)
  - Risk BC: 60%



Pie-chart showing the percentage of mutations across the 25 genes.

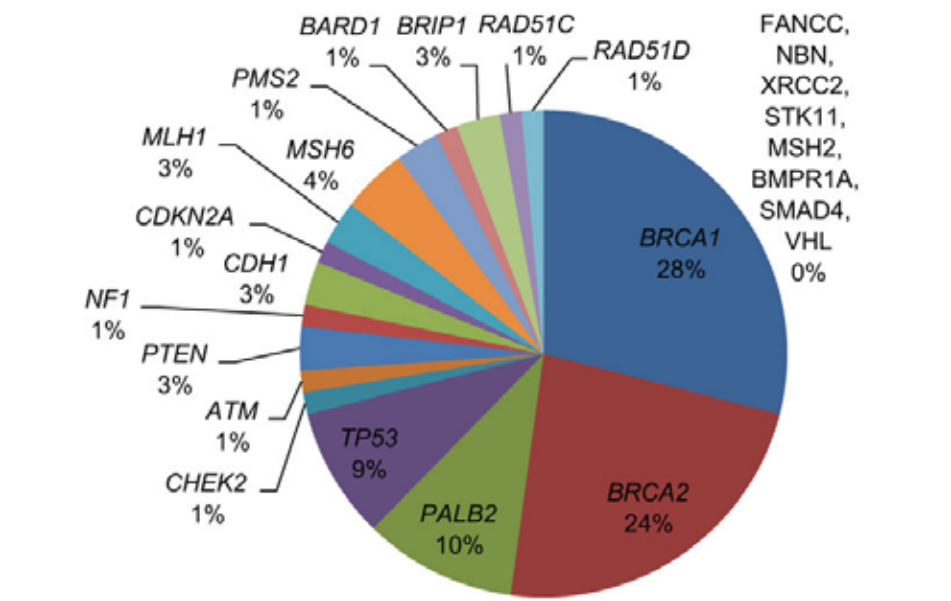
npj Genomic Medicine (2016) 1, 15003; doi:10.1038/npjgenmed.2015.3; published online 13 January 2016

