Penn Medicine

BASSER CENTER FOR BRCA

Genetic Testing Today: What Genes Can Tell Us

Living Beyond Breast Cancer Conference

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the cure is within

ABRAMSON CANCER CENTER

Overview of talk

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- PART 1: Overview of Genetics
- PART 2: *BRCA1/2*
- PART 3: Other breast cancer genes
- PART 4: Tumor genetic testing

PART 1A:

OVERVIEW OF GENETICS

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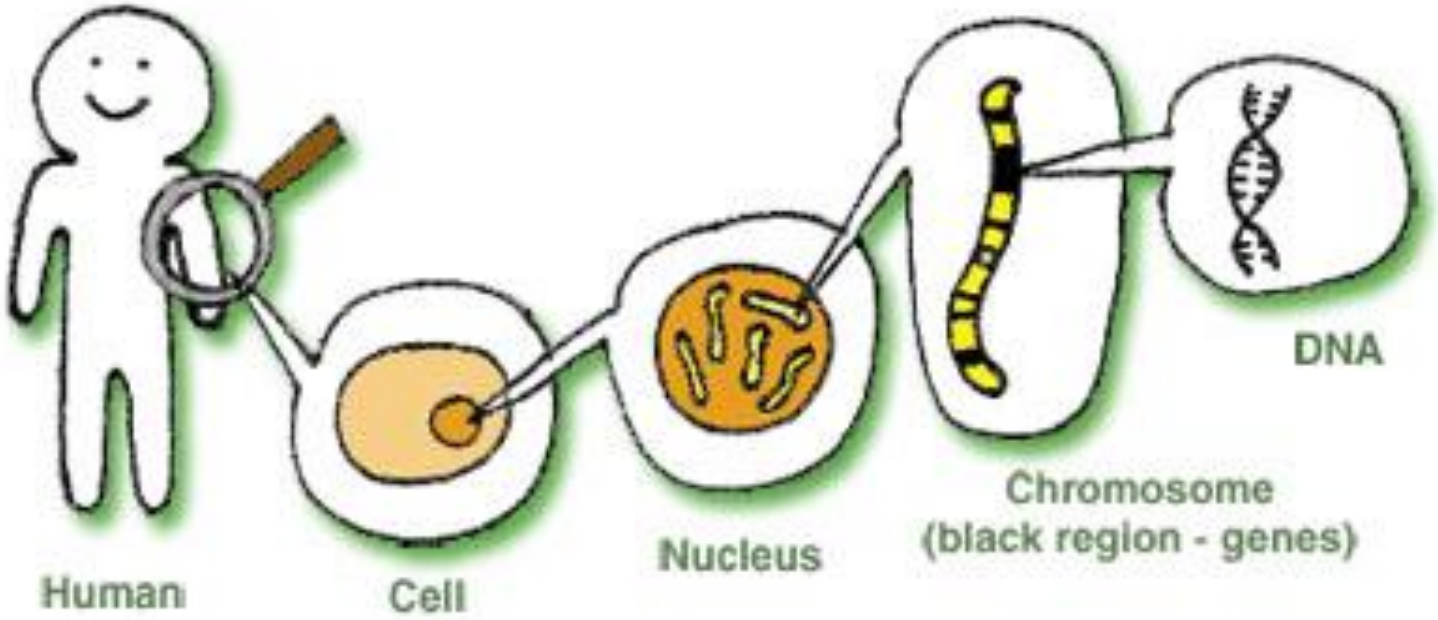
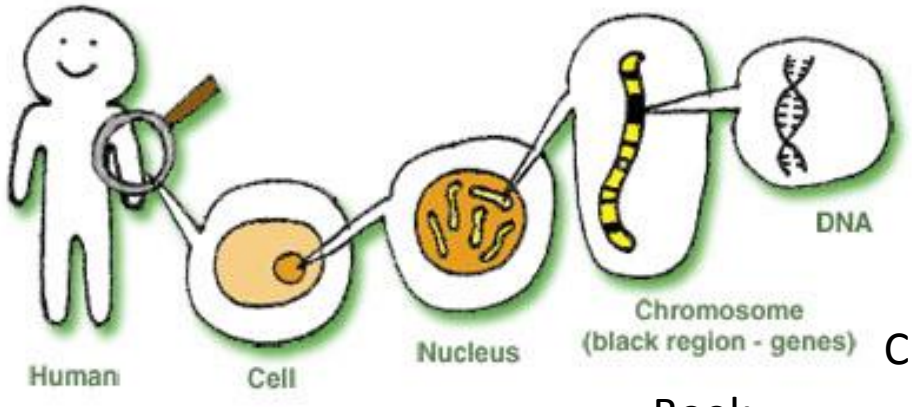
Definitions: Cells, Genes and DNA



