Hôpital général juif
Jewish General Hospital
Centre du cancer Segal Cancer Centre

BREAST CANCER SCREENING

How Do I Know if My Patient is High Risk?

Stephanie M Wong MD MPH
Jewish General Hospital Segal Cancer Centre
Stroll Cancer Prevention Centre High Risk Breast Clinic
McGill Medical School

McGill

Hôpital général juif
Jewish General Hospital
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BREAST CANCER SCREENING

No disclosures except that I am a breast surgical oncologist.

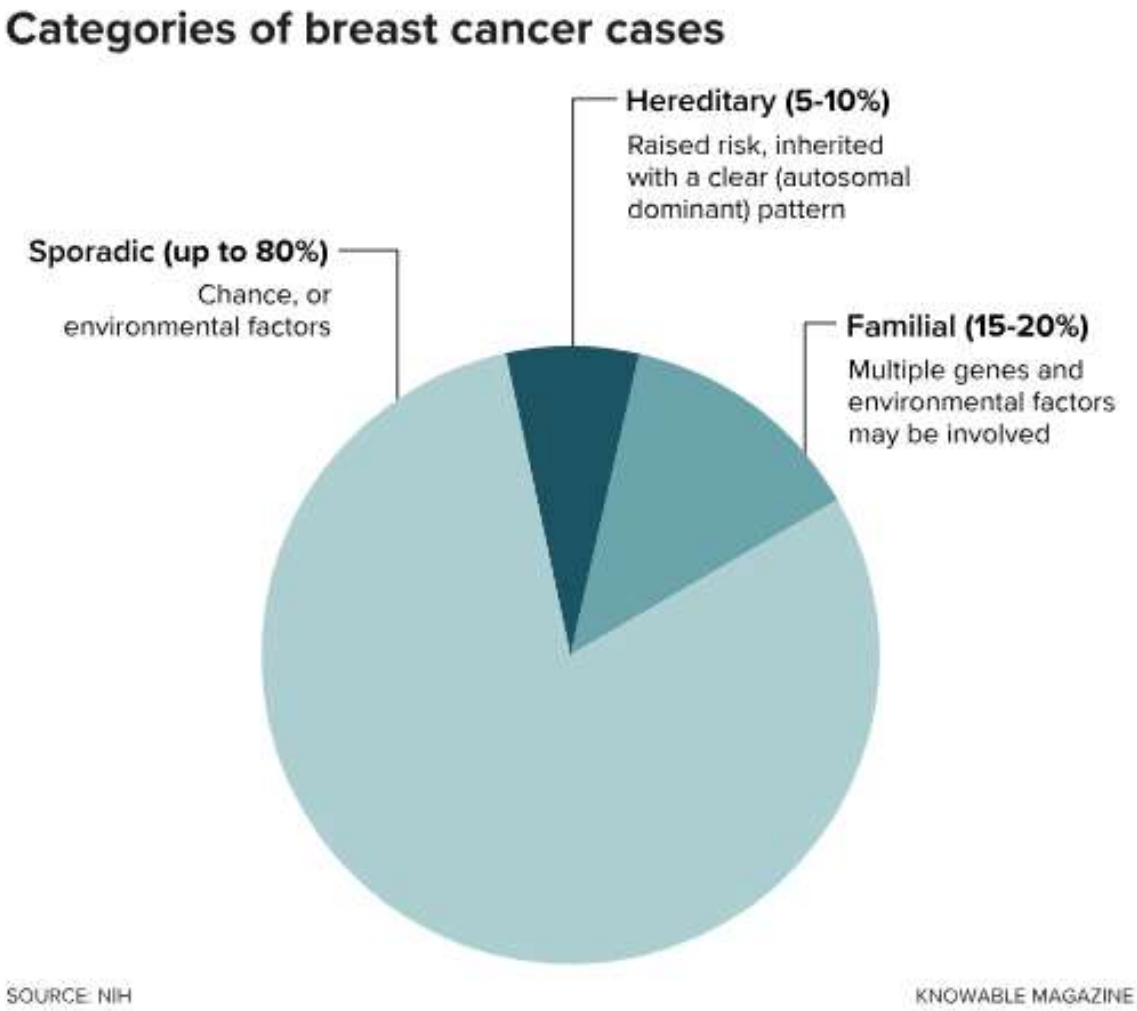
McGill

- Breast cancer is the most common cancer in women worldwide and the second most common cause of cancer related death
  - 26,900 CDN women are diagnosed annually
  - 5,000 CDN women die each year from breast CA

- The lifetime risk of developing breast cancer in average risk women is 12%. In elevated risk women, lifetime risk can vary from 15-80%.

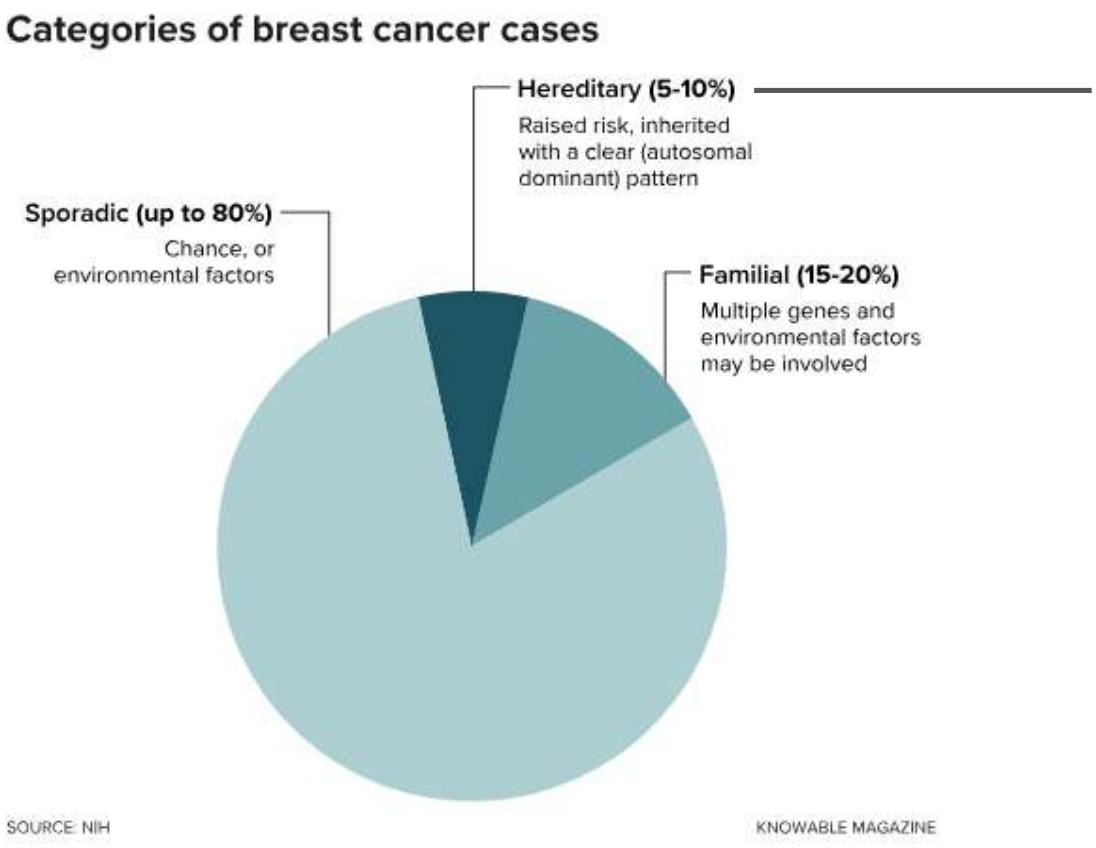
RISK FACTORS

RELATIVE RISK OF BREAST CANCER



RISK FACTORS

HEREDITARY

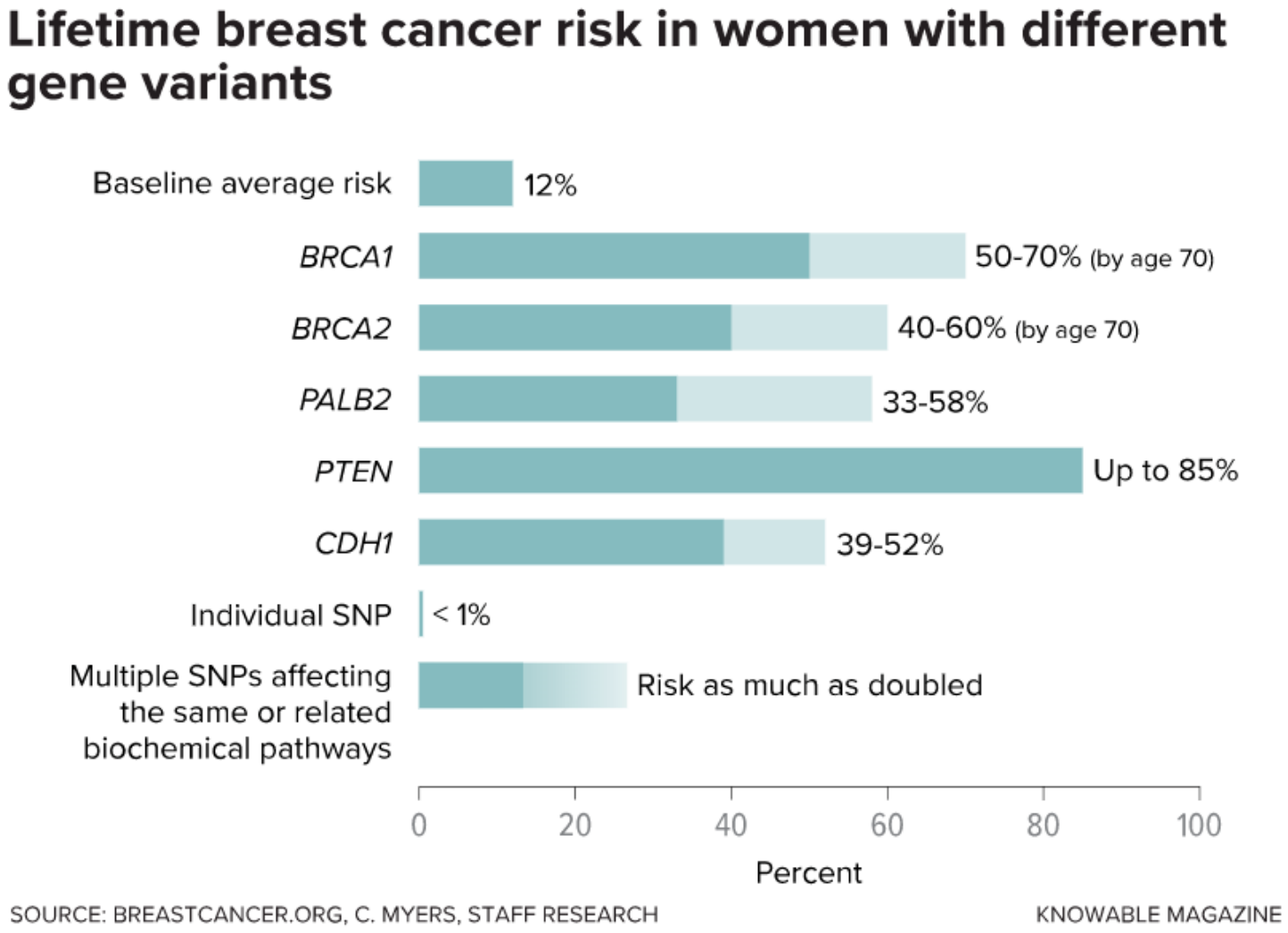


Genetic testing demonstrates a pathogenic variant that explains hereditary breast and other cancers in the family

60% BRCA1/2 genes

40% other moderate-high penetrance genes associated with breast cancer (moderate ATM, CHEK2, NBN; high CDH1, PTEN, TP53, STK11)

Tung N, et al. JCO 2016


Lifetime breast cancer risk in women with different gene variants
Baseline average risk
12%
BRCA1
50-70% (by age 70)
BRCA2
40-60% (by age 70)
PALB2
33-58%
PTEN
Up to 85%
CDH1
39-52%
Individual SNP
< 1%
Multiple SNPs affecting the same or related biochemical pathways
Risk as much as doubled
0
20
40
60
80
100
Percent
SOURCE: BREASTCANCER.ORG, C. MYERS, STAFF RESEARCH
KNOWABLE MAGAZINE

- Families often share the same environmental exposures, as well as sharing genes…
- **SNPs (Single Nucleotide Polymorphisms)**
  - Identified more recently on genome wide association studies (GWAS), usually in regulatory regions that turn a gene on or off
  - We currently know of 150 single small variants that increase the risk of developing breast cancer by a fraction of a percent
  - If multiple SNPs are present, their effect could add up to significant risk = Basis of Polygenic Risk Scores

Couch F, et al. JAMA Oncol

RISK FACTORS

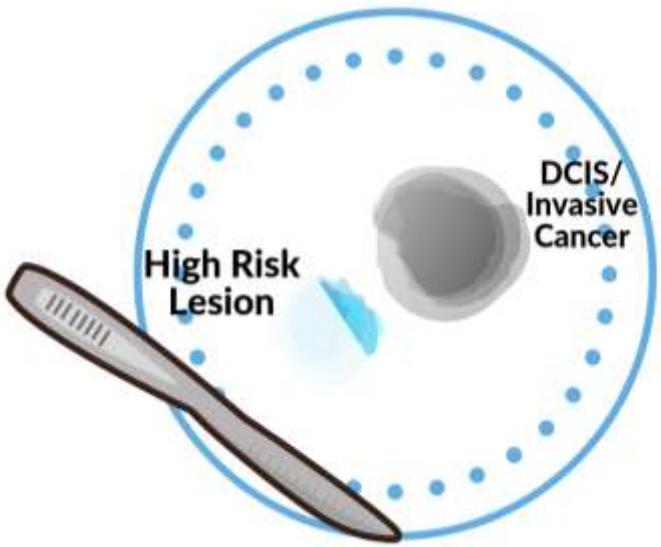
PRIOR CHEST WALL RADIATION

- Adult survivors of childhood cancers with chest wall or mantle radiation
- Four-fold increase in risk (RR 4.2) with mantle radiation
  - Less with other fields
- Correlated to the age at time of RT, time interval from radiation exposure, dose to exposed breast tissue
  - Risk increases 8 years after exposure and does not plateau
  - Women tend to be diagnosed early, 15-20 years earlier than age matched pears
  - Similar clinical characteristics and survival outcomes reported with the exception of high rate of BBC

Overholser et al., Oncology 2016, www.cancernetwork.com

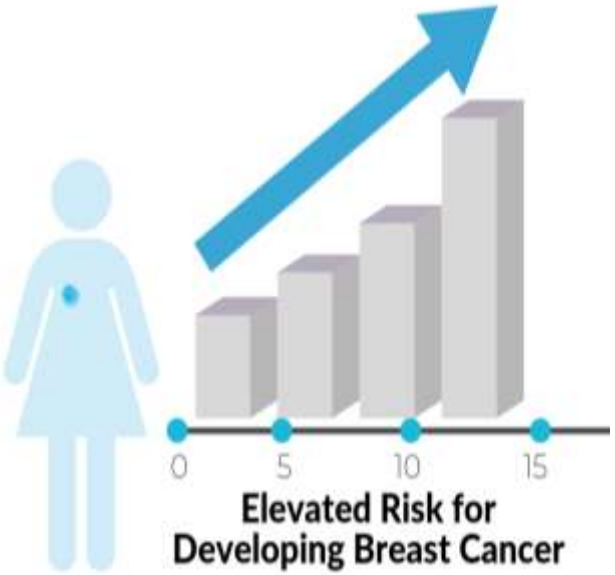
1) High-risk NOW

A lesion diagnosed on core biopsy with a significant chance of being associated with a concurrent cancer.



