An Update on Medical Management of High-Risk Women

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WEXNER MEDICAL CENTER

Disclosures

- Consultant
  - Immunomedics
  - Novartis
  - Biotheranostic
  - Gilead

- Research Support
  - AstraZeneca
  - Immunomedics
  - Gilead
  - Senhwa Biosciences

  - I will be discussing off-label use of oral agents in BC prevention.

Objectives

1.Overview of epidemiology and risk factors for developing breast cancer.

2. General principles of breast cancer risk assessment and screening.

3. Overview of strategies to prevent breast cancer in high-risk individuals

4. Where do we go from here?

Breast Cancer is a Common Disease of Women

Incidence of Invasive Breast cancer in the US	246, 660
Incidence of invasive Breast Cancer in the World	1,300,000 per year
Life time Risk	1 in 8 women
Prevalence in the US	~2.7 million
Median Age of Diagnosis	61
Mortality in US	40,450

Race	Incidence
All Races	125/100,000
White	128 per 100,000 women
Black	125 per 100,000 women
Asian/Pacific Islander	97 per 100,000 women
American Indian/Alaska Native	81 per 100,000 women
Hispanic	92 per 100,000 women

Based on Survaillance Epidemiology and End Result Database; American Cancer Society, Cancer Facts & Figures. 2016

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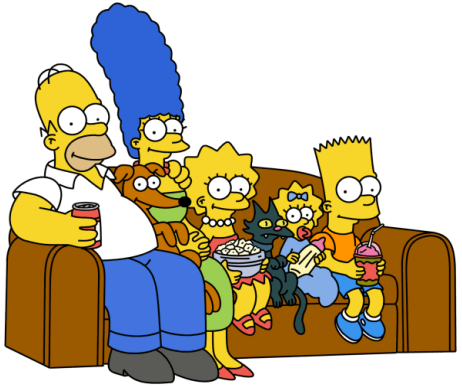
RISK FACTORS FOR BREAST CANCER

Female Sex

Age

Family History



Prolonged Estrogen Exposure

- ✓ Early Age of Menarche
- ✓ Late Age of Menopause
- ✓ Late 1st Pregnancy
- ✓ Hormone Replacement therapy

Other Risk Factors:

- ✓Exposure to ionizing radiation
- ✓Abnormal breast biopsies
- ✓Post-menopausal obesity
- ✓Alcohol

Known Genetic Predisposition

Pathogenic/ Likely Pathogenic Germline Variants

High Penetrance	Mod Penetrance	Insufficient evidence
BRCA1/2	ATM (ER+)	BRIP1
TP53 (LFS, HER 2 +)	CHEK2 (ER+)	NBN
STK11(PJS)	BARD1 (TNBC)	RAD50
PTEN (COWDEN)	NF1	MSH2, MSH6, PMS2, MLH1, EPCAM(Lynch)
PALB2	RAD51C/ RAD 51D (TNBC)	
CDH1 (Lobular)		

The routine use of PRS for breast cancer risk assessment /prevention is discouraged. Further validation is required to understand interaction of SNPs with environmental/ hormonal risk factors as well disease subtype. Ongoing studies will shed light on utility of PRS in comprehensive risk assessment models to guide personalized therapy.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Colorectal. V. 2019

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - ◊ Treatment indications
      - – To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[h,i] (See NCCN Guidelines for Breast Cancer)
      - – To aid in adjuvant treatment decisions with olaparib for high-risk,[j] HER2-negative breast cancer[h]
    - ◊ Pathology/histology
      - – Triple-negative breast cancer
      - – Multiple primary breast cancers (synchronous or metachronous)[k]
      - – Lobular breast cancer with personal or family history of diffuse gastric cancer See NCCN Guidelines for Gastric Cancer
    - ◊ Male breast cancer
    - ◊ Ancestry: Ashkenazi Jewish ancestry
  - Any age (continued):
    - ◊ Family history[l]
      - – ≥1 close blood relative[m] with ANY:
        - ▪ breast cancer at age ≤50
        - ▪ male breast cancer
        - ▪ ovarian cancer
        - ▪ pancreatic cancer
        - ▪ prostate cancer with metastatic,[n] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - – ≥3 total diagnoses of breast cancer in patient and/or close blood relatives[m]
      - – ≥2 close blood relatives[m] with either breast or prostate cancer (any grade)
- Family history of cancer only
  - An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[o]
    - ◊ If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
  - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[p]

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Colorectal. V3. 2022

How do you interpret germline testing results ?

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

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

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Colorectal. V3. 2022

The CARRIERS Study

- Population-based case-control study

Gene	Odds Ratio	95% CI	P Value
ATM	1.8	1.5 – 2.3	<0.001
BRCA1	7.6	5.3 – 11.3	<0.001
BRCA2	5.2	4.1 – 6.8	<0.001
CHEK2	2.5	2.0 – 3.0	<0.001
PALB2	3.8	2.7 – 5.6	<0.001

Investigating Contralateral Breast Cancer in the CARRIERS study

15,104 women with unilateral invasive breast cancer from 10 prospective epidemiological studies in the United States

Inclusion:
-Preserved contralateral breast
-At least one year of follow up

Exclusion:
- DCIS at initial diagnosis

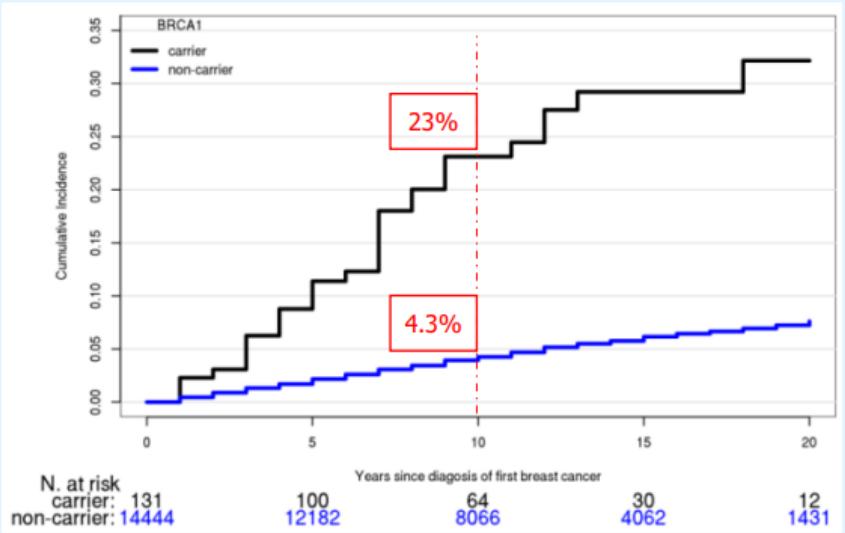
Results of germline sequencing for 5 genes using a QIAseq custom panel