# GENES ASSOCIATED WITH MODERATE BREAST CANCER RISK

- *CHECK 2 (check point kinase 2)*
  - 2-3X increase
  - Several variants

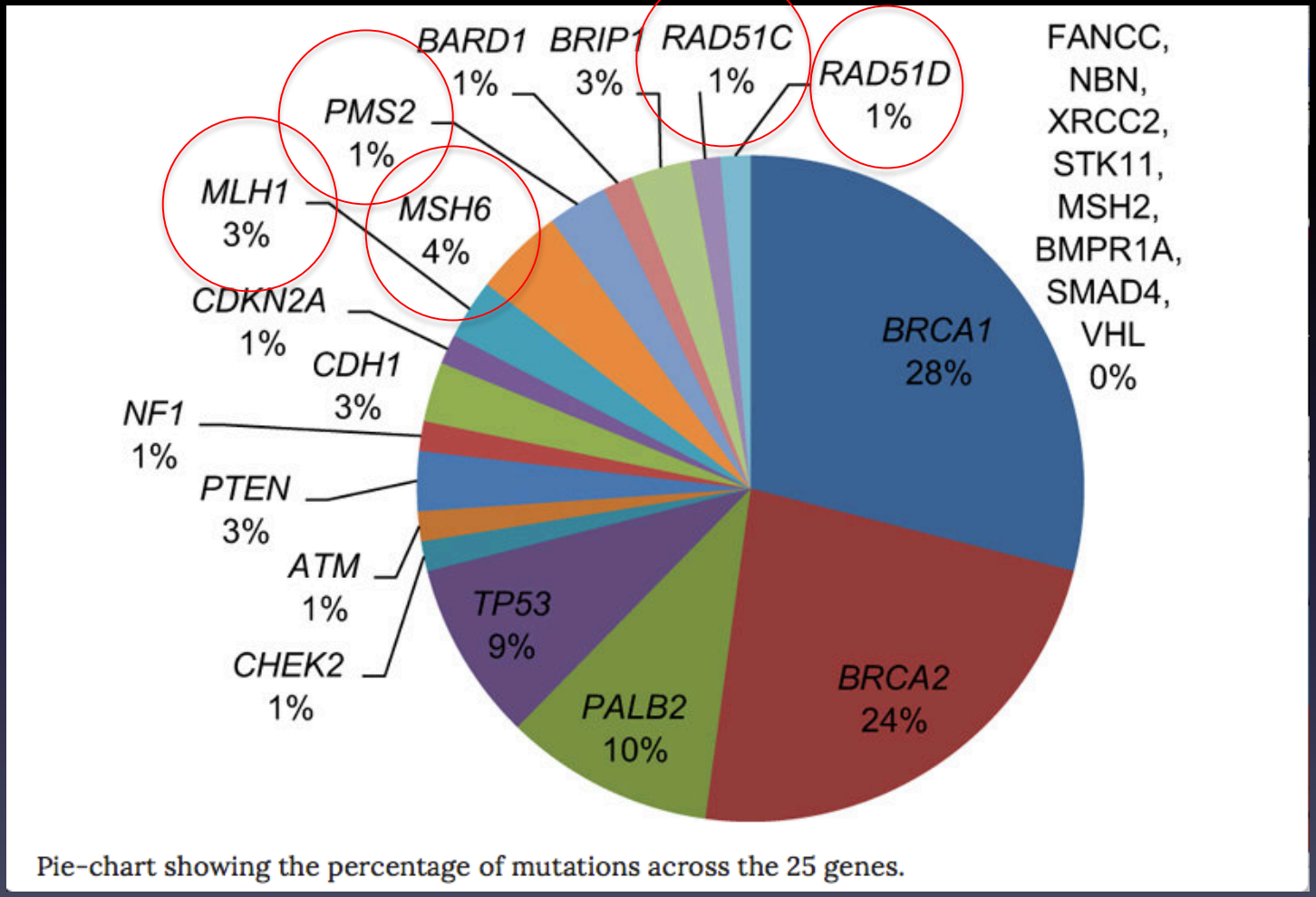
- *PALB2* (partner and localizer of BRCA2)
  - No fam Hx breast cancer: 33%
  - Wt fam Hx BC: 58%

- *ATM* (ataxia-telangiectasia mutated)
  - female heterogygote, risk of BC 2X



Pie-chart showing the percentage of mutations across the 25 genes.

# Unknown risk associated with other genes…




Pie-chart showing the percentage of mutations across the 25 genes.

# Multi-gene testing in breast cancer

- next-generation sequencing technology can analyze a set of genes simultaneously
- Include highly/moderately/less penetrant gene
- Limited data on the degree of cancer risk for many of these genes

## BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a]

**The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.**

| Gene | Breast Cancer Risk and Management | Ovarian Cancer Risk and Management | Other Cancer Risks and Management |
|---|---|---|---|
| *PALB2* | **Increased risk of BC**<br>• Screening: Annual mammogram and consider breast MRI with contrast at 30 y<br>• RRM: Consider based on family history. | **Unknown or insufficient evidence for OC risk** | Unknown or insufficient evidence |
| | Comments: Counsel for risk of autosomal recessive condition in offspring. | | |
| *PTEN* | **Increased risk of BC**<br>• See Cowden Syndrome Management | **No increased risk of OC** | See Cowden Syndrome Management |
| *RAD51C* | **Unknown or insufficient evidence for BC risk** | **Increased risk of OC**<br>• Consider RRSO at 45–50 y | N/A |
| | Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in *RAD51C* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer. | | |
| *RAD51D* | **Unknown or insufficient evidence for BC risk** | **Increased risk of OC**<br>• Consider RRSO at 45–50 y | N/A |
| | Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in *RAD51D* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer. | | |
| *STK11* | **Increased risk of BC**<br>• Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal<br>• RRM: Evidence insufficient, manage based on family history. | **Increased risk of non-epithelial OC**<br>• See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal | See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal |
| *TP53* | **Increased risk of BC**<br>• See Li-Fraumeni Syndrome Management | **No increased risk of OC** | See Li-Fraumeni Syndrome Management |

