What's New in Breast Cancer Genetics

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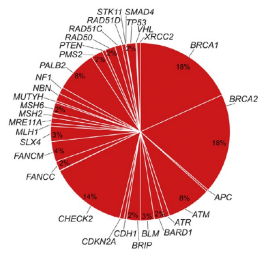
Disclosures

- Natera – advisory board 2022
- No other relevant disclosures

Learning Objectives

- Recognize genes associated with high vs moderate risk for breast cancer
- Outline management differences between high and moderately penetrant genes
- Identify indications for parp inhibitors in the adjuvant and metastatic settings

About 10% of breast cancer is hereditary

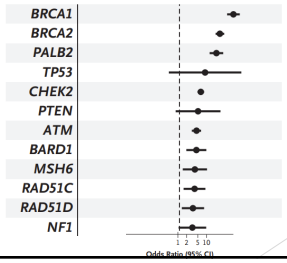


Most Common Mutations:

- **BRCA1, BRCA2**
- **PALB2**
- **CHECK2**
- **ATM**

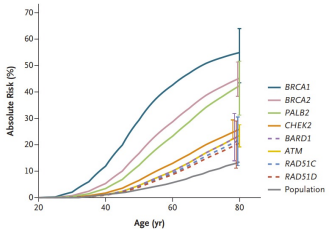
Suszynska GynOnc 2019

Genes Associated with Hereditary Breast Cancer



BCAC NEJM 2021

Cancer Risk

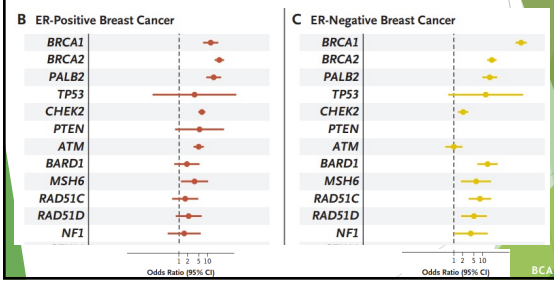


Highest Lifetime Risk

- BRCA1,BRCA2
- PALB 2
- ATM
- CHEK2

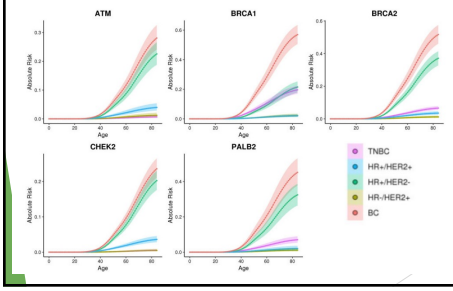
BCAC NEJM 2021

Risk for Er- vs Er+



BCAC NEJM 2021

Cancer Risks and Cancer Types Associated with Common Hereditary Cancers



Hu JNCI 2020

Genes associated with HBC with management guidelines

Highly Penetrant	Moderately Penetrant
BRCA1	CHEK2
BRCA2	ATM
PALB2	NF1
TP53	RAD51C
PTEN	RAD51D
STK11	BARD1

Lifetime Breast Cancer Risk associated with Highly Penetrant genes

Gene	Cancer Risk
BRCA1	60-72%
BRCA2	55-72%
PALB2	32-53%
TP53	>60%
CDH1	37-55%
PTEN	40-60%
STK11	32-54%

NCCN HBOPC Guidelines v1.2025

Lifetime Breast Cancer Risk associated with Moderately Penetrant genes

Gene	Cancer Risk
ATM	21-24*
CHEK2	23-27
BARD1	17-30%
RAD51C	~20%
RAD51D	~20%
NF1	32-53

*ATM 7271T>G ~60%

NCCN HBOPC Guidelines v1.2025

Breast and Ovarian Risk Management by Gene

	Screening breast MRI (>20% lifetime risk)	Discuss risk reducing mastectomy	Discuss risk-reducing BSO
Intervention warranted based on risk - Highly Penetrant Genes	BRCA1 BRCA2 PALB2 TP53 CDH1 PTEN STK11	BRCA1 BRCA2 PALB2 TP53 CDH1 PTEN STK11	BRCA1 BRCA2 PALB2 BRIP1 RAD51C RAD51D PALB2
Intervention warranted based on risk - Moderately Penetrant Genes	ATM CHEK2 NF1 BARD1 RAD51C/D		
Insufficient evidence	BRIP1	ATM, CHEK2, BARD1,NF1 RAD51C/D	TP53

NCCN HBOPC Guidelines v1.2025

Indications for Genetic Testing

- Affected with cancer
  - Cancer type and pathology
  - Family History
  - Ethnicity
- Unaffected
  - Family history
  - Ethnicity

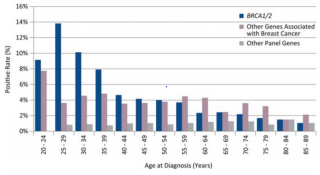
NCCN Guidelines v1.2025
Lu, Wood JCO 2014

Indications for Genetic Testing based on Personal History

- Age ≤65 y
- Any age:
  - To aid in treatment decisions (surgical, adjuvant, metastatic management)
  - Pathology/histology
    - Triple-negative breast cancer
    - Multiple primary breast cancers (synchronous or metachronous)
    - Lobular breast cancer with personal or family history of diffuse gastric
  - Male breast cancer
  - Ancestry: Ashkenazi Jewish ancestry
  - Family history

