McGill EPIB-671 Symposium - 2016

Scientific Program, Friday, May 20

Time	Presenter	Title
13:00-13:15	Host	Introduction to the Symposium and Instructions
13:15-13:30	Milene Gonzalez-Verdecia	Tamoxifen as a risk factor for uterine cancer
13:30-13:45	Katherine Lach	Epidemiology of melanoma
13:45-14:00	Lara Richer	You be the judge: Can talc powder cause ovarian cancer?
14:00-14:15	Enrico Ripamonti	Is bladder cancer associated with pioglitazone use?
14:15-14:30	Mehdi Mousavi	Air pollution as a carcinogen
14:30-14:45	Mariana Usatii	Do genetically modified foods cause cancer? The challenges of investigating the association
14:45-15:00	Talia Malagon	What criteria were used in Canadian recommendations for cervical cancer screening
15:00-15:15	***Coffee Break***	
15:15-15:30	Ali Samkari	Oral contraceptives and breast cancer: What is the evidence?
15:30-15:45	Michel Wissing	Arsenic in drinking water and bladder cancer
15:45-16:00	James Man Git Tsui	Radiation Exposure and Cancer
16:00-16:15	Arif Awan	Risk factors for febrile neutropenia in breast cancer: A retrospective cohort study
Buffer time		
16:30-17:00	Catch-up with content, exam, and end of course: Have a Happy Summer!	

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

TAMOXIFEN AS A RISK FACTOR FOR ENDOMETRIAL CANCER

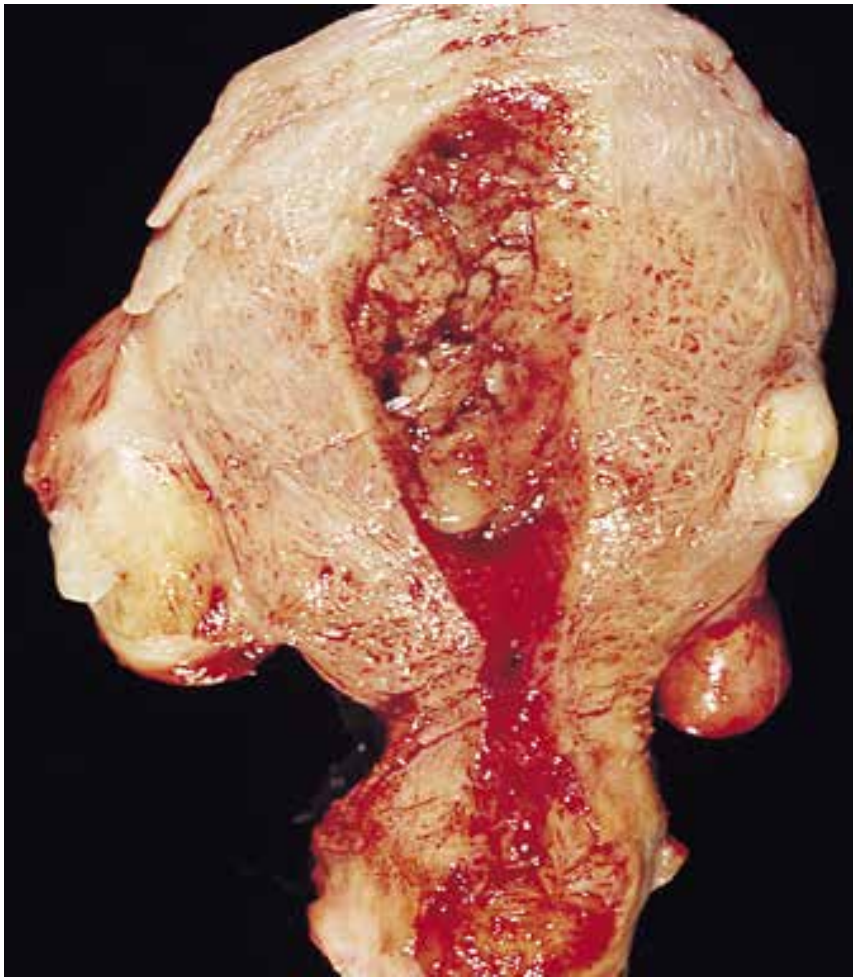
MILENE GONZALEZ-VERDECIA
PGY2 - AP

Endometrial cancer (EC)

- Most common invasive cancer of the female genital tract and the 4th most common cancer in women.
- In 2015: 6,300 women (diagnosed with EC and 1,050 (deaths)
- Two types:

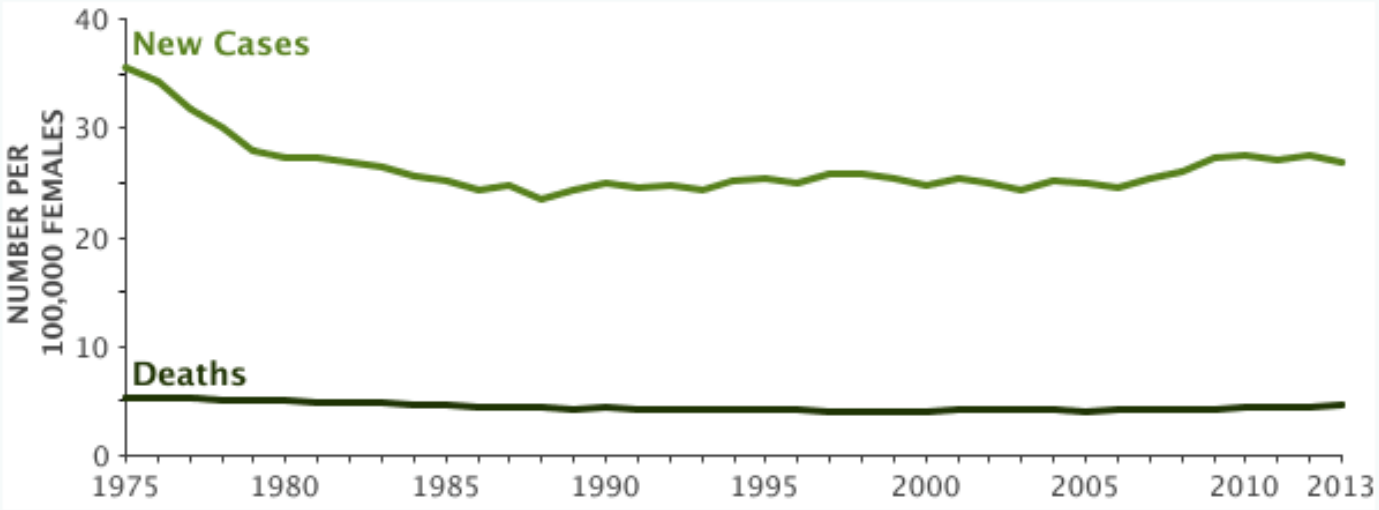
  -Type I (80%) Endometrioid histology, Estrogen driven, better prognosis, may be preceded by endometrial hyperplasia / IEN

  - Type II (10-20%) patients 10 years older, arise in the setting of endometrial atrophy, poorly differentiated tumors, poor prognosis, histology: grade 3 EEC, Serous, clear cell, MMMT...



Endometrial cancer as per SEER database

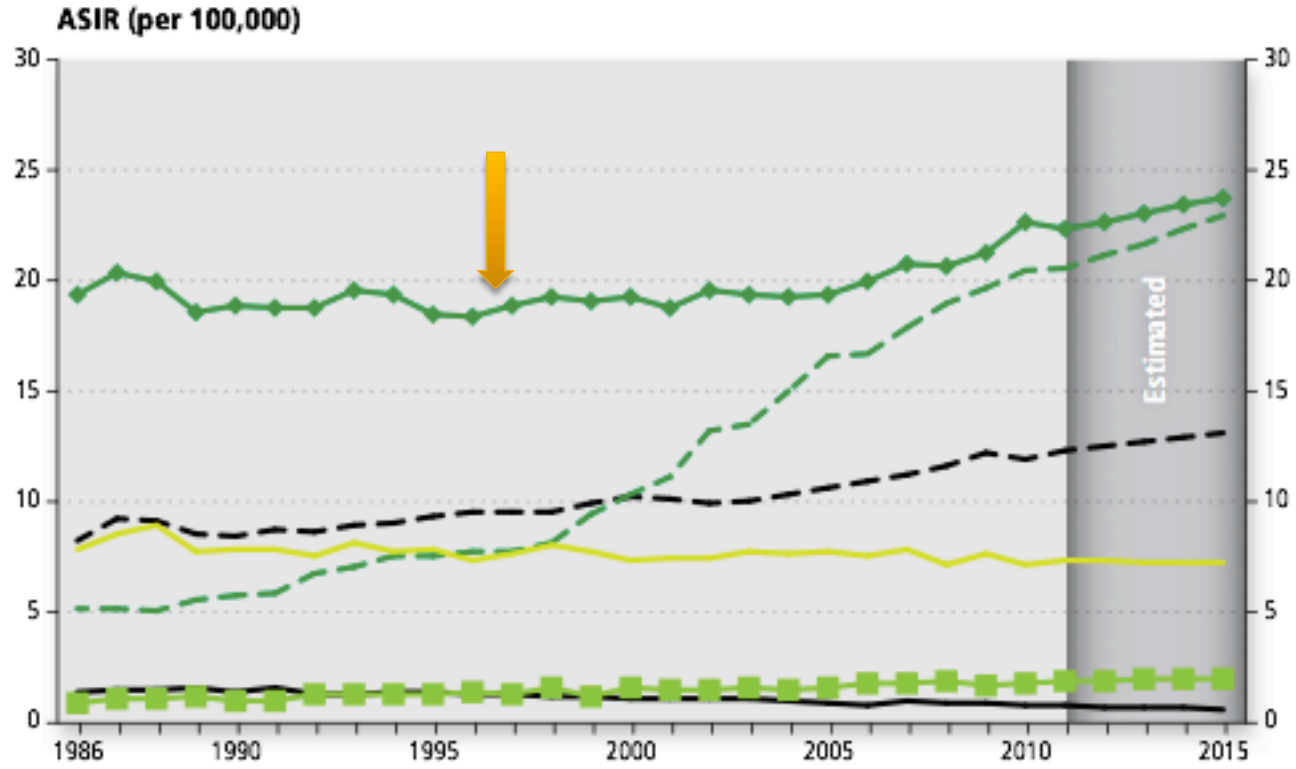
New Cases, Deaths and 5-Year Relative Survival View Data Table



Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	87.8%	79.6%	82.8%	82.5%	84.1%	85.2%	82.6%	82.7%

SEER 9 Incidence & U.S. Mortality 1975-2013, All Races, Females. Rates are Age-Adjusted.

Age-standardized incidence rates (ASiR) for selected cancers, females, Canada, 1986–2015



Analysis by: Surveillance and Epidemiology Division, CCDPC, Public Health Agency of Canada
Data sources: Canadian Cancer Registry, National Cancer Incidence Reporting System databases at Statistics Canada and Quebec Cancer Registry (2008–2010)

* Five most frequent cancers (both sexes combined) and cancers with a statistically significant change in incidence rate of at least 2% per year (see Table 1.5).

Note: Rates are age-standardized to the 1991 Canadian population. See Table 1.4 for data points. Actual data for incidence were available to 2010. The range of scales differs widely between the figures. The complete definition of the specific cancers listed here can be found in Table A10.

Risk factors for Endometrial cancer

Risk factors for endometrial cancer

Risk factor	Relative risk (RR) (other statistics are noted when used)
Increasing age	1.4% endometrial cancer prevalence in women 50 to 70 years old
Unopposed estrogen therapy	2 to 10
Tamoxifen therapy	2
Early menarche	NA
Late menopause (after age 55)	2
Nulliparity	2
Polycystic ovary syndrome (chronic anovulation)	3
Obesity	2 to 4
Diabetes mellitus	2
Estrogen-secreting tumor	NA
Lynch syndrome (hereditary nonpolyposis colorectal cancer)	22 to 50% lifetime risk
Cowden syndrome	13 to 19% lifetime risk
Family history of endometrial, ovarian, breast, or colon cancer	NA

NA: RR not available.

Adapted from data in Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society Guidelines for Early Endometrial Cancer Detection: Update 2001.

Graphic 62089 Version 10.0

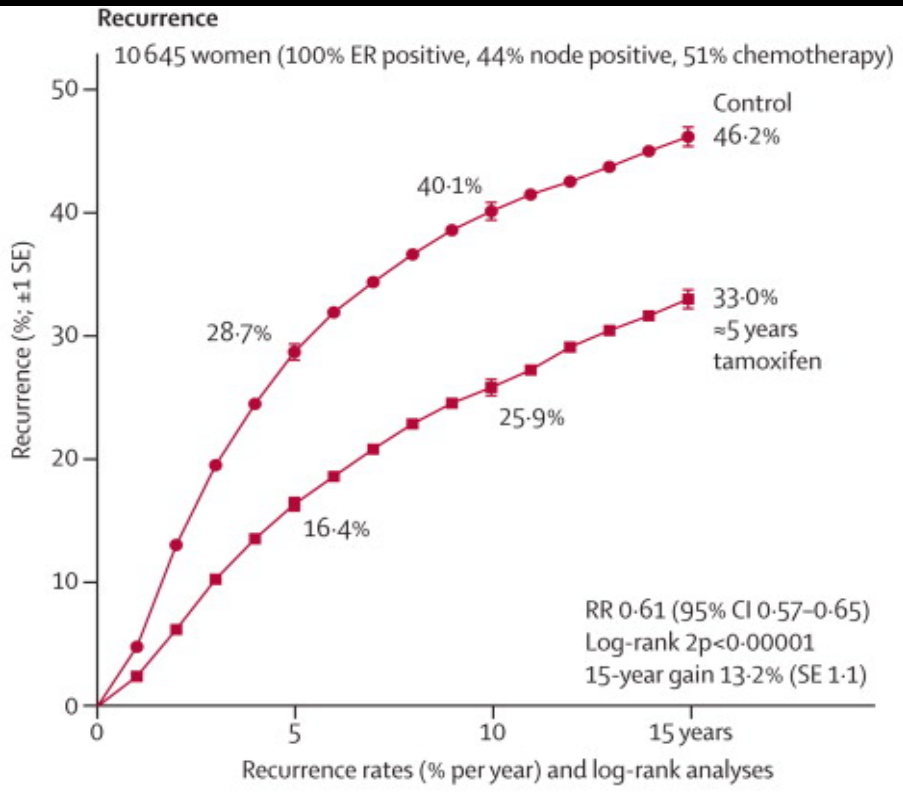
Tamoxifen

- Tamoxifen is a SERM with agonist and antagonist properties depending upon the organ target and the estrogen serum level.

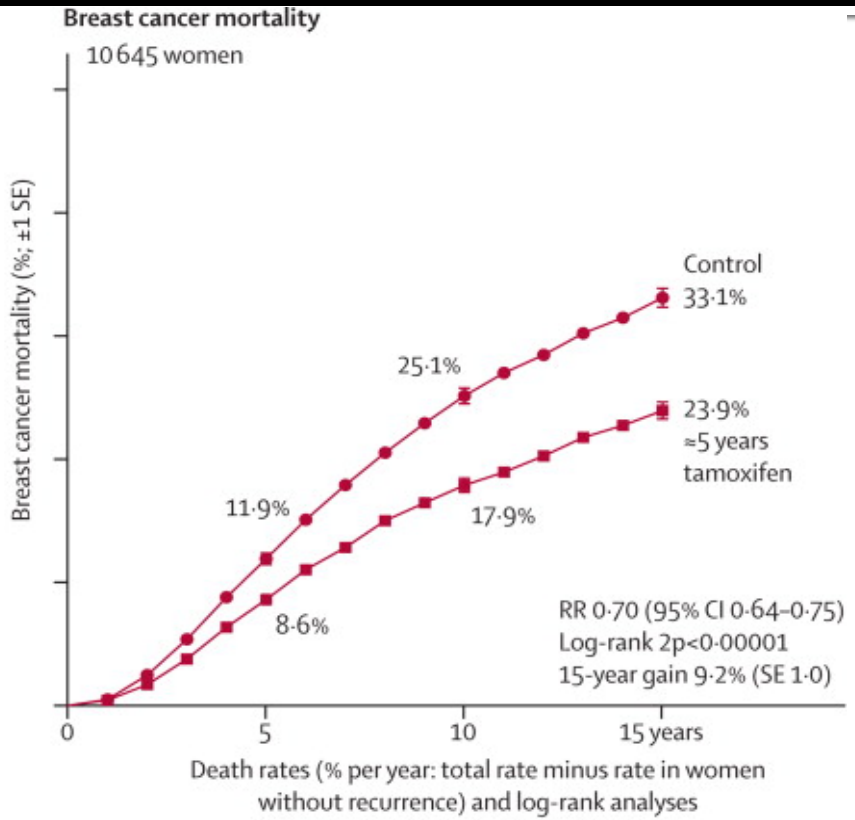
- 1966 - First synthesized: Dr. Walpole team at ICI pharmaceuticals (looking for a contraceptive pill)
- 1971- Introduced to treat advanced breast cancer
- 1978- Aprooved by FDA to treat advanced BrCa
- 1980 - Introduced in the treatment of early BrCa
- 1998 - the meta-analysis of the EBCTCG showed definitively that tamoxifen saved lives and showed:

-41% reduction in the risk of BrCa recurrence (RRR = 0.59)
-34% reduction in mortality (DRR = 0.66)
-1/3 reduction incidence in contralateral BrCa > leading to FDA approving it as chemoprevention in high risk women

Effects of about 5 years of tamoxifen on the 15-year probabilities of recurrence and of breast cancer mortality, for ER-positive disease



	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3	−4·4/35·5



Years 0–4	Years 5–9	Years 10–14	Year 15+
1·79 (SE 0·08)	2·25 (SE 0·11)	1·54 (SE 0·11)	1·48 (SE 0·16)
2·46 (SE 0·10)	3·23 (SE 0·13)	2·28 (SE 0·14)	1·89 (SE 0·19)
0·71 (SE 0·05)	0·66 (SE 0·05)	0·68 (SE 0·08)	0·88 (SE 0·14)
−84·4/244·8	−95·8/233·2	−38·6/99·4	−5·7/42·6

EBCTCG 2011

Tamoxifen's side effects

- Minor side effects: Vasodilation (41%), flushing (33%), hypertension (11%), peripheral edema (11%), Mood changes (12% to 18%), pain (3% to 16%), depression (2% to 12%), Skin changes (6% to 19%), rash (13%), Hot flashes (3% to 80%), fluid retention (32%), altered menses (13% to 25%), amenorrhea (16%), Nausea (5% to 26%), weight loss (23%), vomiting (12%):, Vaginal discharge (13% to 55%), vaginal bleeding (2% to 23%), Weakness (18%), arthritis (14%), arthralgia (11%), Pharyngitis (14%), Lymphedema (11%)
- Main life-threatening SE:

  -DVT

  -Pulmonary embolism

  -Endometrial carcinoma

- As early as 1967 –ICI pharmaceuticals realized that "tamoxifen persists for some days in the uterus" and that it exerts an estrogenic effect in the endometrium
- Since 1970's hundreds of studies have been conducted to prove the association of Tamoxifen and Endometrial cancer
- Most of them showing (among other side effects)

  -Increase incidence of EC in Tamoxifen treated patients

  -Increase incidence of more aggressive forms of EC

  -Increase mortality due to EC in Tamoxifen treated patients

Do still the benefits outweigh the risks?

Example of trials showing increased risk of EC in Tamoxifen exposed patients

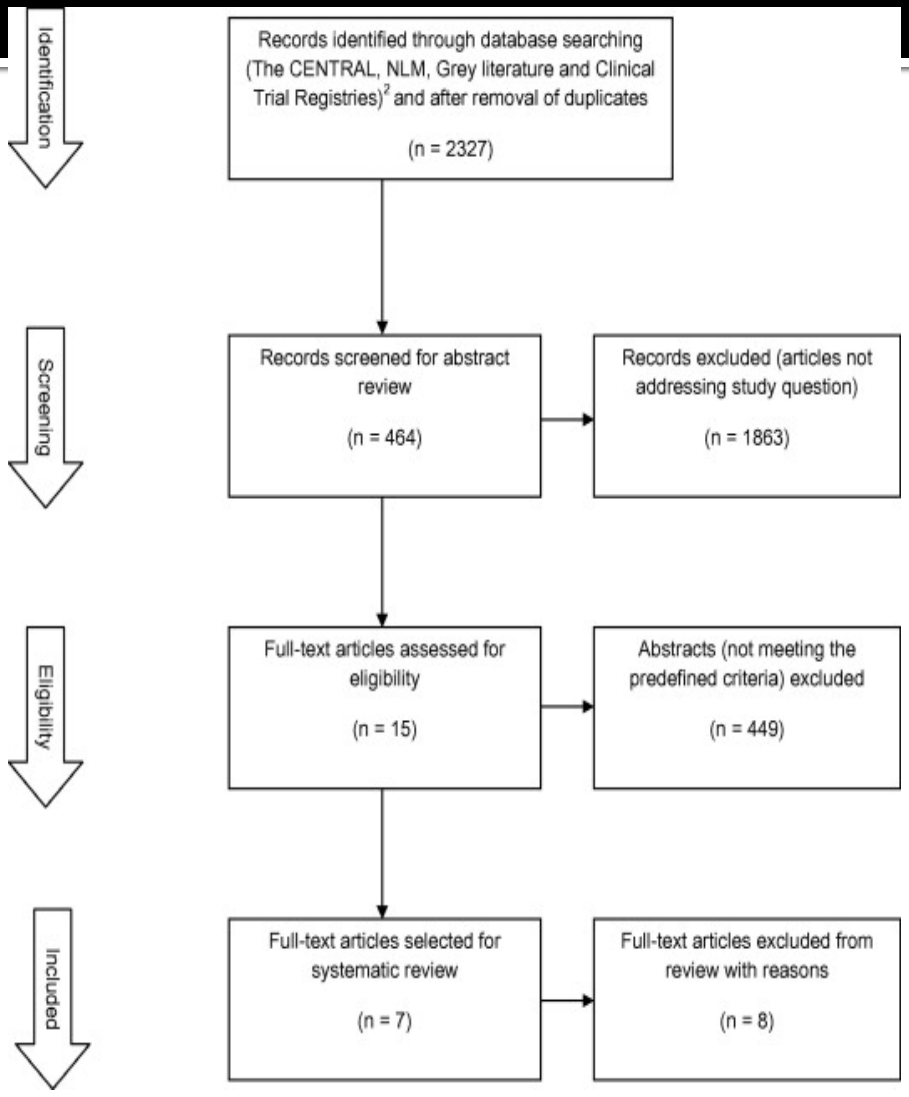
Period studied	Data from	Type of study	Patients enrolled	RR (95% CI)
1976-1990	SBCS	RCC (Tamoxifen40mg 2-5years vs placebo in BrCa patients independent of H status)	2738	6,4 (?)
1982-1988	NSABP-B14	RCC (tamoxifen vs placebo in ER+, LN- BrCa	4063	7,5 (1,7-32,7)
1976-1996 A.Swerdlow	LSHTM	Case control study comparing women with endometrial cancer and without and association to Tamoxifen exposure.	1880	OR: 2,4 (1,8-3,0)

But there was at least one extensive, well conducted study that showed some how slightly different results and that changed the recommendations of the ACOG (American Congress of Obstetricians and Gynecologists)

Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: a systematic review.

- Javaid Iqbal et al. searched for published data from January 1970 to December 2010 in Cochrane Central Register of Controlled Trials and National Library of Medicine >> inclusion and exclusion criteria.
- Criteria for inclusion:
  -Studies that enrolled women <50 years high risk (using modified Gail model)
  -without previous invasive breast cancer or DCIS
  -without previous hysterectomy, DVT or PE

Flow diagram of database search.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6(6):e1000097. doi:10.1371/journal.pmed1000097 . (2) The CENTRAL represents The Cochrane's Central Register of Controlled Trials; NLM represents National Library of Medicine.

- The studies included were Phase III randomized, double-blind, placebo-controlled clinical trials comparing tamoxifen (20 mg per day) vs placebo for five years:
  - Breast Cancer Prevention Trial or BCPT
  - International Breast Cancer Intervention Study-1 (IBIS-1)
  - Royal Marsden hospital tamoxifen breast cancer prevention trial
- Objectives: To estimate incidence and mortality of EC, DVT and PE in Tamoxifen treated patients
- The Cochrane Collaboration's tool to assess the risk of bias was used to judge the credibility and applicability of included studies
- A value of kappa between 0.40 and 0.59 was considered a fair agreement between two authors

Endometrial cancer events in 3 trial in relation to age 50

Study	n, P/T	Placebo	Tamoxifen	RR (95% CI)	P-value	Age-years	Placebo	Tamoxifen	RR (95% CI)	P-value
NSABP P-1	13,165 6599/6576	15	36	2.46 (1.35-4.48)	0.003	<50	8	9	1.13 (0.44-2.93)	0.9
						=>50	7	27	3.86 (1.69-8.86)	0.0002
IBIS-1	7154 3575/3579	11	17	1.51 (0.71-3.22)	0.3	<50	2	1	0.50 (0.05-5.54)	0.9
						=>50	9	16	1.77 (0.78-3.99)	0.2
Royal Marsden study	2471 1233/1238	5	13	2.59 (0.93-7.24)	0.06	<50			No data	
						=>50			No data	

Current recommendations of ACOG (American Congress of Obstetricians and Gynecologists)

- Tamoxifen has been approved by the U.S. FDA for adjuvant treatment of breast cancer, treatment of metastatic breast cancer, and reduction in breast cancer incidence in high-risk women.
- Tamoxifen use may be extended to 10 years based on new data demonstrating additional benefit. Women taking tamoxifen should be informed about the risks of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas, and any abnormal vaginal bleeding, bloody vaginal discharge, staining, or spotting should be investigated.
- Postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial hyperplasia or cancer.
- Premenopausal women treated with tamoxifen have no known increased risk of uterine cancer and require no additional monitoring beyond routine gynecologic care.