2) High-Risk in the FUTURE

A lesion that results in a significantly higher lifetime risk of developing breast cancer.

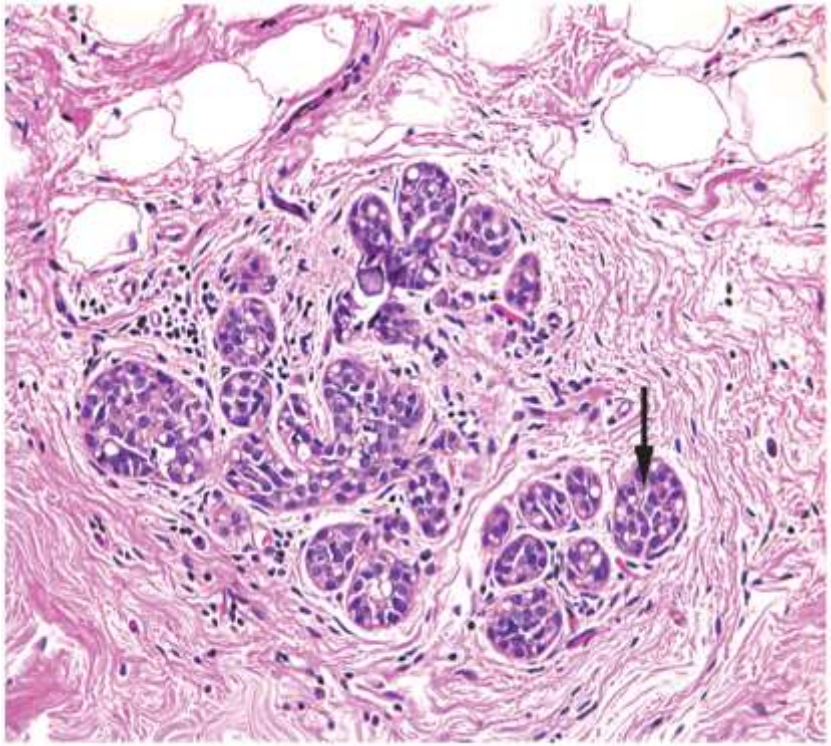


Adapted from TA King, 2019

ATYPICAL LOBULAR HYPERPLASIA (ALH)

- Epithelial proliferative lesion
- Characterized by small, discohesive cells that fill less than half the acinar spaces but does not distend them

  (LCIS = >50% acinar units filled, distended, distorted)

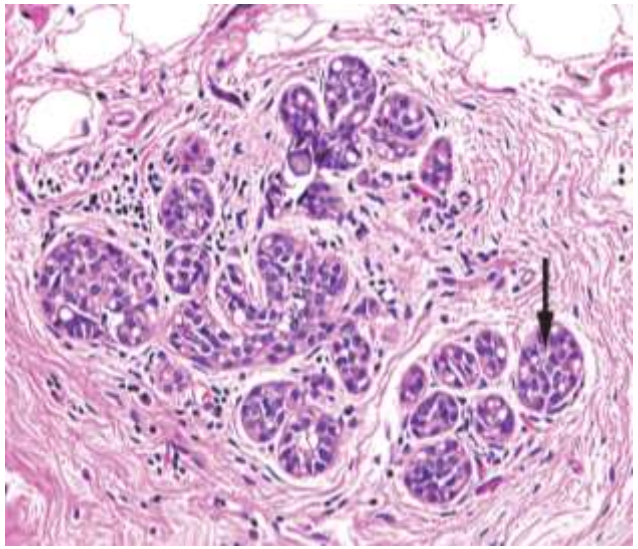


Morrow M, Schnitt S, *et al.* Nat Rev Clin Oncol 2015

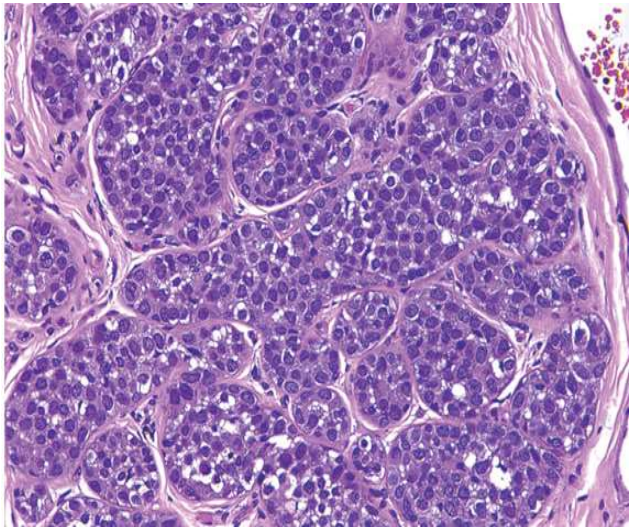
RISK FACTORS

ATYPICAL LOBULAR HYPERPLASIA (ALH)

ALH



LCIS



- Incidental finding that lacks a distinct radiographic correlate
- Identified on 0.3-4% of benign breast biopsies
- Can accompany LCIS, ADH and other high risk lesions

Morrow M, Schnitt S, *et al.* Nat Rev Clin Oncol 2015

	No. patients with atypia + FU	No. with ALH (%)	RR_{ALH} (95% CI)
Nashville Cohort (1985)	283	126 (45%)	4.2 (2.6-6.9)*
Mayo Clinic Cohort (2007)	331	142 (43%)	3.7 (2.5-5.1)
Nurses Health Study (2016)	124	55 (44%)	6.6 (4.2-10.3)

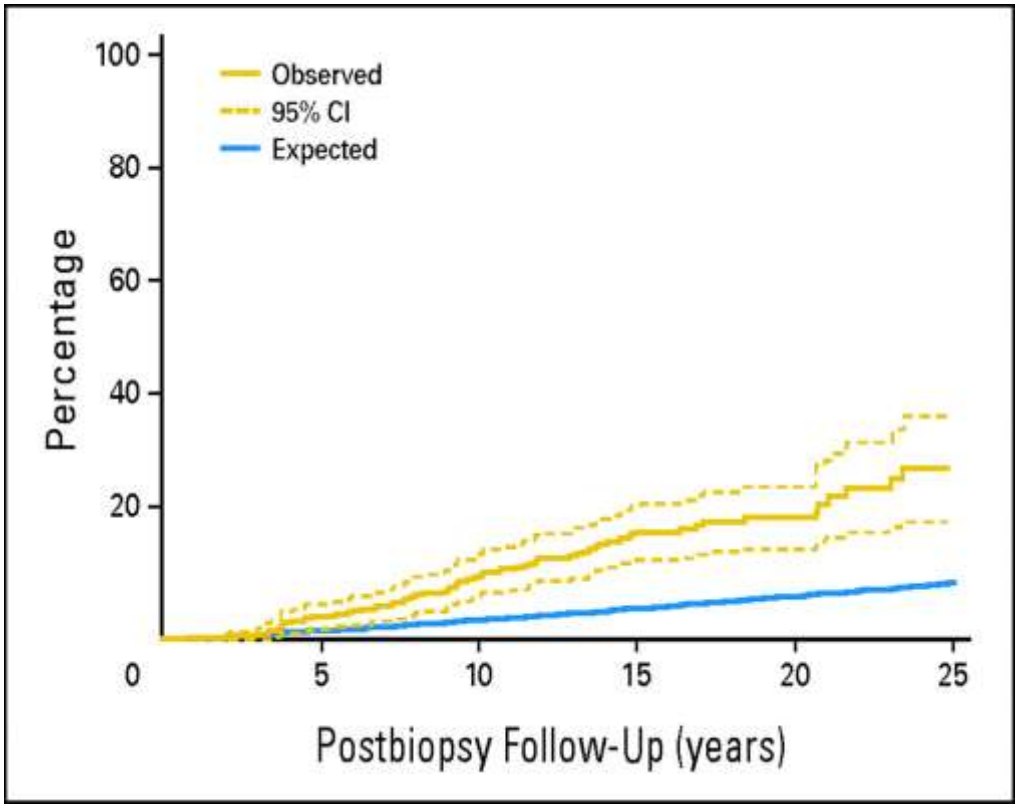
*RR for invasive cancer only

Women with ALH have a relative risk of breast cancer that is 4-fold higher than the general population.

Page DL, Dupont WD, *et al.* Cancer 1985
Degnim AC *et al.* JCO 2007
Collins LC *et al.* Cancer 2016

ATYPICAL LOBULAR HYPERPLASIA (ALH)

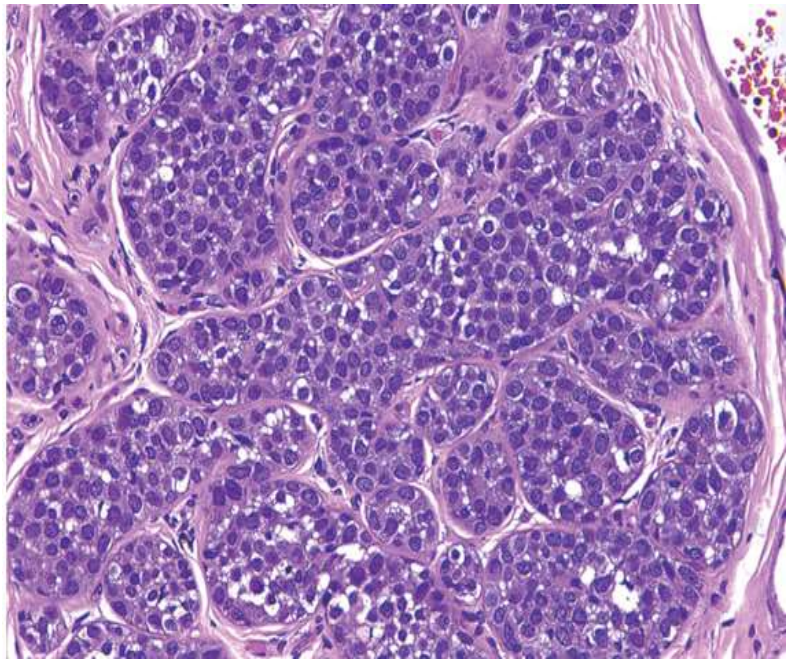
This translates to an absolute risk of ≈ 1% per year.



Degnim AC et al. JCO 2007
Hartmann LC et al. Cancer Prev Res 2014

LOBULAR CARCINOMA IN SITU (LCIS)

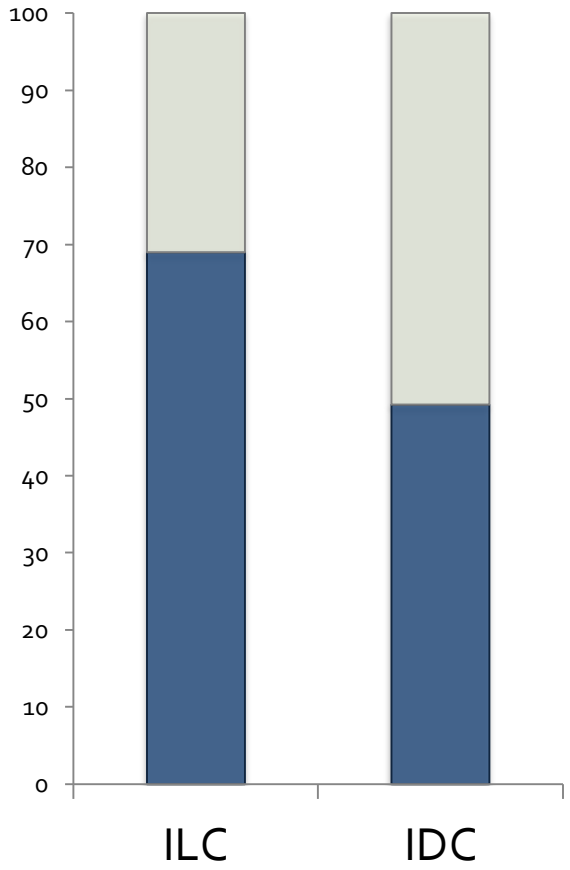
- Characterized by discohesive cells with scant cytoplasm and small, uniform nuclei that fill more than half the acinar spaces in a lobule, resulting in their distension
- Previously thought to be a breast cancer precursor similar to DCIS (hence “carcinoma in situ”)



Morrow M, Schnitt S, *et al.* Nat Rev Clin Oncol 2015

RISK FACTORS

LOBULAR CARCINOMA IN SITU (LCIS)



Ipsilateral to the breast with prior LCIS:
69% ILC vs. 49.2% IDC (p<0.001)

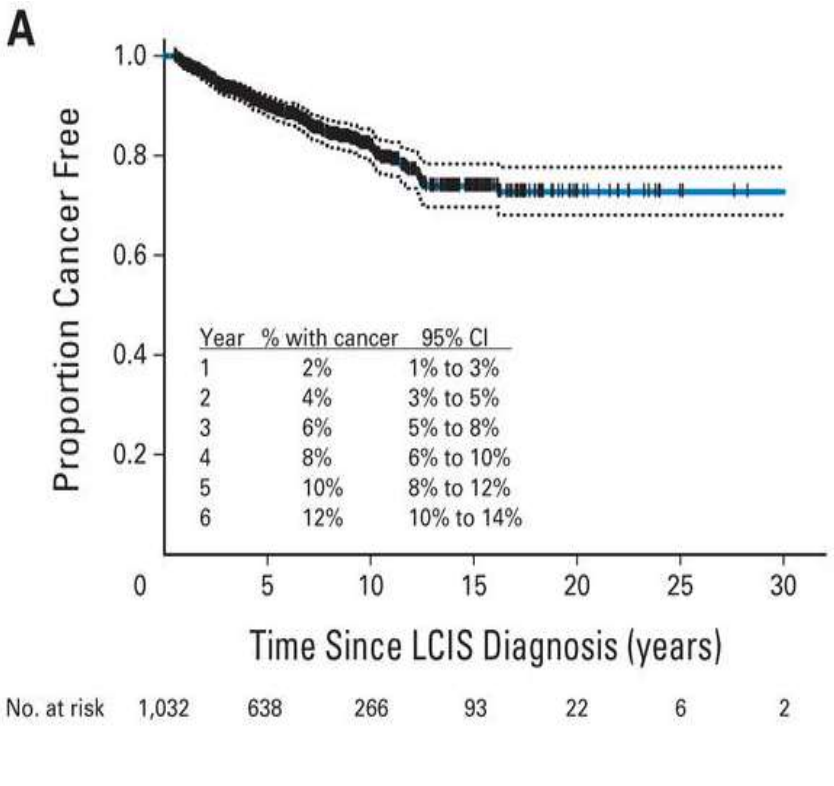
Wong SM, King TA, et al. Ann Surg Onc 2017