- Time-to-event analysis comparing contralateral breast ca risk between carriers in each gene vs. non-carriers
  - Multivariate proportional hazard regression analysis accounting for competing risk of death[1]
    - Censoring at last follow-up or contralateral prophylactic mastectomy
- Adjusting for contributing study, race/ethnicity, age at diagnosis, menopausal status, histology and ER status of the first breast cancer and the use of endocrine therapy

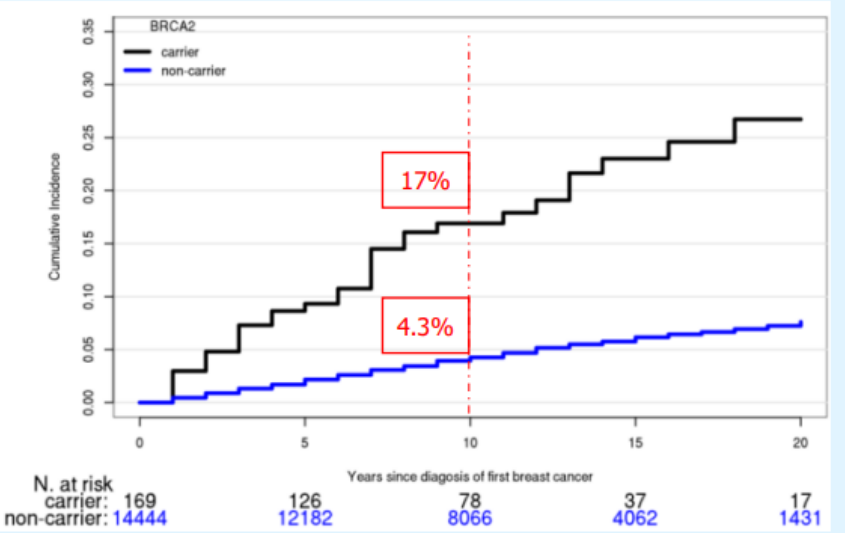
1. Fine JP and Gray RJ. Journal of the American Statistical Association 1999; 94:496-509