REFERENCES

- Javaid J Iqbal. Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: a systematic review. Cancer Treatment Reviews , 2012. Volume:38 , Issue:4. p 318-328
- Committee of Gynecologic practice. Tamoxifen and Uterine Cancer. ACOG. Number 601, June 2014
- EBCTCG. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011 Aug 27; 378(9793): 771–784.
- J. Tubiner et al. Clinicopathological and molecular analysis of endometrial carcinoma associated with tamoxifen. Modern Pathology. (2008) 21, p 925–936
- A. J. Swerdlow et al. Tamoxifen Treatment for Breast Cancer and Risk of Endometrial Cancer: A Case–Control Study. Lancet
- O. Lavie et al. The risk of developing uterine sarcoma after tamoxifen use. IJGC. Volume 18(2), March/April 2008, p 352–356
- Ju-Yin Chen et al. Endometrial Cancer Incidence in Breast Cancer Patients Correlating with Age and Duration of Tamoxifen Use: a Population Based Study. J of Cancer. 2014; 5(2):p 151-155.

EPIDEMIOLOGY OF MELANOMA

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PGY-1, Anatomical Pathology

Epidemiology 671

McGill University

2016

MELANOMA

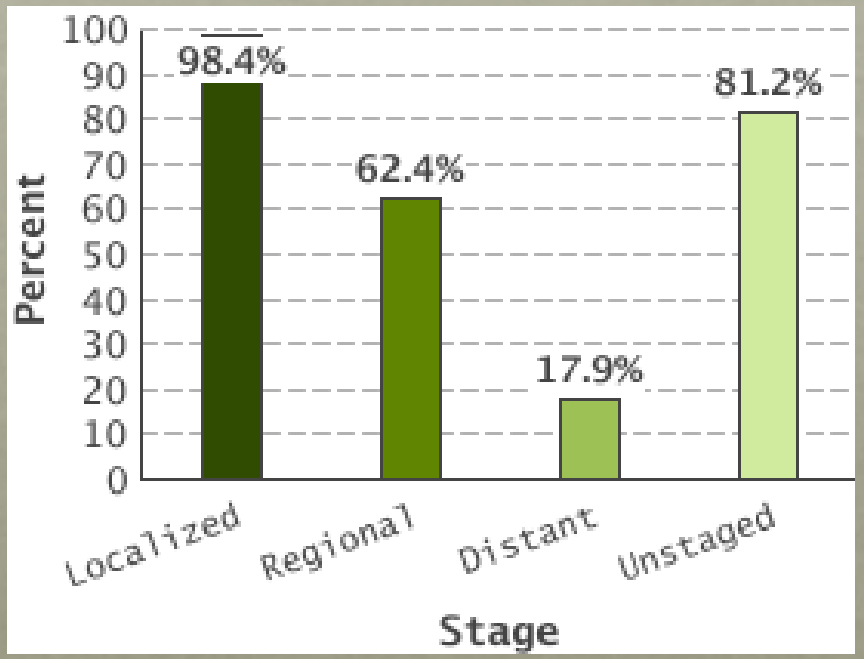
- Malignant, aggressive disease histologically derived from melanocytes; responsible for >75% of skin cancer deaths[1]
- Initial: radial growth phase
  - Horizontal growth: through superficial (papillary) dermis à irregular contours and variegated pigmentation.
- Later: vertical growth phase
  - Dermal invasion signals metastatic potential à papules, nodules
- Vertical DEPTH is the most important prognostic indicator:
  - Highly curable when detected at early stage i.e. less than **1mm** thickness;
  - Five-year survival rates decline steadily as tumour thickness & cancer stage increase

1. Bolognia, Jean et al. Dermatology, 3rd edition. Claus Garbe and Jurgen Bauer, Melanoma. Elsevier, 2012: 1885.

AJCC & PROGNOSIS

- Thickness of tumor ("Breslow depth"),
  - T1: equal to or <1mm,
  - T2: 1.01 to 2mm
  - T3: 2.01 to 4mm
  - T4: >4mm
- Stage I and II cancers (no regional/distant mets): surgical excision often cures
  - even T1aN0M0 has 10-year disease-specific mortality of 5 - 10%
- Thick melanomas (stage IIB and IIC) have 10-year survival of 32.3 – 53.9%[2]

5-year relative survival[1]



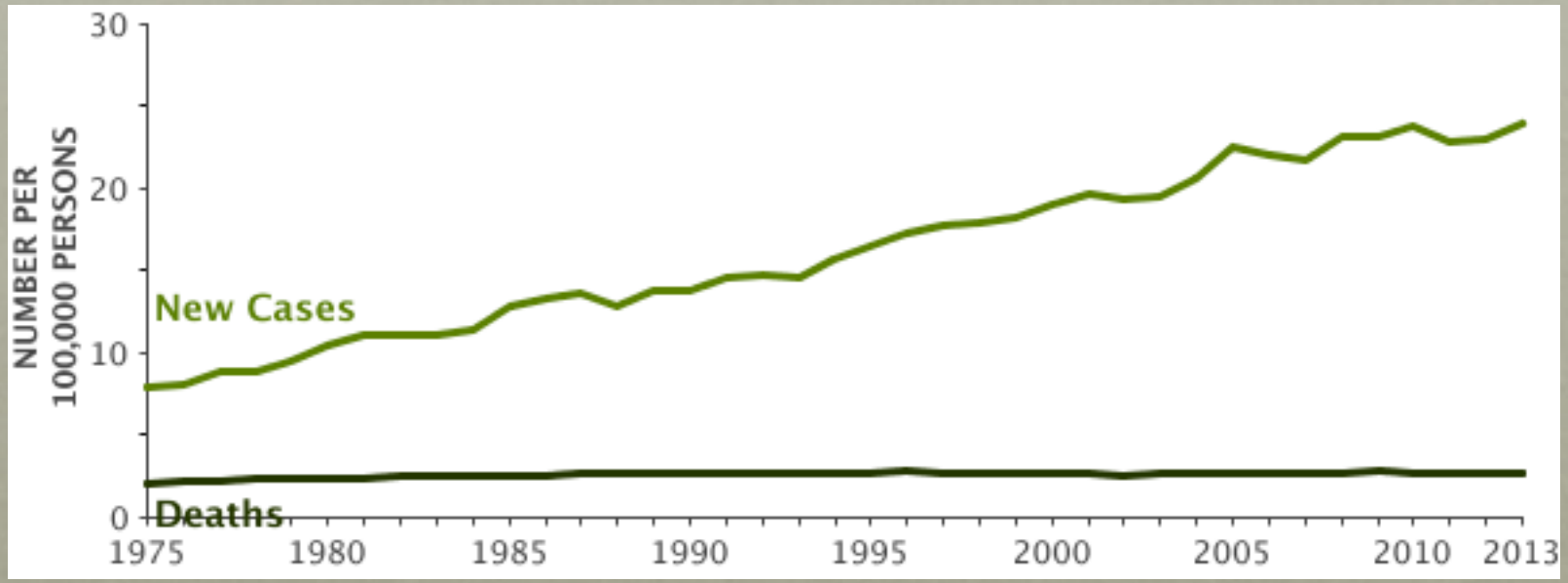
1. SEER Stat Fact Sheets, Melanoma of the Skin. Percent of Cases & 5-year relative survival by stage at diagnosis www.seer.cancer.gov/statfacts/html.melan.html Accessed: 14 May 2016
2. Bruce A. Chabner, Dan N. Longo. Harrison's Manual of Oncology, 2nd edition. New York: McGraw-Hill, 2014.

EPIDEMIOLOGY OF MELANOMA

- Dramatically rising incidence reported worldwide since the 1970s: doubling in rates per decade; annual 3 – 7% increase until 1990s[1] – now 1.4% in last 10 years
- USA SEER statistics: now 6th most common cancer among men and women[2]
- Estimated new cases in 2016: 76,380
  - 4.5% of all new cancer cases
- Estimated deaths in 2016 due to melanoma: 10,130
  - 1.7% of cancer deaths
- 1992 – 2012: incidence increase - average annual percent change of 2.0% (males); 0.9% (females)[3]
- 1992 – 2012: mortality – average annual percent change + 0.3% (males) vs. – 0.5% (females)

1. WHO Skin Tumours. Lyon: 2006: 53.
2. SEER Stat Fact Sheets, Melanoma of the Skin. Number of New Cases and Deaths. www.seer.cancer.gov/statfacts/html.melan.html Accessed: 14 May 2016
3. Rebecca L. Siegel et al. Cancer Statistics, 2016. CA: Cancer J. Clin. 66, 1: Jan/Feb 2016: 7-30.

TRENDS – INCIDENCE & MORTALITY (U.S.)



Year	1975	1980	1985	1990	1995	2000	2004	2008
5-year survival	81.8%	83.9%	86.1%	89.2%	90.1%	92.0%	93.1%	93.3%

SEER Stat Fact Sheets, Melanoma of the Skin. New Cases, Deaths and 5-year Relative Survival. www.seer.cancer.gov/statfacts/html.melan.html Accessed: 14 May 2016

RISK FACTORS – WHO GETS MELANOMA?

- Common pigmentation genes responsible for light complexion, poorly tanning skin, red or blonde hair, numerous melanocytic nevi in complex interplay with environmental risk due to UVR, both UVA and UVB

- Genetics: Familial melanomas make up 10% of cases
  - Germline genetic mutations and polymorphisms that predispose to melanoma; CDKN2A Encodes p16 and $p14^{ARF}$ – regulatory mechanisms on cell cycle through Rb and P53 à ~2% of all melanomas

- Pigmentation genes: germline mutations in melanocortin1 receptor (MCR1) gene convey risk in addition to phenotypic susceptibility
  - Risk 1.5- to 3-fold of any cutaneous melanoma[1]

- BRCA 2: relative risk 2.58[2]

- Substantial change in genetic risk factors in most populations unlikely to account for observed increases in melanoma.

1. Bolognia, Jean et al. Dermatology, 3rd edition. Claus Garbe and Jurgen Bauer, Melanoma: 1885 – 1914. Elsevier, 2012: 1889.
2. Bruce Chabner, Dan L. Longon. Harrison's Manual of Oncology: 729.

WHO IS AFFECTED: WORLDWIDE

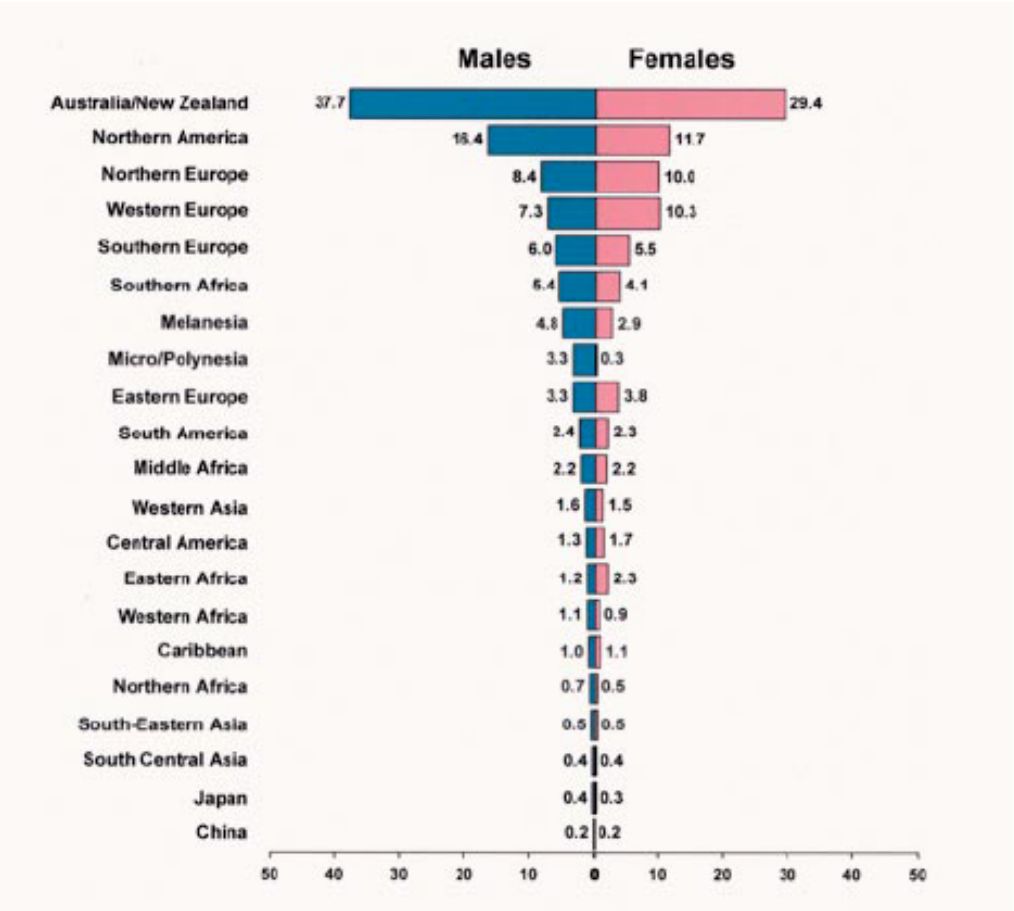
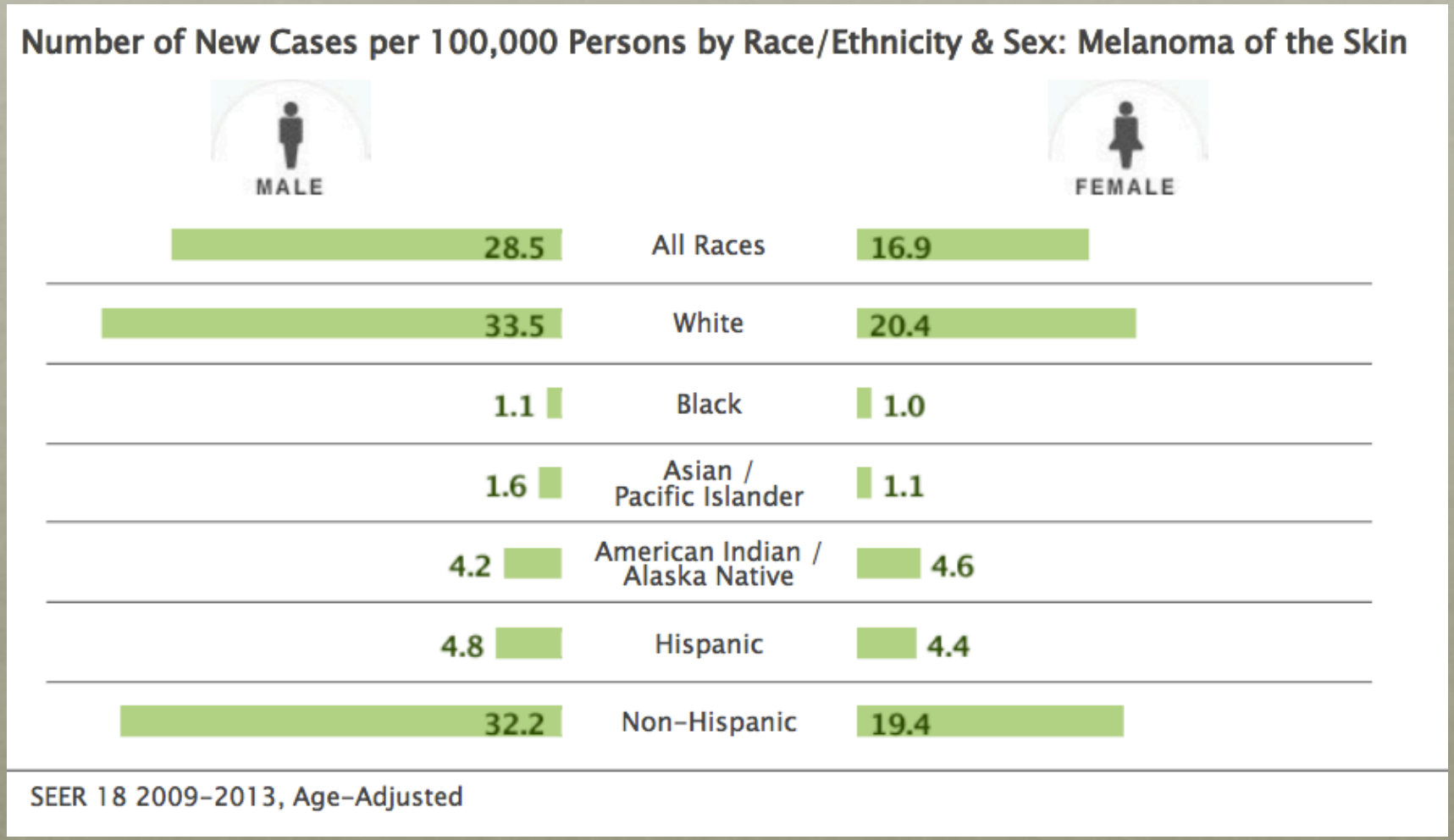


Fig. 2.2 Age-standardized incidence rates for malignant melanoma of skin, per 100 000 population and year, adjusted to the world standard population. From D.M. Parkin et al. {1779}.

- Incidence greatest in Australia / New Zealand
- Caucasian populations with proximity to equator
  - Possible relationship with latitude – conflicting studies. Ex: relationship to latitude not reproducible in N.A.
- Higher ambient sunshine levels, lighter-skinned population, with high wealth – corresponding high melanoma rate & low mortality.

Paul Kleuhues, editor, et al. Pathology and Genetics of Skin Tumours. Lyon, France. IARC Press: 2006.

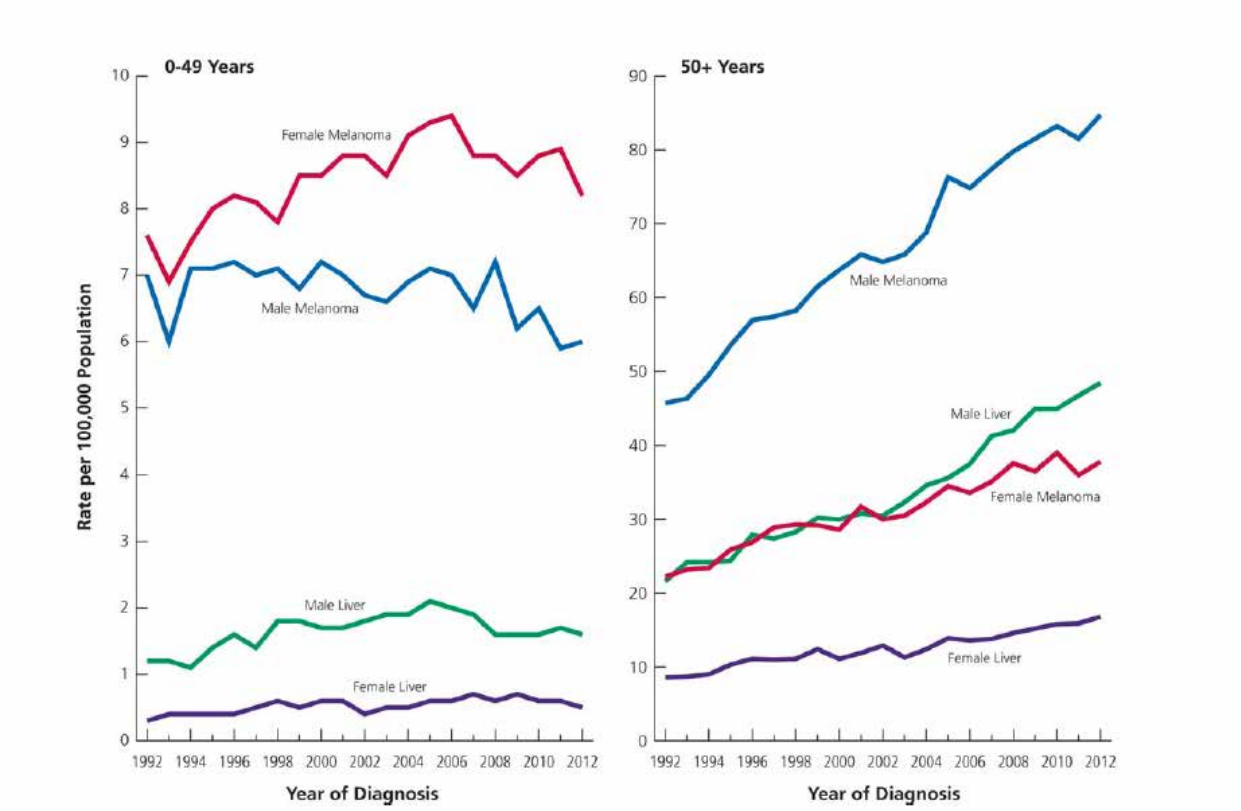
WHO IS AFFECTED? (USA)



SEER Stat Fact Sheets, Melanoma of the Skin. www.seer.cancer.gov/statfacts/html.melan.html Accessed: 14 May 2016

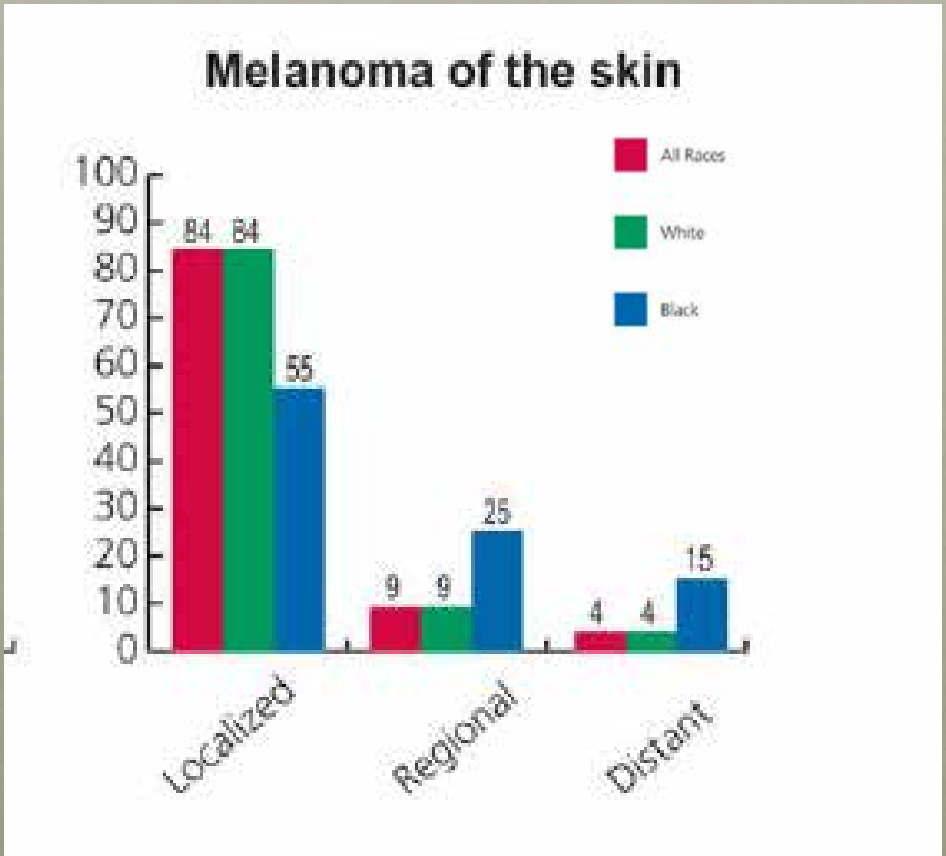
WHO IS AFFECTED? MEN VS WOMEN

FIGURE 4. Incidence Trends for Melanoma and Liver Cancer by Age, United States, 1992 to 2012.
Rates are age adjusted to the 2000 US standard population and adjusted for delays in reporting.



Rebecca L. Siegel, Kimberly D. Miller, Ahmedin Jemal. Cancer Statistics, 2016. Ca Cancer J Clin 2016; 66: 7-30.

WHO IS AFFECTED? RACE



- Although incidence much greater in whites in USA, blacks are more likely to be diagnosed at later stage
- 80% of cutaneous melanomas in black population Acral lentiginous (vs. 2% in whites);
  - Clinical misdiagnosis common à delay
  - Aggressive type with rapid clinical evolution from radial to vertical growth phases

Rebecca L. Siegel, Kimberly D. Miller, Ahmedin Jemal. Cancer Statistics, 2016. Ca Cancer J Clin 2016; 66: 7-30.