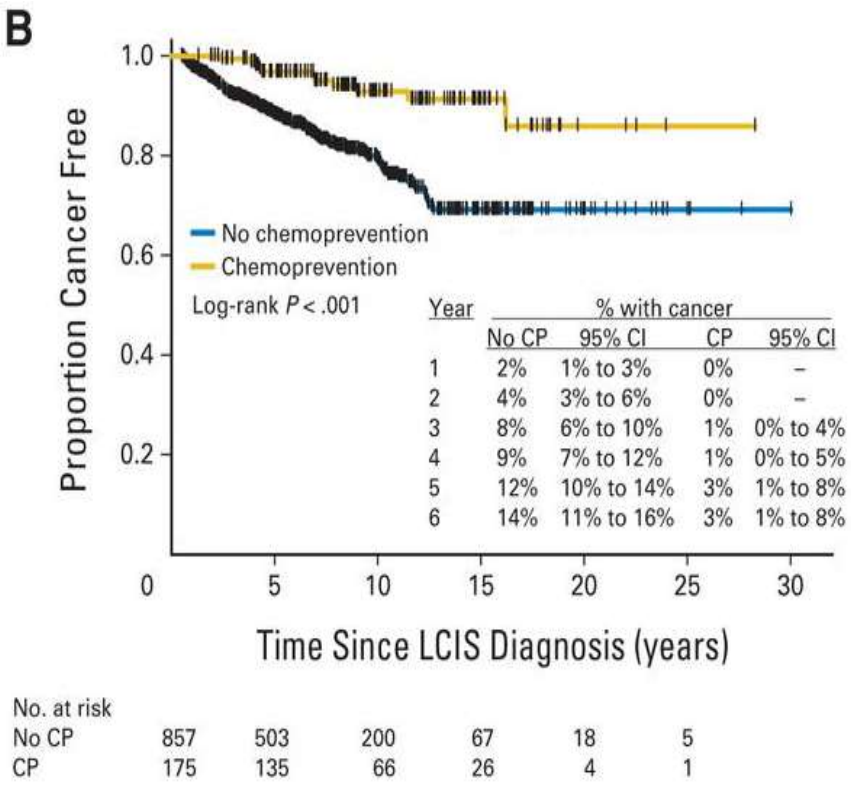
- Bilateral Risk, RR:3-8
- Recent studies exploring clonal relationship between LCIS and ILC support role as a non-obligate precursor to invasive disease

Hwang ES et al. Cancer 2004
Begg et al. Breast Cancer Res 2016
Lee JK et al. Clin Cancer Res 2019

RISK FACTORS

LOBULAR CARCINOMA IN SITU (LCIS)





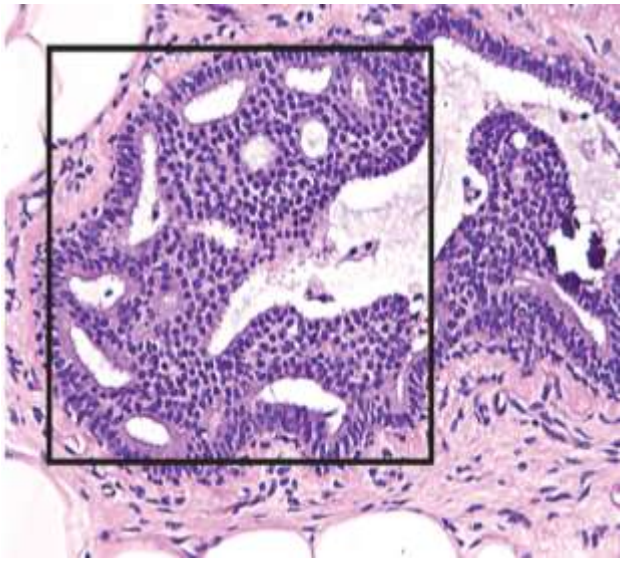
Absolute risk of breast cancer of ≈ 1-2% per year.

King TA, Pilewskie M, et al. JCO 2015

RISK FACTORS

ATYPICAL DUCTAL HYPERPLASIA (ADH)

ADH



Morrow M, Schnitt S, *et al.* (2015) *Nat. Rev. Clin. Oncol.*

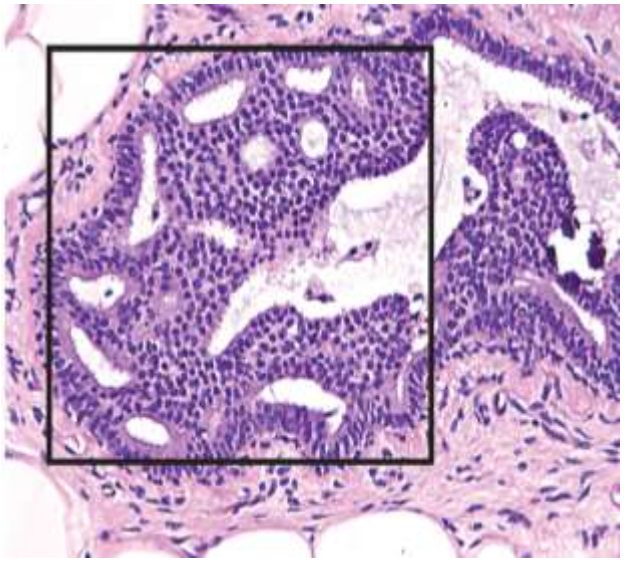
- Identified in 8-17% of all benign breast biopsies
- Similar in appearance and shares genetic and molecular similarities with low grade DCIS*

(*distinction can be difficult)

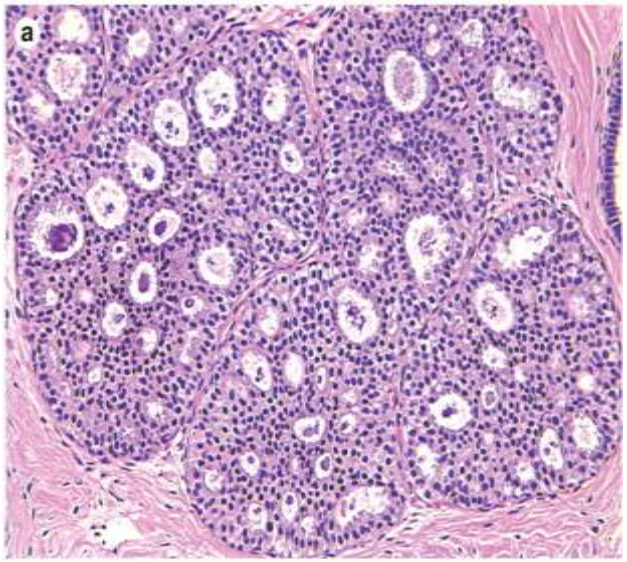
RISK FACTORS

ATYPICAL DUCTAL HYPERPLASIA (ADH)

ADH



DCIS



Morrow M, Schnitt S, *et al.* (2015) *Nat. Rev. Clin. Oncol.*

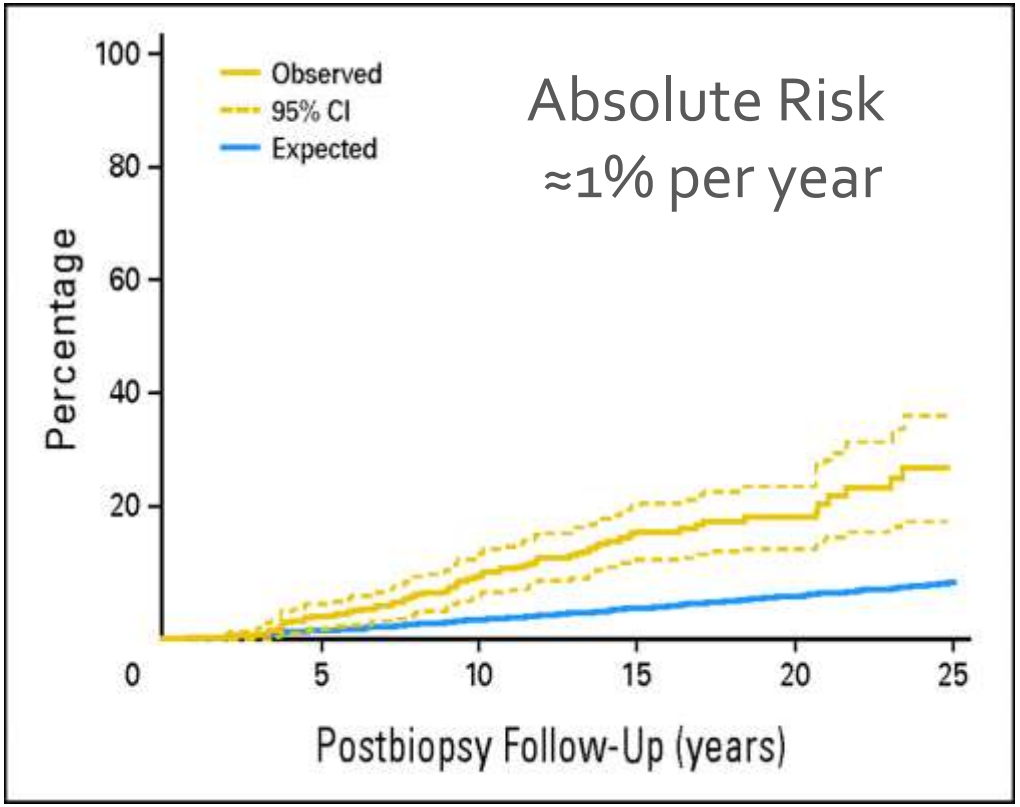
- Identified in 8-17% of all benign breast biopsies
- Similar in appearance and shares genetic and molecular similarities with low grade DCIS*

(*distinction can be difficult)

- Twenty-year cumulative risk of 21%

- Risk similar for ALH and ADH
  - ⇧ younger age at dx
  - ⇧ multiple foci of atypia

- Strong family history results in no additional risk if ADH/ALH already present



Degnim AC et al. JCO 2007; Hartmann LC et al. Cancer Prev Res 2014

RISK FACTORS

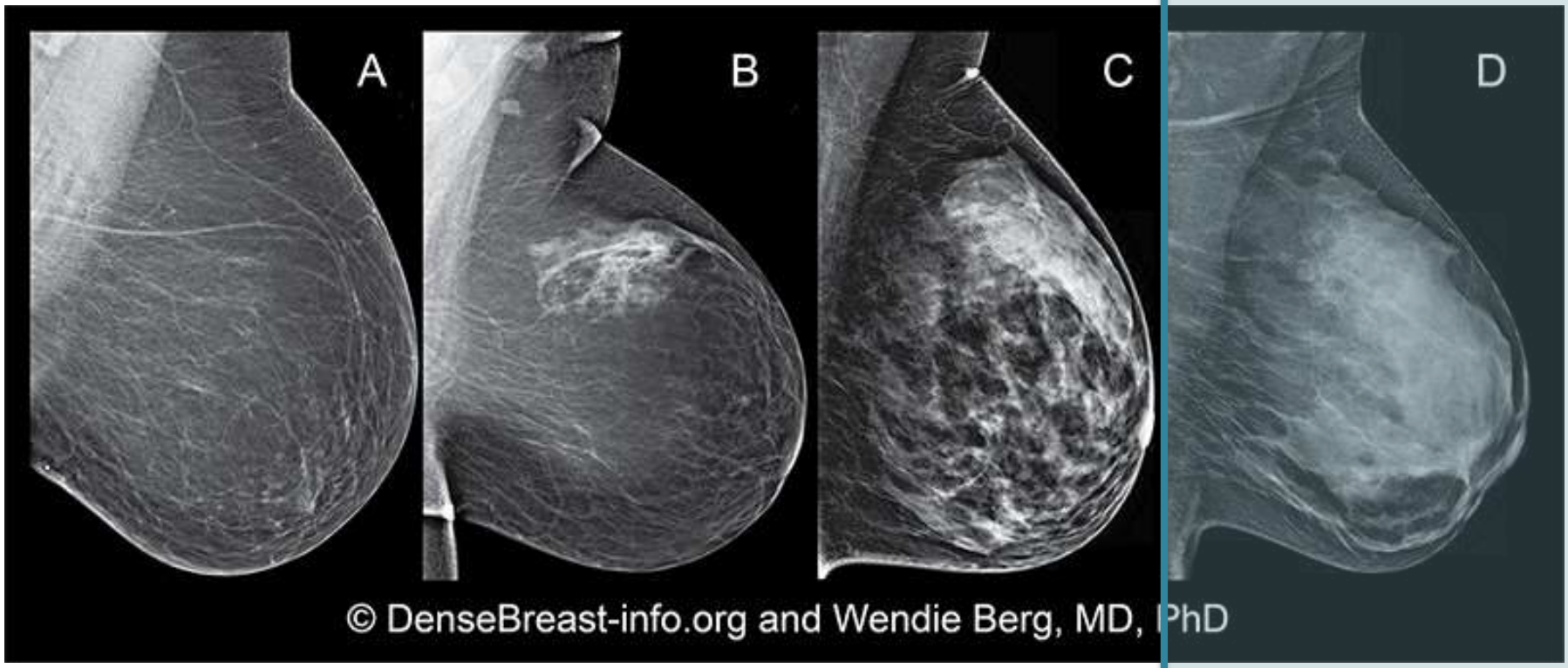
ATYPICAL BREAST BIOPSIES

	Risk of Upgrade to Malignancy	Surgical Excision	Breast Cancer Risk	Risk Reduction/ Prevention
ALH	0-1%	Not required	1% per year	Yes
LCIS	1-3%	Not required[a]	1-2% per year	Yes
ADH	20%	Yes[b]	1% per year	Yes
Focal FEA	7.5-11%	Yes	≈0.5% per year	No

[a] Unless discordant, pleomorphic LCIS, or multifocal/extensive LCIS (>4 TDLUs);
[b] Unless >95% calcs removed, <3 TDLUs involved, well sampled;
[c] Unless suspicious imaging findings, symptomatic, enlarging clinically;