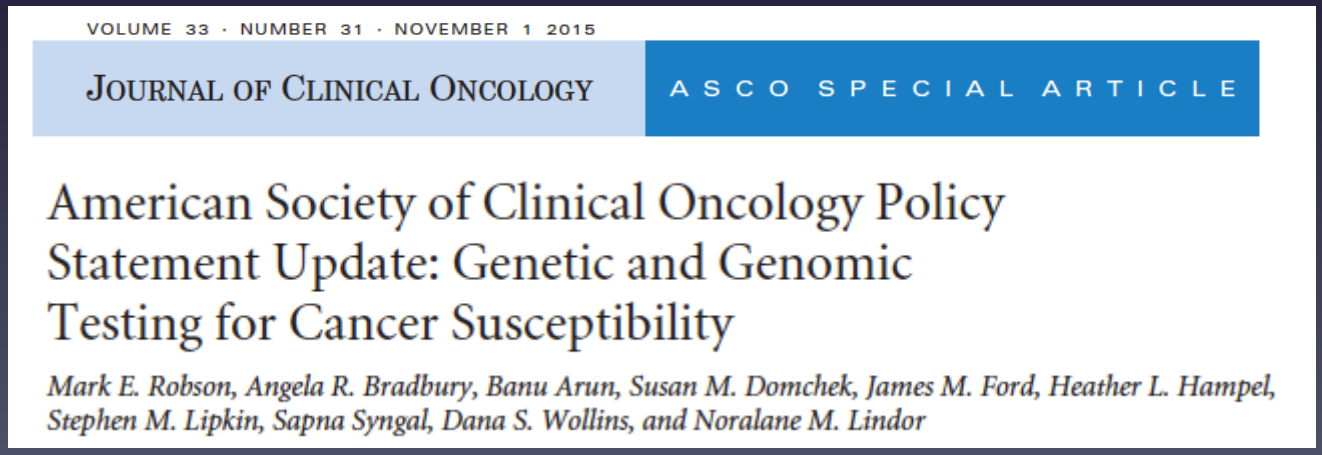
NCCN Guidelines Version 2.2017 Genetic/Familial High-Risk Assessment: Breast and Ovarian

**Table 2. Genetic Test Results to Determine the Presence of a Cancer-Predisposing Gene**

| *Result* | *Description* |
|---|---|
| *True-positive* | The person is a carrier of an alteration in a known cancer-predisposing gene. |
| *True-negative* | The person is not a carrier of a known cancer-predisposing gene that has been positively identified in another family member. |
| *Indeterminate (uninformative)* | The person is not a carrier of a known cancer-predisposing gene, and the carrier status of other family members is either also negative or unknown. |
| *Inconclusive (variants of unknown significance)* | The person is a carrier of an alteration in a gene that currently has no known significance. |

# Genetic testing in breast cancer-conclusions

1. Targeted screening
2. Knowledge of risk associated with results
3. Multi-gene testing can provide data with unknown clinical utility...so far...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ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility

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PROMPT

WHAT WE DO | GENES | TAKE ACTION

- ATM
- CDH1
- CHEK2
- PALB2
- RAD51C
- RAD51D
- STK11
- TP53
- BRCA1 & BRCA2

## ABOUT PR

PROMPT is an online research registry for people who ls—a newer form of genetic testing that looks for mutations in several diffe es on the panels have been linked to an increased risk of cancer, but some ris others.

Our objective is to follow people with mutations or variants in genes on these panels, so that patients, physicians, and researchers can more clearly understand these lesser-known risks.