WHO IS AFFECTED? DEATHS

TABLE 6. Trends in 5-Year Relative Survival Rates* (%) by Race and Year of Diagnosis, United States, 1975 to 2011

	ALL RACES			WHITE			BLACK		
	1975 TO 1977	1987 TO 1989	2005 TO 2011	1975 TO 1977	1987 TO 1989	2005 TO 2011	1975 TO 1977	1987 TO 1989	2005 TO 2011
All sites	49	55	69†	50	57	70†	39	43	62†
Brain & other nervous system	22	29	35†	22	28	33†	25	32	40†
Breast (female)	75	84	91†	76	85	92†	62	71	81†
Colorectum	50	60	66†	50	60	67†	45	52	59†
Esophagus	5	10	20†	6	11	21†	4	7	14†
Hodgkin lymphoma	72	79	88†	72	80	89†	70	72	86†
Kidney & renal pelvis	50	57	74†	50	57	74†	49	55	74†
Larynx	66	66	63†	67	67	65	58	56	51
Leukemia	34	43	62†	35	44	63†	33	35	55†
Liver & intrahepatic bile duct	3	5	18†	3	6	18†	2	3	13†
Lung & bronchus	12	13	18†	12	13	19†	11	11	16†
Melanoma of the skin	82	88	93†	82	88	93†	57‡	79‡	70
Myeloma	25	27	49†	24	27	48†	30	30	50†
Non-Hodgkin lymphoma	47	51	72†	47	51	73†	49	46	64†
Oral cavity & pharynx	53	54	66†	54	56	68†	36	34	45†
Ovary	36	38	46†	35	38	46†	42	34	38
Pancreas	3	4	8†	3	3	8†	2	6	7†
Prostate	68	83	99†	69	84	>99†	61	71	98†
Stomach	15	20	30†	14	18	29†	16	19	28†
Testis	83	95	97†	83	95	97†	73‡§	88‡	91
Thyroid	92	94	98†	92	94	99†	90	92	97†
Urinary bladder	72	79	79†	73	80	79†	50	63	67†
Uterine cervix	69	70	69	70	73	71	65	57	60†
Uterine corpus	87	82	83†	88	84	85†	60	57	66†

*Survival rates are adjusted for normal life expectancy and are based on cases diagnosed in the Surveillance, Epidemiology, and End Results (SEER) 9 areas from 1975 to 1977, 1987 to 1989, and 2005 to 2011, all followed through 2012.

Rebecca L. Siegel, Kimberly D. Miller, Ahmedin Jemal. Cancer Statistics, 2016. Ca Cancer J Clin 2016; 66: 7-30.

PRIMARY PREVENTION

- Known link with UVR: melanoma attributed to sun exposure est. > 90% in Canada, Australia, USA; 78-90% in other European countries[1]
- Sunscreen: widely promoted; clear preventive, proven effects against squamous cell carcinoma
- Despite clear link with UVR and melanoma, some studies showed sunscreen increased sunbathing time, contributing formation; others with no significant effect
- Only RCT (finally) in 2011, Australia
  - 1621 adults randomized to sunscreen +/- from 1992 – 1996, followed until 2006
  - All melanomas Hazard ratio 0.50; 95% CI 0.24 – 1.02 p0.051
  - Invasive Hazard ratio 0.27; 95% CI 0.08 – 0.97 p0.045

Howard L Kaufman, Janice M. Mehnert, eds. Melanoma. New York: Springer, 2016.

SECONDARY PREVENTION

- AAD: Has offered education and free screening since 1985 in the U.S.: 1992 – 1994 found higher percentage of lesions <1.50mm than in cases in SEER: 10% vs 2%
- USPSTF: there insufficient (I) evidence to assess balance/harms of FBSE or patient self-examination for early detection of melanoma
- No randomized studies directly examined whether screening à reduced morbidity, mortality
- *However* "screening consistently identifies thinner melanomas than usual care;" suggests that high-risk populations may benefit from screening
- Canadian Task Force on Preventive Health Care (1994): poor evidence to warrant including/excluding skin cancer screening from PHE; fair evidence to support whole-body skin exam for very select group.

U.S. Preventive Services Task Force. Final Recommendation Statement. Skin Cancer: Screening, February 2009. http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/skin-cancer-screening Accessed: May 19, 2016.

SO, WHY THE INCREASE?

- Some theories:
- Rising incidence of melanoma due to genuine increase in disease: particularly men >50
  - Deaths (in USA) at plateau while incidence rising
  - Increased awareness & vigilance, patient education à caught in earlier stages à *mortality* plateau despite surge in incidence
  - Also possible: change in biology of melanoma? Tendency toward less aggressive biology consistent with rising incidence, corresponding stabilization of mortality.
- Increase correlates with lifestyle changes post 1950s, generation in whom incidence has peaked
  - "induction time" 20-40 years
  - More common in higher SES: outdoor sports, beach holidays, Western countries.
  - Suntan as symbol of health & wealth.

Paul Kleuhues, editor, et al. Pathology and Genetics of Skin Tumours. Lyon, France. IARC Press: 2006: 55.

Thank you

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You be the judge

Does talc powder increase the risk of developing ovarian cancer?

Lara Richer, PGY1 Pathology

EPIB 671

May 20, 2016

Background

- There are approximately >1000 law suits pending against a pharmaceutical company alleging that talc found in their baby powder contributes to ovarian cancer
- About ovarian cancer
  - 14000 deaths in USA yearly
  - Highest mortality of gynecological malignancies
  - Inflammation involved in ovarian carcinogenesis
- About talc
  - Mineral that absorbs water
  - IARC considers it a “possible” carcinogen (since 2006)

History

- 1960s
  - Asbestos found in some talc powders
- 1970s
  - Talc particles found in ovaries and uterii of women with those malignancies
- 1980s
  - Case control study linked talc use and ovarian malignancy

Exhibit A: case-control

(*Epidemiology* 2016;27: 334–346)

- 2041 women diagnosed with epithelial ovarian cancer between 18 and 80yo
- 2100 controls found via random digit dialing, driver licenses and town residents matched by area of residence and within 5 years of age
- Asked about “regular” or “at least monthly” applied powder to genital or rectal area, sanitary napkins, or other, type of powder, frequency of use, years used

Exhibit A: case-control

TABLE 1. Type, Timing, and Duration of Genital Talc Use

	Control Subjects N (%)	Case Subjects N (%)	Adjusted[a] OR (95% CI)
Personal use			
None			1.00 (referent)
Body use only			0.99 (0.84, 1.16)
Genital use only			1.42 (1.04, 1.96)
Type of genital powder used			
No genital use			1.00 (referent)
Cornstarch use only			0.58 (0.19, 1.74)
Johnson and Johnson Baby Powder or Shower to Shower			1.30 (1.10, 1.54)
Other brand(s)			1.35 (1.12, 1.64)
Time since exposure ended			
No genital use			1.00 (referent)
≥35 years			1.18 (0.79, 1.75)
25–34 years			1.24 (0.91, 1.70)
15–24 years			1.30 (0.94, 1.80)
5–14 years			1.36 (1.00, 1.85)
Currently using or recently stopped			1.38 (1.15, 1.65)
Frequency of use			
No genital use			1.00 (referent)
1–7 days per month			1.17 (0.96, 1.44)
8–29 days per month			1.37 (1.05, 1.78)
≥30 days per month			1.46 (1.20, 1.78)
Adjusted for all variables	-		1.32 (1.15, 1.53)

Cross examination

- NHS
  - Causality: no data for these women of finding talc in the diseased ovaries
  - Recall bias: self-reported use
    - Would need 18% misclassification to lose OR of 1.3
    - OR are decreasing over the years, whereas publicity about potential danger of talc use increasing à expect higher OR in more recent studies
  - Confounding
    - Addressed in table 2

Exhibit B: cohort

DOI:10.1093/jnci/dju208
First published online September 11, 2014

ARTICLE

Perineal Powder Use and Risk of Ovarian Cancer

Serena C. Houghton, Katherine W. Reeves, Susan E. Hankinson, Lori Crawford, Dorothy Lane, Jean Wactawski-Wende, Cynthia A. Thomson, Judith K. Ockene, Susan R. Sturgeon

Manuscript received October 31, 2013; revised May 21, 2014; accepted June 5, 2014.

- 61285 women from Women's Health Initiative-Observational Study
  - 29066 never used perineal powder, 32219 ever used perineal powder
  - Avg age 65, followed for avg 12.2-12.6 yrs
  - Caucasians, obese, less than a college degree
- Aim: to assess different areas of perineal powder use and durations of use on ovarian cancer diagnoses

Exhibit B: cohort

Table 2. Age and multivariable-adjusted hazard ratios of ovarian cancer by area of perineal powder application (n = 61 576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR (95% CI)	P_{trend} †	Multivariable HR* (95% CI)	P_{trend} †
Powder use on genitals						
Never	247				1.0 (referent)	.67
Ever‡	181				1.12 (0.92 to 1.36)	
Less than 9 years	112				1.23 (0.98 to 1.54)	
10 or more years	68				0.98 (0.75 to 1.29)	
Powder use on sanitary napkins						
Never	336				1.0 (referent)	.69
Ever‡	93				0.95 (0.76 to 1.20)	
Less than 9 years	62				0.96 (0.73 to 1.26)	
10 or more years	30				0.95 (0.65 to 1.37)	
Powder use on diaphragm						
Never	373				1.0 (referent)	.67
Ever‡	52				0.92 (0.68 to 1.23)	
Less than 9 years	35				0.91 (0.64 to 1.30)	
10 or more years	17				0.95 (0.58 to 1.56)	
Combined ever powder use§						
Never	197				1.0 (referent)	.77
Ever‡	232				1.06 (0.87 to 1.28)	
Less than 9 years	135				1.09 (0.88 to 1.36)	
10 or more years	97				1.02 (0.80 to 1.30)	

Table 4. Age and multivariable-adjusted hazard ratios for combined ever powder use by subtype of ovarian cancer (n = 61 576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR* (95% CI)	Multivariable HR* (95% CI)
Serous†				
Never				1.0 (referent)
Ever				1.16 (0.88 to 1.53)
Serous Invasive				
Never				1.0 (referent)
Ever				1.13 (0.84 to 1.51)
Mucinous				
Never				1.0 (referent)
Ever				1.03 (0.47 to 2.27)
Endometrioid				
Never				1.0 (referent)
Ever				1.29 (0.64 to 2.61)

Cross examination

- WHI-OS:
  - Did not recollect data after baseline
    - Prophylactic oophorectomy
    - Women who started using powder
    - Therefore, misclassification risk from erroneous reporting
  - Only duration data, no frequency of use data
  - No data on the content of talc or asbestos in perineal powder

Exhibit C: meta-analysis

Research Article

Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls

Kathryn L. Terry[1,3,4], Stalo Karageorgi[2], Yurii B. Shvetsov[5], Melissa A. Merritt[4], Galina Lurie[5], Pamela J. Thompson[6], Michael E. Carney[5], Rachel Palmieri Weber[9], Lucy Akushevich[6], Wei-Hsuan Lo-Ciganic[11], Kara Cushing-Haugen[12], Weiva Sieh[8], Kirsten Moysich[13], Jennifer A. Doherty[12,15], Christina M. Nagle[16], Andrew Berchuck[10], Celeste L. Pearce[7], Malcolm Pike[7,14], Roberta B. Ness[17]; Penelope M. Webb[16] for the Australian Cancer Study (Ovarian Cancer), and the Australian Ovarian Cancer Study Group; Mary Anne Rossing[12], Joellen Schildkraut[9], Harvey Risch[18], and Marc T. Goodman[6], on behalf of the Ovarian Cancer Association Consortium

- Eight studies with a combined 8525 patients with ovarian, FT or peritoneal cancer and 9859 controls
- Harmonized data by comparing questionnaires
- Aim: to assess “association between genital powder use and risk of ovarian cancer overall, by invasiveness and by histologic type in a pooled analysis of eight population-based case control studies with relevant data from the OCAC”

Exhibit C: meta-analysis

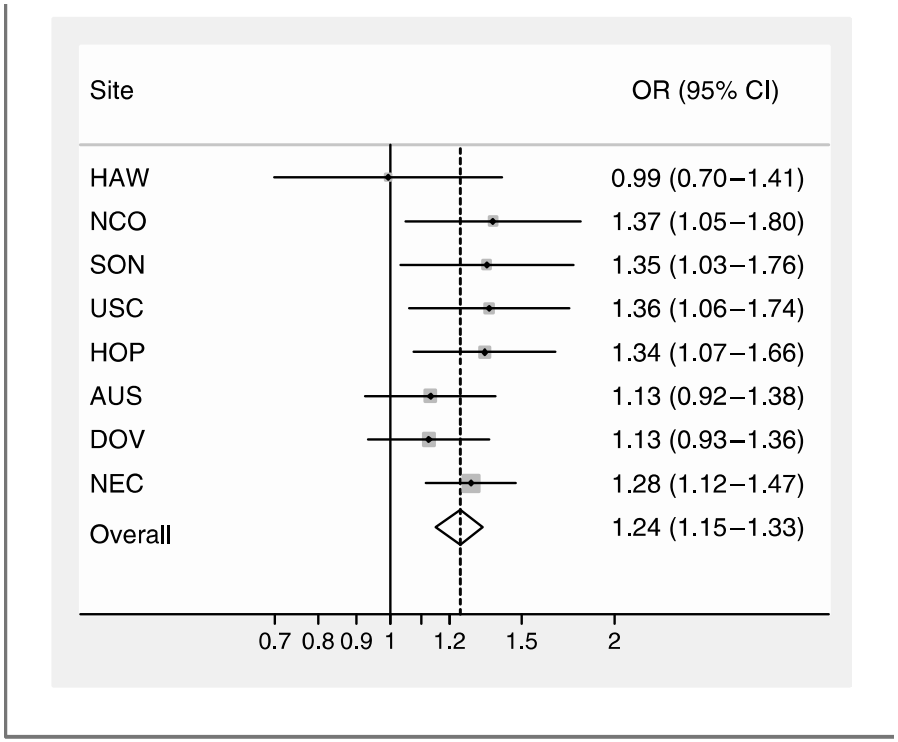

Exhibit C: meta-analysis

Table 5. Association between estimated lifetime applications of genital powder and risk of ovarian cancer (borderline and invasive combined)

Lifetime number of applications[a]		All cases ($N = 7,587$)		Nonmucinous cases ($N = 6,361$)	
	Controls (%)	Cases (%)	OR[b] (95% CI)	Cases (%)	OR[b] (95% CI)
Never users	6,175 (76)	5,384 (71)	1.00	4,472 (70)	1.00
Quartile 1	509 (6)	534 (7)	1.14 (1.00–1.31)	467 (7)	1.18 (1.02–1.36)
Quartile 2	512 (6)	541 (7)	1.23 (1.08–1.41)	456 (7)	1.22 (1.06–1.41)
Quartile 3	497 (6)	542 (7)	1.22 (1.07–1.40)	457 (7)	1.22 (1.06–1.40)
Quartile 4	486 (6)	586 (8)	1.32 (1.16–1.52)	509 (8)	1.37 (1.19–1.58)
P_{trend}[c]			0.17		0.17

[a]Age-specific 25th, 50th, and 75th percentile cutoff points are 612, 1,872, and 5,400 for participants < 40 years old; 612, 2,160, and 7,200 for 41–50 years; 720, 3,600, and 10,800 for 51–60 years; 1,440, 5,760, and 14,440 for 61–70; 840, 7,200, and 18,000 for > 70 years.
[b]ORs were estimated using conditional logistic regression conditioned on 5-year age groups and adjusted for age (continuous), oral contraceptive duration (never use, <2, 2–<5, 5–<10, or ≥10 years), parity (0, 1, 2, 3, or 4+ children), tubal ligation history (no or yes), BMI (quartiles), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, or other).
[c]Trend excludes never users.

Cross examination

- Relation is less than what is shown by previous studies
  - Used published and unpublished data
- No dose-response relationship: difficult to get accurate assessment of exposure
- Meta-analysis
  - Questionnaires differed
  - Missing data excluded

You've been selected for jury duty!

- Does talc powder use increase the risk of ovarian cancer?
- Was the pharmaceutical company negligent for not warning consumers about the potential dangers of talc powder?
- Is the pharmaceutical company responsible for increasing the cancer risk in these women?

Real verdicts

- GR vs Johnson & Johnson
  - 62yo F , used talc on genitals for many years and developed ovarian cancer
  - Awarded $55 million
- JF vs Johnson & Johnson
  - 62yo F, history of talc use on genitals, died of ovarian cancer
  - Family awarded $72 million

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Is bladder cancer associated with pioglitazone use?

Enrico Ripamonti

Montréal- May 20, 2016 - McGill University

Course in Cancer Epidemiology and Prevention

The rise of pharmacoepidemiology

The Promise of Pharmacoepidemiology in Helping Clinicians Assess Drug Risk

Jerry Avorn, MD

Circulation. 2013;128:745-748
doi: 10.1161/CIRCULATIONAHA.113.003419

Improving Automated Database Studies

Wayne A. Ray[a,b]

Epidemiology • Volume 22, Number 3, May 2011

Textbook of Pharmacoepidemiology

WILEY

Editors BRIAN L. STROM *and* STEPHEN E. KIMMEL

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Bladder cancer at a glance

10 MAJOR CANCERS, ASR (WORLD) PER 100 000

Male		Female	
Prostate	105.0	Breast	85.3
Trachea, bronchus and lung	53.5	Trachea, bronchus and lung	36.4
Colon	23.7	Colon	18.8
Bladder	21.3	Corpus uteri	16.9
Non-Hodgkin lymphoma	15.4	Thyroid	12.3
Melanoma of skin	15.1	Melanoma of skin	11.1
Kidney	13.2	Non-Hodgkin lymphoma	10.9
Rectum	11.2	Ovary	9.2
Pancreas	8.2	Kidney	7.1
Other and unspecified	7.4	Rectum	6.8
All sites	363.4	All sites	284.6

US National Program of Cancer Register, in Cancer incidence in five continents, IARC, Lyon, 2014

Descriptive epidemiology (EU-US):

- 4th most common malignancy in men
- Accounts for 5% to 10% of all malignancies in men
- The risk of developing bladder cancer at 75 years of age is 2% to 4% for men and 0.5% to 1% in women

Epidemiology, Staging and Grading, and Diagnosis Committee of the Bladder Cancer Consensus Conference, 2005

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Risk factors

Well-established risk factors:
•Tobacco smoking
•Exposure to β-naphthylamile, 4-aminobiphenil (ABP) and benzidine, principally among workers in the textile dye and rubber tyre industries
•Chronic urinary tract infection
•*Schistosoma haematobium* infection
•Use of cyclophosphamide, an agent used in the treatment of malignant neoplasms
•Radiotherapy/chemotherapy

Possible risk factors:
•For workers and former workers in the dye, rubber, chemical industries, following exposure to amines
•Exposure to constituents of paints, such as benzidine
•Diesel exhaust exposure

Uncertain risk factors:
•Coffee consumption
•Use of artificial sweeteners
•Use of hair dyes

Epidemiology, Staging and Grading, and Diagnosis Committee of the Bladder Cancer Consensus Conference, 2005

Oral therapies for type-2 diabetes:
A brief history

- **1997:** the oral antihyperglycaemia market was significantly affected by the launch of troglitazone, the first drug in a new class of agents known as thiazolidinedione (or glitazones)
- **1999:** two other drugs of this class were launched: rosiglitazone and pioglitazone
- **2000**: the FDA withdrew troglizatone from the market because of hepatotoxicity
- **2010:** the FDA restricted the use of rosiglitazone and the European Medicines Agency suspended it from the market due to safety concerns (hearth failure)
- **2016**: Pioglitazone is the only thiazolidinedione commonly used worldwide today

Current controversies:

Association of pioglitazone use with bladder cancer

- **2000s**: animal models showed an association with bladder neoplasia
- **2003**: the FDA and the manufacturer agreed to this 10-year observational study to evaluate the potential risk of bladder cancer with pioglitazone use in humans
- **2003**: the European Medicines Agency requested a second postmarketing investigation of pioglitazone use and risk of cancer at other sites
- **2011**: A 5-year interim analysis (Lewis et al., 2011) showed no increased risk of bladder cancer overall. However, persons receiving more than 2 years of pioglitazone treatment had a small but statis-tically significant 1.4-fold elevated risk of bladder cancer (hazard ratio [HR], 1.4; 95% CI, 1.0-2.0)

Current controversies:

Association of pioglitazone use with bladder cancer

- **2011**: both the European Medicines Agency and FDA requested updates to the product safety information and allowed continued marketing of pioglitazone
- **2013:** A metanalysis (Ferwana et al., 2013) confirmed the risk of bladder cancer for pioglitazone users
- **2015**: Lewis et al. (2015) at the end of their study reported that pioglitazone use is not associated with statistically significant increased risk of bladder cancer. They report increased prostate and pancreatic cancer, which deserve further investigation

Commentary on Lewis et al.'s results

Although the authors present their results as conclusive, excluding concerns with respect to pioglitazone use association with bladder cancer, their paper presents with several limitations. In particular:

•It has to be explained the difference in the results between the 5-years interim analysis (positive result) and the 16-years total follow-up (negative result). The authors exclude that this difference can be due to chance or to methodological differences, but no other hypotheses are set forth

•In 16 years (period of observation) pioglitazone had a different degree of popularity among physicians (very high at the beginning, lower at the end, also due to the alarms for its association with cancer). This popularity – prescription relation could have led to non-proportional hazards along the period of observation, and this could explain the difference in the results at different thresholds

Two meta-analyses

Thiazolidinediones and associated risk of bladder cancer: a systematic review and meta-analysis

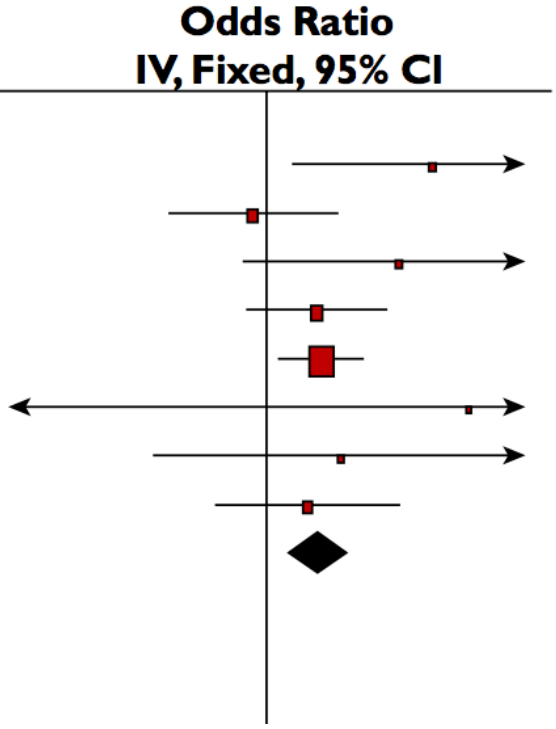
BJCP British Journal of Clinical Pharmacology

Richard M. Turner,[1,2] Chun S. Kwok,[3] Chen Chen-Turner,[2] Chinedu A. Maduakor,[3] Sonal Singh[4] & Yoon K. Loke[3]

Study or Subgroup	Weight	Odds Ratio IV, Fixed, 95% CI
Pioglitazone		
Azoulay 2012 [46]	4.5%	1.83 [1.10, 3.05]
Chang 2012 [47]	12.4%	0.95 [0.70, 1.29]
Hsiao 2013 [51]	3.6%	1.62 [0.92, 2.86]
Lewis 2011 [41]	17.8%	1.20 [0.93, 1.55]
Neumann 2012 [19]	48.6%	1.22 [1.05, 1.42]
Song 2012 [52]	0.3%	2.09 [0.26, 16.80]
Tseng 2012 [44]	2.5%	1.31 [0.66, 2.59]
Wei 2013 [45]	10.4%	1.16 [0.83, 1.62]
Subtotal (95% CI)	100.0%	1.21 [1.09, 1.35]

Heterogeneity: $Chi^2 = 6.34$, $df = 7$ ($P = 0.50$); $I^2 = 0\%$

Test for overall effect: $Z = 3.48$ ($P = 0.0005$)



Two meta-analyses

Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies

M. Ferwana[1,2], B. Firwana[1,3,4], R. Hasan[1,3,4], M. H. Al-Mallah[1,5], S. Kim[4,6], V. M. Montori[4,7] and M. H. Murad[4,8]

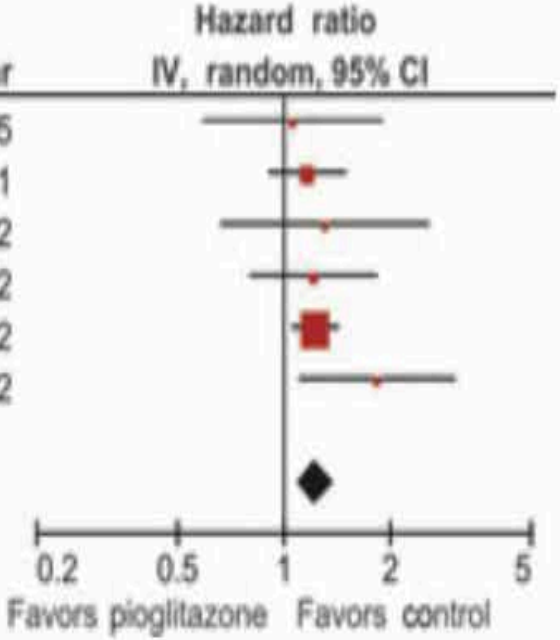
DIABETICMedicine

(a)

Study or subgroup	log[Hazard ratio]	SE	Weight	Hazard ratio IV, random, 95% CI	Year
Dormandy	0.0556	0.2995	4.0%	1.06 [0.59, 1.90]	2005
Lewis	0.1501	0.1303	21.3%	1.16 [0.90, 1.50]	2011
Tseng	0.2661	0.347	3.0%	1.30 [0.66, 2.58]	2012
Li	0.1933	0.2125	8.0%	1.21 [0.80, 1.84]	2012
Neumann	0.2032	0.0788	58.3%	1.23 [1.05, 1.43]	2012
Azoulay	0.6052	0.2602	5.3%	1.83 [1.10, 3.05]	2012
Total (95% CI)			**100.0%**	**1.23 [1.09, 1.39]**	

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.82$, df = 5 ($P = 0.73$); $I^2 = 0\%$