RISK FACTORS

DENSE BREASTS



Almost Entirely Fatty (10%)	Scattered Fibroglandular (40%)	Heterogeneously Dense (40%)	Extremely Dense (10%)
Not Dense: MG Sensitivity 80-98%[1]		"Dense" Breasts: MG Sensitivity 30-48%[1]	
Ref	$OR_{BreastCA}$: 2.1 (1.6-2.6)[2]	$OR_{BreastCA}$: 2.4 (1.8-3.3)[2]	$OR_{BreastCA}$: 4.7 (3.0-7.4)[2]

[1]Hooley RJ et al, Radiology 2012 [2]Boyd et al, NEJM 2007 (Canadian Screening Programs)

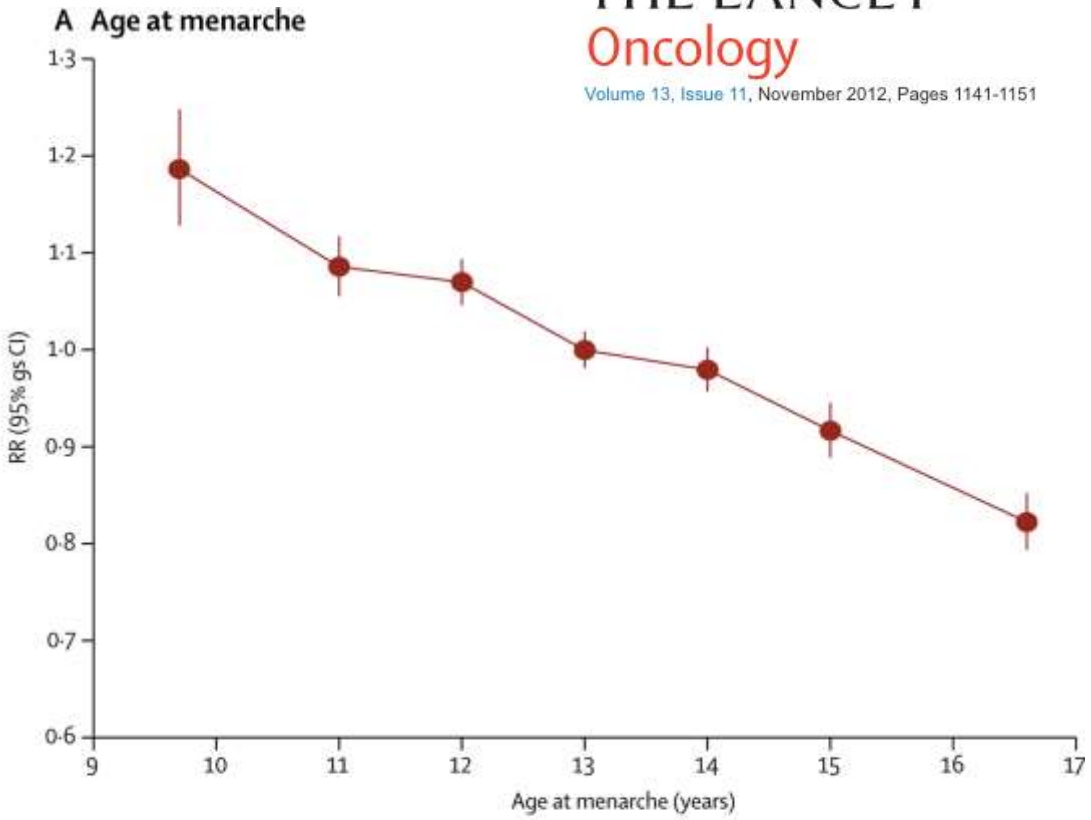
HORMONAL EXPOSURES MODESTLY AFFECT RISK: MENARCHE

Age at Menarche

5% increased risk for every year younger than 13 at menarche

(5% decrease in risk for every year older than 13 at menarche)

THE LANCET
Oncology
Volume 13, Issue 11, November 2012, Pages 1141-1151



Age group (mean, years)	<11 (9·7)	11 (11·0)	12 (12·0)	13 (13·0)	14 (14·0)	15 (15·0)	≥16 (16·6)
Cases/controls	5511/11 685	15 855/37 779	25 806/61 512	31 759/83 389	20 599/53 212	10 576/31 390	8858/27 124
RR	1·19	1·09	1·07	1·00	0·98	0·92	0·82
(95% qs CI)	(1·13–1·25)	(1·06–1·12)	(1·05–1·09)	(0·98–1·02)	(0·96–1·00)	(0·89–0·95)	(0·79–0·85)

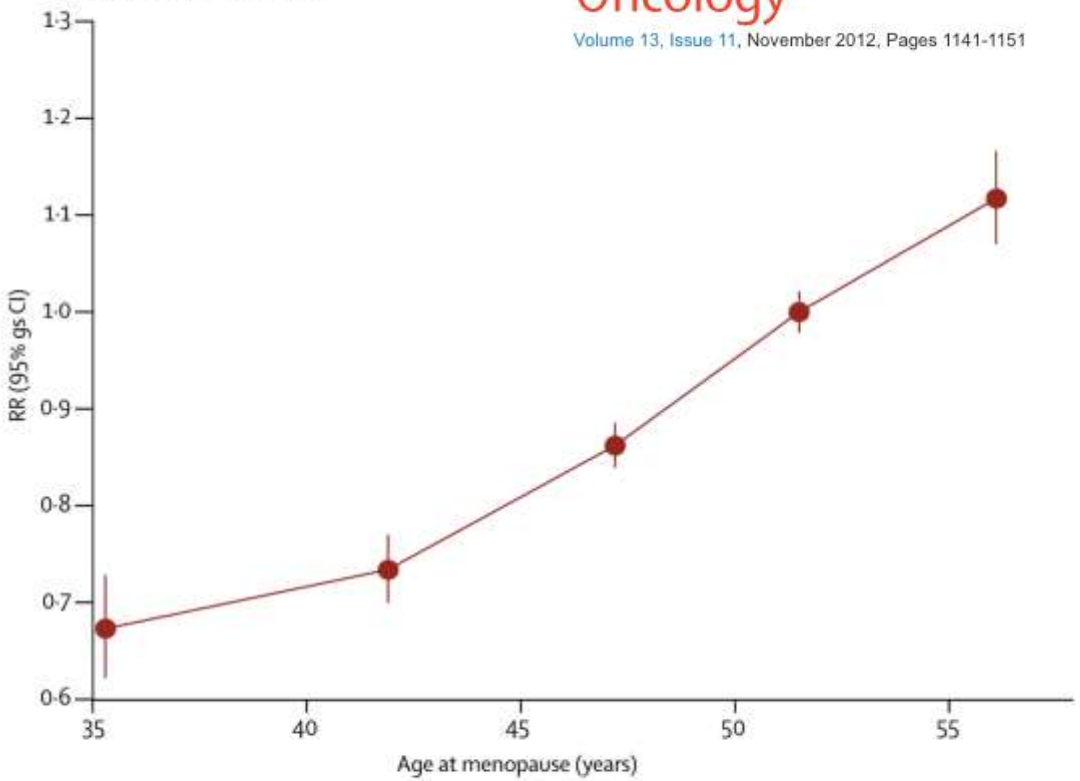
HORMONAL EXPOSURES MODESTLY AFFECT RISK: MENOPAUSE

Age at Menopause

3% increased risk for every year older than 50 at menopause

(3% decreased risk for every year younger than 50 at menopause)

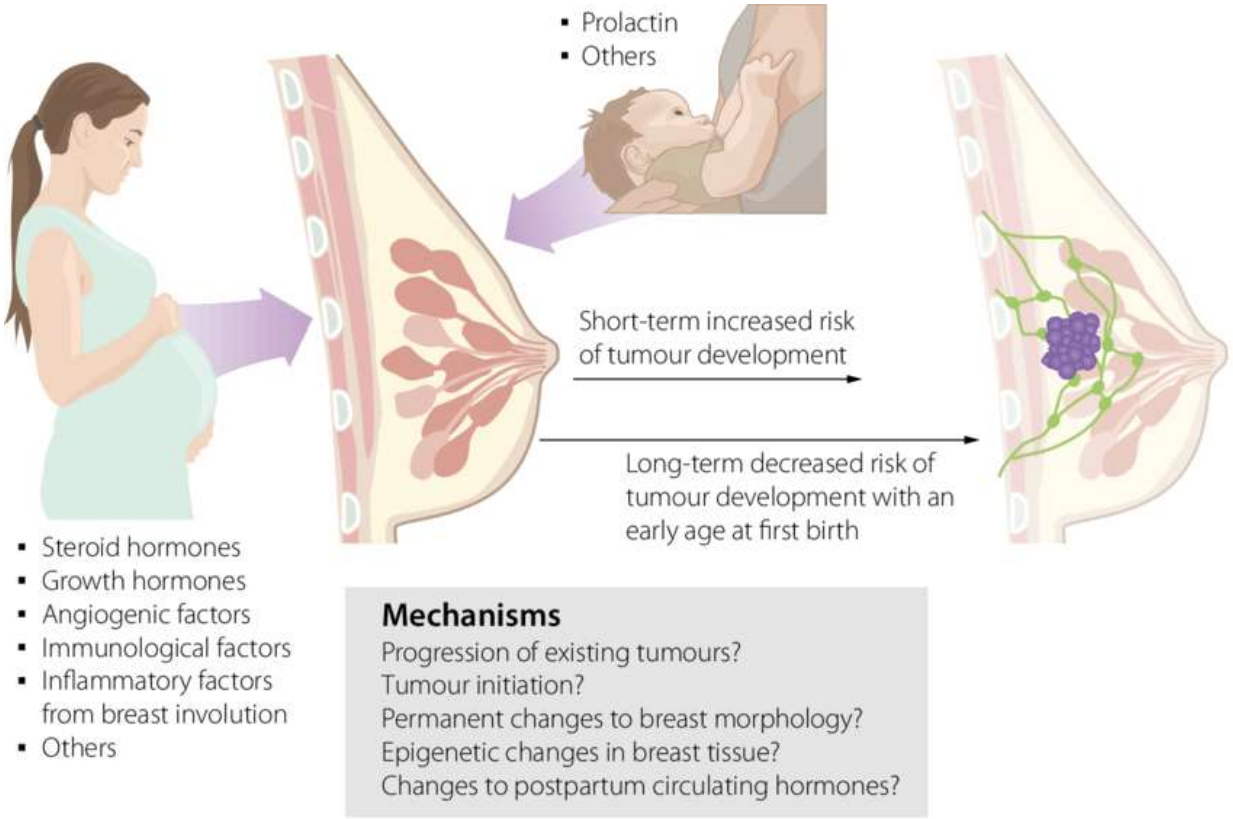
THE LANCET Oncology
Volume 13, Issue 11, November 2012, Pages 1141-1151



Age group (mean, years)	<40 (35·3)	40–44 (41·9)	45–49 (47·2)	50–54 (51·5)	≥55 (56·1)
Cases/controls	2397/7741	5516/18 544	17 336/52 040	28 197/75 944	6891/16 144
RR (95% gs CI)	0·67 (0·62–0·73)	0·73 (0·70–0·77)	0·86 (0·84–0·89)	1·00 (0·98–1·02)	1·12 (1·07–1·17)

RISK FACTORS

HORMONAL EXPOSURES MODESTLY AFFECT RISK: NUMBER OF & AGE AT FIRST PREGNANCY



Pregnancy:

- Increases short term risk for approximately 10 years
- Lowers long term risk to lower than that of nulliparous women (unless if older 35 at FB)
- Multiple pregnancies over short duration = lower risk

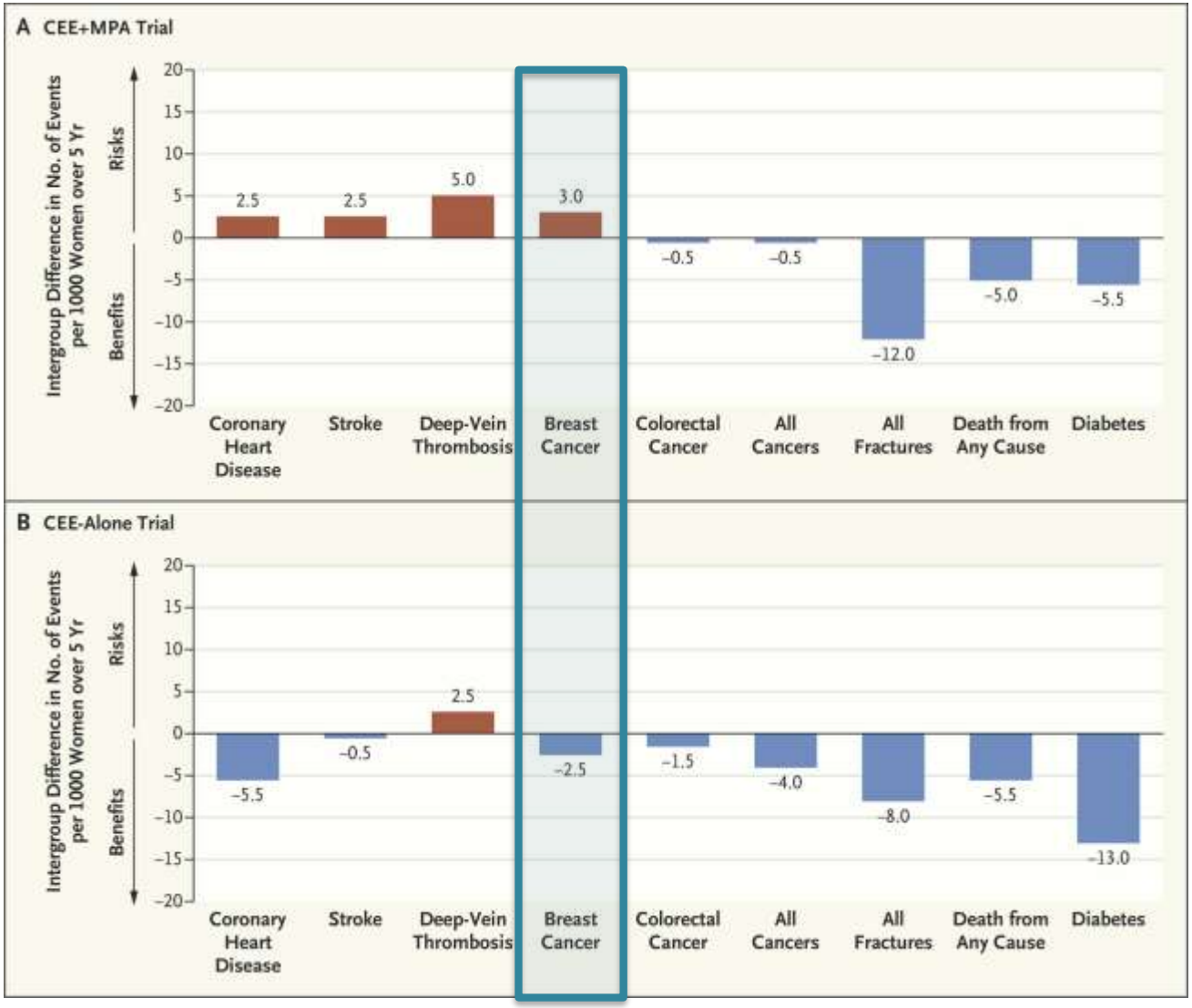
Age at First Birth:

The early studies establishing risk related to age at first birth demonstrated a 40% risk increase with FB at 35 years compared to women who gave birth <20 years

Troisi et al. J Int Med 2018; Lambe M et al. NEJM 1994; Colditz et al. Am J Epidem 2000

- Women's Health Initiative (WHI)
  - Long term (>5 yr) use of combined HRT in 16,608 women with an intact uterus associated with elevated risk of breast cancer
    - Combined HRT associated with 26% increased breast cancer risk (HR 1.26, 95% CI 1·00–1·59)
  - Long term follow up of 10,739 post-menopausal women who had undergone TAH BSO + taking estrogen-alone
    - HRT had no increased risk (HR 0·77, 95% CI 0·62–0·95) of breast cancer
    - CAUTION: Significantly increased risk in patients with a family history of breast cancer (25%) or benign breast disease (22%)

1) WHI investigators, JAMA 2002 2) Anderson et al. Lancet Oncol 2012



Manson et al. JAMA 2013; NEJM 2016

- Increases breast cancer risk in post menopausal women
  - Post menopausal weight loss of 4-11 lbs associated with a 20% risk reduction in breast cancer[1]
  - Post menopausal weight gain associated with an increase in breast cancer risk[2]
- Bariatric surgery in obese (BMI >35) patients associated with 30-45% reduction in pre- and post-menopausal risk[3]
- Effect mediated through decreased adiposity associated estrogen and insulin levels

1) Eliassen AH et al. JAMA, 2006 2) Ahn J et al. Arch Int Med, 2007 3) Felgelson HS et al. Ann Surg 2019

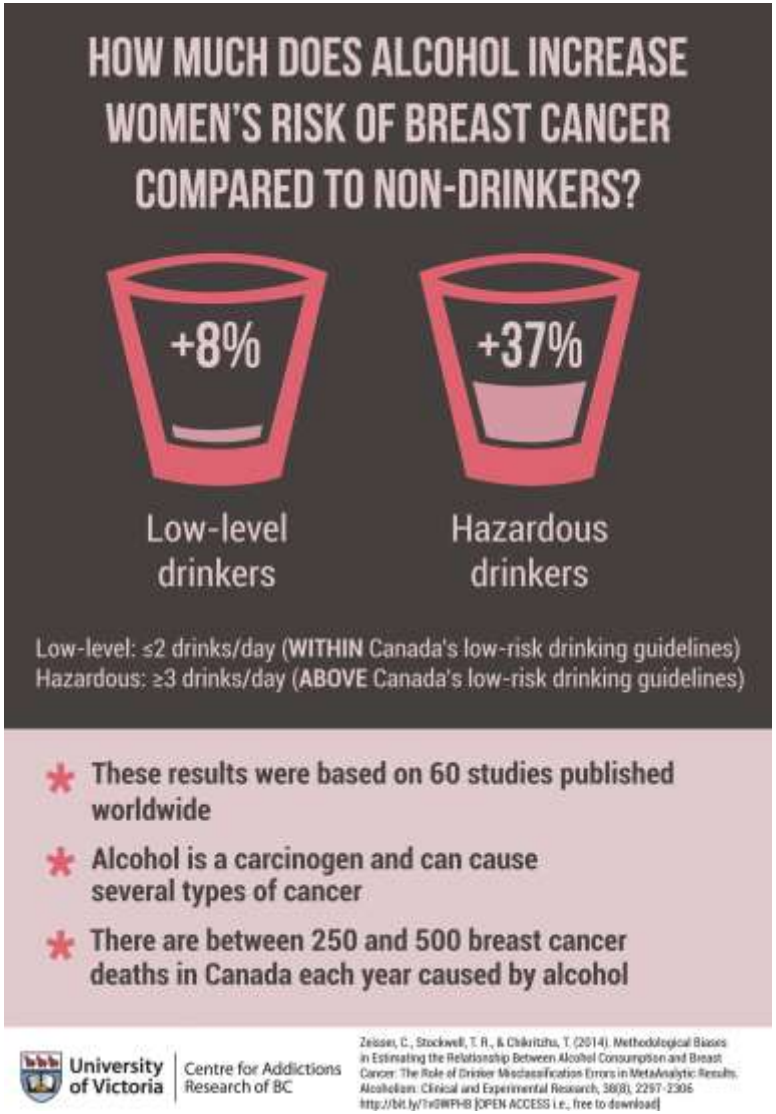
RISK FACTORS

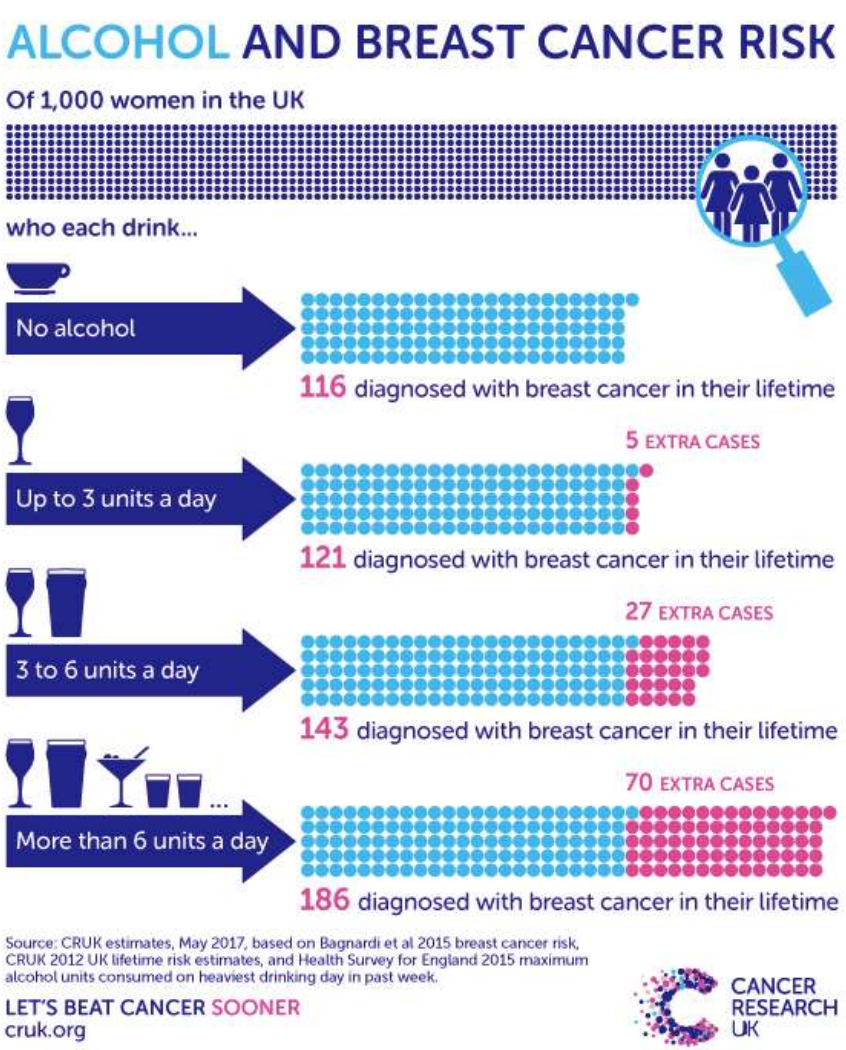
LIFESTYLE FACTORS: OBESITY

- Alcohol affects the way the body metabolizes estrogen
  - Estrogen levels higher in women with an alcohol intake greater than 1 drink/day
  - Women who drink 2-3 glasses/day = 20% higher risk of breast cancer than non-drinkers
  - Women who drink 3+ drinks per day = 37% risk

- Smoking
  - Associated with a 24% increased risk in current smokers and a 13% increased risk in prior smokers

1) Hamajima et al., BJC 2002 2) Gaudet et al. JNCI 2013


HOW MUCH DOES ALCOHOL INCREASE WOMEN'S RISK OF BREAST CANCER COMPARED TO NON-DRINKERS?
+8%
+37%
Low-level drinkers
Hazardous drinkers
Low-level: ≤2 drinks/day (WITHIN Canada's low-risk drinking guidelines)
Hazardous: ≥3 drinks/day (ABOVE Canada's low-risk drinking guidelines)
These results were based on 60 studies published worldwide
Alcohol is a carcinogen and can cause several types of cancer
There are between 250 and 500 breast cancer deaths in Canada each year caused by alcohol
University of Victoria
Centre for Addictions Research of BC
Zeisser, C., Stockwell, T. R., & Chikritzhs, T. (2014). Methodological Biases in Estimating the Relationship Between Alcohol Consumption and Breast Cancer: The Role of Drinker Misclassification Errors in MetaAnalytic Results. Alcoholism: Clinical and Experimental Research, 38(8), 2297-2306
http://bit.ly/1v0WPHB [OPEN ACCESS i.e., free to download]


ALCOHOL AND BREAST CANCER RISK
Of 1,000 women in the UK
who each drink...
No alcohol
116 diagnosed with breast cancer in their lifetime
Up to 3 units a day
5 EXTRA CASES
121 diagnosed with breast cancer in their lifetime
3 to 6 units a day
27 EXTRA CASES
143 diagnosed with breast cancer in their lifetime
More than 6 units a day
70 EXTRA CASES
186 diagnosed with breast cancer in their lifetime
Source: CRUK estimates, May 2017, based on Bagnardi et al 2015 breast cancer risk, CRUK 2012 UK lifetime risk estimates, and Health Survey for England 2015 maximum alcohol units consumed on heaviest drinking day in past week.
LET'S BEAT CANCER SOONER
cruk.org
CANCER RESEARCH UK

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  - Associated with a 24% increased breast cancer risk in current smokers and a 13% increased risk in prior smokers

1) Hamajima et al., BJC 2002 2) Gaudet et al. JNCI 2013

REFERRAL

CONSULTATION

High Risk Evaluation

RISK ASSESSMENT
TYRER-CUZICK V8, BOADICEA

BIO-BANKING
BLOOD, BIOPSY TISSUE BLOCKS IF AVAILABLE

GENETICS

- Pre-test Counselling and Testing
- Post-test Counseling
- Cascade Testing for Family members

ALLIED HEALTH PARTNERS

- Bariatrics for Weight Loss Surgery (BMI >40)
- Nutrition for Weight Loss Program (BMI 30-40)
- Smoking Cessation Program
- GI for CRC/ Pancreatic Screening
- Gynecology for Ovarian Cancer Risk
- Dermatology for Melanoma Screening

BREAST SCREENING

- Mammo-graphic Screening
- Screening MRI
- Bone health BMD/DEXA

PREVENTION

- SERMs/AI
- Bilateral Prophylactic Mastectomy
- RRS/ RRSO

FOLLOW UP

Hôpital général juif
Jewish General Hospital
Centre du cancer Segal Cancer Centre

RISK MODELS

EVALUATING BREAST CANCER RISK

Risk Model	Outcomes	Factors Assessed
Breast Cancer Risk Assessment Tool (Gail Model)	5-year risk and lifetime risk	Age, ethnicity, menarche, age at first live birth, number of previous breast biopsies (atypia), first degree relatives with breast cancer
IBIS tool (Tyrer-Cuzick Model) v.8	10-year risk and lifetime risk	Age, menarche, parity, age at first birth, meno status, HRT, BMI, breast density*, AH/LCIS, breast biopsy, PRS, Family history of breast or ovarian cancer, bilateral breast cancer, AJ ancestry, BRCA1/2 status
BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm model) v.4 *beta*	10-year risk and risk of genetic mutation	Age, FH of breast, ovarian, pancreatic or prostate cancer, bilateral breast cancer, subtype of cancer, BRCA1/2, PALB2 CHEK2, ATM status, AJ ancestry
BRCApro	10-year risk and risk of BRCA mutation	Age, race, personal or FH of breast and ovarian cancer, bilateral breast cancer, subtype of cancer, BRCA1/2 status, AJ ancestry

BCRT (Gail Model)

http://bcrisktool.cancer.gov

NIH NATIONAL CANCER INSTITUTE

Breast Cancer Risk Assessment Tool

RISK CALCULATOR | ABOUT THE CALCULATOR

Patient Eligibility 1 — Demographics 2 — Patient & Family History 3

Patient Eligibility

Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) or has she received previous radiation therapy to the chest for treatment of Hodgkin lymphoma?

- ○ Yes
- ○ No

Does the woman have a mutation in either the *BRCA1* or *BRCA2* gene, or a diagnosis of a genetic syndrome that may be associated with elevated risk of breast cancer?

- ○ Yes
- ○ No
- ○ Unknown

Demographics

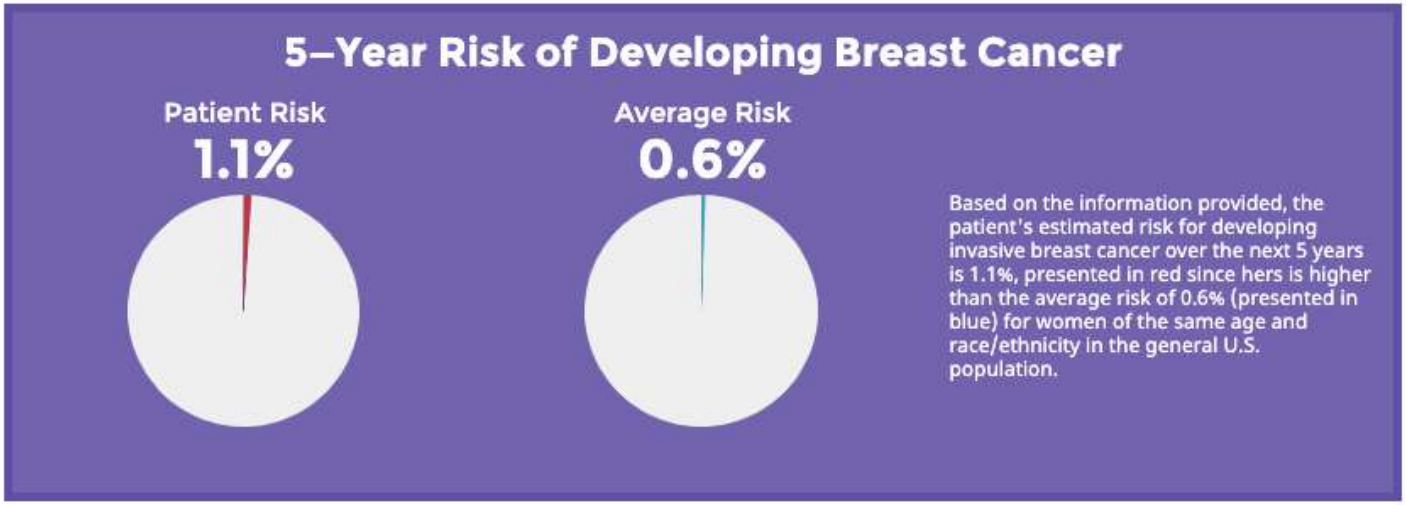
What is the patient's age?