Unadjusted Cumulative Incidence of CBC from the First Breast Cancer Diagnosis

BRCA1



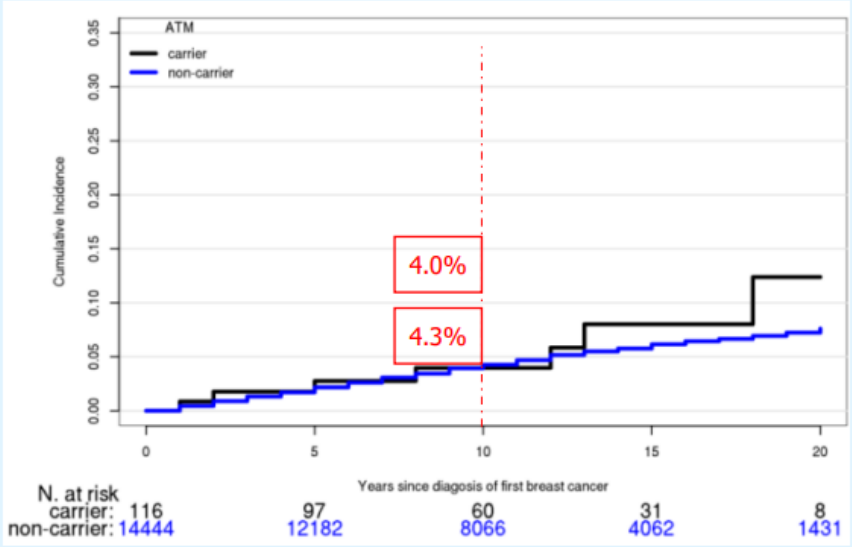
BRCA2



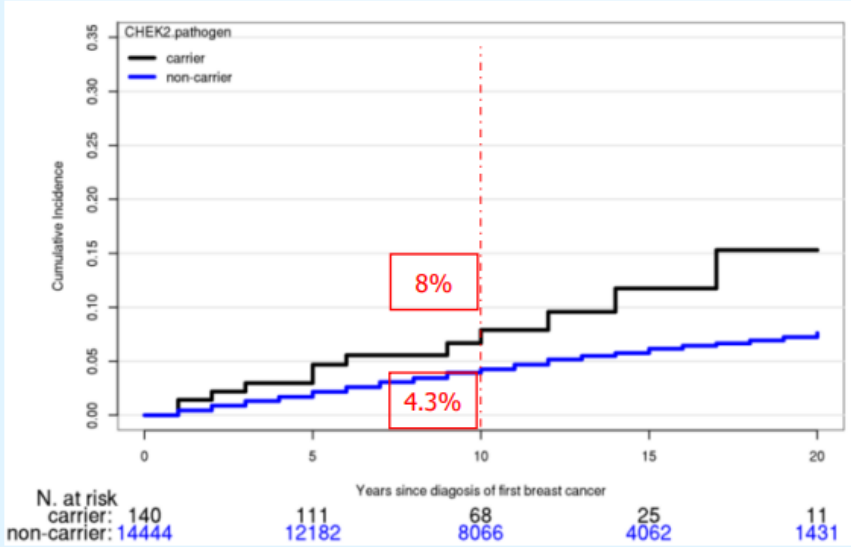
JCO 2023 Mar 20;41(9):1703-1713

Unadjusted Cumulative Incidence of CBC from the First Breast Cancer Diagnosis

ATM

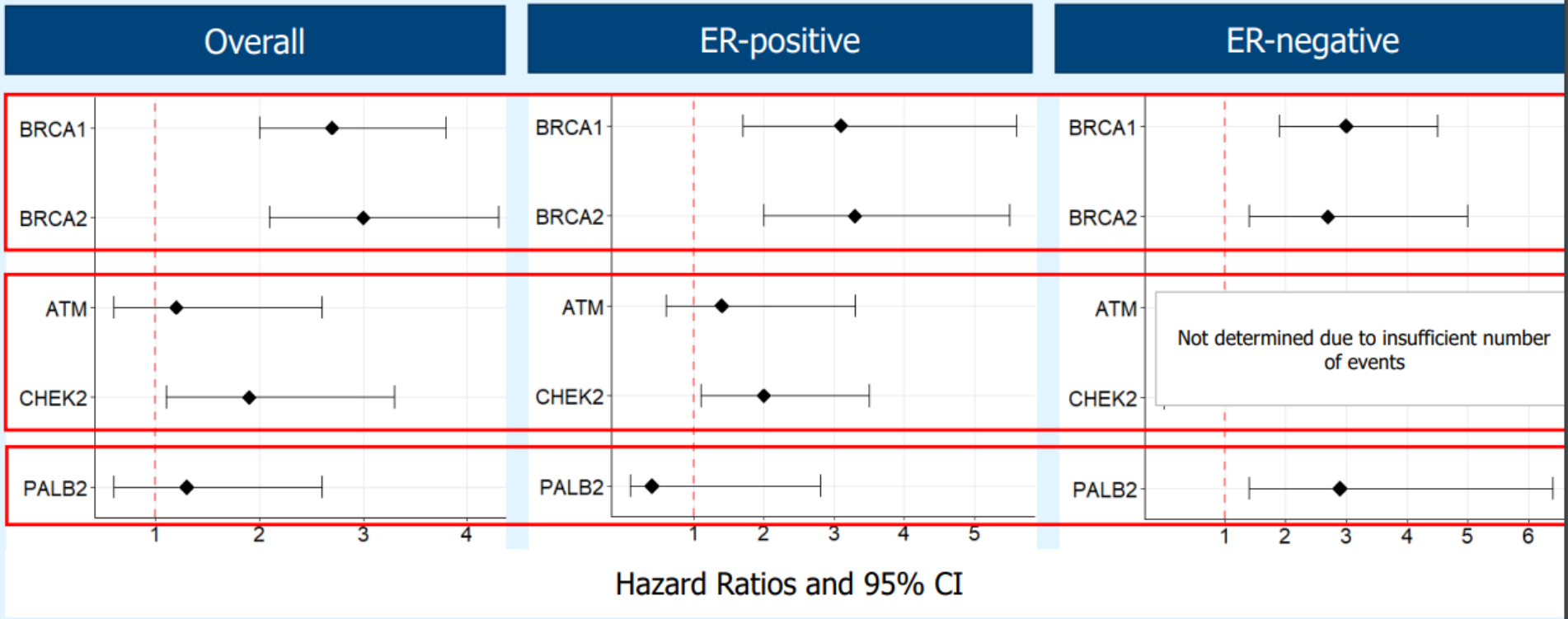


CHEK2



JCO 2023 Mar 20;41(9):1703-1713

Adjusted CBC Risk: Overall and by ER-Status of First Breast Cancer



JCO 2023 Mar 20;41(9):1703-1713

San Antonio Breast Cancer Symposium®, December 6-10, 2022

Contralateral Breast Cancer Risk in **women over the age of 65** at first breast ca diagnosis

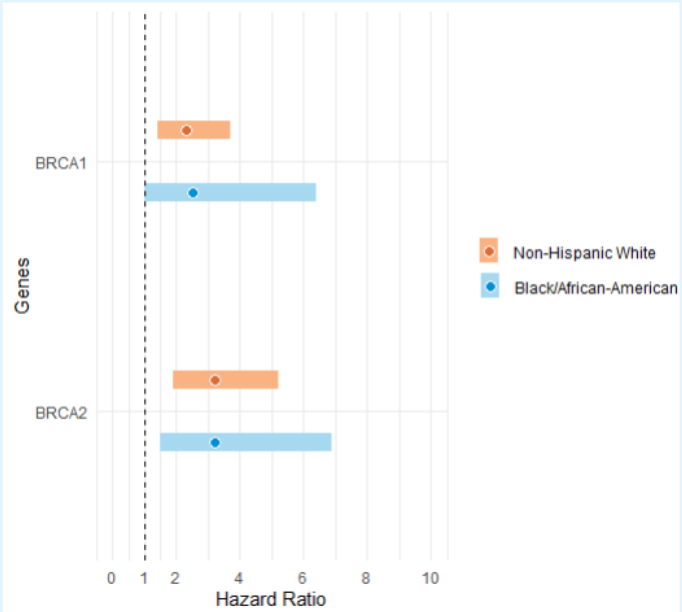
- Total, **N=6010**
- PV carriers in *ATM, BRCA1, BRCA2, CHEK2* and *PALB2*= **153 (2.6%)**
- Median follow-up duration: **10 years**
- Number of contralateral breast cancer events in PV carriers: **3**

Age and menopausal status at initial breast cancer diagnosis significantly influence the contralateral breast cancer risk in PV carriers

- Important for decision-making on risk management strategies such as contralateral prophylactic mastectomy or supplemental MRI screening in PV carriers with breast cancer.

JCO 2023 Mar 20;41(9):1703-1713

Contralateral Breast Cancer Risk by **Race/ethnicity**



Black women with *BRCA1* or *BRCA2* PVs have a similarly elevated risk of CBC as non-Hispanic White women.

- Risk-management strategies should be similar

JCO 2023 Mar 20;41(9):1703-1713

Breast Cancer Risk Assessment

1. Gail
2. IBIS
3. Claus
4. BRCAPRO
5. BOADICEA

Which one to go with?

Breast Cancer Risk Assessment - GAIL

- Gail Model predicts life time risk of developing breast cancer (*http://www.cancer.gov/bcrisktool)*
  - Personal history of breast cancer
  - Age
  - Age of 1st Period
  - Age of 1st life birth
  - Number of 1st degree relatives with breast cancer
  - History of breast biopsy
  - History of pre-malignant changes (atypical ductal hyperplasia)

  - *Limitation:* Does not consider family history beyond first-degree relatives with breast cancer. It does not factor in any other cancers or any paternal relatives with cancer. NOT useful for making recommendations for screening / risk reduction on individual basis

Gail et al. J Natl Cancer Inst 1999

What about other risk assessment models?

- Tyrer-Cuzick (IBIS)

-Considers nongenetic risk factors such as age at menarche, first term birth, biopsy history, height and weight, age at menopause, etc.

-Considers a family history of breast and ovarian cancer beyond first-degree relatives.

-Often predicts breast cancer risks that are higher than other mathematic models.