Test for overall effect: $Z = 3.47$ ($P = 0.0005$)



Conclusions

- Thiazolidinedions have become a very popular drug for treatment of type II diabetes
- The association of pioglizatone with bladder (and other types) of cancer is currently a hot topic of pharmacoepidemiology
- Recent results from a 16-years observational study by Lewis et al. (2015) seem non-conclusive and present with methodological drewbacks
- Two meta-analyses (Ferwana et al., 2013; Turner et al., 2014) failed to present accurate evidence in favor of the association, as biased and very heterogeneous studies were pooled together
- In conclusion, this still remains a debated topic and a challenging field of future research

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Air Pollution and Lung Cancer

EPIB 671

Mehdi Mousavi

Sources in air pollution

- Anthropogenic: Transport, power generation, industrial activity, biomass burning, and domestic heating and cooking
- Particulate matter with diameter <10 μm **(PM10)**
- Fine particulate matter (<2.5 μm) **(PM2·5)**
- Nitrogen dioxide **(NO2)**
- Sulfur dioxide **(SO2)**
- Ozone **(O3)**
- Nitrogen oxides **(NOx)**

European Study of Cohorts for Air Pollution Effects (n=312 944) [1]

- **Risk for lung cancer**

PM10: HR 1.22 [95% CI 1.03–1.45] per 10 μg/m³

PM2.5: HR 1.18 (0.96–1.46) per 5 μg/m³

Nox: HR 1.01 [0.95–1.07] per 20 μg/m³

- **Adenocarcinomas of the lung**

PM10: HR 1.51 (1·10–2·08)

PM2.5: HR 1.55 (1·05–2·29)

- **↑ in road traffic** of 4000 vehicle-km per day within 100 m of the residence

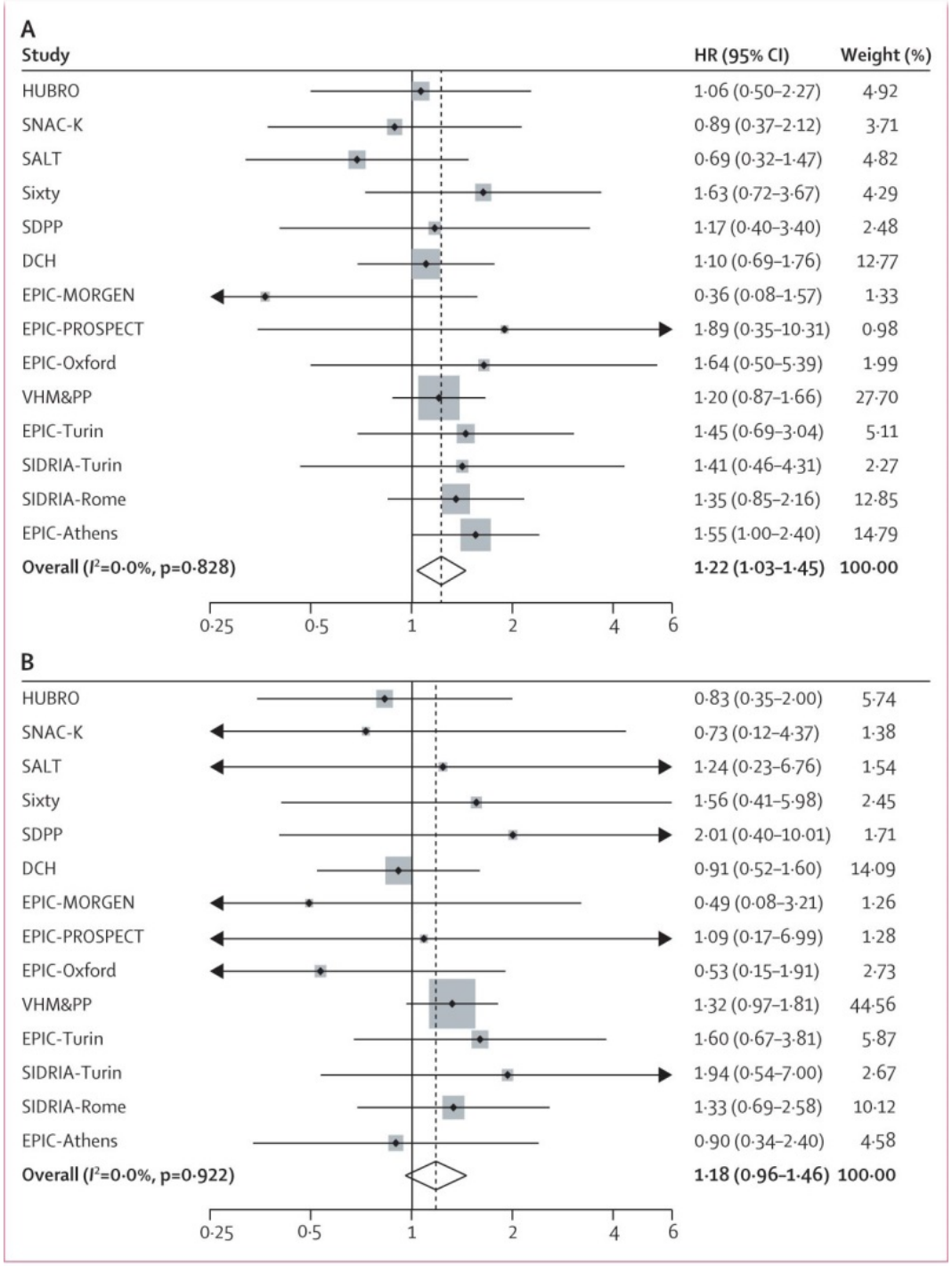
HR for lung cancer 1.09 (0.99–1.21).

European Study of Cohorts [1]

Hazard ratio (HR) for lung cancer according to PM10 concentration (A)

HR for lung cancer according to PM2·5 concentration (B)

Data points show HR; lines show 95% CI; boxes show the weight with which each cohort contributed to the overall HR; vertical dashed line shows overall HR.



Cancer Prevention II study, American Cancer Society, (500 000 out of 1.2 million) [2]

- Fine particulate (PM2.5) and sulfur oxide (SO2)-related pollution were associated with all-cause, lung cancer, mortality.
- Each 10 μg/m³ ↑ in PM2.5 → ~ 8% ↑ risk of all-cause, lung cancer mortality
- Coarse particle fraction and total suspended particles were not consistently associated with mortality.

Cancer Prevention Study II (American Cancer Society) [3]

- RRs against estimated daily dose of PM2.5
- Risk ↑ **linearly**, reaching maximum RRs > 40 among long-term heavy smokers for lung cancer mortality

Cancer Prevention Study–II by ACS (188,699 lifelong never-smokers) [4]

- Each 10 mg/m3 ↑ in PM2.5 → 15–27% ↑ in lung cancer mortality.
- The association between PM2.5 and lung cancer mortality was similar in men and women and across categories of attained age and educational attainment, but was **stronger** in those with a normal body mass index and a history of **chronic lung disease at enrollment** (P = 0.05)

Meta-analysis 21 cohort studies [5]

The risk of lung cancer mortality or morbidity

- 7.23 (95% CI: 1.48–13.31)% /10 μg/m3 ↑ PM2.5
- 13.17 (95% CI: 5.57–21.30)%/10 ppb ↑ NO2
- 0.81 (95% CI: 0.14–1.49)% 10 ppb ↑ NOx
- 14.76 (95% CI: 1.04–30.34)%/10 ppb ↑ SO2

The association of fine particles with lung cancer was suggestively stronger among never smokers

- RR per each 10 μg/m3=1.18, 95% CI: 1.06–1.32.

Null association for carbon monoxide and ozone.

Carcinogenicity of outdoor air pollution

- Evidence from many studies [1, 2,3, 5].
- Increased risk was also seen in studies restricted to never smokers [4,5].
- Occurrence of cancer in animals exposed to outdoor air pollution [6].
- Changes in the expression of genes involved in DNA damage and repair, inflammation, immune and oxidative stress response, as well as altered telomere length and epigenetic effects such as DNA methylation [7]

IARC Working Group [6]

- The IARC unanimously classified outdoor air pollution and particulate matter from outdoor air pollution as carcinogenic to humans (IARC Group 1).
- Particularly, an increased risk of lung cancer
- limited epidemiological evidence for bladder cancer (occupational and residential exposure)

Canadian multi-site population-based case– control study [7]

- Positive associations between incident breast cancer and all three measures of NO2 exposure from 1975 to 1994. (1) satellite-derived observations; (2) satellite derived observations scaled with historical fixed-site measurements of NO2; and (3) a national land-use regression (LUR) model.
- 10 ppb increase in NO2 exposure ORs of 1.26 (95% CIs: 0.92–1.74), 1.32 (95% CI: 1.05–1.67) and 1.28 (95% CI: 0.92–1.79).
- For postmenopausal breast cancer, ORs of 1.10 (95% CI: 0.88–1.36), 1.10 (95% CI: 0.94–1.28) and 1.07 (95% CI: 0.86–1.32).
- Some support for association of traffic-related air pollution and breast cancer, especially in premenopausal women.

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- **6.** Loomis D, Grosse Y, Lauby-Secretan B, Ghissassi FE, Bouvard V, Benbrahim-Tallaa L, et al. The carcinogenicity of outdoor air pollution. The Lancet Oncology. 2013;14(13):1262-3.
- **7.** DeMarini DM. Genotoxicity biomarkers associated with exposure to traffic and near-road atmospheres: a review. Mutagenesis. 2013;28(5):485-505.

Do GMO's cause cancer ? The challenges investigating the association.

Mariana Usatii, PGY1

Pathology, McGill

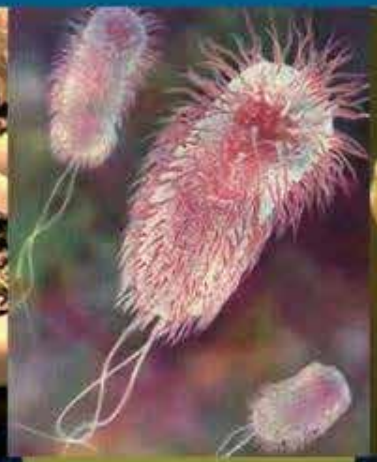
How "RoundUp Ready" GMO Corn is Made:

GENETIC ENGINEERING IS COMPLETELY DIFFERENT FROM TRADITIONAL BREEDING & CARRIES UNIQUE RISKS

Corn

\+ DNA

from soil bacteria that is naturally resistant to RoundUp herbicide



\+ e.coli

gaps are created in e.coli DNA & are recombined with RoundUp resistant bacteria

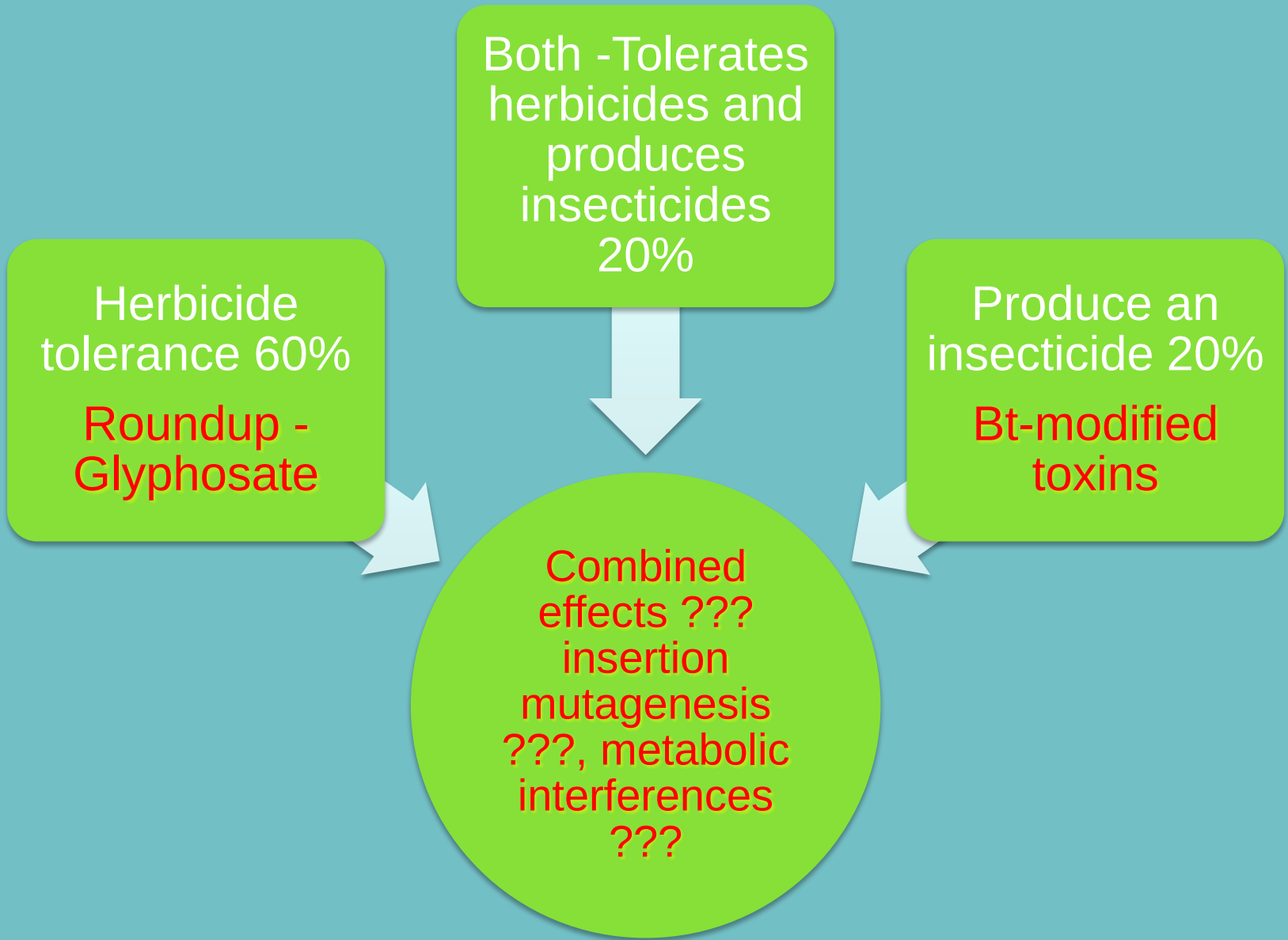
\+ bacteria

that causes tumors in plants are used to breach the cell wall

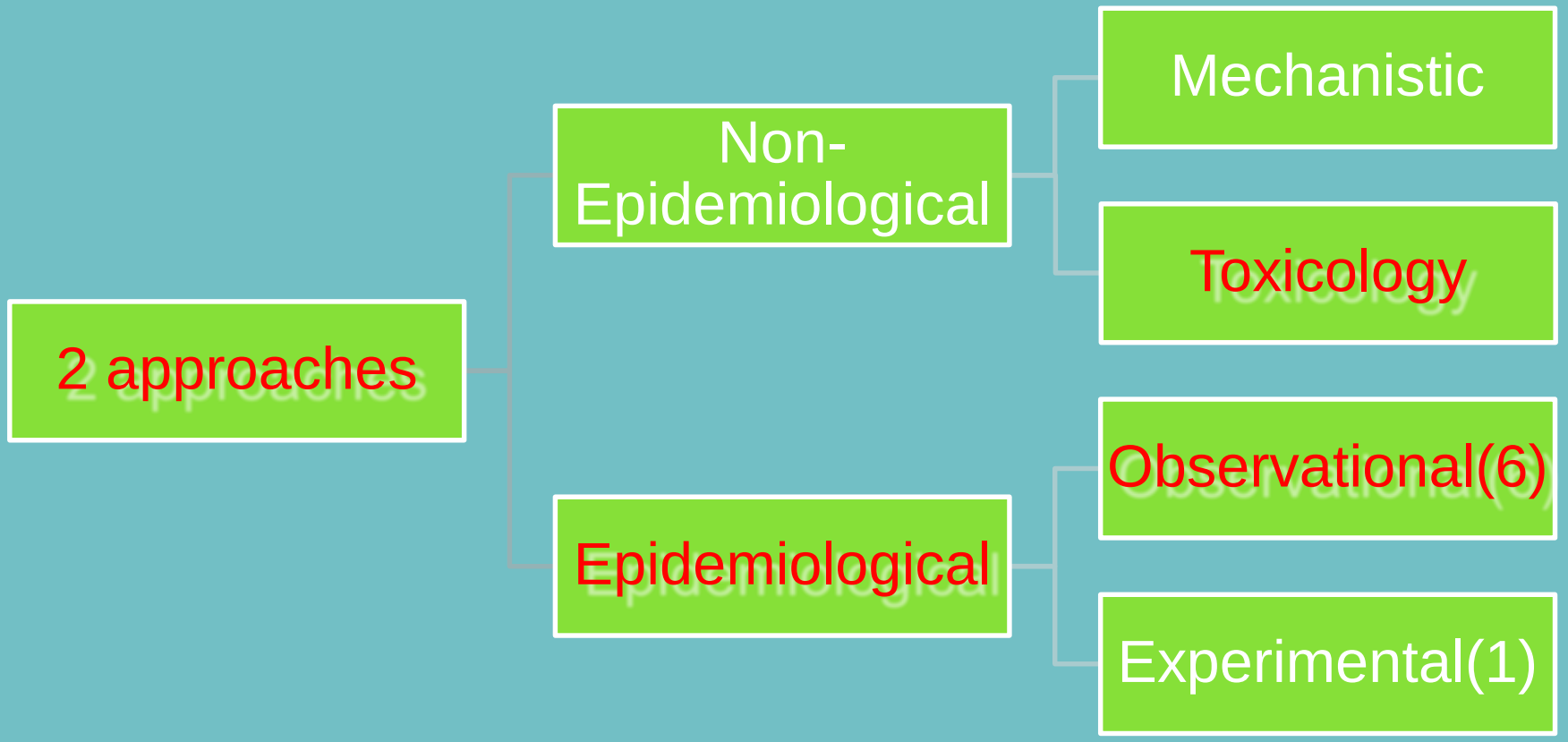
Monsanto

GMOINSIDE.org
Coalition Powered by Green America

Agricultural GMO's 1995-2010



How do we discover carcinogens ?



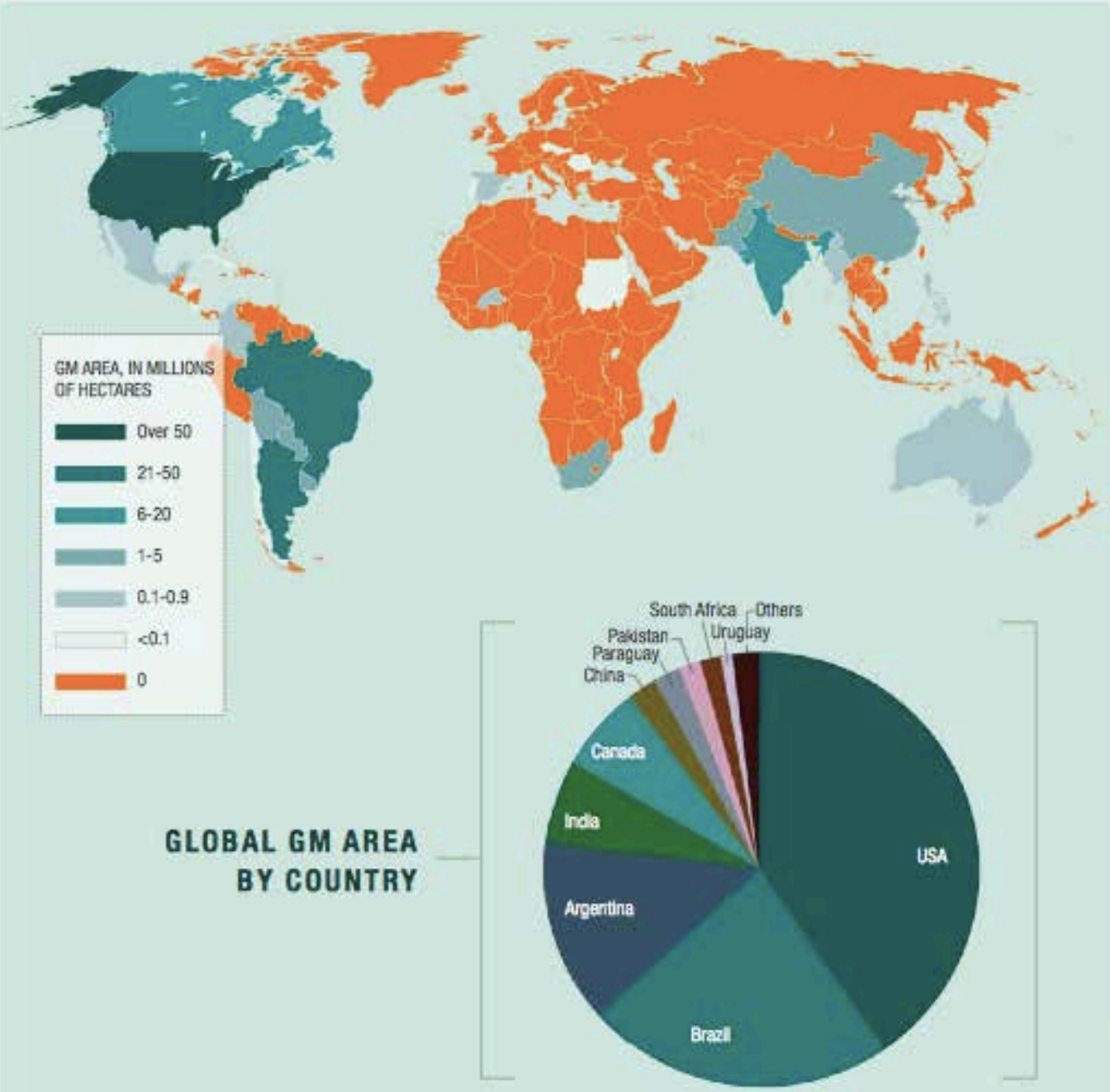
Mechanisms of carcinogenesis for diet

- Direct ingestion of carcinogens
- Carcinogens formed in the body
  - Altered bacterial flora (fecopectins)
- Transport of carcinogens
- Promotion (vitamin deficiency)
- Storage of carcinogens (fat)

Observational studies

- Non-inferential, descriptive (case reports)
- Population based
  - Surveillance (documentation of baseline)
  - Ecologic studies
    - Coarse verification of correlation between exposure and disease burden.
- Individual studies - do not fit the situation
    - Cross-sectional, Case-control, Cohort

Who is exposed ?
To What, since When and Where ?


GM AREA, IN MILLIONS OF HECTARES
Over 50
21-50
6-20
1-5
0.1-0.9
<0.1
0
GLOBAL GM AREA BY COUNTRY
South Africa
Others
Uruguay
Pakistan
Paraguay
China
Canada
India
USA
Argentina
Brazil

Ecologic studies

- METHODOLOGIC PROBLEMS
  - Ecologic Bias
    - Within-group bias
    - Confounding by group
    - Effect modification by group
  - Problems of Confounder Control
  - Within-Group Misclassification
  - Other Problems
    - LACK OF ADEQUATE DATA
    - TEMPORAL AMBIGUITY
    - COLLINEARITY
    - MIGRATION ACROSS GROUPS

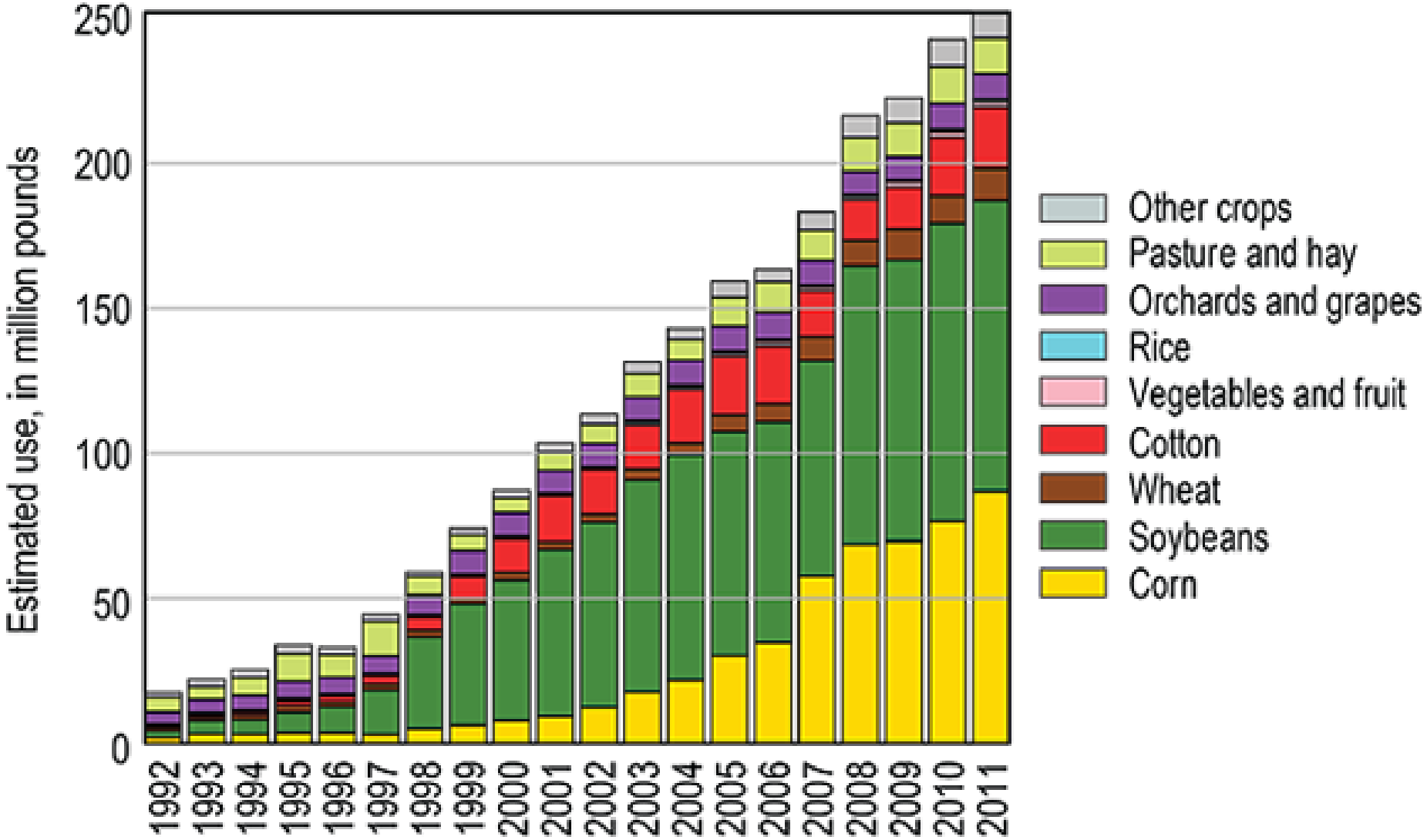
Criteria to Establish Causality

- Most important
  - Experimental evidence
  - Strength of association
  - Consistency
  - Biologic gradient
- Least important
  - Coherence, Plausibility, Analogy, Specificity

» Hill, 1965


Glyphosate use by year and crop (Next slide)

Glyphosate Use by Year and Crop



Source: U.S. Geological Survey, National Water Quality Assessment Program,
Pesticides in U.S. Streams and Rivers: Occurrence and Trends during 1992-2011
http://water.usgs.gov/nawqa/pnsp/pubs/pest-streams/

USGS
science for a changing world

Evidence of carcinogenicity

- De Roos AJ, Zahm SH, Cantor KP, et al. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med* 2003; 60: E11.
- WHO/FAO. Glyphosate. Pesticides residues in food 2004 Joint FAO/WHO Meeting on Pesticides Residues. Part II Toxicological. IPCS/WHO 2004; 95–162. http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/(accessed March 6, 2015).
- Bolognesi C, Carrasquilla G, Volpi S, Solomon KR, Marshall EJ. Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: association to occupational exposure to glyphosate. *J Toxicol Environ Health A* 2009; 72: 986–97.