This tool calculates risk for women between the ages of 35 and 85.

Select age

BCRT (Gail Model)

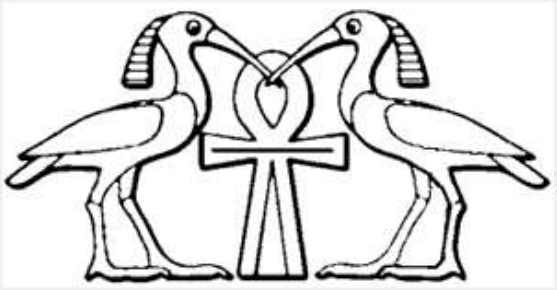
40F Caucasian, Menarche 12, 31 at FB, mother with breast cancer…



www.ems-trials.org/riskevaluator

IBIS Breast Cancer Risk Evaluation Tool

NEW! v8 [ZIP]



Description of breast cancer risk program

The program assumes that there is a gene predisposing to breast cancer in addition to the *BRCA1/2* genes. The woman's family history is used to calculate the likelihood of her carrying an adverse gene, which in turn affects her likelihood of developing breast cancer. The risks of developing breast cancer for the general population were taken from data on the first breast cancer diagnosis (ICD-10 code C50) in Thames Cancer Registry area (UK) between 2005-2009. The risk from family history (caused by the adverse genes) is modelled to fit the results in "Familial Breast and Ovarian Cancer: A Swedish Population-based Register Study, Anderson H et al., American Journal of Epidemiology 2000, 152: 1154-1163".

The risk from other classical factors including age at first child and benign disease are combined with familial risk.

The latest version of the model (v8) incorporates mammographic density.

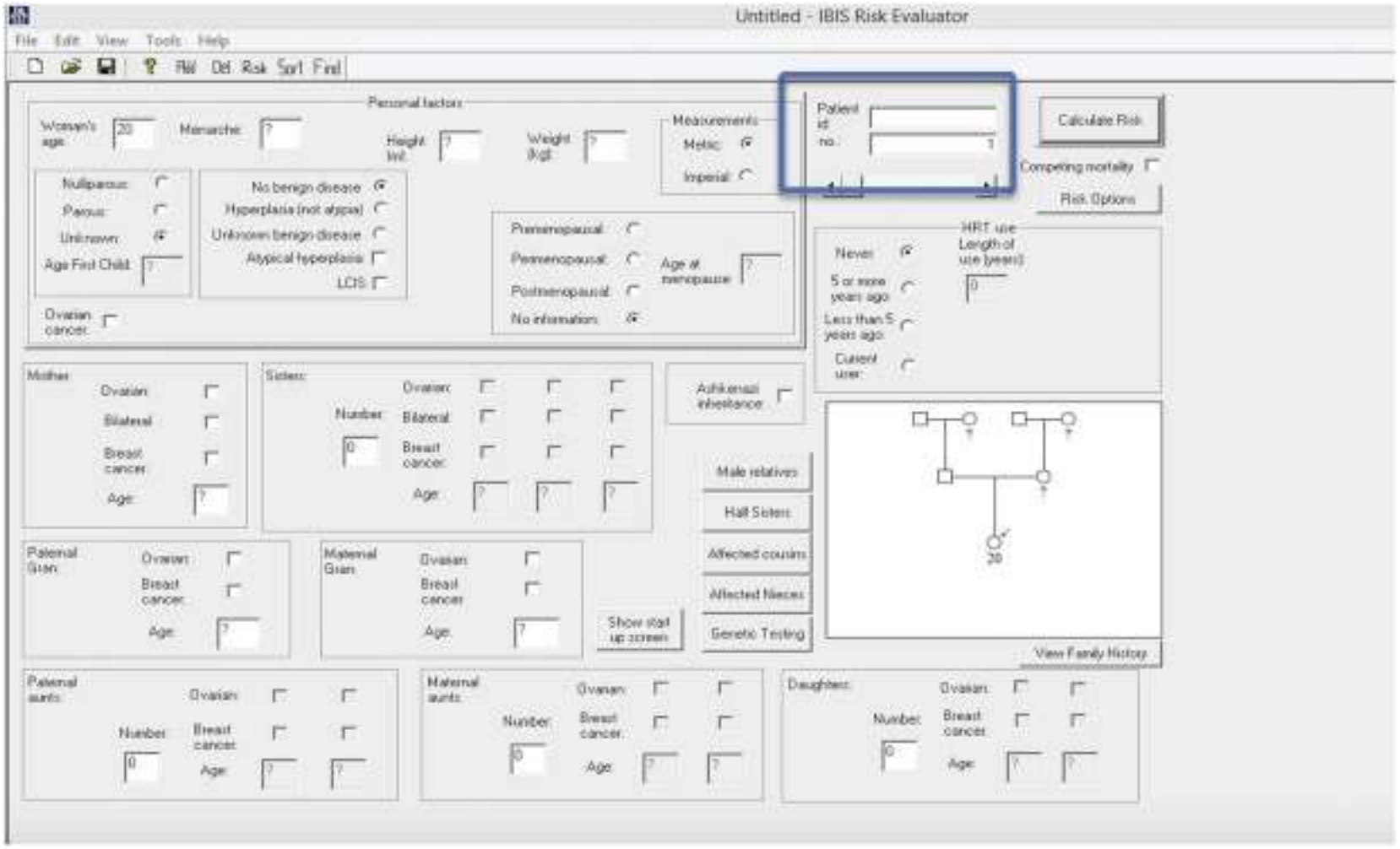
Contact Details

Prof. Jack Cuzick
Centre for Cancer Prevention,
Wolfson Institute of Preventive Medicine,
Charterhouse Square,
London
EC1M 6BQ

email: riskevaluator@ems-trials.org

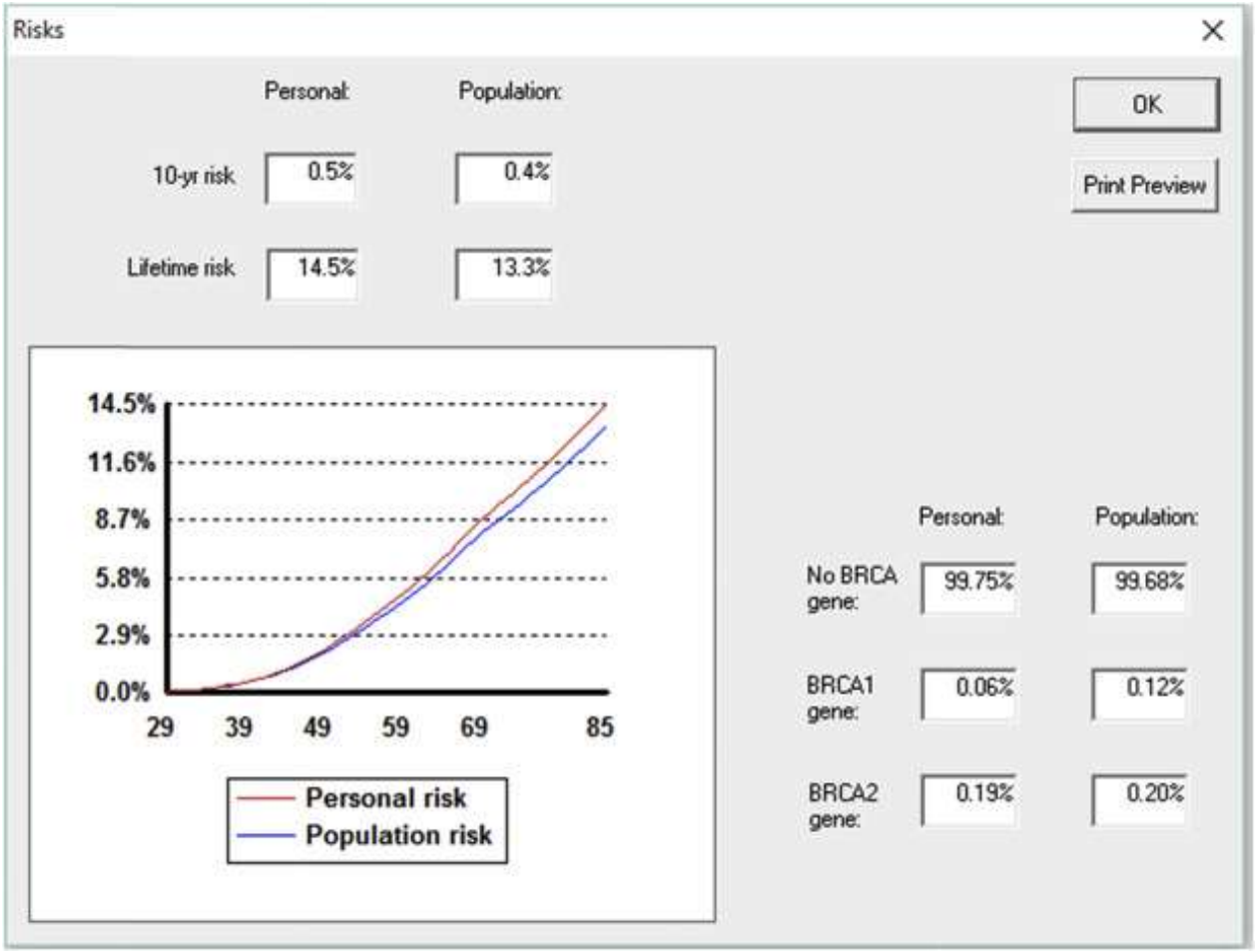
IBIS (Tyrer-Cuzick)

DESKTOP VERSION



IBIS (Tyrer-Cuzick)

MODEL OUTPUT



BOADICEA:

https://Ccge.medschl.cam.ac.uk/boadicea

BRCApro:

https://projects.iq.harvard.edu/bayesmendal/brcapro

Centre for Cancer Genetic Epidemiology

Centre for Cancer Genetic Epidemiology

BOADICEA

- BOADICEA model description
- BOADICEA Web Application
- Setup your BOADICEA user account
- Login to BWA v3
- Login to BWA v4 *Beta*
- Advice for the public
- Publications
- Contact

BOADICEA

The **Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm** (BOADICEA) is a computer program that is used to calculate the risks of breast and ovarian cancer in women based on their family history. It is also used to calculate the probability that they are carriers of cancer-associated mutations in the BRCA1 or BRCA2 gene. To access BOADICEA, all you need is a BOADICEA is a user account, which you can setup online in a minutes here.

You can access two different versions of the BOADICEA program using the links in the menu to the left:

(i) BWA v3 considers the explicit effects of BRCA1 and BRCA2 mutations;

(ii) BWA v4 *Beta* considers the explicit effects of BRCA1, BRCA2, PALB2, CHEK2 and ATM mutations.

This tool is provided for research use only. The BOADICEA software is at an early stage of development and is provided "as is" (ie. it is not error-free). BOADICEA is designed for research use only and is not designed for providing information on which to base clinical decisions. BOADICEA has not been approved for use by any regulatory authority.

For general BOADICEA inquiries please contact Alex Cunningham (apc40@medschl.cam.ac.uk) or Antonis Antoniou (aca20@medschl.cam.ac.uk).

BWA v4 *Beta* is not for commercial use. For commercial BOADICEA inquiries please contact Vibha Tamboli (Vibha.Tamboli@enterprise.cam.ac.uk) or Terry Parlett (Terry.Parlett@enterprise.cam.ac.uk).

UNIVERSITY OF CAMBRIDGE

Centre for Cancer Genetic Epidemiology

Consultand Consultand

Enter details of the consultand...

Clinical history | Breast cancer pathology | Genetic testing

First name/ID	Jane Doe				
Personal details	Sex and status	○ Male ◉ Female	◉ Alive ○ Dead	☐ Ashkenazi origin	
	Age or Age at death	◉ Exact	○ Approx Age range	○ Unknown	
	Year of birth	◉ Exact	○ Approx Year range	○ Unknown	
Breast cancer ☐	Age at diagnosis	◉ Exact	○ Approx Age range	○ Unknown	
Contralateral BC ☐	Age at diagnosis	◉ Exact	○ Approx Age range	○ Unknown	

search a-z contact

UNIVERSITY OF CAMBRIDGE

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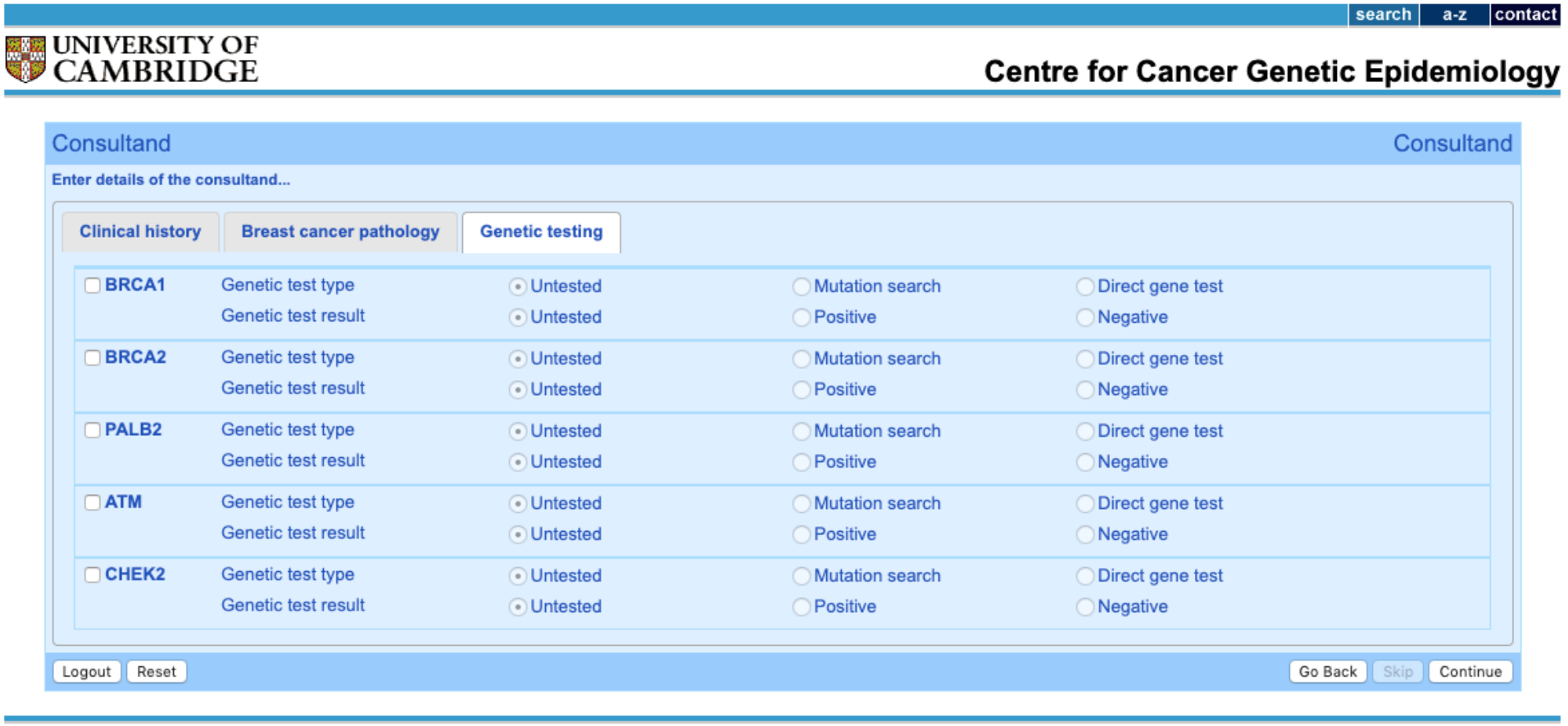
Consultand Consultand

Enter details of the consultand...