- CanRisk (BOADICEA)

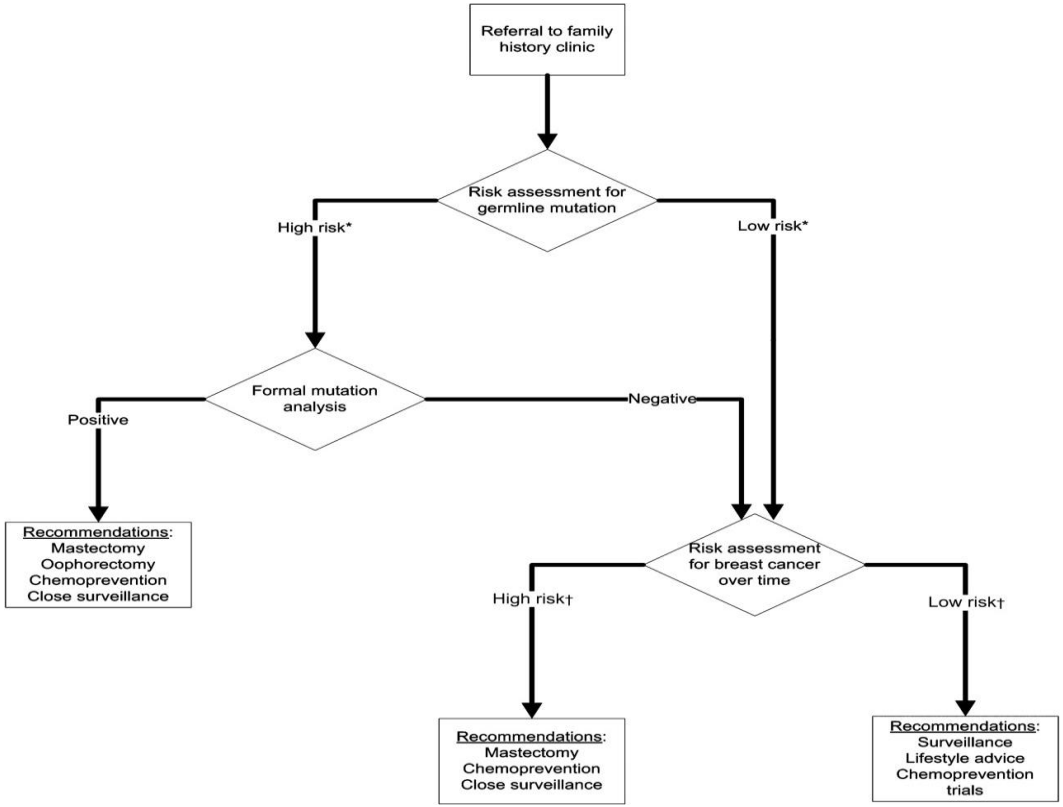
-Models the risks of breast and ovarian cancer based on family history and genotypes for variants in BRCA1/2, PALB2, CHEK2, ATM, BARD1, RAD51C, and RAD51D.

-Incorporates the effects of common genetic variants (summarized as polygenic risk scores, PRS),

-Includes lifestyle, hormonal and clinical features, breast density, and disease pathology.

-Prospectively validated, both for the prediction of carrier probabilities and prediction of subsequent cancer risk.

Flowchart of the management of women who are referred to HRB Clinic.

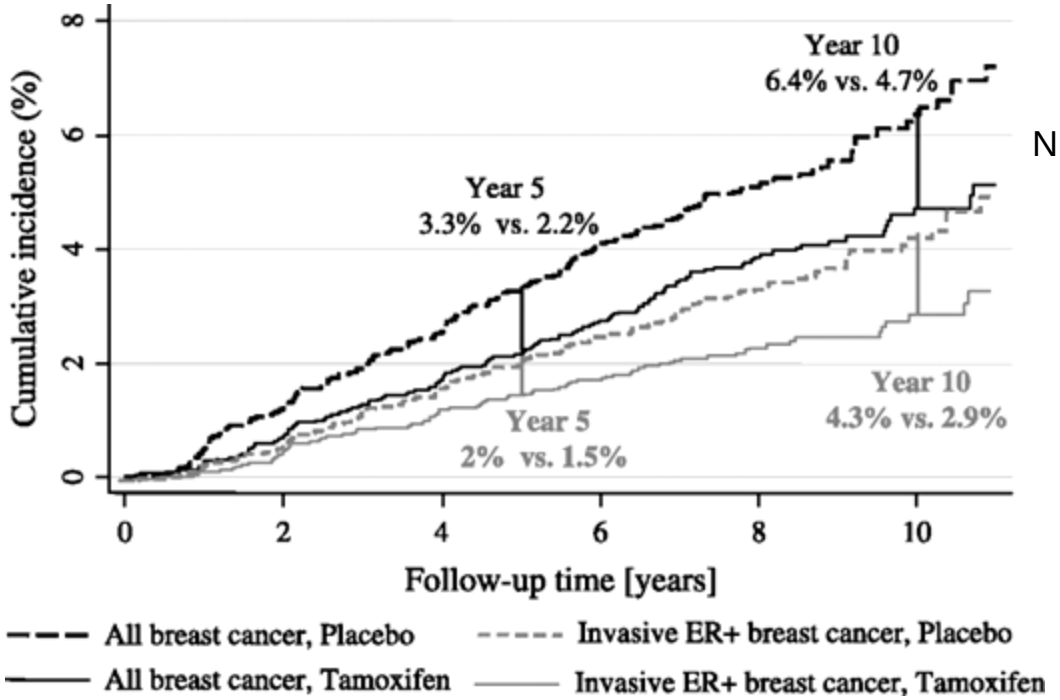


J Natl Cancer Inst, Volume 102, Issue 10, 19 May 2010, Pages 680–691, https://doi.org/10.1093/jnci/djq088

What can be done to prevent breast cancer in individuals with high risk?

- Increased screening (breast exams, mammograms and breast MRI)
- Endocrine Therapy
  - Tamoxifen
  - Raloxifene (post-menopausal women)
  - Exemestane (post-menopausal women
  - Anastrozole
- Risk Reducing Mastectomy
- Targeting modifiable risk factors

Cumulative incidence rates for all breast cancers and invasive estrogen receptor (ER)-positive breast cancers according to treatment arm



N = 13,338

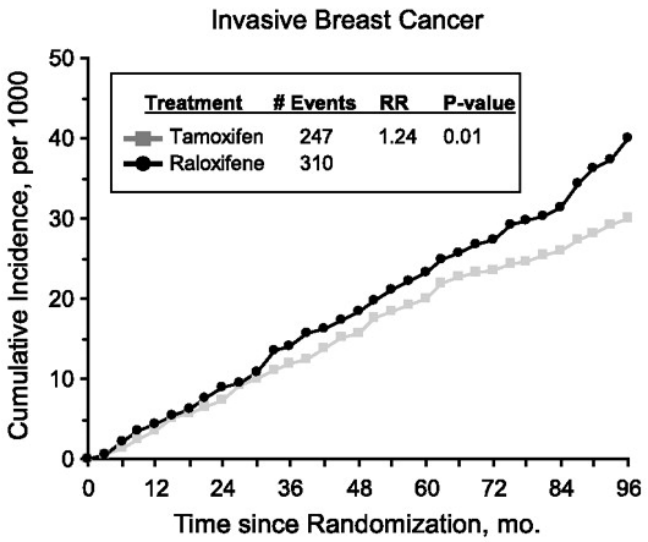
Uterine Cancer :