Evaluation of carcinogenicity (IARC vol. 112, WHO)

- ***Glyphosate is in Group 2A category.***
- ***Group 2A:*** *exposure circumstance is probably carcinogenic to humans (N=66)*
  - Limited evidence in humans but sufficient in experimental animals.
  - Inadequate evidence in humans but sufficient in experimental animals and strong evidence that in exposed humans the agent acts through a relevant carcinogenic mechanism.

Evaluation of carcinogenicity
(U.S. Environmental Protection Agency)

- ***Group A:*** *Human carcinogens*
  - Sufficient evidence from epidemiologic studies
  - There is virtually no epidemiologic evidence regarding GMO carcinogenicity and it's practically impossible to obtain with currently applicable methods.

Conclusion

- At this moment there is no clear cut answer if GMO's will directly hurt us.
  - High quality animal studies are missing
  - Epidemiological studies remain challenging
  - Accurate labeling of GMO's is imperative.
- There is an important concern that the increased use of glyphosate will increase the cancer incidence, particularly in countries where GMO's are cultivated.


•STATE LAW•
GENETICALLY MODIFIED FOOD MUST HAVE LABEL
WOULD BE EASIER TO LABEL THE FEW ITEMS THAT HAVEN'T BEEN MODIFIED!
GMO LIST
GMO
GMO!
DAVE GRANLUND © www.davegranlund.com

ETHAN HAWKE

UMA THURMAN

JUDE LAW

G A T T A C A

There is no gene for the human spirit

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- Hill, 1965
- IARC, WHO, Vol 112
- Hal Morgenstein An.Rev.Pub.Health 1995.
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- CBAN, Can. Biotech. Act. Network, 2015
- Featured image by theGlobal Water Partnership and licensed by Creative Commons.
- Seralini et al, 2010
- The Lancet Oncology, www.thelancet.com/oncology March 20, 2014http://dx.doi.org/10.1016/S1470-2045(15)70134-8


THANK YOU

Does cervical cancer screening meet criteria for a suitable screening program in Canada?

Talía Malagón

EPIB 671 Symposium, March 20th 2016

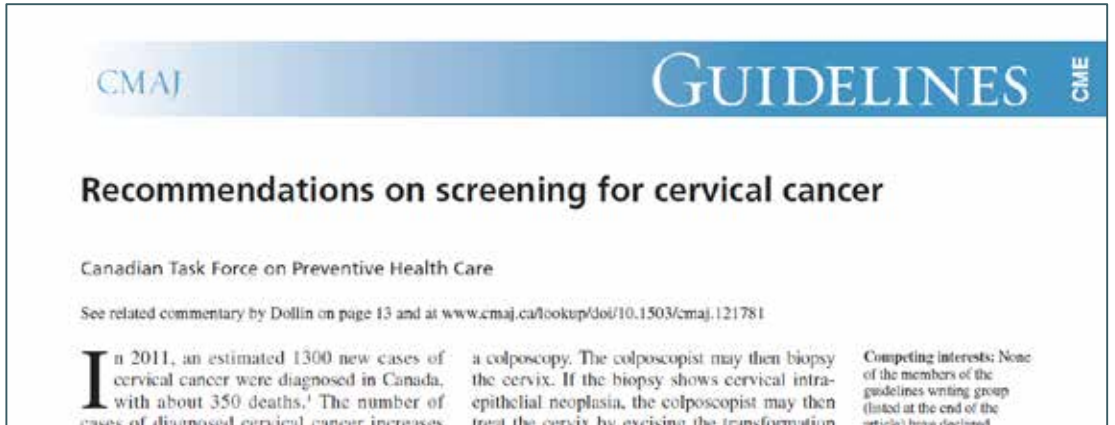
Cervical cancer screening in Canada

§ Started in 1949 in British Columbia.

§ Coverage increased across Canada mostly in 60-70s.

§ In 2013, Canadian Task Force on Preventive Health Care (CTFPHC) updated 1994 recommendations for cervical cancer screening.

§ Do recommendations follow criteria for a screening program?


CMAJ GUIDELINES CME

Recommendations on screening for cervical cancer

Canadian Task Force on Preventive Health Care

See related commentary by Dollin on page 13 and at www.cmaj.ca/lookup/doi/10.1503/cmaj.121781

In 2011, an estimated 1300 new cases of cervical cancer were diagnosed in Canada, with about 350 deaths.[1] The number of

a colposcopy. The colposcopist may then biopsy the cervix. If the biopsy shows cervical intra-epithelial neoplasia, the colposcopist may then

Competing interests: None of the members of the guidelines writing group (listed at the end of the

CMAJ. 2013 Jan 8;185(1):35-45.

What to consider when evaluating a screening program?

§ Wilson and Jungner criteria (1968):

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding should be economically balanced in relation to possible expenditure on medical care.
10. Case-finding should be a continuing process and not a "once and for all" project.

§ Additional criteria proposed (WHO 2008) (subset):

1. There should be scientific evidence of screening programme effectiveness.
2. The programme should ensure informed choice, confidentiality and respect for autonomy.
3. The programme should promote equity and access to screening for the entire target population.
4. The overall benefits of screening should outweigh the harm.

1. *Wilson, Jungner. WHO 1968. 2. Andermann et al. WHO 2008.*

What to consider when evaluating a screening program?

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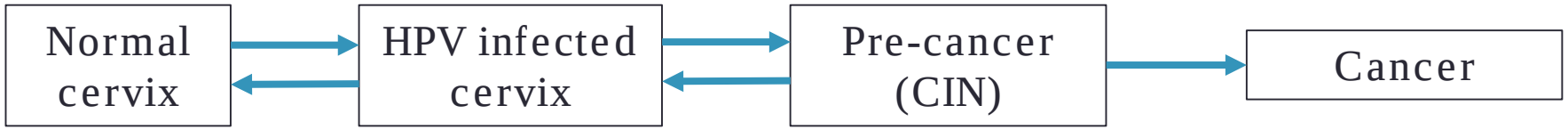
1. *Wilson, Jungner. WHO 1968. 2. Andermann et al. WHO 2008.*

Natural history of disease

§ The natural history of the condition should be adequately understood. þ



- § Not explicitly discussed in 2013 guidelines.
- § 1994 guidelines: cervical cancer "*possibly*" associated with HPV infection and there were "*uncertainties concerning the progression of dysplasia to invasive cancer*".[1]

§ There should be a recognizable latent or early symptomatic stage. þ

- § Persistent HPV infection, CIN

1. *Morrison. Public Health Agency of Canada 1994.*

Screening test/treatment properties

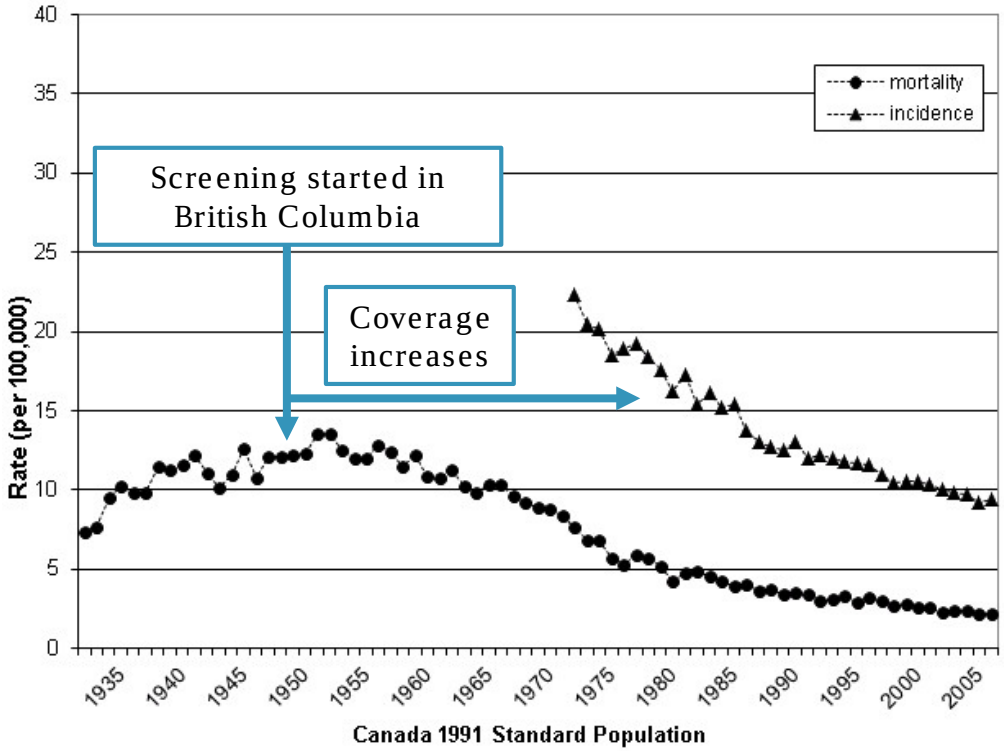
- There should be a suitable test or examination. þ
  - *"Screening for cervical cancer using the Pap test detects precursor lesions." CMAJ 2013*
- There should be an accepted treatment for patients with recognized disease. þ
  - *"The colposcopist may then biopsy the cervix. If the biopsy shows CIN, the colposcopist may treat the cervix by excising the transformation zone." CMAJ 2013*
- The test should be acceptable to the population. þ
  - Not considered in 2013 guidelines.
  - High screening coverage in Canada (72-80%)[1] suggests Pap tests are generally acceptable.

1. *Canadian Partnership Against Cancer 2011*

Importance of health problem + effectiveness

- The condition sought should be an important health problem. (?)
  - *"Lifetime incidence was 1.5% in 1972, and is now 0.7%."* CMAJ 2013
  - 12th most incident female cancer.[1]
- There should be scientific evidence of screening programme effectiveness. þ
  - Systematic review of RTCs and observational studies evaluating screening effectiveness against cancer incidence and mortality.[2]
  - *"The evidence suggests substantial protective effects for screening women 30 years and older."*[2]
  - *"More research is needed on the effectiveness and optimal use of HPV screening." CMAJ 2013*

Age-standardized mortality and incidence of cervical cancer in Canada



Dickinson et al. BMC Public Health 2012, 12:992

1. *Canadian Cancer Statistics 2015. 2. CTFPHC 2013.*

Ethical considerations

- Facilities for diagnosis and treatment should be available. þ
- Case-finding should be a continuing process. þ
- The programme should ensure informed choice, confidentiality and respect for autonomy. (?)
  - *"The potential harms and benefits should be discussed between patient and provider for informed decision-making." CMAJ 2013*
- The programme should promote equity and access to screening for the entire target population. (?)
  - Cervical cancer screening covered by public health care.
  - *"Certain subgroups of women are less likely to receive adequate screening, including immigrant groups, Aboriginal women and women with very low socioeconomic status." CMAJ 2013*

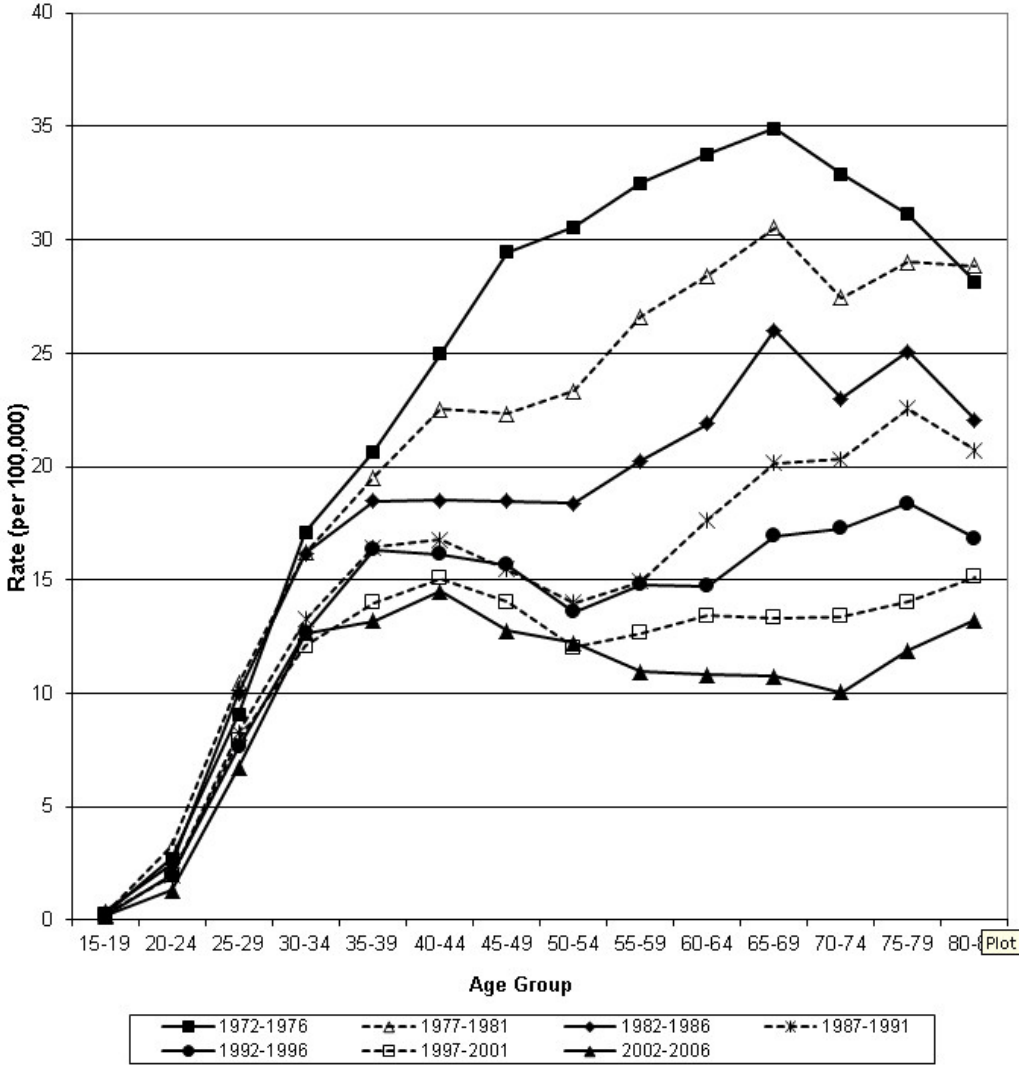
Balance of harms, costs, and benefits

- The cost of case-finding should be economically balanced in relation to possible expenditure on medical care. þ
  - Not a traditional consideration for cervical cancer screening.
  - *"A Canadian economic modelling study suggests that screening with either cytology or HPV testing is highly cost-effective compared with no screening." CMAJ 2013*
- The overall benefits of screening should outweigh the harm. þ
  - *"The benefits of screening must be balanced against its potential harms." CMAJ 2013*

Benefits	Harms
§ Reduced cervical cancer incidence § Reduced cervical cancer mortality	§ Anxiety § Stigmatization § Bleeding, pain from treatment § Overtreatment § Adverse obstetric outcomes (preterm births, underweight births, fetal loss)

Balance of harms and benefits

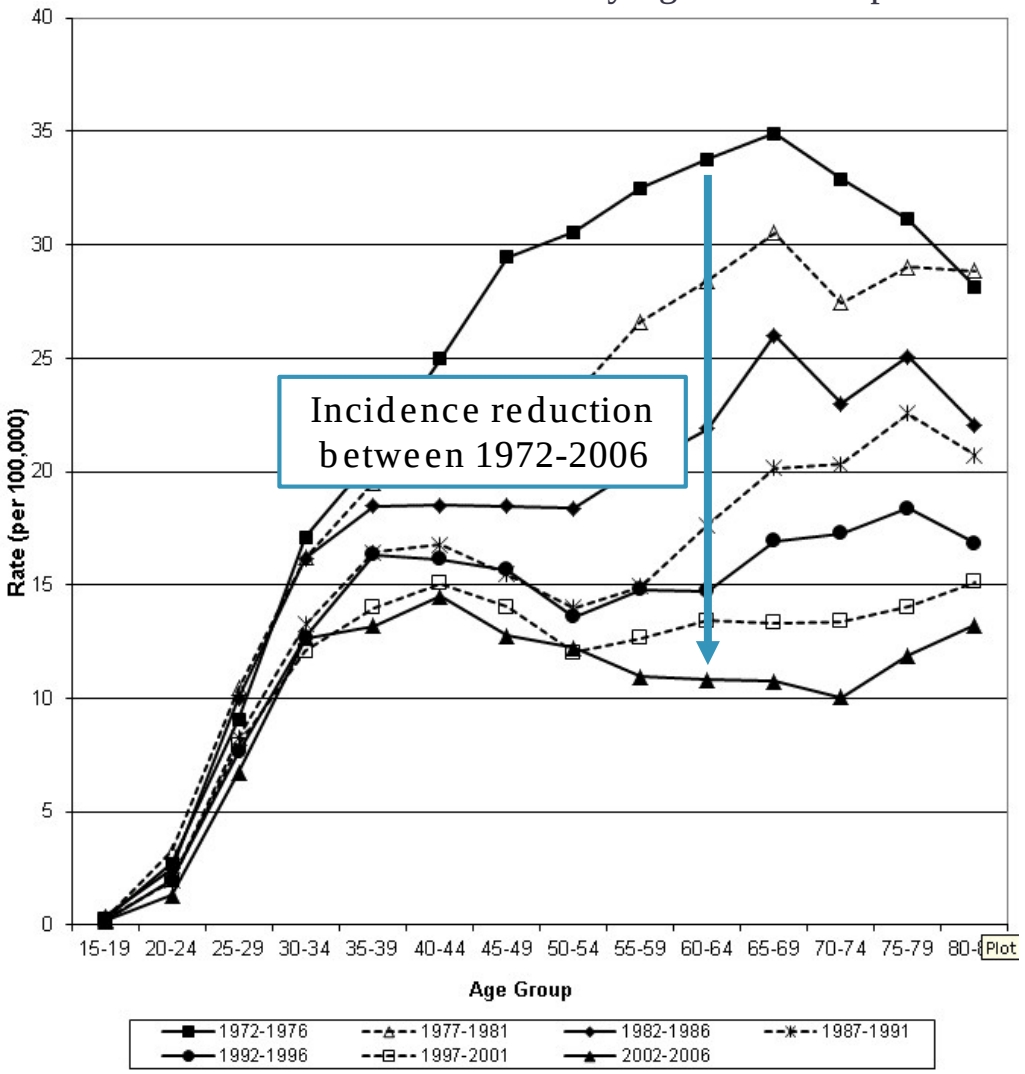
Incidence of cervical cancer by age and time period



Dickinson et al. BMC Public Health 2012, 12:992

Balance of harms and benefits

Incidence of cervical cancer by age and time period

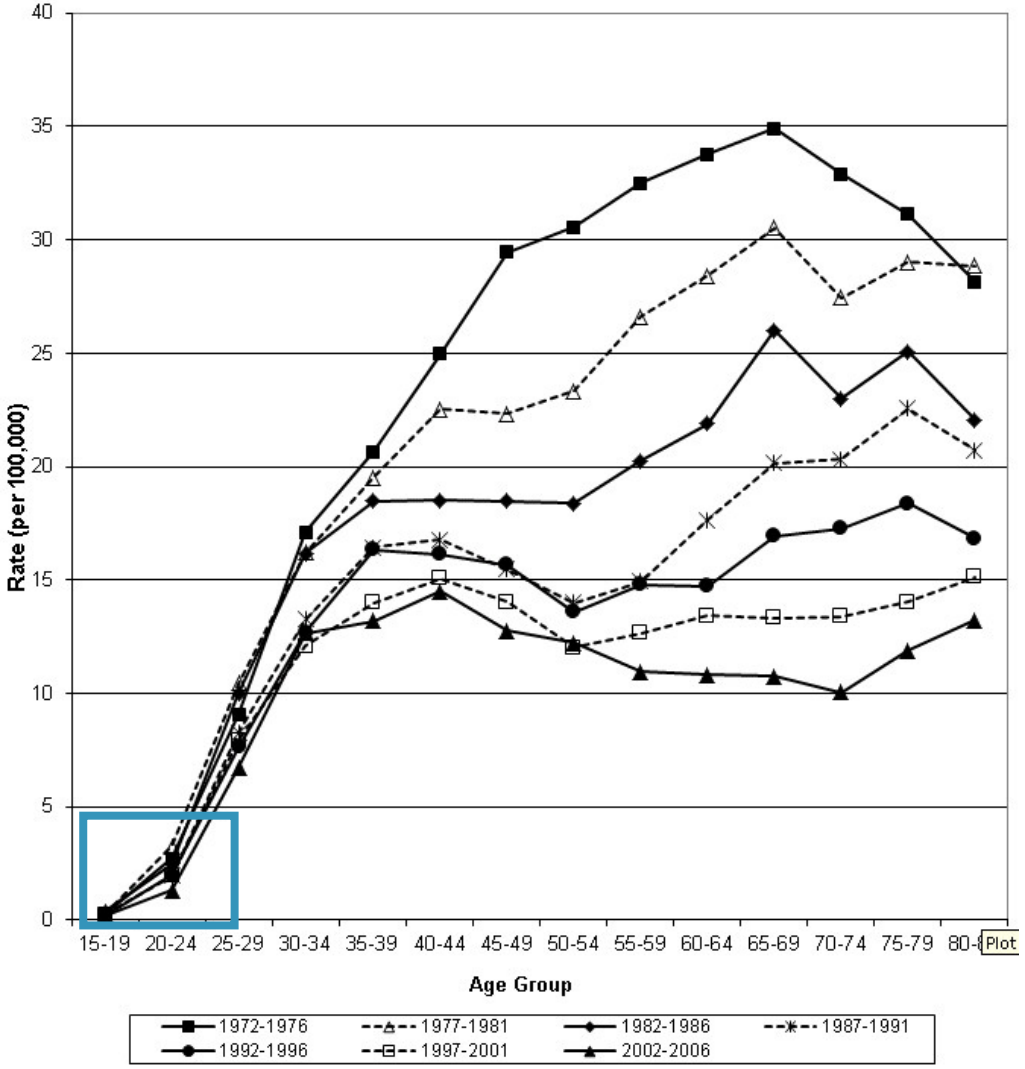


Dickinson et al. BMC Public Health 2012, 12:992

Balance of harms and benefits

- <25 years:
  - *BENEFITS*
    "No reduction in mortality due to cervical cancer among women aged 20–24 years in Canada since the 1970s"
  - *HARMS*
    "High incidence of minor harms and the potential for future early pregnancy loss or premature labour for women in this age group."
  - ***"We conclude that the harms of screening for cervical cancer in women aged 20–24 years outweigh any potential benefits" CMAJ 2013***