Clinical history | Breast cancer pathology | Genetic testing

☐ Estrogen Receptor (ER)	◉ Unknown	○ Positive	○ Negative
☐ Progestrogen Receptor (PR)	◉ Unknown	○ Positive	○ Negative
☐ Human Epidermal Growth Factor Receptor Two (HER2)	◉ Unknown	○ Positive	○ Negative
☐ Cytokeratin Fourteen (CK14)	◉ Unknown	○ Positive	○ Negative
☐ Cytokeratin Five/Six (CK5/6)	◉ Unknown	○ Positive	○ Negative

Logout Reset Go Back Skip Continue


search
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UNIVERSITY OF CAMBRIDGE
Centre for Cancer Genetic Epidemiology
Consultand
Consultand
Enter details of the consultand...
Clinical history
Breast cancer pathology
Genetic testing
BRCA1
Genetic test type
Untested
Mutation search
Direct gene test
Genetic test result
Untested
Positive
Negative
BRCA2
Genetic test type
Untested
Mutation search
Direct gene test
Genetic test result
Untested
Positive
Negative
PALB2
Genetic test type
Untested
Mutation search
Direct gene test
Genetic test result
Untested
Positive
Negative
ATM
Genetic test type
Untested
Mutation search
Direct gene test
Genetic test result
Untested
Positive
Negative
CHEK2
Genetic test type
Untested
Mutation search
Direct gene test
Genetic test result
Untested
Positive
Negative
Logout
Reset
Go Back
Skip
Continue

BayesMendel Lab
450 Brookline Ave
Boston, MA 02215
Contact

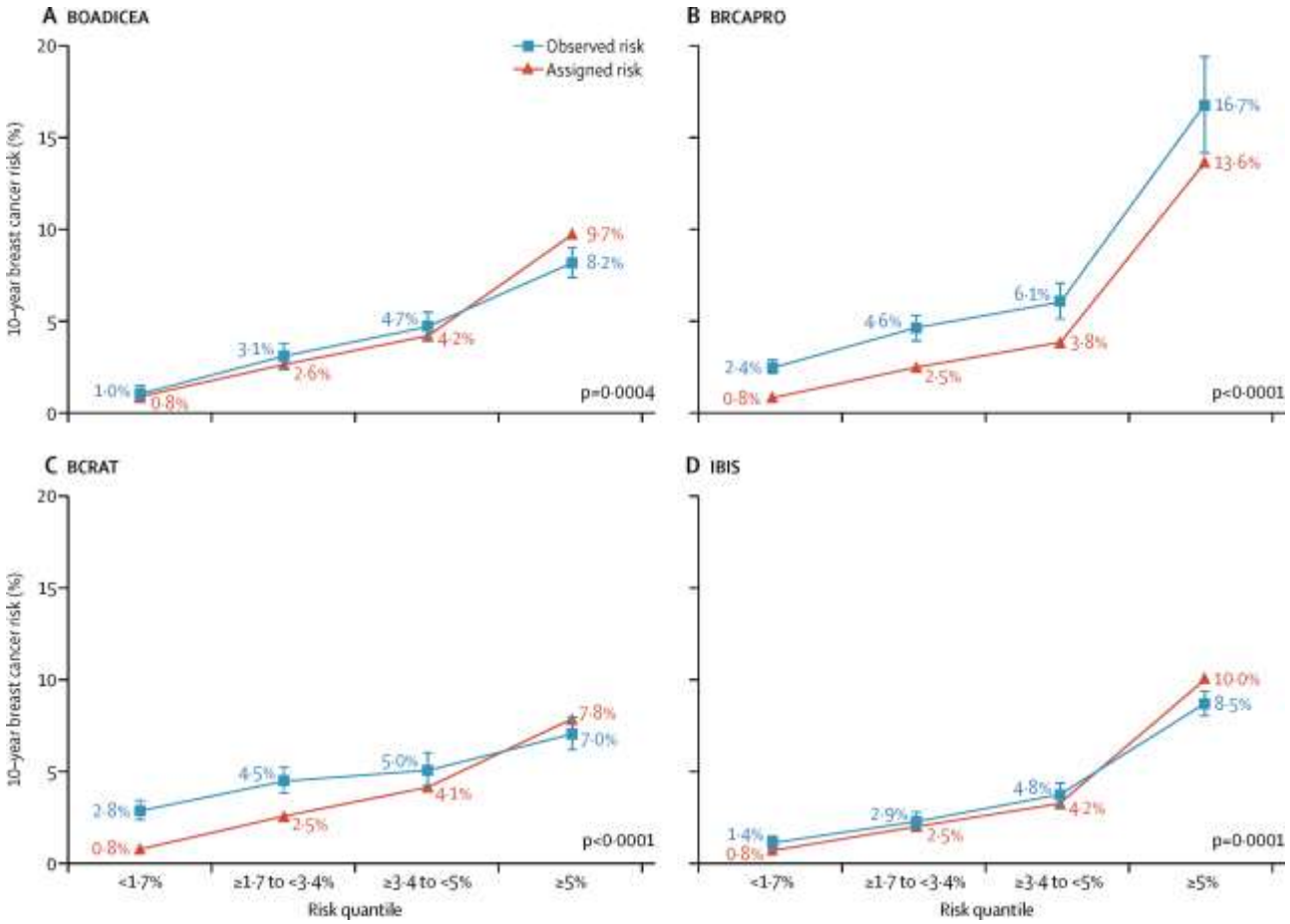
BRCAPRO

BRCAPRO is a statistical model, with associated software, for assessing the probability that an individual carries a germline deleterious mutation of the BRCA1 and BRCA2 genes, based on family history of breast and ovarian cancer, based on his or her family's history of breast and ovarian cancer, including male breast cancer and bilateral synchronous and asynchronous diagnoses. BRCAPRO uses a Mendelian approach that assumes autosomal dominant inheritance. This assumption is supported extensively by previous linkage analyses. Age-dependent penetrances and prevalences are based on a systematic review of the literature.

Recent updates to the BRCAPRO software include:

- BRCAPRO has been re-calibrated and improved with updated penetrances for contralateral breast cancer.
- Package now allows for input on ethnicity for each family member, in order to better characterize families containing more than one ethnic groups, each of which may present different allele frequencies for the mutations of interest.
- Mastectomy as an intervention has been added to BRCAPRO.
- Improved the error message returned when there is a problem with the Twins input.

MODEL CALIBRATION

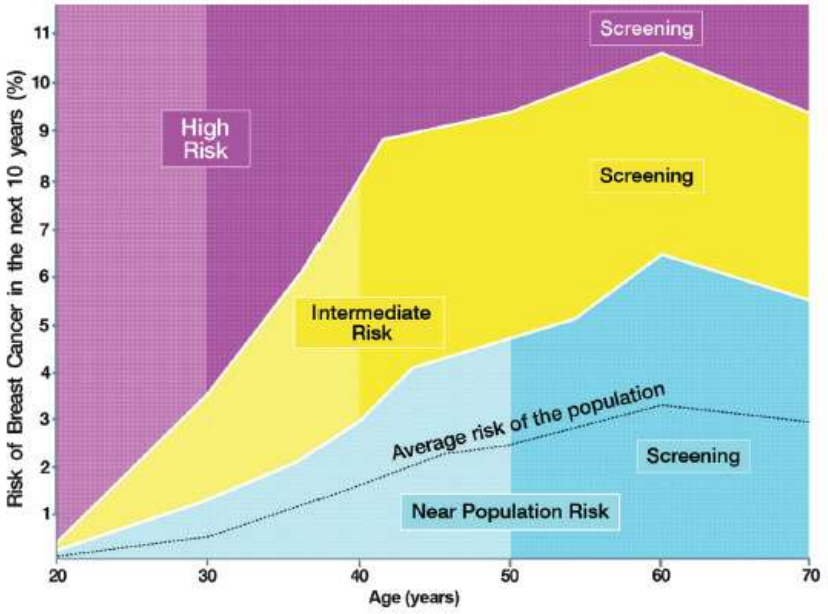


THE LANCET
Oncology
Volume 20, Issue 4, April 2019, Pages 504-517

"Our results suggest that models that include multigenerational family history, such as BOADICEA and IBIS, have better ability to predict breast cancer risk, even for women at average or below-average risk of breast cancer."

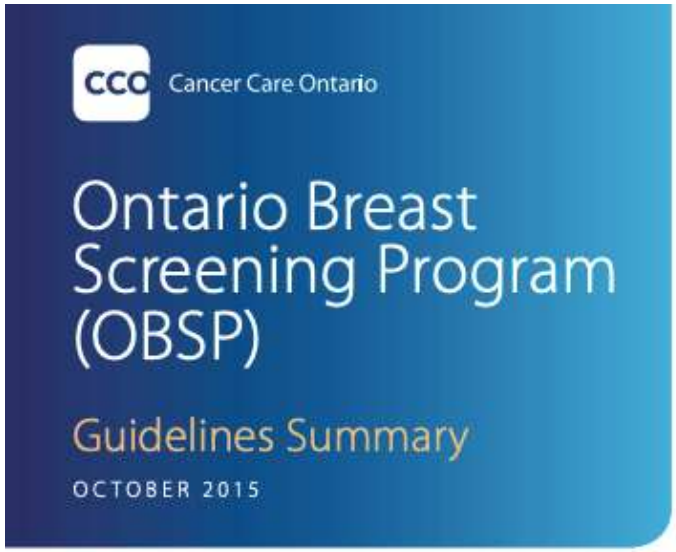
TRANSLATING RISK ESTIMATES INTO SCREENING RECOMMENDATIONS

- 30 year old patient: 10-year risk >3%, lifetime risk >25%
  - Consider starting mammographic + MRI screening at 30 years
  - Consider referral to genetics
- 40 year old: 10-year risk between 3-8%, lifetime risk >25%
  - Consider starting mammographic screening at 40 years
  - If less, discuss routine screening at 50



HIGH RISK PATIENTS

PRE-EXISTING SCREENING PROGRAMS

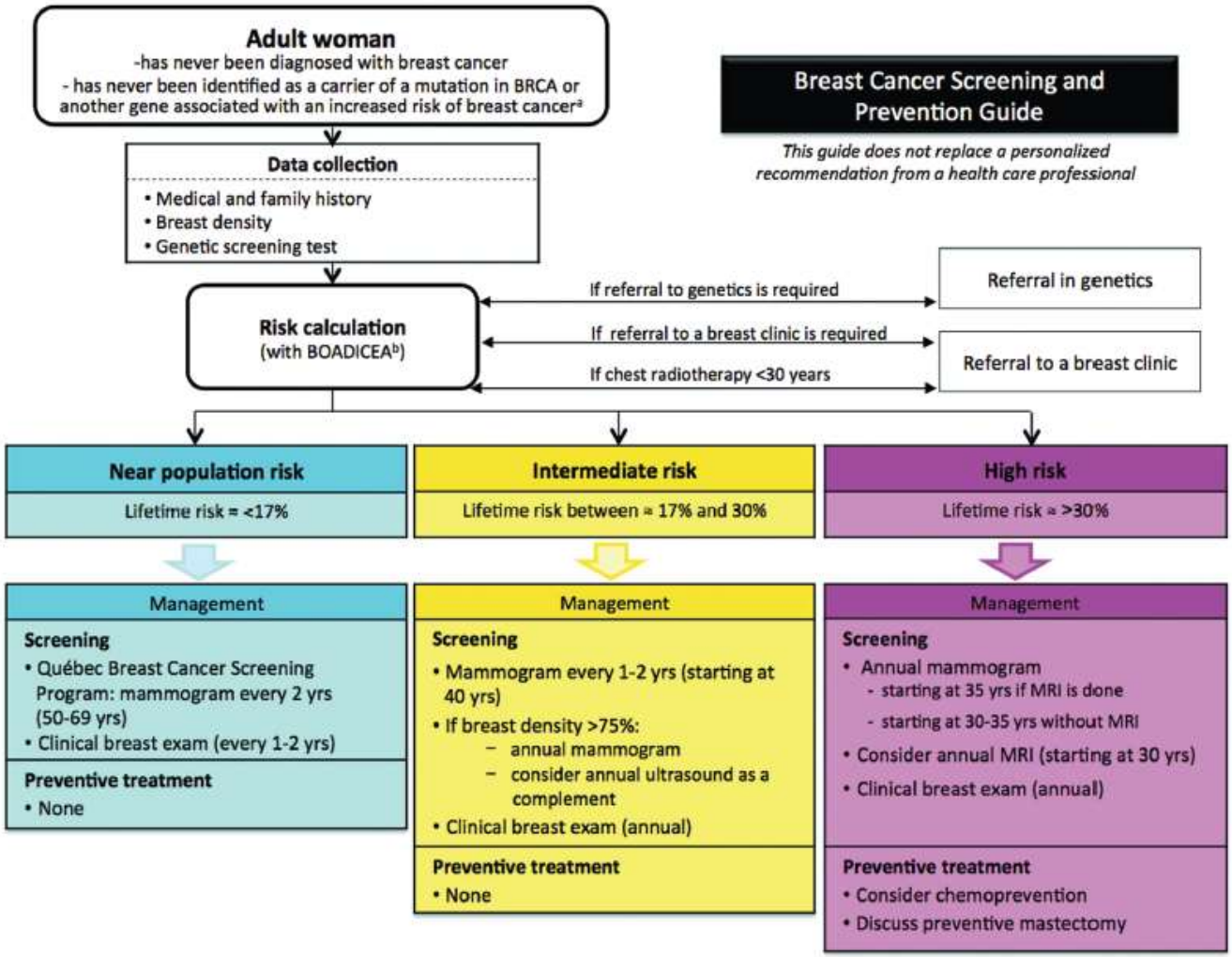


Eligible for direct entry into the high risk breast screening program based on personal and family history. Must meet one of the following risk criteria:

- Known to be a carrier of the BRCA1/2, PALB2, PTEN, CDH1, TP53 gene mutation;
- First-degree relative of a mutation carrier, has had genetic counselling and has declined genetic testing;
- Previously assessed by a genetic clinic (using the IBIS/Tyrer-Cuzick or BOADICEA tools) as having a ≥25 per cent personal lifetime risk of breast cancer based on family history; or
- Received radiation therapy to the chest before age 30 and at least eight years ago.