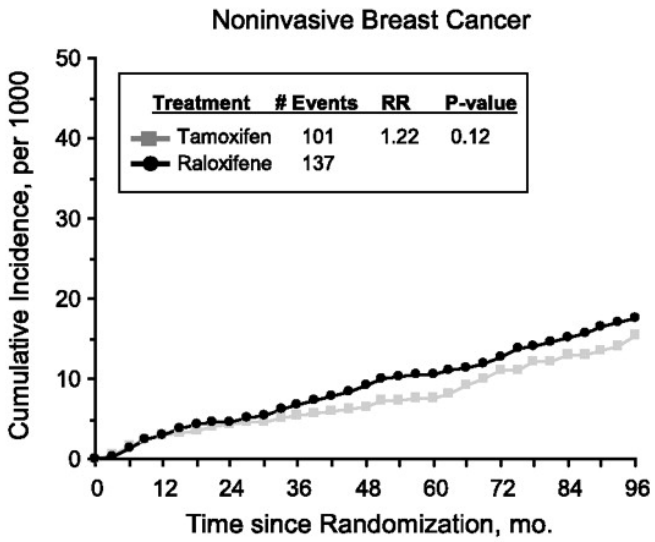
0.5% risk in the tamoxifen group

0.3% risk in the placebo group

Cuzick, J. et al. J. Natl. Cancer Inst. 2007 99:272-282

STAR, NSABP P2 : Raloxifene *vs.* Tamoxifen in high risk women

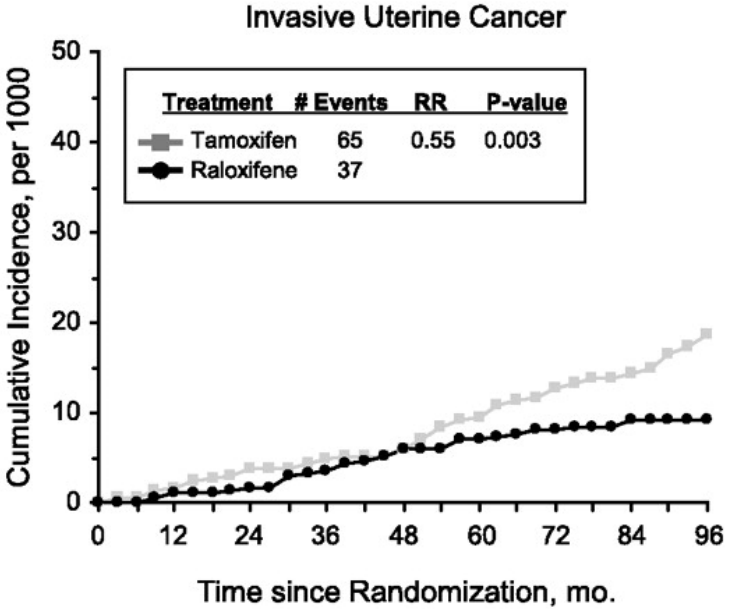




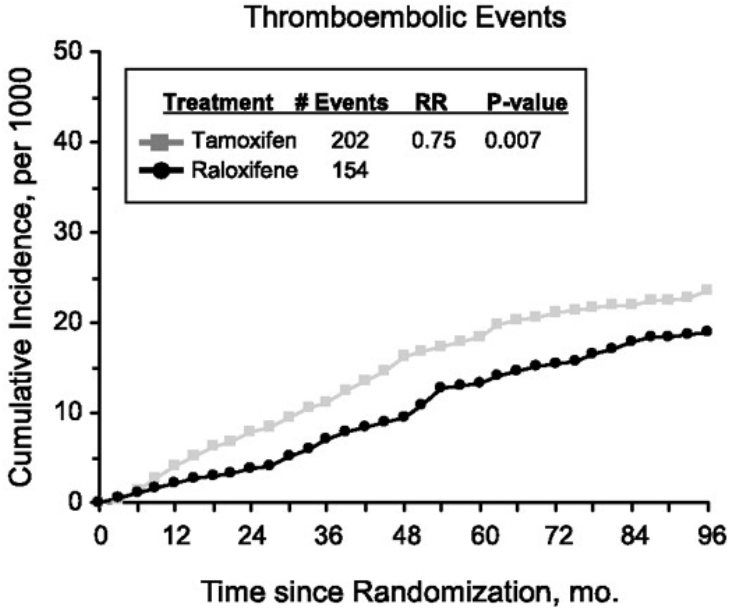
No. at Risk							
Raloxifene	9754	9398	8973	8196	5999	4453	2650
Tamoxifen	9736	9387	8939	8059	5833	4326	2621

No. at Risk							
Raloxifene	9754	9365	8925	8125	5938	4405	2616
Tamoxifen	9736	9359	8901	8019	5793	4290	2593

Cancer Prev Res (Phila). 2010;3(6):696-706



No. at Risk							
Raloxifene	4717	4556	4368	3976	2913	2157	1295
Tamoxifen	4739	4504	4238	3769	2686	2017	1204



No. at Risk							
Raloxifene	9754	9439	9049	8277	6079	4515	2706
Tamoxifen	9736	9391	8962	8094	5868	4351	2649

Cancer Prev Res (Phila). 2010;3(6):696-706.

Chemoprevention

- SERM's have shown to reduce breast cancer incidence in high-risk women by ~ 40% with greatest benefit in women with intraepithelial neoplasia (ADH/ALH, LCIS/ DCIS)

- Uptake remains low, likely from lack of mortality benefit and poor adherence given duration and frequency of AE's.