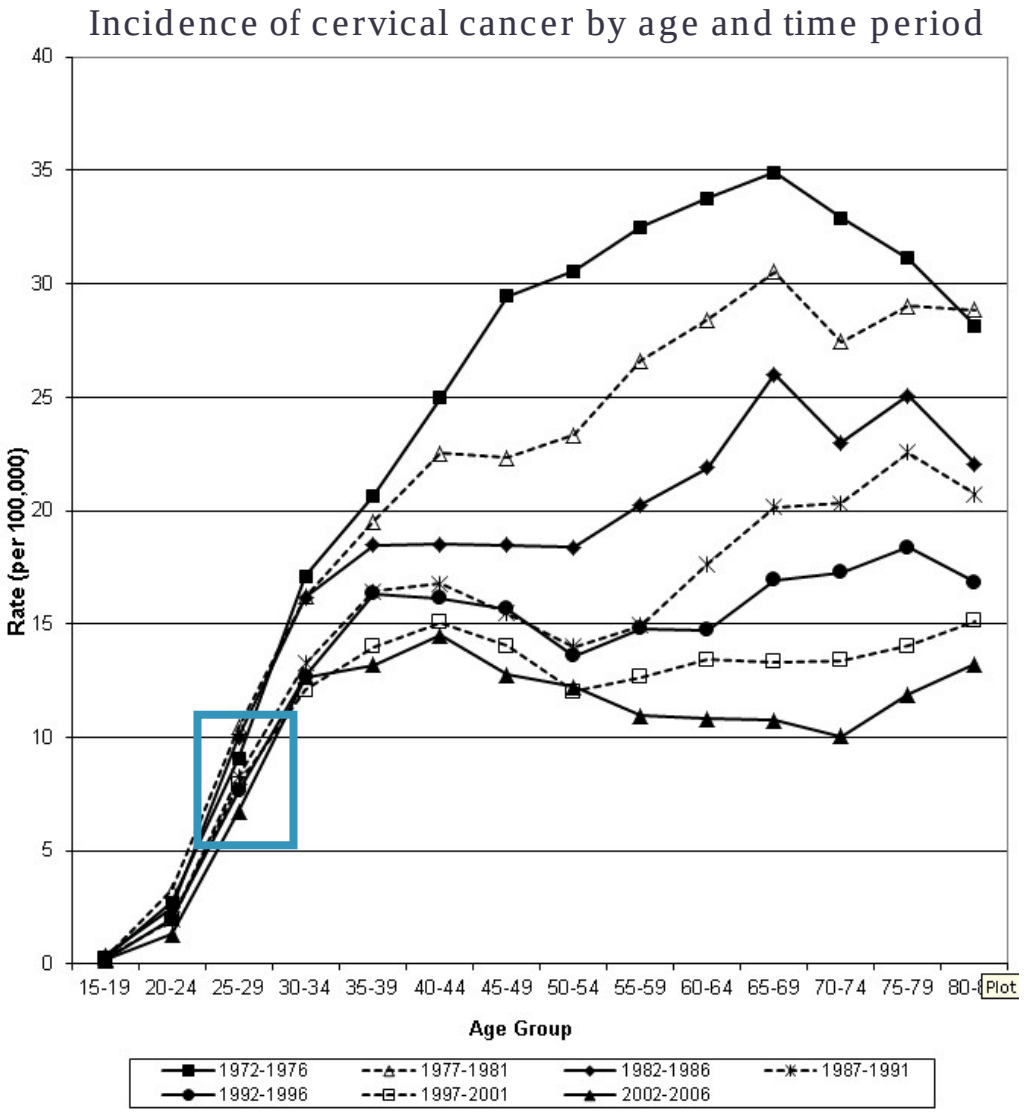
Incidence of cervical cancer by age and time period



Dickinson et al. BMC Public Health 2012, 12:992

Balance of harms and benefits

- 25-29 years:
  - *BENEFITS*
    "Higher incidence and mortality due to cervical cancer in this age group."
  - *HARMS*
    "High incidence of minor harms and the potential for future early pregnancy loss or premature labour for women in this age group."
  - ***"For women aged 25–29 years, we recommend routine screening for cervical cancer every 3 years. We assigned a weak recommendation for this age group, reflecting our concerns about the harms of overtreatment." CMAJ 2013***



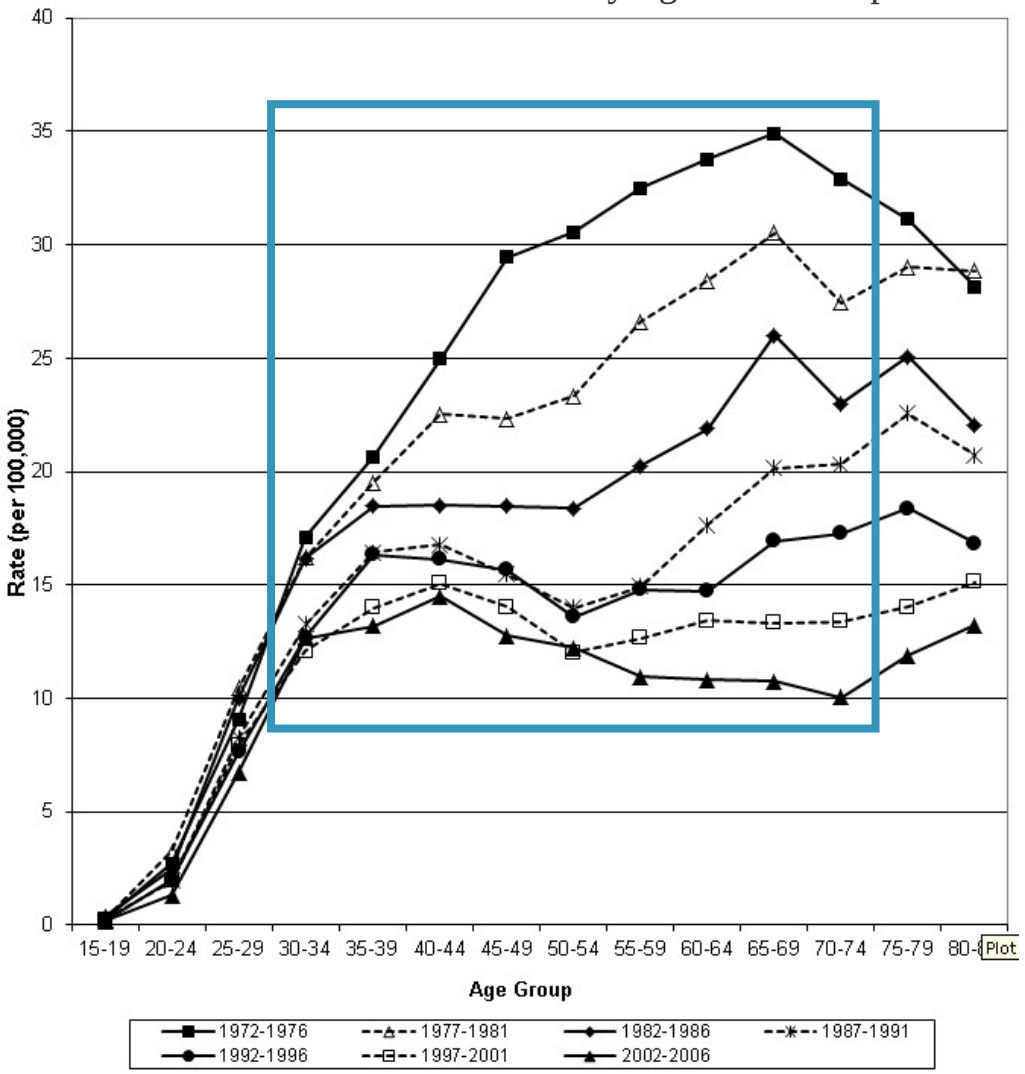
Dickinson et al. BMC Public Health 2012, 12:992

Balance of harms and benefits

§ 30-69 years:

- § *BENEFITS*
  "Screening was associated with a decrease in incidence of cervical cancer."
- § *HARMS*
  "Pregnancy-related harms become less important as women complete their childbearing."
- § ***"The desirable effects of screening outweigh the undesirable effects and most women would be best served by [routine screening for cervical cancer every 3 years]." CMAJ 2013***

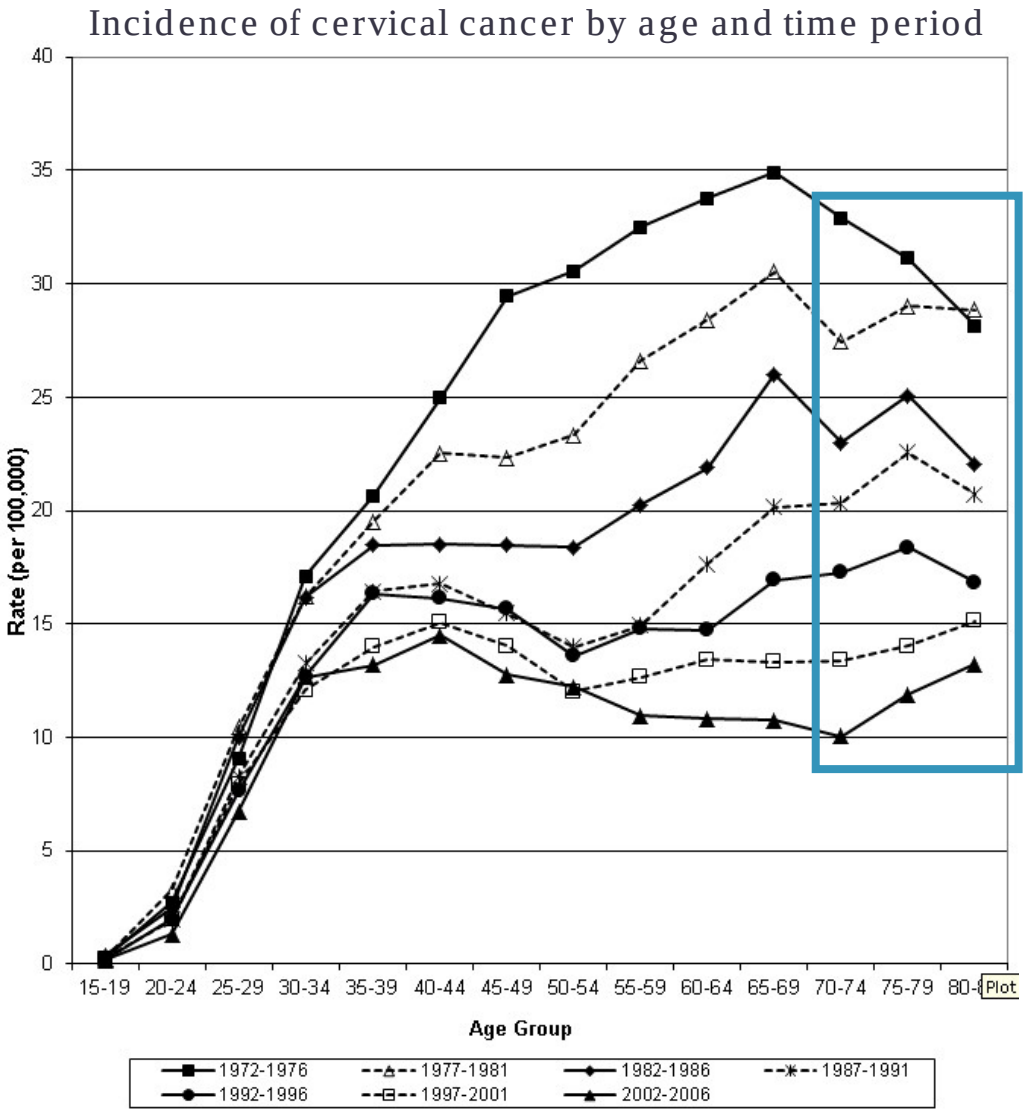
Incidence of cervical cancer by age and time period



Dickinson et al. BMC Public Health 2012, 12:992

Balance of harms and benefits

- >69 years:
  - *BENEFITS*
    "Mortality from cervical cancer in Canada increases with age."
    "There is limited evidence for the benefits of screening in older women."
  - ***"For women aged 70 years and older who have undergone adequate screening, we recommend that routine screening may end" CMAJ 2013***



Dickinson et al. BMC Public Health 2012, 12:992

Conclusion

- Most important considerations in CTFPHC recommendations:
  - Effectiveness
  - Balance of harms/benefits
- Further considerations:
  - Equity of access for underserved populations
  - HPV testing (meets most criteria but was not recommended)
- Criteria which may no longer be met in the future due to HPV vaccination:
  - The condition sought should be an important health problem. ý
  - The cost of case-finding should be economically balanced in relation to possible expenditure on medical care. (?)
  - The overall benefits of screening should outweigh the harm. (?)

OCP& Breast Cancer:What's the Evidence?

Ali Samkari
Surgical Oncology Fellow
McGill University


1 in 9
Canadian women will develop breast cancer
Take Action
Fight Breast Cancer
Canadian Cancer Society
Société canadienne du cancer


4%
OF BREAST CANCERS IN CANADA
OCCURRED IN WOMEN
UNDER THE AGE OF 40
(APPROXIMATELY 1,055 CASES)
40 years
50 years
IN 2013
4%
18%
18%
OF ALL NEW BREAST CANCER CASES
IN CANADA ARE DIAGNOSED
IN WOMEN LESS THAN
50

Age

It's the strongest risk factor for breast cancer, and aging increases your risk.

Genetic alterations

Inherited changes in certain genes (including BRCA and PTEN) affect your risk.

Family history

A breast cancer diagnosis in your mother, sister and/or daughter, especially before age 50.

Dense breast tissue

A high percentage of dense breast tissue can make it more difficult to detect an abnormality on a mammogram.

Reproductive and menstrual history

Having your first menstrual period before age 12, going through menopause after age 55, or having your first full-term pregnancy after age 30 raises your risk.

Body weight

The chance of getting breast cancer is higher for postmenopausal women who are overweight or obese.

Radiation therapy

Undergoing radiation therapy to the chest before age 30 puts you at increased risk.

Menopausal hormonal therapy

Long term combined estrogen and progestin menopausal hormone therapy raises your breast cancer risk.

Alcohol

Drinking alcohol frequently may increase breast cancer risk.

Side Effects of OCPs

1. Bloating, nausea, and breast tenderness.
2. Breakthrough bleeding and amenorrhea.
3. CHD, HTN and stroke.
4. Venous thromboembolic disease.
5. Risk of cancer
6. Liver disorders and pancreatitis
7. Weight gain

BMJ

RESEARCH

Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study

Philip C Hannaford, professor,[1] Sivasubramaniam Selvaraj, research fellow,[2] Alison M Elliott, senior research fellow ,[1] Valerie Angus, data manager,[3] Lisa Iversen, research fellow,[1] Amanda J Lee, professor of medical statistics[1]

- Cohort study
- Statistically significant lower rates of cancers of the large bowel or rectum, uterine body, and ovaries.
- Statistically significant trends of increasing risk of cervical and central nervous system
- Oral contraception was not associated with an overall increased risk of cancer

Articles

Breast cancer and hormone-replacement therapy in the Million Women Study

Million Women Study Collaborators

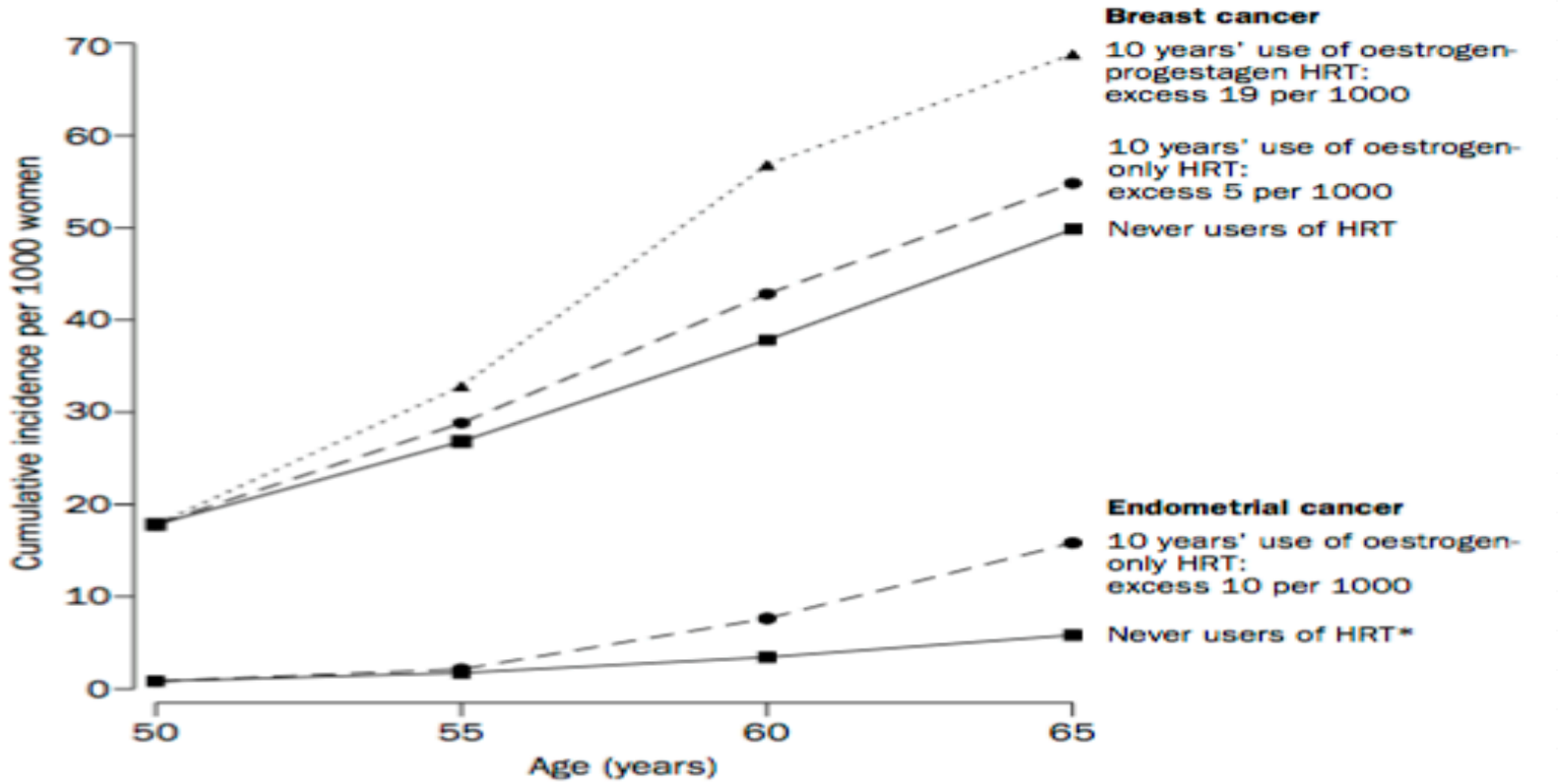


Figure 7: **Estimated cumulative incidence of breast and endometrial cancer per 1000 women in developed countries who never used HRT and who used HRT for 10 years, beginning at age 50 years**

*10 years' use of oestrogen-progestagen HRT estimated to result in little change in culmulative incidence of endometrial cancer.

ELSEVIER

Contraception

Contraception 88 (2013) 678–683

Original research article

Oral contraceptive use and cancer: final report from the Oxford–Family Planning Association contraceptive study

Martin Vessey*, David Yeates

Unit of Health Care Epidemiology, Oxford University, Old Road Campus, Headington, Oxford OX3 7LF UK

Received 30 May 2013; revised 16 August 2013; accepted 22 August 2013

- 17032 women aged 25–39 years recruited from 1968 to 1974
- Breast cancer findings (1087 cases) were entirely negative; the rate ratio (RR) comparing ever users of OCs with never users was 1.0 [95% confidence interval (CI): 0.9–1.1]

Cancer Causes and Control, 1997, 8, pp. 65-72

A prospective study of oral contraceptive use and risk of breast cancer (Nurses' Health Study, United States)

Susan E. Hankinson, Graham A. Colditz, JoAnn E. Manson,
Walter C. Willett, David J. Hunter, Meir J. Stampfer and Frank E. Speizer

Received 2 May 1996; accepted in revised form 4 October 1996)

- 3,383 cases of breast cancer from 1976 to 1992 among 1.6 million person-years of follow-up
- no overall relationship between duration of OC use and breast cancer risk, even among women who reported using OCs for 10 or more years
- The risk associated with five or more years of OC use prior to a first full-term pregnancy compared with never-use was 0.96 (CI=0.65-1.43)

The New England
Journal of Medicine

VOLUME 346 JUNE 27, 2002 NUMBER 26

ORAL CONTRACEPTIVES AND THE RISK OF BREAST CANCER

POLLY A. MARCHBANKS, PH.D., JILL A. MCDONALD, PH.D., HOYT G. WILSON, PH.D., SUZANNE G. FOLGER, PH.D., MICHELE G. MANDEL, B.A., JANET R. DALING, PH.D., LESLIE BERNSTEIN, PH.D., KATHLEEN E. MALONE, PH.D., GISKE URSIN, M.D., PH.D., BRIAN L. STROM, M.D., M.P.H., SANDRA A. NORMAN, PH.D., AND LINDA K. WEISS, PH.D.

- A population-based, case-control study
- 4574 women with breast cancer and 4682 controls
- The relative risks (RRs) of breast cancer for current or previous OC use were 1.0 (95% CI 0.8-1.2) and 0.9 (95% CI 0.8-1.0)
- Breast cancer risk was not associated with estrogen dose, duration of use, initiation at a young age (age <20 years), or race.

Risk of Breast Cancer With Oral Contraceptive Use in Women With a Family History of Breast Cancer

FREE

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JAMA. 2000;284(14):1791-1798. doi:10.1001/jama.284.14.1791.

- Historical cohort study of 426 families of breast cancer probands diagnosed between 1944 and 1952 at the Tumor Clinic of the University of Minnesota Hospital. Follow-up data on families were collected by telephone interview between 1991 and 1996
- The elevated risk among women with a first-degree family history of breast cancer was most evident for OC use during or prior to 1975, when formulations were likely to contain higher dosages of estrogen and progestins (RR, 3.3; 95% CI, 1.5-7.2). A small number of breast cancer cases (n = 2) limited the statistical power to detect risk among women with a first-degree relative with breast cancer and OC use after 1975.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Oral Contraceptives and Risk of Ovarian Cancer and Breast Cancer Among High-Risk Women: A Systematic Review and Meta-Analysis

Patricia G. Moorman, Laura J. Havrilesky, Jennifer M. Gierisch, Remy R. Coeytaux, William J. Lowery, Rachel Peragallo Urrutia, Michaela Dinan, Amanda J. McBroom, Vic Hasselblad, Gillian D. Sanders, and Evan R. Myers

- Eight studies examining breast cancer risk in BRCA1/2 mutation carriers.
- meta-analysis showed a non statistically significant association with breast cancer (OR, 1.21; 95% CI, 0.93 to 1.58), Data were inadequate to perform meta-analyses examining duration or timing of use.
- For women with a family history of breast cancer, three studies were identified. The differences between them precluded combining the data for meta-analyses, and no overall pattern could be discerned.

Conclusion

- Unlike the use of hormone replacement therapy, there is no evidence to support any relation between the use of OCP and breast cancer even in high risk groups

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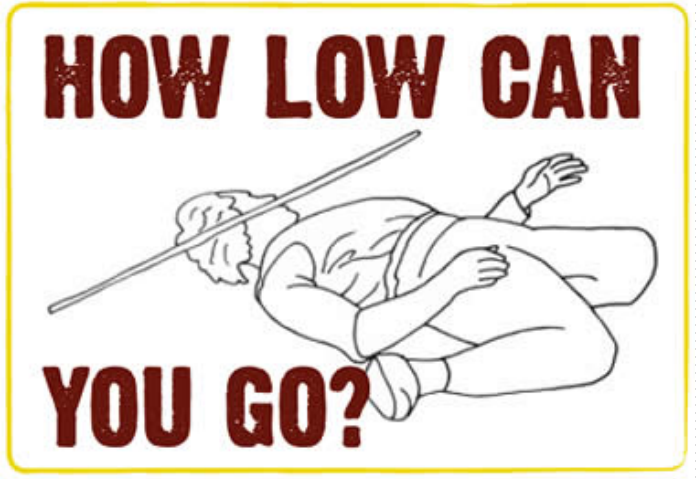
How low can it go?