HIGH RISK PATIENTS

PRE-EXISTING SCREENING PROGRAMS



HIGH RISK
BREAST CLINIC

DESIGNED TO FOLLOW PATIENTS WITH...

ATYPICAL BREAST BIOPSIES	Lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH) & atypical ductal hyperplasia (ADH), and other atypias (flat epithelial atypia, atypical papillomas)
PERSONAL OR FAMILY HISTORY OF CANCER	Patients who have multiple close (1st or 2nd degree) relatives with breast cancer, a first degree relative with early onset breast cancer, any family history of ovarian cancer, or themselves have a history of cancer treated with chest wall radiation.
KNOWN GENETIC SUSCEPTIBILITY	Patients or families with known BRCA1/2 and PALB2 mutations, as well as women with other high penetrance (TP53, PTEN CDH1, STK11) or moderate penetrance mutations (ATM, CHEK2, NBN, etc.)
DENSE BREASTS	Women with extremely dense breasts (Category D) on screening mammography, tomosynthesis, or MRI.
OTHER RISK FACTORS	Women with actionable lifestyle risk factors such as obesity (BMI >40), smoking, and increased alcohol consumption (>7 drinks/week)

HIGH RISK PATIENTS

EARLIER INITIATION OF SCREENING

Risk Factor	Age of Initiation of Screening	Frequency of Screening
Extremely Dense Breasts	50 years	Annual Mammo +/- discuss DBT or US
Family history of onset breast cancer	10 years prior to youngest diagnosed family member or 50, whichever occurs first	Annual Mammo +/- DBT or US if dense
Atypical breast biopsy (ALH, ADH, LCIS)	40 years or at time of breast biopsy showing atypia	Annual Mammo +/- DBT or US if dense, consider MRI*
Moderate Penetrance Mutation Carrier (ATM, CHEK2, NBN, PALB2 without FHx)	10 years prior to youngest diagnosed family member, or starting at age 40, whichever occurs first*	Annual Mammo +/- DBT or US if dense, consider MRI*
High Penetrance Mutation Carrier (BRCA1/2, PTEN, CDH1, TP53, PALB2 with family history breast caner)	25-30 years	Annual Mammo + Annual MRI (alternating every 6 months)
History of Chest Wall Radiation in Childhood	25-30 years	Annual Mammo + Annual MRI (alternating every 6 months)

*Insufficient evidence to support or refute/evidence in evolution

REFERRAL

CONSULTATION

High Risk Evaluation

RISK ASSESSMENT
TYRER-CUZICK V8, BOADICEA

BIO-BANKING
BLOOD, BIOPSY TISSUE BLOCKS IF AVAILABLE

GENETICS

- Pre-test Counselling and Testing
- Post-test Counseling
- Cascade Testing for Family members

ALLIED HEALTH PARTNERS

- Bariatrics for Weight Loss Surgery (BMI >40)
- Nutrition for Weight Loss Program (BMI 30-40)
- Smoking Cessation Program
- GI for CRC/ Pancreatic Screening
- Gynecology for Ovarian Cancer Risk
- Dermatology for Melanoma Screening

BREAST SCREENING

- Mammo-graphic Screening
- Screening MRI
- Bone health BMD/DEXA

PREVENTION

- SERMs/AI
- Bilateral Prophylactic Mastectomy
- RRS/ RRSO

FOLLOW UP

Hôpital général juif
Jewish General Hospital
Centre du cancer Segal Cancer Centre

PREVENTION

CLINICAL TRIALS: SERMs/AIs

	No. Patients	Agent used	Median Follow Up (months)	Breast Cancer Risk Reduction (RR/HR, 95% CI)
NSABP P-1 (BCPT) Fisher et al. (2005)	13,388	Tamoxifen 20 mg/d x 5 yrs vs. Placebo	84	0.57 (0.46-0.70)
IBIS-I, 2014 Cuzick et al. (2015)	7,154	Tamoxifen 20 mg/d x 5 yrs vs. Placebo	192	0.71 (0.60-0.83)
NSABP P-2 (STAR) Vogel et al. (2010)	19,747	Raloxifene 60 mg/d vs. Tamoxifen 20 mg/d x 5 yrs	81	1.24 (1.05-1.47)
TAM-01 DeCensi et al. (2019)	500	Tamoxifen 5 mg/d vs. Placebo x 3 yrs	61	0.48 (0.26-0.92)
MAP.3 Goss et al. (2011)	4,560	Exemestane 25 mg/d x 5 yrs vs. Placebo	35	0.35 (0.18-0.70)
IBIS-II Cuzick et al. (2013)	3,684	Anastrozole 1 mg/d x 5 yrs vs. Palcebo	60	0.47 (0.32-0.68)

PREVENTION

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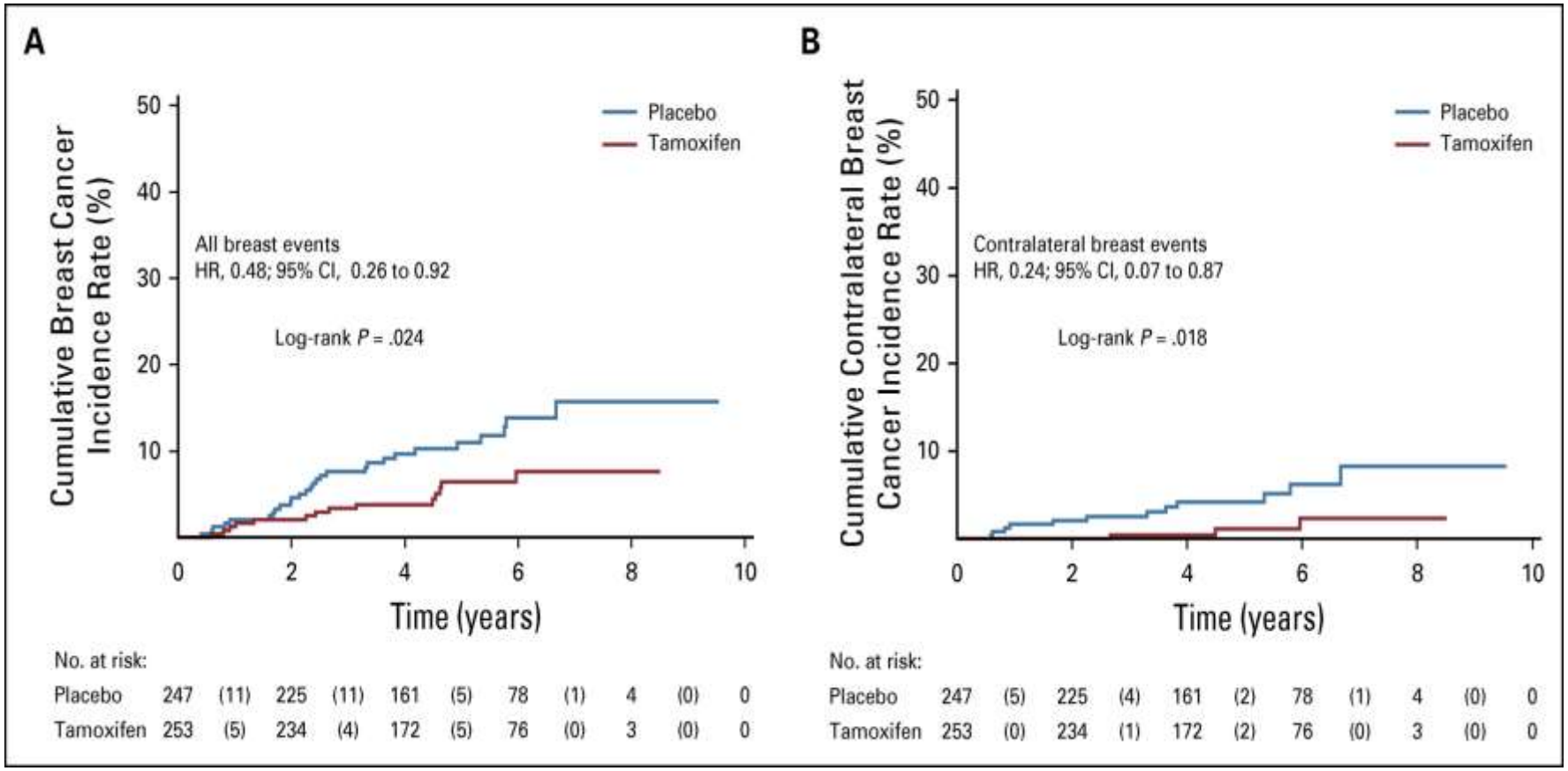
- Multicenter TAM-01 trial (Italy)
  - Biomarker studies:
    - Tam 5 mg not inferior to 20 mg in decreasing breast cancer proliferation
  - N=500, mean age 50 years
  - 20% ADH, 10% LCIS, 70% DCIS
  - Randomized to Tamoxifen 5 mg/day vs. Placebo for 3 years

PREVENTION

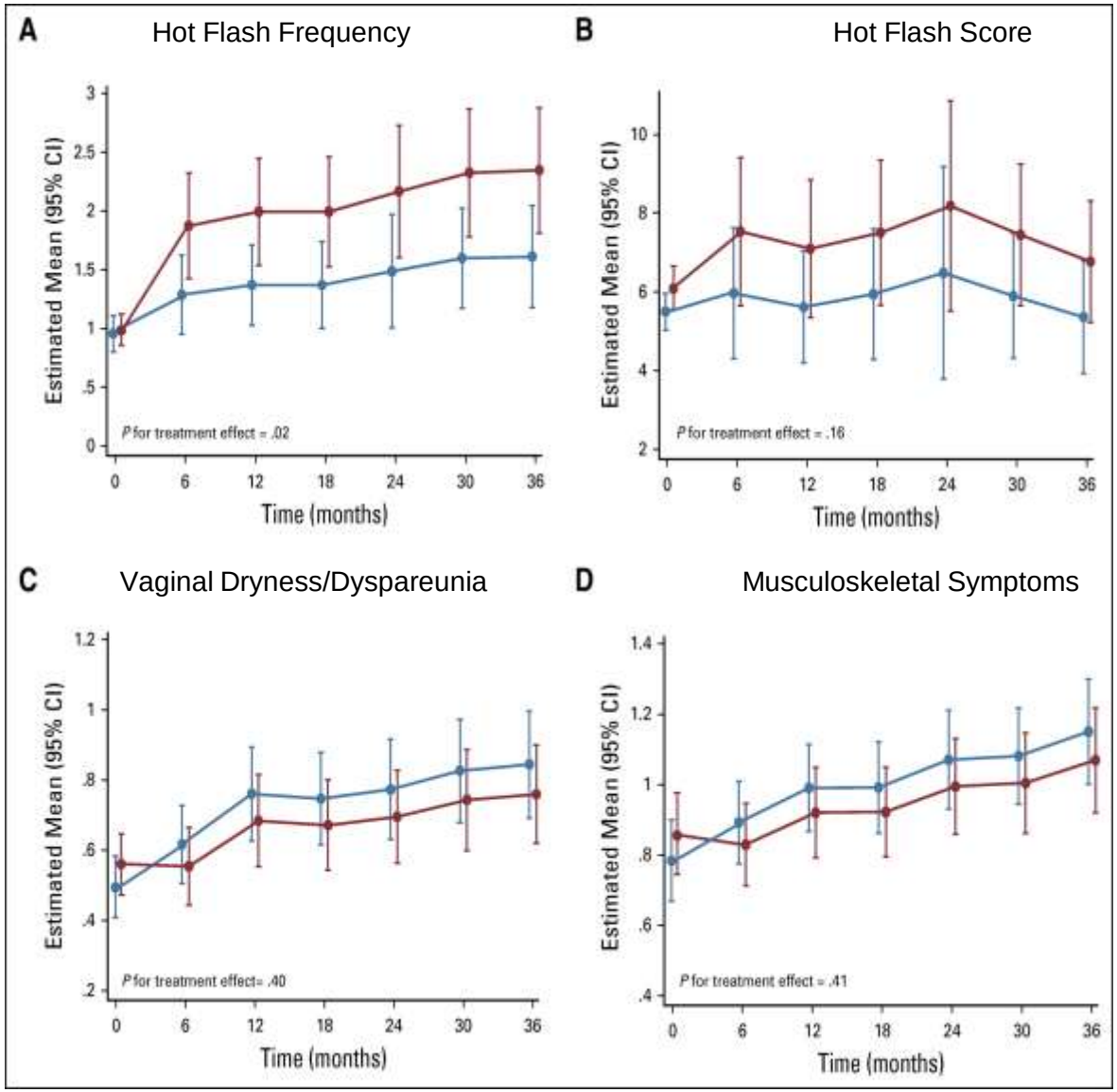
LOW DOSE TAMOXIFEN (Baby-TAM)



DeCensi A, et al. JCO 2019

PREVENTION

LOW DOSE TAMOXIFEN (Baby-TAM)



DeCensi A, et al.
JCO 2019

CORE NEEDLE BX

PATHOLOGY

High Risk Lesion

ALH, LCIS, ADH

PREMENOPAUSAL

- Tamoxifen 5 mg/d x 3 years
- Tamoxifen 20 mg/d x 5 years

POSTMENOPAUSAL

TAH-BSO + Osteoporosis	Intact Uterus + Osteoporosis	Intact Uterus + Normal BMD
Tamoxifen 20 mg or 5 mg x 3-5 years	Raloxifene 60 mg/d x 5 years	Exemestane 25 mg or Anastrozole 1 mg/d x 5 years

BREAST SCREENING

- Mammographic Screening
- Consider Screening MRI*
- Bone health BMD/DEXA

LIFESTYLE

- 1 glass ETOH/day
- Smoking Cessation
- Moderate Intensity Exercise

FOLLOW UP

Hôpital général juif
Jewish General Hospital
Centre du cancer Segal Cancer Centre

Hôpital général juif
Jewish General Hospital
Centre du cancer Segal Cancer Centre

BREAST CANCER SCREENING

Thank you!

SM.WONG@MCGILL.CA

High Risk Breast Clinic (HRBC)
at the JGH Stroll Cancer Prevention Center
Accepting Referrals via Fax To: (514) 340-8302
www.mcgill.ca/cancerprev

McGill