Waters , Breast cancer research, 2012
Noonan S et al, CaPR 2018

San Antonio Breast Cancer Symposium®, December 6-10, 2022

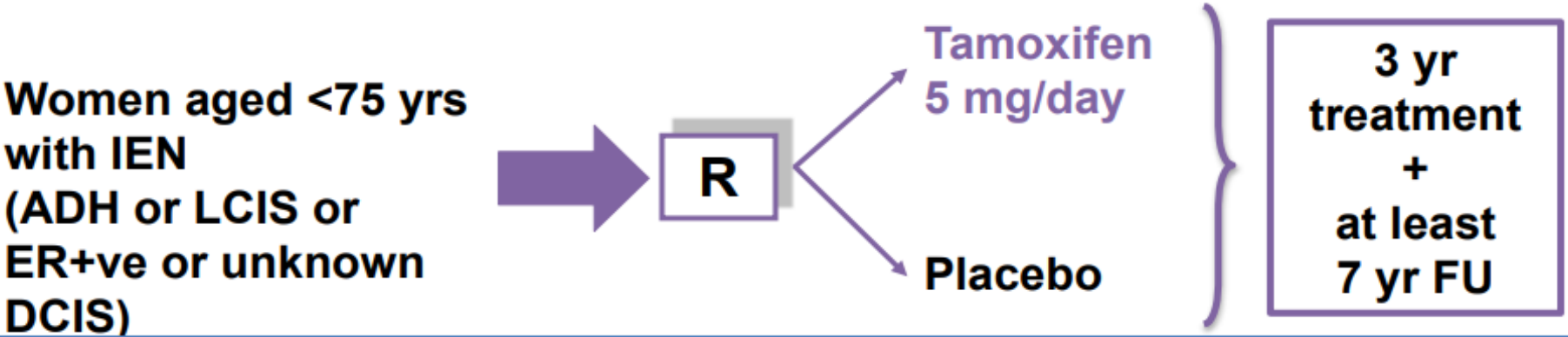
GS408

10 YEAR RESULTS OF A PHASE 3 TRIAL OF LOW-DOSE TAMOXIFEN IN NONINVASIVE BREAST CANCER

Andrea De Censi[1], Matteo Lazzeroni[2], Matteo Puntoni[3], Luca Boni[4], Aliana Guerrieri Gonzaga[2], Tania Buttiron Webber[1], Marianna Fava[1], Irene Maria Briata[1], Livia Giordano[5], Maria Digennaro[6], Laura Cortesi[7], Katia Cagossi[8], Elisa Gallerani[9], Alessia De Simone[10], Anna Cariello[11], Giuseppe Aprile[12], Maria Renne[13], Bernardo Bonanni[2]

(1) E.O. Ospedali Galliera, Genova, Italy; (2) IEO - European Institute of Oncology IRCCS, Milan; (3) Clinical & Epidemiological Research Unit, University Hospital of Parma; (4) IRCCS Ospedale Policlinico San Martino, Genoa; (5)Azienda Ospedaliera-Universitaria Città della Salute e della Scienza di Torino; (6) IRCCS Istituto Tumori Giovanni Paolo II, Bari; (7) Azienda Ospedaliera-Universitaria Policlinico di Modena; (8) Ospedale Bernardino Ramazzini, Carpi; (9) ASST Settelaghi Varese; (10) ICS Maugeri -Centro Medico di Pavia; (11) Ospedale Santa Maria delle Croci, Ravenna; (12) Azienda ULSS8 Berica- Ospedale di Vicenza; (13) Chirurgia Generale Azienda Ospedaliera Mater Domini Catanzaro.

TAM 01- Study Design



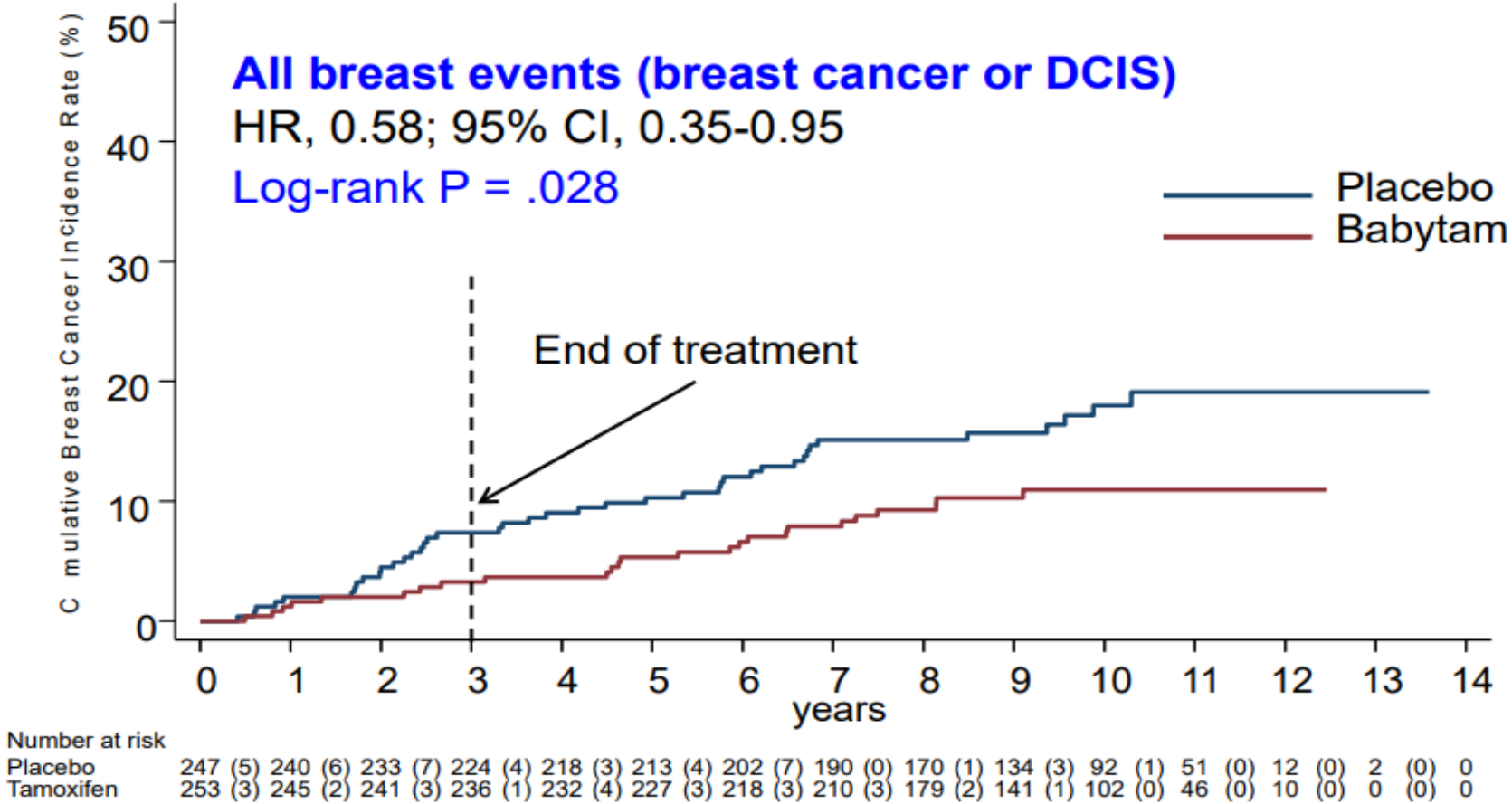
Primary endpoint:
Incidence of invasive breast cancer or DCIS

- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months for 3 yrs, Mx every year for 10 yrs

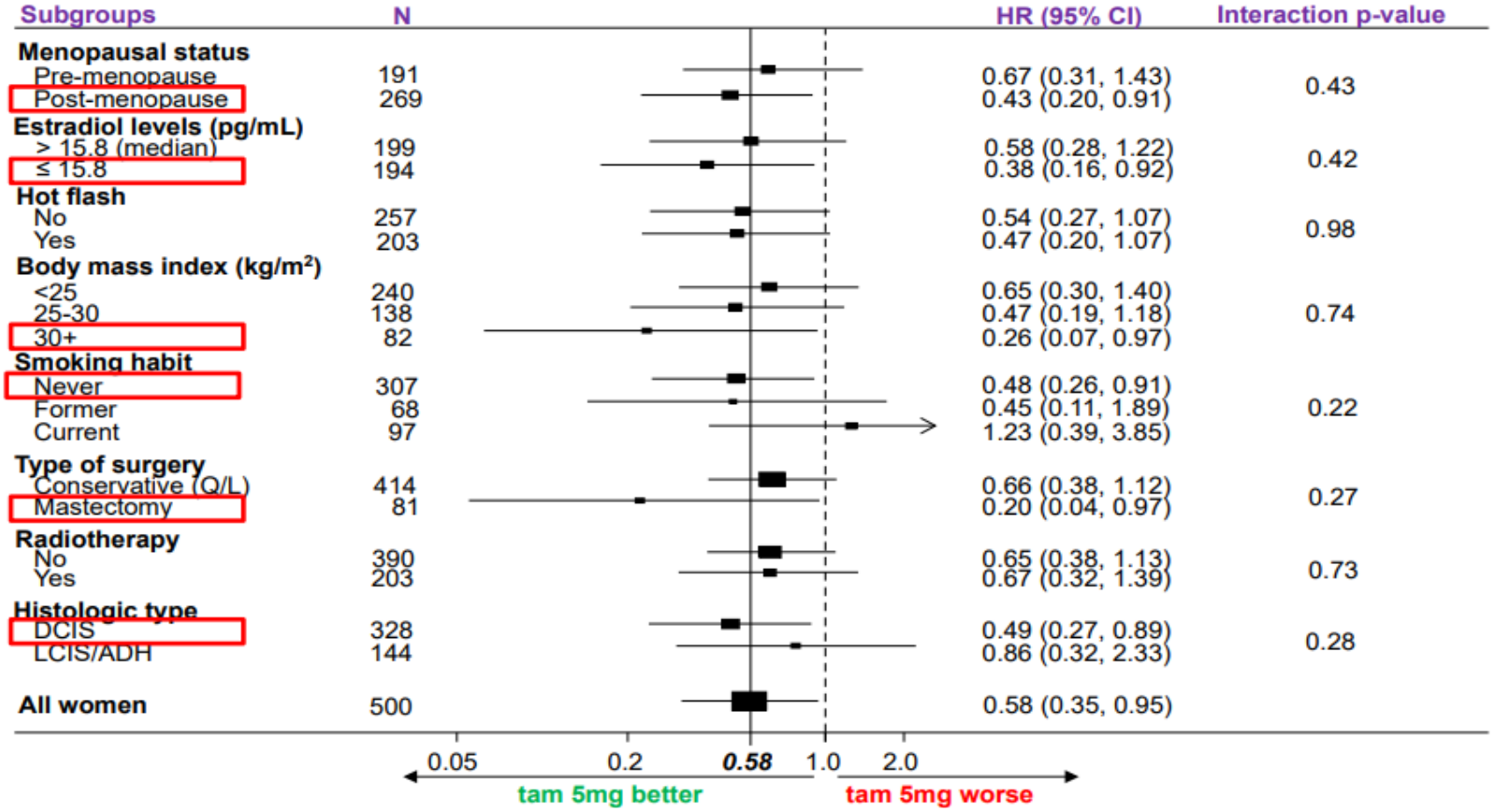
Main subject and tumor characteristics (n=500)

	Babytam N=253	Placebo N=247
Age, mean (SD)	54 (9.6)	54 (9.1)
Pre-menopausal, %	43	40
BMI, mean (SD)	25.7 (4.8)	25.3 (4.2)
ADH, %	20	20
LCIS, %	11	10
DCIS, %	69	70
ER/PR+ve/unk DCIS, %	66 / 34	67 / 33
Radiotherapy for DCIS, %	61	61

DeCensi et al. *J Clin Oncol.* 37(19):1629-1637, 2019


All breast events (breast cancer or DCIS)
HR, 0.58; 95% CI, 0.35-0.95
Log-rank P = .028
Placebo
Babytam
End of treatment
Cumulative Breast Cancer Incidence Rate (%)
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
years
Number at risk
Placebo 247 (5) 240 (6) 233 (7) 224 (4) 218 (3) 213 (4) 202 (7) 190 (0) 170 (1) 134 (3) 92 (1) 51 (0) 12 (0) 2 (0) 0
Tamoxifen 253 (3) 245 (2) 241 (3) 236 (1) 232 (4) 227 (3) 218 (3) 210 (3) 179 (2) 141 (1) 102 (0) 46 (0) 10 (0) 0 (0) 0