Arsenic levels in drinking water and bladder cancer



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Arsenic (As)

- Natural metalloid
- Pesticide
- Growth stimulant in animal industry
- Cigarettes
- Strengthening alloys of copper and lead
- Semiconductor
- Pigment

Arsenic and its role in cancer

- Sufficient evidence in humans (group 1) for its role in lung, skin and bladder cancer
- Limited evidence in humans (group 2A/B) in kidney, liver and prostate cancer

IARC monographs on the evaluation of carcinogenic risks to humans volume 100C – Arsenic, metals, fibres, and dusts (2009)

Arsenic in drinking water and bladder cancer

- Dose-response relationship in incidence, with a RR up to 40 with high levels of exposure (up to >1mg/L)
- Incidence RR:
  - 10 µg/L: 1.4 (0.35-4.0) / 2.7 (1.2-4.1)
  - 50 µg/L: 2.3 (0.59-6.4) / 4.2 (2.1-6.3)
  - 150 µg/L: 3.1 (0.80-8.9) / 5.8 (2.9-8.7)
- Mortality SMR:
  - 10 µg/L: 1.0 (0.15-38)
  - 50 µg/L: 1.7 (0.49-40)
  - 150 µg/L: 2.2 (0.54-41)

IARC monographs on the evaluation of carcinogenic risks to humans volume 100C – Arsenic, metals, fibres, and dusts (2009); Saint-Jacques et al., Environ Health, 2014 Jun 2:13:44, PMID 24889821

Arsenic in drinking water - guidelines

- Canada/EU: 10 µg/L
- WHO guideline: 10 µg/L

- WHO/JECFA 2010:
  - >50 µg/L: some evidence of adverse effects
  - 10-50 µg/L: possibility of adverse effects
  - <10 µg/L: adverse effects too low to measure in epidemiology studies

WHO Factsheet Arsenic (Dec 2012), http://www.who.int/mediacentre/factsheets/fs372/en/; Government of Canada Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Arsenic (Jan 2008), http://healthycanadians.gc.ca/publications/healthy-living-vie-saine/water-arsenic-eau/index-eng.php?page=3#a2

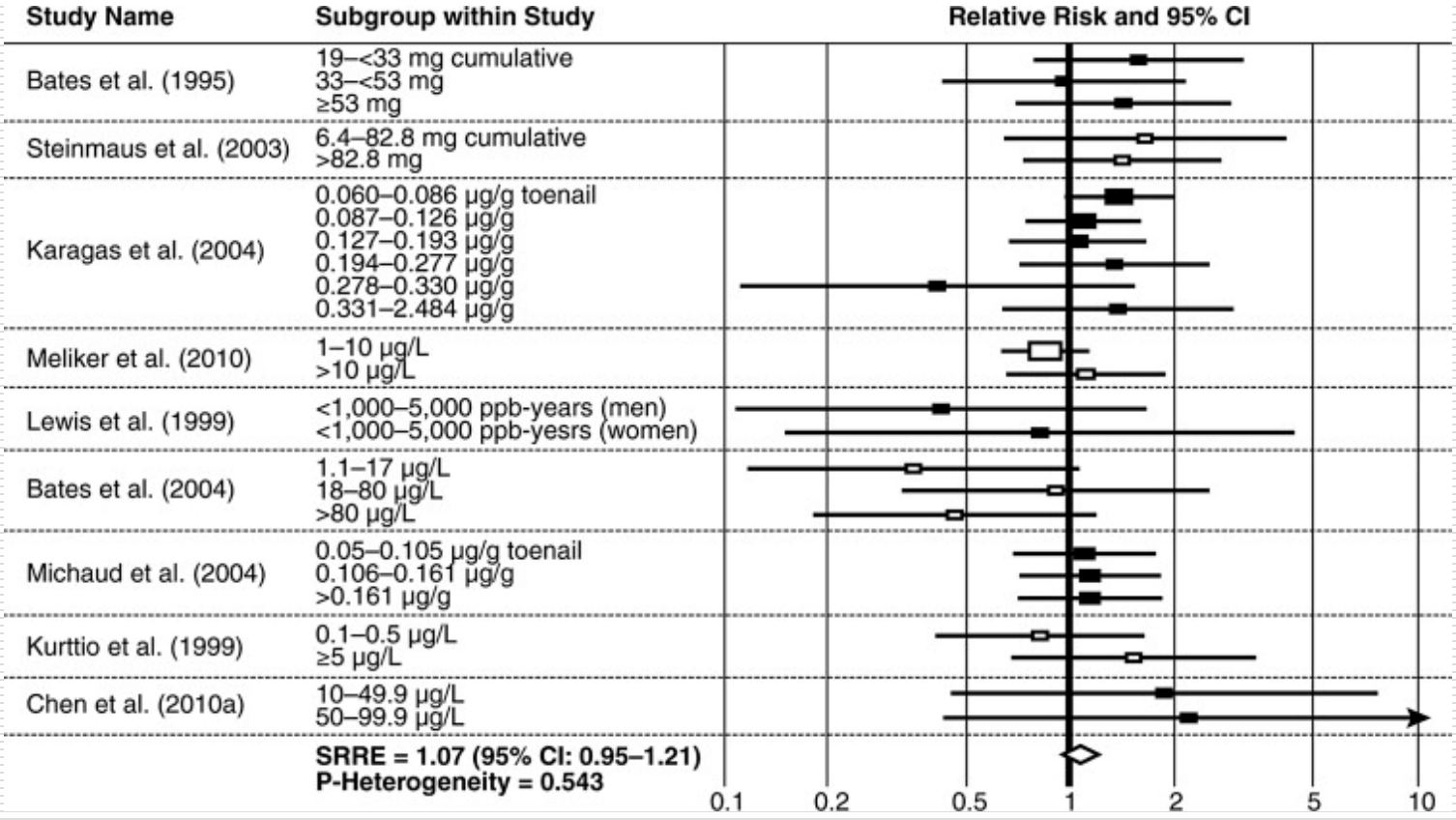
Low-level arsenic exposure and bladder cancer – meta-analysis (1)

- Inclusion criteria:
  - Case-control or cohort studies
  - Water-arsenic concentration **<100µg/L** or biomarkers that would be within the low-level range
  - Available RR and measures of variability
  - Analysis of varying levels of arsenic exposure and bladder cancer
  - Control for smoking (if needed)
  - Nutritionally sufficient regions
- 9 studies included

Tsuji et al., Toxicology, 2014 Mar 20:317:17-30, PMID 24462659

Low-level arsenic exposure and bladder cancer – meta-analysis (2)

Referent population: lowest arsenic dose category



Tsuji et al., Toxicology, 2014 Mar 20:317:17-30, PMID 24462659

Low-level arsenic exposure and bladder cancer – meta-analysis (3)

Table 3
Summary of meta-analysis findings.

Type of analysis	Analysis characteristics	All study participants	Never smokers[a,b]	Ever smokers[a,c]
All studies[1–9]	SRRE (95% CI)	1.07 (0.95–1.21)	0.85 (0.66–1.08)	1.18 (0.97–1.44)
	p-Value for heterogeneity	0.543	0.915	0.034
	Number of studies in analysis	9	7	7
Incident cases only[1–4,6,7,9]	SRRE (95% CI)	1.08 (0.96–1.22)	0.86 (0.66–1.13)	1.16 (0.96–1.41)
	p-Value for heterogeneity	0.500	0.799	0.047
	Number of studies in analysis	7	5	6
Water exposure studies[1,2,4–6,8,9]	SRRE (95% CI)	1.01 (0.82–1.03)	0.81 (0.60–1.08)	1.21 (0.80–1.84)
	p-Value for heterogeneity	0.327	0.836	0.009
	Number of studies in analysis	7	6	5
Cumulative exposure[1,2,8]	SRRE (95% CI)	1.10 (0.81–1.49)	0.79 (0.49–1.30)	2.35 (1.51–3.66)
	p-Value for heterogeneity	0.301	0.776	0.786
	Number of studies in analysis	3	3	3
United States studies[1–5]	SRRE (95% CI)	1.09 (0.95–1.26)	0.87 (0.66–1.14)	1.31 (1.05–1.65)
	p-Value for heterogeneity	0.562	0.782	0.119
	Number of studies in analysis	5	5	4

Note: SRRE – summary relative risk estimate; $p \leq 0.10$ considered to indicate heterogeneity; (1) Bates et al. (1995), (2) Steinmaus et al. (2003), (3) Karagas et al. (2004), (4) Meliker et al. (2010), (5) Lewis et al. (1999), (6) Bates et al. (2004), (7) Michaud et al. (2004), (8) Kurttio et al. (1999) and (9) Chen et al. (2010a).

[a] Excluding Chen et al. (2010a); adjusted for smoking but did not stratify by smoking status.

[b] Excluding Michaud et al. (2004); all participants were smokers.

[c] Excluding Lewis et al. (1999); participants were largely non-smokers.

Tsuji et al., Toxicology, 2014 Mar 20:317:17-30, PMID 24462659

Increased levels of arsenic in bladder cancer patients – case-control

- Cases: 124 male bladder cancer patients
- Controls: 220 male controls
- Median arsenic concentration in blood in cases is higher than in controls (0.48 vs 1.44 µg/L, p<0.02)

Table 4 Logistic regression per median groups of metal exposure for bladder cancer risk and potential confounding variables

Exposure variables	Median groups			
	1	*p* value	2	*p* value
Blood As (µg/L)	0.15–0.70		0.70–167.00	
N (cases/controls)	37/104		49/92	
As	0.18 (0.01–2.95)	0.232	2.44 (1.11–5.35)	0.026
Age	2.14 (0.93–4.92)	0.074	1.24 (0.57–2.67)	0.586
Smoking	2.77 (1.62–4.75)	<0.001	2.27 (1.37–3.75)	0.001

The following variables were entered into the model: age (0: <66 years old; 1: >66 years old); smoking (0: never; 1: former; 2: current smoker); building dust exposure (0: no; 1; yes); rainwater consumption (1: yes; 0: no)

Feki-Tounsi et al., Environ Sci Pollut Res Int, 2013 Jun,20(6):3923-31, PMID 23184132

Low-level arsenic in drinking water and bladder cancer – Baris et al. (1)

- Bladder cancer incidence is about 20% higher in New England, cause is unknown
- 1079 histologically confirmed bladder carcinoma patients (incl. CiS):
  - Diagnosed 2001-2004
  - Age 30-79
  - White race
  - Known information on arsenic exposure
- 1287 randomly selected control patients, matched by state, sex, age at diagnosis, race

Baris et al., JNCI, 2016 May 2, 108(9), PMID 27140955

Low-level arsenic in drinking water and bladder cancer – Baris et al. (2)

- Interview:
  - Ancestry, smoking, occupation, use of wood-burning stoves, shellfish & bracken fern intake
  - Average water intake during lifetime
  - Wells used
- Arsenic levels in wells (modelled)
- ORs adjusted for age, sex, Hispanic ethnicity, state of residence, smoking, education, high-risk occupation and exposure to THM

Baris et al., JNCI, 2016 May 2, 108(9), PMID 27140955

Low-level arsenic in drinking water and bladder cancer – Baris et al. (3)

Risk factor	Case patients†	Control subjects†	OR (95% CI)
Smoking status§			
Never smoker	171	444	1.00 (Referent)
Occasional smoker	21	39	1.46 (0.82 to 2.60)
Former smoker	578	664	2.22 (1.79 to 2.77)
Current smoker	352	186	5.20 (4.00 to 6.75)
High-risk occupation‖			
Never	276	456	1.00 (Referent)
Ever	837	869	1.50 (1.24 to 1.82)

Baris et al., JNCI, 2016 May 2, 108(9), PMID 27140955

Low-level arsenic in drinking water and bladder cancer – Baris et al. (4)

Drinking water intake from all sources, L/d†	Case patients	Control subjects	OR (95% CI)	Case patients	Control subjects	OR (95% CI)
	Overall					
≤1.1	226	327	1.00 (Referent)			
>1.1–1.5	246	328	1.07 (0.83 to 1.38)			
>1.5–2.2	282	325	1.17 (0.91 to 1.50)			
>2.2–3.8	243	254	1.22 (0.94 to 1.59)			
>3.8	82	53	1.86 (1.23 to 2.81)			
			P_{trend}‡ = .003			
	Never-used private well			Ever-used private well§		
≤1.1	61	62	1.00 (Referent)	165	265	1.00 (Referent)
>1.1–1.5	68	82	0.85 (0.50 to 1.43)	178	246	1.15 (0.85 to 1.54)
>1.5–2.2	65	92	0.70 (0.42 to 1.17)	217	233	1.38 (1.03 to 1.84)
>2.2–3.8	63	48	1.16 (0.66 to 2.03)	180	206	1.25 (0.93 to 1.69)
>3.8	17	9	1.94 (0.76 to 4.98)	65	44	1.84 (1.15 to 2.93)
			P_{trend}‡ = .13			P_{trend}‡ = .01
						$P_{heterogeneity}$ = .71
	Ever-used drilled well and never-used dug well§			Ever-used dug well and never-used drilled well§		
≤1.1	89	144	1.00 (Referent)	21	34	1.00 (Referent)
>1.1–1.5	86	105	1.25 (0.82 to 1.90)	15	38	0.58 (0.22 to 1.48)
>1.5–2.2	108	117	1.42 (0.95 to 2.13)	19	24	1.01 (0.40 to 2.59)
>2.2–3.8	69	110	0.85 (0.55 to 1.31)	33	18	2.28 (0.91 to 5.71)
>3.8	29	16	2.03 (0.96 to 4.30)	12	5	4.01 (1.06 to 15.14)
			P_{trend}‡ = .48			P_{trend}‡ = .002
						$P_{heterogeneity}$ = .01

Baris et al., JNCI, 2016 May 2, 108(9), PMID 27140955

Low-level arsenic in drinking water and bladder cancer – Baris et al. (5)

Unlagged				Lagged 40 y			
Arsenic exposure	Case patients	Control subjects	OR (95% CI)	Arsenic exposure	Case patients	Control subjects	OR (95% CI)
Average arsenic concentration, μg/L†				Average arsenic concentration, μg/L†			
≤0.5	303	325	1.00 (Referent)	≤0.4	280	314	1.00 (Referent)
>0.5–1.0	226	318	0.77 (0.60 to 0.98)	>0.4–0.7	260	309	0.91 (0.71 to 1.17)
>1.0–2.1	281	323	0.97 (0.76 to 1.24)	>0.7–1.6	233	304	0.93 (0.72 to 1.20)
>2.1–7.0	225	259	0.98 (0.74 to 1.28)	>1.6–5.7	220	248	1.06 (0.81 to 1.40)
>7.0–10.4	18	30	0.64 (0.33 to 1.23)	>5.7–8.7	26	33	0.92 (0.51 to 1.66)
>10.4	26	32	1.10 (0.61 to 2.00)	>8.7	37	29	1.49 (0.85 to 2.61)
			P_{trend}‡ = .82				P_{trend}‡ = .16
Average daily arsenic intake, μg/d†				Average daily arsenic intake, μg/d†			
≤0.7	244	327	1.00 (Referent)	≤0.5	250	315	1.00 (Referent)
>0.7–1.6	270	323	1.05 (0.82 to 1.35)	>0.5–1.0	250	311	0.98 (0.76 to 1.27)
>1.6–3.6	292	324	1.16 (0.91 to 1.49)	>1.0–2.5	266	309	1.15 (0.89 to 1.48)
>3.6–13.2	213	251	1.16 (0.88 to 1.52)	>2.5–8.5	210	243	1.16 (0.88 to 1.53)
>13.2–19.8	28	33	0.95 (0.53 to 1.69)	>8.5–13.5	37	30	1.69 (0.96 to 2.96)
>19.8	32	29	1.53 (0.86 to 2.74)	>13.5	43	29	1.81 (1.05 to 3.12)
			P_{trend}‡ = .28				P_{trend}‡ = .01
Cumulative arsenic intake, mg†				Cumulative arsenic intake, mg†			
≤15.7	228	327	1.00 (Referent)	≤3.5	233	313	1.00 (Referent)
>15.7–34.5	288	321	1.18 (0.92 to 1.52)	>3.5–8.8	269	308	1.13 (0.87 to 1.47)
>34.5–77.0	263	321	1.13 (0.88 to 1.46)	>8.8–22.4	260	311	1.21 (0.92 to 1.58)
>77.0–291.0	235	257	1.32 (1.00 to 1.73)	>22.4–83.5	213	247	1.28 (0.95 to 1.72)
>291.0–483.6	33	32	1.30 (0.74 to 2.28)	>83.5–124.8	34	29	1.72 (0.96 to 3.10)
>483.6	32	29	1.60 (0.90 to 2.87)	>124.8	47	29	2.24 (1.29 to 3.89)
			P_{trend}‡ = .12				P_{trend}‡ = .004

Baris et al., JNCI, 2016 May 2, 108(9), PMID 27140955

Low-level arsenic in drinking water and bladder cancer – Baris et al. (6)

Unlagged

Cumulative arsenic intake, mg†			
≤15.7	228	327	1.00 (Referent)
>15.7–34.5	288	321	1.18 (0.92 to 1.52)
>34.5–77.0	263	321	1.13 (0.88 to 1.46)
>77.0–291.0	235	257	1.32 (1.00 to 1.73)
>291.0–483.6	33	32	1.30 (0.74 to 2.28)
>483.6	32	29	1.60 (0.90 to 2.87)
			P_{trend}‡ = .12

Lagged 40 years

Cumulative arsenic intake, mg†			
≤3.5	233	313	1.00 (Referent)
>3.5–8.8	269	308	1.13 (0.87 to 1.47)
>8.8–22.4	260	311	1.21 (0.92 to 1.58)
>22.4–83.5	213	247	1.28 (0.95 to 1.72)
>83.5–124.8	34	29	1.72 (0.96 to 3.10)
>124.8	47	29	2.24 (1.29 to 3.89)
			P_{trend}‡ = .004

PAR 13.8% (95% CI 0-29.2%)

Baris et al., JNCI, 2016 May 2, 108(9), PMID 27140955

Low-level arsenic in drinking water and bladder cancer – Baris et al. (7)

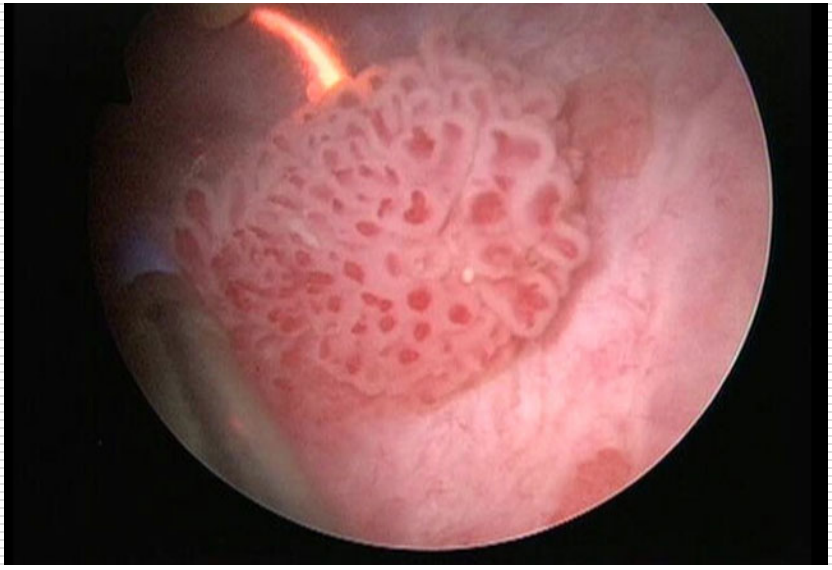
- Limitations:
  - Exposure misclassification due to limited data on arsenic levels x years ago
  - Recall bias on daily water intake
  - Other water contaminant may be a confounder
  - Selection bias
  - Small OR differences

Baris et al., JNCI, 2016 May 2, 108(9), PMID 27140955

Conclusion – How low can it go?

While it has been proven that high levels of arsenic are a cause of bladder cancer, a first large-scale case-control study suggests that low levels of arsenic in drinking water (<10µg/L) may also increase bladder cancer risk, although the study has various limitations.

Discussion



IMAGING RADIATION EXPOSURE AND CANCER

James Tsui

Radiation Oncology PGY1

Intro

- Medical Imaging becoming more common

- More patients are exposed to radiation
  - Diagnostic
  - Surveillance
  - Intervention
  - Treatment

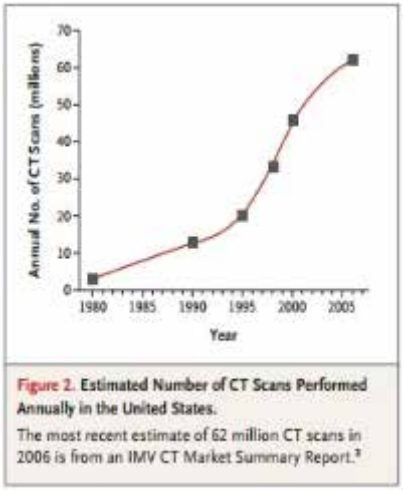


Figure 2. Estimated Number of CT Scans Performed Annually in the United States.
The most recent estimate of 62 million CT scans in 2006 is from an IMV CT Market Summary Report.[3]

Brenner and Hall, NEJM 2007[1]

- Risk
  - CT scan may account for 1.5 to 2% of all future cancers in the US[1]
  - No large-scale epidemiological studies
  - Estimates come from atomic-bomb survivors data
    - Radiation Effects Research Foundation (RERF)
    - Linear no-threshold (LNT) model

CT scan

- Single abdominal CT ≈ 400 chest x-rays
- Ionizing radiation
  - Gray – absorbed dose 1Gy = 1J/Kg
  - Sievert – equivalent dose

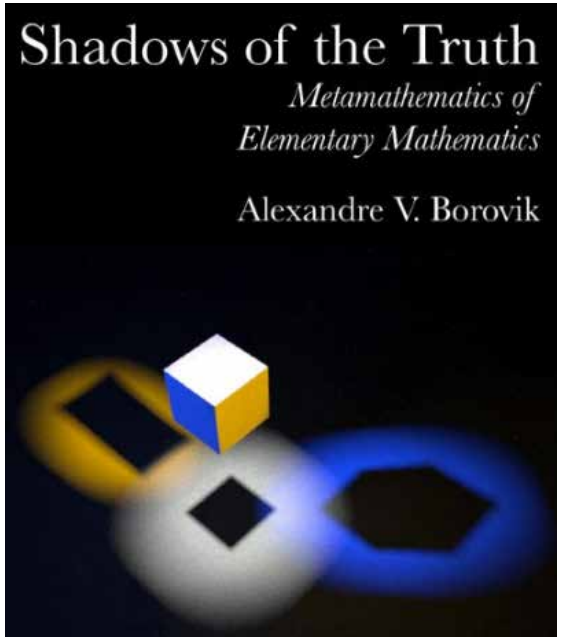


Table 1. Approximate mean doses relevant to societal low-dose radiation exposures and to low-dose radiation risk estimation

	Approximate mean individual dose, mSv*
Some societally relevant exposures	
Round-trip flight, New York to London	0.1
Single screening mammogram (breast dose)	3
Background dose due to natural radiation exposure	3/yr
Dose (over a 70-year period) to 0.5 million individuals in rural Ukraine in the vicinity of the Chernobyl accident	14
Dose range over 20-block radius from hypothetical nuclear terrorism incident [FASEB scenario 1: medical gauge containing cesium (6)]	3–30
Pediatric CT scan (stomach dose from abdominal scan)	25
Radiation worker exposure limit (1)	20/yr
Exposure on international space station	170/yr
Some low-dose epidemiological studies	
A-bomb survivors [mean dose in LSS cohort (2)]	200
Medical x-rays [breast dose in scoliosis study (4)]	100
Nuclear workers [mean dose from major studies (5)]	20
Individuals diagnostically exposed *in utero* (3)	10

Brenner et al., PNAS 2003

ICRP

International Commission on Radiological Protection

1 Sv à 4-5% increased RR of fatal cancer

(~33 CT scan)

Atomic bomb survivors

Radiation-Related Cancer Risks at Low Doses among Atomic Bomb Survivors

Donald A. Pierce[1] and Dale L. Preston

Radiation Effects Research Foundation, Hijiyama Park, Hiroshima 732-0815, Japan

- Exposure and Cancer incidence for 1958-1994
  - RERF, Nagasaki tumor registries
- Cohort
  - Exposed – survivors within 2.5km from ground-zero
    - n = 54,000 (~half of all survivors within the distance)
    - Individuals were interviewed
      - Location
      - Shielding
  - Unexposed – survivors from 2.5-10km from ground-zero
    - n = 40,000

Pierce and Preston, Radiation Research 2000

Atomic bomb survivors – cont'd

- Results
  - Age at exposure >30
  - Age-specific rates
    - 1958-1994
- Confound
  - Rural vs urban
    - >3km VS proximal but not exposed – 5% higher cancer rates
  - Smoking negligible
  - Health care access negligible

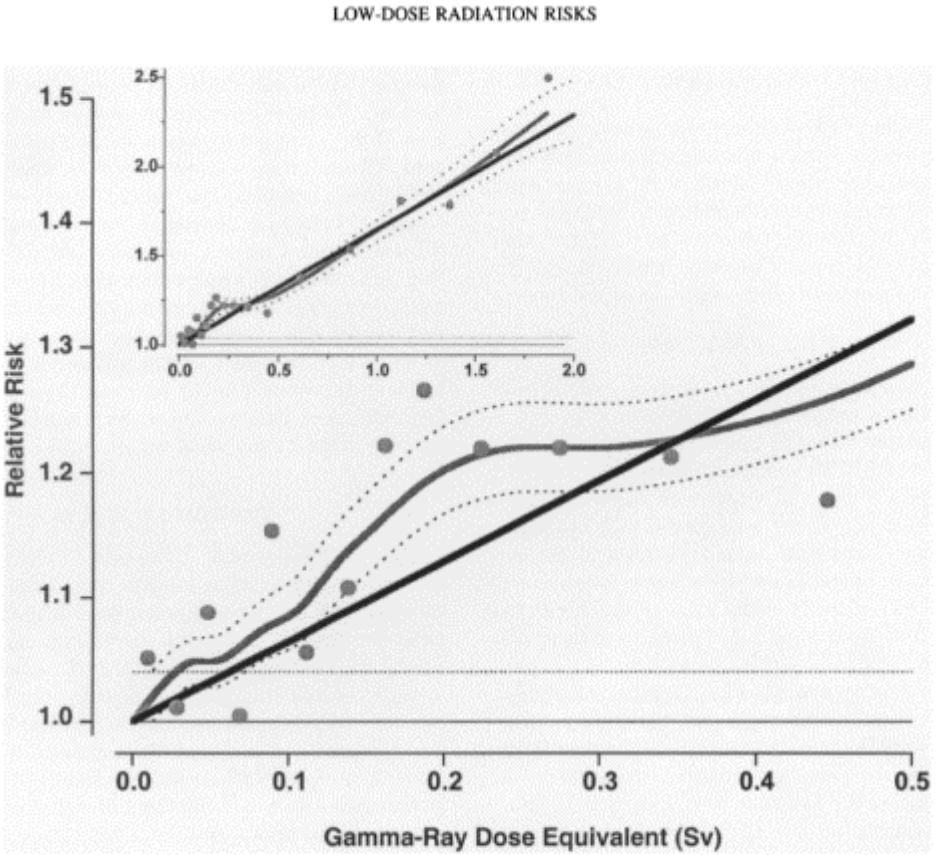


FIG. 1. Estimated low-dose relative risks. Age-specific cancer rates over the 1958–1994 follow-up period relative to those for an unexposed person, averaged over the follow-up and over sex, and for age at exposure 30. The dashed curves represent ±1 standard error for the smoothed curve. The straight line is the linear risk estimate computed from the range 0–2 Sv. Because of an apparent distinction between distal and proximal zero-dose cancer rates, the unity baseline corresponds to zero-dose survivors within 3 km of the bombs. The horizontal dotted line represents the alternative baseline if the distal survivors were not omitted. The inset shows the same information for the fuller dose range.