NCCN Guidelines v1.2025
Bedrosian JCO 2024
Lu, Wood JCO 2014

Panel Testing for breast cancer



Early age at diagnosis increases the likelihood of finding a mutation

- Mutation rates:
  - Women <40: 13-18%
  - Women 41-49: 8.6-9.0%

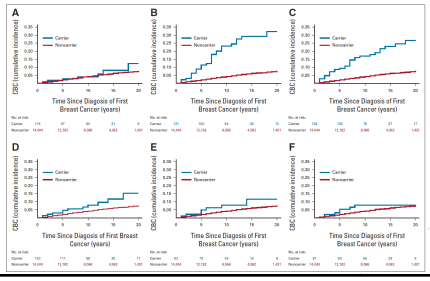
BRCA genes and HBC genes most commonly associated with early onset

Buys Cancer 2017

Implications of Genetic Testing for Women with Breast Cancer

- At Diagnosis
  - Surgical decision making
    - Bilateral mastectomies are an option for highly penetrant genes (i.e.BRCA1, BRCA2, PALB2)
    - Avoid radiation for TP53 mutation carriers
  - Surveillance
    - Annual Screening Breast MRI + Annual Mammogram for moderate and highly penetrant genes

Contralateral Breast Cancer Risk by Gene

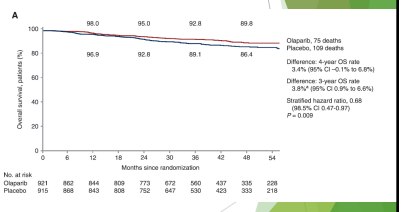


A:ATM
B: BRCA1
C: BRCA2
D: CHEK2
E: CHEK2 (1100delC)
F: PALB2

Yadev JCO 2022

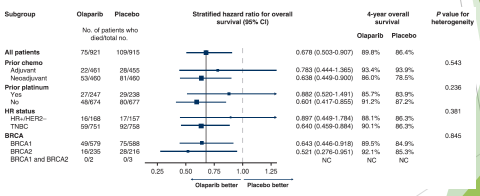
Adjuvant therapy for BRCA associated cancers

- Eligibility:
  - Er- >2cm/LN+ or no pCR
  - ER+ ≥4LN+ or no pCR (CPS+EG score 3)
- Olaparib for one year



Masuda NEJM 2017, Geyer AnnOnc 2022

Parp inhibitor as adjuvant therapy



Geyer AnnOnc 2022

Parp inhibitor as adjuvant therapy

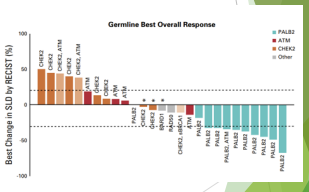
Table 2. Summary of adverse events in the safety analysis set[a]

Adverse event, no. of patients (%)	Olaparib (n = 911)	Placebo (n = 904)
Any adverse event	836 (91.8)	758 (83.8)
Serious adverse event	79 (8.7)	78 (8.6)
Adverse event of special interest[b]	31 (3.4)	51 (5.6)
MDS/AML	2 (0.2)	3 (0.3)
Pneumonitis[c]	9 (1.0)	12 (1.3)
New primary malignancy[d]	21 (2.3)	36 (4.0)
Grade ≥3 adverse event	223 (24.5)	102 (11.3)
Grade 4 adverse event[e]	17 (1.9)	4 (0.4)
Adverse event leading to permanent discontinuation of treatment[f]	98 (10.8)	42 (4.6)
Adverse event leading to death[g]	1 (0.1)	2 (0.2)

Geyer AnnOnc 2022

Management of metastatic hereditary breast cancer

- PARP inhibitor
  - Olaparib, talazoparib
  - BRCA1, BRCA2, PALB2
  - NOT ATM/CHECK 2
- Improved PFS
  - olaparib 4.2 v 7 months
  - talazoparib 5.6 v 8.6 months
- Less toxicity compared to chemotherapy



Robson NEJM 2017
Litton NEJM 2018
Tung JCO 2020

Cascade testing

- Definition: Genetic testing in blood relative who have known pathogenic variants.
  - 1st degree relatives: 50% risk
  - 2nd degree relatives: 25% risk
- Impact of testing
- Positive
  - Have cancer risk associated with mutation
  - Cancer screening and prevention can improve survival
- Negative
  - Population cancer risk
  - Need to evaluate non-mutation side of the family

Summary

- Reviewed Genes and Breast Cancer Risk associated high and moderately penetrant genes
- Reviewed management for both high and moderately penetrant gene mutation carriers
- Discussed
  - Risk for Er+ vs ER – disease by gene
  - Risk for Contralateral disease by gene
- Impact on management of breast cancer
- Importance of cascade testing!!!

Who should receive adjuvant parp inhibitor

- 35 year old BRCA 1 mutation carrier with LN+ ER+ disease who has significant residual disease after neoadjuvant Adriamycin+Cytoxan followed by taxol
- 65 year old BRCA 2 mutation carrier with 7LN+ ER+ disease and undergoes bilateral mastectomy
- 40 year old BRCA 1 mutation carrier with LN+ ER-/HER2+ disease who has residual disease after neoadjuvant therapy

Which mutation carriers are not candidates for risk reducing mastectomies

- PALB2 mutation carriers
- ATM mutation carriers
- CHECK 2 mutation carriers
- TP 53 mutation carriers

Thank you!