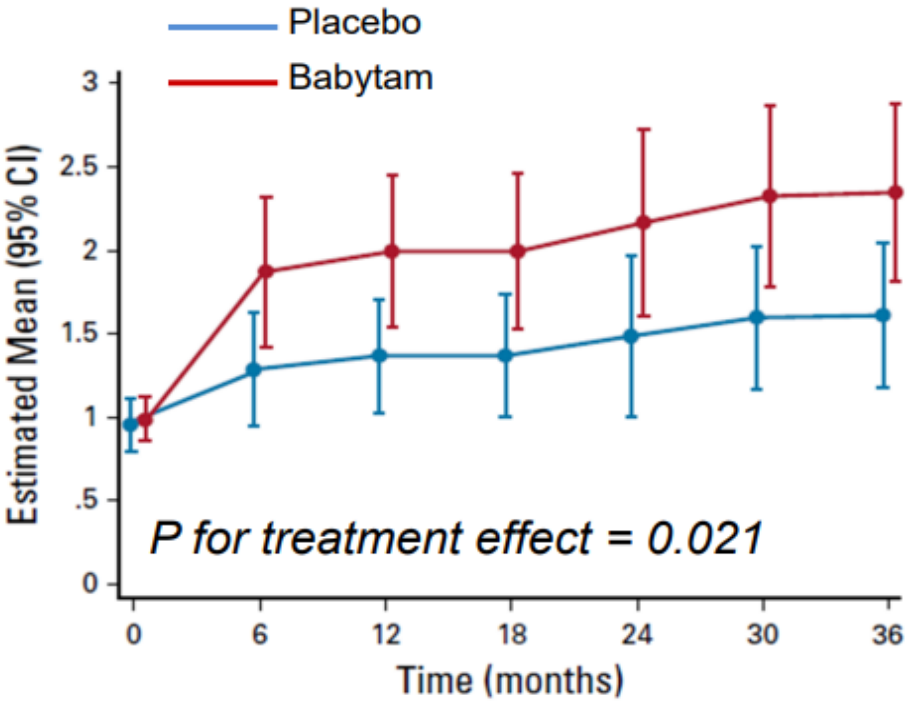
San Antonio Breast Cancer Symposium®, December 6-10, 2022



Adverse events by allocated arm

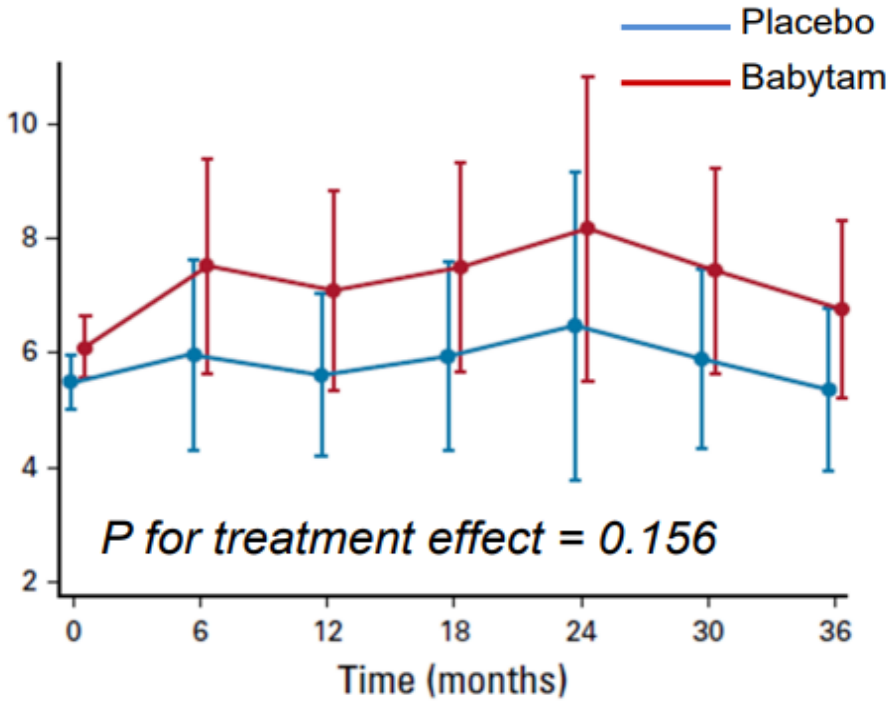
	Tamoxifen N=249	Placebo N=246	P Value
Adverse Events, n			
Endometrial cancer	1	0	1.0
Other neoplasms	16	9	0.22
Deep vein thrombosis or pulmonary embolism	1	1	1.0
Superficial phlebitis	2	0	0.50
Coronary heart disease	2	2	1.0
Bone fracture	4	2	0.69
Cataract	5	5	1.00
Endometrial polyps	20	13	0.28
Death from other causes	5	2	0.45
Death from breast cancer	1	2	0.62
Other serious adverse events	3	6	0.34

Daily hot flashes frequency



Daily hot flashes score

Frequency by Intensity



DeCensi et al. *J Clin Oncol.* 37(19):1629-1637, 2019

Conclusions

- Babytam 5 mg/day for 3 years lowers recurrence from non-invasive breast cancer at 10 y without AEs
- Effect on contralateral ca. opens door for primary prevention
- Benefit seen across all subgroups, though with low power
- Low-risk of death (0.6% at 10 y) supports treatment de-escalation in DCIS.
- Tamoxifen another example of a missed optimal dose for a targeted agent[1]

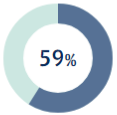
1. Shah M. *N Engl J Med* 2021;385:1445

Ongoing high-risk studies at OSUCCC

S1904 SWOG clinical trial number

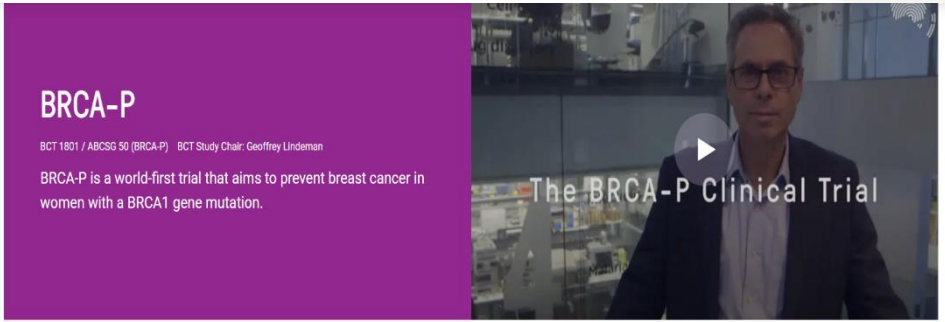
Cluster Randomized Controlled Trial of Patient and Provider Decision Support to Increase Chemoprevention Informed Choice Among Women with Atypical Hyperplasia or Lobular Carcinoma In Situ - Making Informed Choices on Incorporating Chemoprevention into Care (MiCHOICE)

Open Phase



Accrual

Abbreviated Title	Decision Support Tool
Activated	09/01/2020
Participants	Limited: Institutions Listed on the Title Page



Where do we go from here…

- Target specific high-risk populations:
  - Women with atypical hyperplasia, LCIS, and DCIS
  - Women with hereditary breast cancer syndromes
- Minimize side effects with:
  - Alternative SERMs (Duavee®), oral SERDs
  - Low-dose or topical tamoxifen/endoxifen
  - Combination chemoprevention regimens (sulindac + AI)
- Identify novel agents with activity against ER-negative breast cancer (denosumab for *BRCA1* mutation carriers)
- Validate short-term surrogate endpoint biomarkers which correlate with breast cancer development


Thank You!