Pierce and Preston, Radiation Research 2000

Multinational epi study

The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Estimates of Radiation-Related Cancer Risks

- Few small epidemiological studies - radiation workers and cancer risk
  - Some increase in overall cancer mortality
  - No consistent pattern for single cancer
  - Small studies
  - Subject to substantial uncertainty

- Largest analytical study – low-dose exposures
  - Total duration 5,192,710 person-years
  - Quantitative measurements – personal dosimeter

Cardis et al., Radiation Research 2007

Multinational epi study – cont'd

- Retrospective cohort study
  - n = 600,000 in 15 countries

(Australia, Belgium, Canada, Finland, France, Hungary, Japan, Korea, Lithuania, Slovak Republic, Spain, Sweden, Switzerland, UK, US)

  - Employed >1year
  - Monitored for external radiation exposure
  - Doses to individual organs calculated
  - Cumulated dose divided by 11 categories of exposure
  - Cancer related mortality rate was calculated for each category, weighted by person-year
  - Excess relative risk (ERR) / Sievert
  - Expected mortality obtained from GETRATES module in Epicure (age, sex, calendar year – specific mortality rates from the standard national population)

Cardis et al., Radiation Research 2007

Multinational epi study – cont'd

- Results

TABLE 1
Observed and Expected Numbers of Deaths by Cumulative Radiation Dose, Trend Test Statistics and ERRs per Sv for Specific Causes of Death

Cause of death	No.		Cumulative dose (mSv)[a] <5	5– 10–	500+	Trend test (*P* value)	ERR/Sv	90% CI	RR at 100 mSv[b]
A. Main groupings of causes of death									
All causes	18,993	Observed	11,525	14		2.12	0.42	(0.07, 0.79)	1.04
		Expected	11,681.9	13.2		(0.017)			
Cancers	5,233	Observed	3129	6		2.52	0.97	(0.28, 1.77)	1.10
		Expected	3190.4	4.2		(0.006)			
All excluding leukemia	5,024	Observed	3010	5		2.43	0.97	(0.27, 1.80)	1.10
		Expected	3062.1	4.1		(0.007)			
All excluding leukemia, lung and pleura	3,528	Observed	2185	3		1.30	0.59	(−0.16, 1.51)	1.06
		Expected	2193.7	2.3		(0.097)			
Solid cancers	4,770	Observed	2855	4		2.12	0.87	(0.16, 1.71)	1.09
		Expected	2902.5	3.9		(0.017)			
Smoking-related solid cancers	2,737	Observed	1569	3		1.86	0.91	(0.04, 1.98)	1.09
		Expected	1597.3	3.4		(0.032)			
Smoking-related solid cancers other than lung	1,280	Observed	773	0		0.06	0.21	(<0[c], 1.68)	1.02
		Expected	766.9	1.3		(0.477)			
Nonsmoking-related solid cancers	2,033	Observed	1275	2		0.92	0.62	(−0.36, 1.92)	1.06
		Expected	1283.1	1.1		(0.180)			
Non-cancer causes	13,315	Observed	8076	8		0.87	0.20	−0.19, 0.63	1.02
		Expected	8164.7	9.0		(0.193)			
Unknown cause of death	445	Observed	320	0		0.14	0.29	(<0, 4.04)	1.03
		Expected	326.8	0.0		(0.443)			
B. Specific types of cancer									
Buccal and pharynx	113	Observed	74	0		0.18	0.40	(<0, 5.99)	1.04
		Expected	71.9	0.1		(0.427)			
Oesophagus	144	Observed	84	0		−0.78	<0	—	0.84[d]
		Expected	81.3	0.3		(0.782)			*(0.57, 1.15)*
Stomach	347	Observed	204	0		0.41	0.49	(<0, 3.92)	1.05
		Expected	203.5	0.3		(0.341)			
Small intestine	12	Observed	10	0		0.10	3.18	(<0, 28.3[c])	1.32
		Expected	8.3	0.0		(0.460)			
Colon	410	Observed	248	0		0.14	0.21	(<0, 3.07)	1.02
		Expected	254.1	0.4		(0.443)			
Rectum	185	Observed	108	0		0.53	1.27	(<0, 7.62)	1.13
		Expected	114.0	0.2		(0.298)			
Liver	62	Observed	44	0		1.29	6.47	(<0, 27.0)	1.65
				0.0		(0.099)			
				0		−0.67	<0	—	0.58[d]

image 4

Cardis et al., Radiation Research 2007

Multinational epi study – cont'd

- Results
  - All causes death
    - ERR 0.42/Sv (90% CI 0.07-0.79) à RR 1.04 at 100 mSv
      - Statistically significant increasing trend with cumulative dose (p=0.02)
  - Cancer mortality (excluding leukemia)
    - ERR 0.97/Sv (90% CI 0.28-1.77) à RR 1.10 at 100 mSv
      - Including leukemia does not change ERR
  - Solid cancers
    - ERR 0.87/Sv
      - 30% of data driven by lung and pleural CA (for <200mSv)
      - Smoking-related lung cancer showed a stronger association with cumulative radiation dose
  - Non-cancer mortality
    - ERR 0.20/Sv (90% CI 0.19-0.63)

Cardis et al., Radiation Research 2007

Multinational epi study – cont'd

TABLE 6
Effects of Socio-economic Status (SES), Duration of Employment, Excluded Cohorts, and Associated Causes of Death on ERR per Sv and RR at 100 mSv and Corresponding 90% Confidence Intervals (CI) for Deaths from all Cancers Excluding Leukemia, from all Cancers Excluding Leukemia, Lung and Pleural Cancer, from Lung Cancer, and from Leukemia Excluding CLL: Results from Linear Models

	No.	ERR/Sv	90% CI		RR at 100 mSv
All cancers excluding leukemia					
standard analysis	5,024	0.97	0.27	1.80	1.10
no adjustment for SES	5,024	1.24	0.52	2.07	1.12
no adjustment for SES, including OH, Japan, INEL	6,519	0.64	0.04	1.29	1.06
no adjustment for duration of employment	5,024	0.31	−0.23	0.93	1.03
including associated causes	5,346	0.94	0.26	1.72	1.09
All cancers excluding leukemia, lung, and pleura					
standard analysis	3,528	0.59	−0.16	1.51	1.06
no adjustment for SES	3,528	0.61	−0.12	1.50	1.06
no adjustment for SES, including OH, Japan, INEL	4,578	0.33	−0.31	1.08	1.03
no adjustment for duration of employment	3,528	0.21	−0.41	0.96	1.02
including associated causes	3,760	0.38	−0.31	1.24	1.04
Lung cancer					
standard analysis	1,457	1.86	0.47	3.81	1.19
no adjustment for SES	1,457	2.88	1.34	4.79	1.29
no adjustment for SES, including OH, Japan, INEL	1,895	1.33	0.23	2.68	1.13
no adjustment for duration of employment	1,457	0.48	−0.42	1.62	1.05
including associated causes	1,545	2.24	0.86	3.99	1.22
Leukemia excluding CLL					
standard analysis	196	1.93	<0	7.14	1.19
no adjustment for SES	196	2.19	<0	7.59	1.22
no adjustment for duration of employment	196	0.82	<0	4.62	1.08
including associated causes	205	1.74	<0	6.75	1.17

Cardis et al., Radiation Research 2007

Radiation exposure from CT in childhood

- Retrospective cohort study
  - n = ~180,000
  - < 22 yo, no prev cancer
  - Great Britain 1985 to 2002
- Outcome
  - Cancer incidence – Leukemia / Brain
- Findings
  - Leukemia (74/174,604)
    - **ERR** 0.036/mGy CI 0.005-0.12 p=0.0097
    - <5mGy vs >30mGy **RR 3.18** (95% CI 1.49-6.94)
  - Brain tumor (135/176,587)
    - **ERR** 0.023/mGy CI 0.01-0.049 p<0.0001
    - <5mGy vs 50-74mGy **RR 2.82** (95% CI 1.33-6.03)

Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study

Mark S Pearce, Jane A Salotti, Mark P Little, Kieran McHugh, Choonsik Lee, Kwang Pyo Kim, Nicola L Howe, Cecile M Ronckers, Preetha Rajaraman, Sir Alan W Craft, Louise Parker, Amy Berrington de González

	Male patients		Female patients	
	Brain dose (mGy)	Red bone marrow dose (mGy)	Brain dose (mGy)	Red bone marrow dose (mGy)
Age at brain CT				
0 years	28	8	28	8
5 years	28	9	28	9
10 years	35	6	35	6
15 years	43	4	44	6
20 years	35	2	42	2
Age at chest CT				
0 years	0·4	4	0·4	4
5 years	0·3	3	0·3	3
10 years	0·3	3	0·3	3
15 years	0·2	4	0·3	4
20 years	0·2	4	0·3	4
Age at abdominal CT				
0 years	0·2	3	0·2	3
5 years	0·1	2	0·1	2
10 years	0·1	3	0·1	3
15 years	0·0	3	0·0	3
20 years	0·0	3	0·0	4
Age at extremity CT				
0 years	0·0	1	0·0	1
5 years	0·0	0·2	0·0	0·2
10 years	0·0	0·1	0·0	0·1
15 years	0·0	0·0	0·0	0·0
20 years	0·0	0·0	0·0	0·0

Table 1: Estimated radiation doses to the brain and red bone marrow from one CT scan, by scan type, sex, and age at scan, as used in this study for scans after 2001

Pearce et al., Lancet 2012

Radiation exposure from CT in childhood

- Conclusion
  - Triple the risk, but cancer relatively rare
    - 10 years after first scan to patients younger than 10
      - 1 excess leukemia & 1 excess brain

      / 10,000 head CT scans

	Cases	ERR per mGy (95% CI)	p value (test for dose-response)
Red bone marrow dose			
All leukaemia, including myelodysplastic syndromes	74	0·036 (0·005 to 0·120)	0·0097
Acute lymphoblastic leukaemia	26	1·719* (>0 to 17·73†)	0·0053
Acute myeloid leukaemia	18	0·021 (−0·042† to 0·155)	0·2653
Myelodysplastic syndromes	9	6·098* (>0 to 145·4†)	0·0032
Leukaemia excluding myelodysplastic syndromes	65	0·019 (−0·012† to 0·079)	0·1436
Brain dose			
All brain	135	0·023 (0·010 to 0·049)	<0·0001
Glioma	65	0·019 (0·003 to 0·070)	0·0033
Schwannoma and meningioma	20	0·033 (0·002 to 0·439)	0·0195

ERR=excess relative risk. *Iteratively reweighted least-squares algorithm failed to converge, so parameter estimates might be unreliable. †Calculated using Wald-based CI.

Table 3: Excess relative risk per mGy for cancer subtypes in relation to organ-specific radiation doses received from CT scans

	Leukaemia		Brain tumours	
	ERR per mGy	p value	ERR per mGy	p value
Sex				
Male*	0·031	0·6300	0·016	0·0850
Female	0·042		0·028	
Years since first exposure				
0–<5	0·048	0·8061	0†	0·6468
5–<10	0·033		0·025	
≥10	0·026		0·021	
Years since last exposure				
0–<5	0·052	0·3004	0†	0·1976
5–<10	0·015		0·026	
≥10	0·014		0·016	
Number of CT scans				
1	0·013	0·8013	0·007	0·1213
2–4	0·028		0·021	
≥5	0·035		0·018	
Age at exposure (years)‡				
0–<5	0·030	0·5381	0·005	0·0003
5–<10	0·072		0·028	
10–<15	−0·002		0·037	
≥15	0·049		0·041	
Years since exposure‡				
2–<5	0·055	0·5357	..	0·2399
5–<10	0·021		0·026	
10–<15	0·005		0·023	
≥15	0·026		0·005	

ERR=excess relative risk. ..=not applicable (follow-up started at 5 years). *Includes individual of unknown sex. †Aliased parameter, set to zero. ‡Time-dependent variable.

Table 4: Excess relative risk per mGy for leukaemia and brain tumours, by various personal characteristics

Pearce et al., Lancet 2012

Questions?

- THANK YOU J

RISK FACTORS FOR FEBRILE NEUTROPENIA IN BREAST CANCER PATIENTS ON AC CHEMOTHERAPY: A RETROSPECTIVE COHORT STUDY

Arif Ali Awan
EPIP-671; Dr. E. Franco
May 20th, 2016

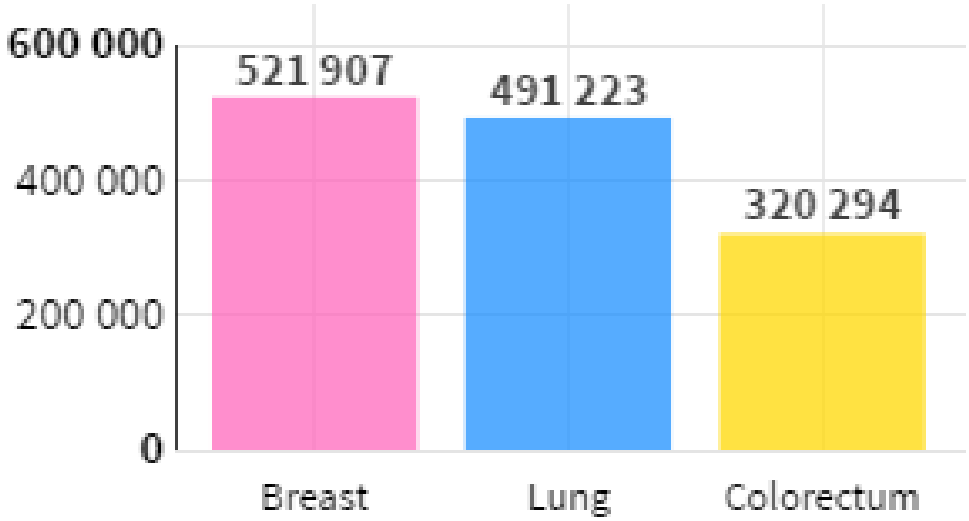
BACKGROUND

Breast cancer accounted for 521,907 deaths in 2012, the highest among cancers in females.[1]

The lifetime risk of developing breast cancer is 1 in 8 women. [2]

Mainstay of treatment is surgery for local/regional disease with a combination of chemotherapy, hormonal therapy and radiation therapy.

Adjuvant chemotherapy and hormonal therapy can reduce breast cancer mortality by approximately a half. [3]



Estimated Global Cancer Mortality – Females (2012)

[1]FERLAY J, SOERJOMATARAM I, ERVIK M, DIKSHIT R, ESER S, MATHERS C, REBELO M, PARKIN DM, FORMAN D, BRAY, F. GLOBOCAN 2012 V1.0, CANCER INCIDENCE AND MORTALITY WORLDWIDE: IARC CANCERBASE NO. 11 [INTERNET]. LYON, FRANCE: INTERNATIONAL AGENCY FOR RESEARCH ON CANCER; 2013. AVAILABLE FROM: HTTP://GLOBOCAN.IARC.FR, ACCESSED ON 19/MAY/2016

[2] HTTP://WWW.CANCER.ORG/CANCER/CANCERBASICS/LIFETIME-PROBABILITY-OF-DEVELOPING-OR-DYING-FROM-CANCER

[3] EARLY BREAST CANCER TRIALISTS' COLLABORATIVE, G. (2005). EFFECTS OF CHEMOTHERAPY AND HORMONAL THERAPY FOR EARLY BREAST CANCER ON RECURRENCE AND 15-YEAR SURVIVAL: AN OVERVIEW OF THE RANDOMISED TRIALS. LANCET *365*, 1687-1717.

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ADJUVANT CHEMOTHERAPY

The mainstay chemotherapy is an **anthracycline**-based regimens with a **taxane**.

A common regimen is Adriamycin and cyclophosphamide (**AC**) followed by taxane (T).

6-7 % of patients develop febrile neutropenia with this treatment regimen. [1]

Febrile neutropenia is defined as: [2]

- **Fever** (≥ 38.3 ºC once or ≥38 ºC) AND
- **Neutropenia** (Absolute neutrophil count (ANC) < 500 cells/mm3 or projected to be in 48 hours).

2.6% in-patient mortality for breast cancer patients diagnosed with febrile neutropenia[3].

[1] SPARANO, J. A., ET AL. (2008). "WEEKLY PACLITAXEL IN THE ADJUVANT TREATMENT OF BREAST CANCER." N ENGL J MED **358**(16): 1663-1671

[2] FREIFELD, A. G., ET AL. (2011). "CLINICAL PRACTICE GUIDELINE FOR THE USE OF ANTIMICROBIAL AGENTS IN NEUTROPENIC PATIENTS WITH CANCER: 2010 UPDATE BY THE INFECTIOUS DISEASES SOCIETY OF AMERICA." CLINICAL INFECTIOUS DISEASES **52**(4): 427-431.

[3] PATHAK, R., ET AL. (2015). "MORTALITY, LENGTH OF STAY, AND HEALTH CARE COSTS OF FEBRILE NEUTROPENIA-RELATED HOSPITALIZATIONS AMONG PATIENTS WITH BREAST CANCER IN THE UNITED STATES." SUPPORT CARE CANCER **23**(3): 615-617.

RISK FACTORS FOR FEBRILE NEUTROPENIA

Patient-related	Chemotherapy-related	Disease-related
Age ≥ 65	Chemotherapy regimen	Tumour type
Performance status	Prophylaxis	Advanced disease
Gender		Genetic Risk Factor
Co-morbidities		
Low pre treatment ANC/ ANC nadir		
Body mass index/Body surface area		

WHAT ARE THE RISK FACTORS FOR FEBRILE NEUTROPENIA IN BREAST CANCER PATIENTS ON AC CHEMOTHERAPY?

Not previously established in patients on AC chemotherapy.

A **retrospective cohort study** with medical chart review.

We obtained the local Institutional Review Board approval.

ALL patients that received AC chemotherapy for breast cancer in the adjuvant/neoadjuvant setting between 2008-2012 from pharmacy records (n = 419)

Electronic and paper chart review until end of chemotherapy.

Identified patients with febrile neutropenia (n = 39, 9.3% of all patients)

Assessed risk factors for febrile neutropenia in all patients (no febrile neutropenia vs febrile neutropenia)

- Patient-related: age, Absolute neutrophil count pre-chemotherapy and in between chemotherapy
- Tumour related: ER/PR/Her-2/Tumour (T)/Node (N)/Histology/chemotherapy setting

Data analysis was performed using Microsoft Excel Data Analysis ® and PERL computer programming to determine odds ratios.

RISK FACTORS: HER2 STATUS ASSOCIATED WITH RISK OF FEBRILE NEUTROPENIA

	No Febrile Neutropenia (n = 380)	Febrile neutropenia (n = 39)	OR (95% CI) or *p-value*
Mean Age (years)	53.9 (SD 10.8)	55.3 (SD 9.0)	*0.43*
Estrogen receptor status			
positive (%)	274 (72.1)	32 (82.1)	1.8 (0.8-4.1)
negative (%)	106 (27.9)	7 (17.9)	
Progesterone receptor status			
positive (%)	239 (62.9)	27 (69.2)	1.3 (0.7-2.7)
negative (%)	141 (37.1)	12 (30.8)	
Her2 receptor status			
positive (%)	113 (29.7)	20 (51.3)	**2.6 (1.3-5.0)**
negative (%)	261 (68.7)	18 (46.2)	
equivocal (%)	6 (1.6)	1 (2.6)	

RISK FACTORS: T/N, GRADE, HISTOLOGY NOT ASSOCIATED WITH RISK OF FEBRILE NEUTROPENIA

	No Febrile Neutropenia (n = 380)	Febrile neutropenia (n = 39)	OR (95% CI) or *p-value*
Tumour Size (T)			
T1-2 (%)	290 (76.3)	34 (87.2)	2.6 (0.9-7.4)
T3-4 (%)	91 (21.7)	4 (10.3)	
Node (N)			
negative (%)	149 (39.2)	17 (43.6)	1.2 (0.6-2.3)
positive (%)	231 (60.8)	22 (56.4)	
Grade			
1-2 (%)	214 (56.3)	20 (51.3)	0.9 (0.4-1.7)
3 (%)	165 (43.4)	18 (46.2)	
Histology			
IDC (%)	318 (83.7)	37 (94.8)	1.6 (0.4-6.9)
ILC (%)	27 (7.1)	2 (5.1)	

RISK FACTORS: TIMING OF CHEMOTHERAPY

Chemotherapy setting not associated with risk of febrile neutropenia.

	No Febrile Neutropenia (n = 380)	Febrile neutropenia (n = 39)	OR (95% CI) or *p-value*
Adjuvant	246 (64.7)	29 (74.4)	1.6 (0.7-3.3)
Neoadjuvant	133 (35)	10 (25.6)	

RISK FACTORS: PRE-CYCLE 1 CHEMOTHERAPY ABSOLUTE NEUTROPHIL COUNT (ANC)

Low absolute neutrophil count (< 2.5 x 10^9/L) not associated with febrile neutropenia.

	No Febrile Neutropenia (n = 380)	Febrile neutropenia (n = 39)	OR (95% CI) or *p-value*
ANC pre-cycle 1 mean x10^9/L (SD)	4.1 (1.78)	3.56 (1.67)	*0.07*
ANC pre-cycle 1 < 2.5x10^9/L (%)	46 (12.1)	9 (23.1)	**2.2 (1.0-4.8)**
ANC pre-cycle 1 ≥ 2.5 x 10^9/L (%)	334 (87.9)	30 (76.9)	

RISK FACTORS: INTERIM ABSOLUTE NEUTROPHIL COUNT STRONGLY ASSOCIATED WITH RISK OF FEBRILE NEUTROPENIA

N = 204/419 = 49% patients had an Interim Absolute Neutrophil count.

	Interim ANC cycle 1 (x 10^9/L)	No febrile neutropenia (% total)	Febrile Neutropenia (% total)	Odds Ratio (95% CI)
Cycle 1	≤ 0.1	22 (10.8)	10 (59)	**10.7 (3.7-31)**
	> 0.1	165 (80.9)	7 (41)	
	≤ 0.5	97 (47.5)	18 (95)	**16.3 (2.1-124)**
	> 0.5	88 (43.1)	1 (5)	
All Cycles	≤ 0.1	21 (10.3)	11 (42.3)	**5.5 (2.2-13.5)**
	> 0.1	157 (77.0)	15 (57.7)	
	≤ 0.5	94 (46.1)	21 (81)	**3.8 (1.4-10.4)**
	> 0.5	84 (41.2)	5 (19)	

INTERIM ABSOLUTE NEUTROPHIL COUNT CAN LIKELY BE USED TO PREDICT FEBRILE NEUTROPENIA

An absolute neutrophil count $\leq 0.5 \times 10^9/L$ has a 18% positive predictive value and a 94 % negative predictive value:

	Interim ANC cycle 1 Threshold (x10^9/L)	Sens. (%)	Spec. (%)	Positive predictive Value (%)	Negative Predictive value (%)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Cycle 1	0.1	42.3	88.7	34.3	91.7	3.8 (2.1-6.9	0.65 (0.47-0.91)
	0.5	94.7	47.6	15.7	98.9	1.8 (1.5-2)	0.11 (0.02-0.75)
All cycles	0.1	42.3	88.2	34.3	91.3	3.6 (2.0-6.6)	0.65 (0.47-0.91)
	0.5	**80.1**	**47.2**	**18.3**	**94.3**	**1.5 (1.2-1.9)**	**0.41 (0.18-0.91)**

STUDY FINDINGS

Her2 receptor positive patients 2.6 times more likely to develop febrile neutropenia (univariate analysis!)

Interim absolute neutrophil count (ANC) during cycle 1 was a strong predictor of febrile neutropenia during the subsequent chemotherapy cycles (OR 3.8-5.5).

The lower the ANC, the higher the chance of developing febrile neutropenia.

Biological reasoning: as per definition of febrile neutropenia, patients with lower absolute neutrophil count higher risk of febrile neutropenia

STUDY LIMITATIONS

Her2 receptor positive patients associated with increased risk in a univariate analysis (analysis not shown, but these patients had non-statistically significant interim ANC counts).

Single-institution, which may limit reproducibility.

High potential for selection bias as only 49% patients had interim absolute neutrophil count. Were these patients considered higher risk by treating physicians?

- Analysis was repeated with a physician who treated 40% of the patients and performed interim ANC counts in 80% of his patients with similar results.

CONCLUSION

A retrospective cohort study assessing risk factors for febrile neutropenia patients in breast cancer patients receiving AC chemotherapy revealed:

- Strong prediction value of interim absolute neutrophil count
- Her2 receptor positive patients more likely to have febrile neutropenia

Future directions:

- Validation of Her2 patients with other data-sets and multi-variate analysis
- Design of a prospective trial assessing risk and prophylaxis of febrile neutropenic patients.

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