Definitions: Mutations



Building Room Shelf Book Chapter

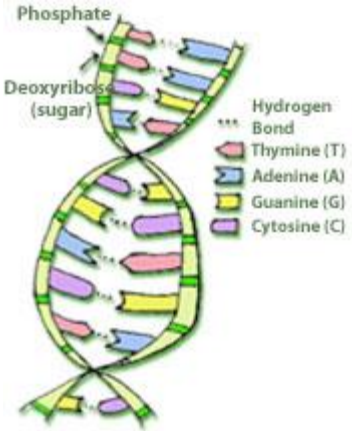
Mutations change the story:

-> remove or add a letter

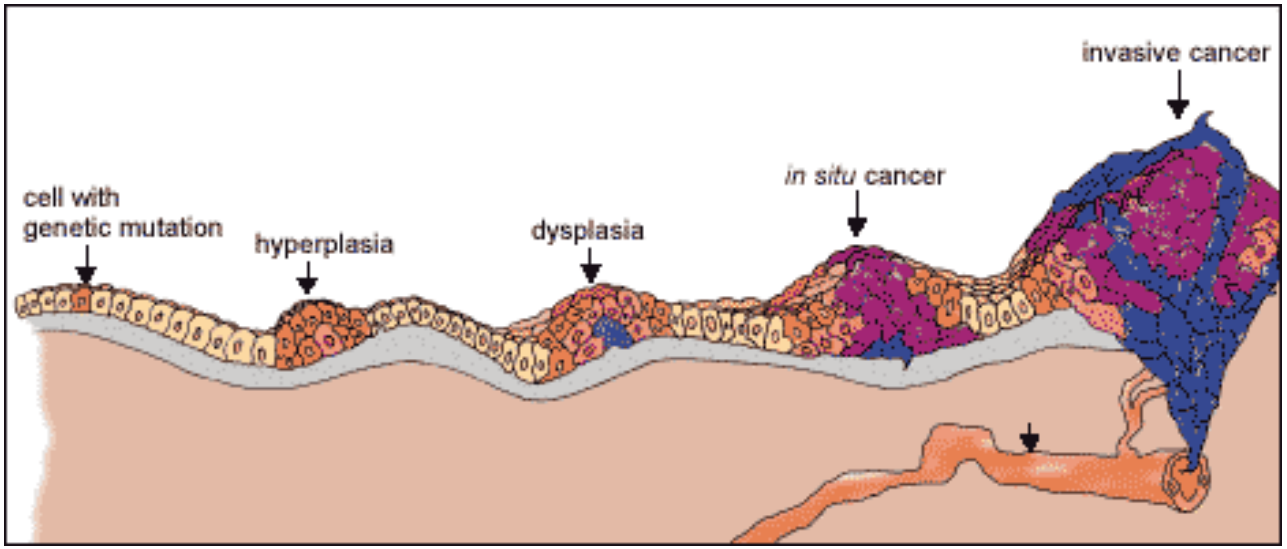
-> change a letter

-> remove or add a whole page

There are only 4 letters in this story!



How do mutations in genes cause cancer?

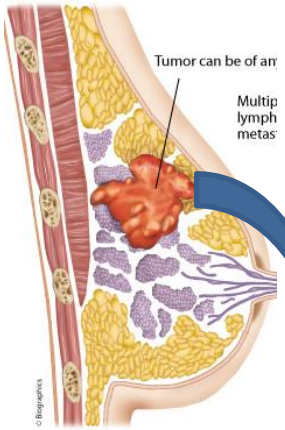


Brakes =
Tumor suppressors
Active in normal cells
Mutations->cancer

Accelerator =
Oncogenes
Inactive in normal cells
Mutations->cancer

Germline (Inherited) versus Somatic (Tumor)

We can test both



"Germline" or "Constitutional" or "Inherited" genetic changes that lead to cancer predisposition
e.g
BRCA1, *BRCA2*
TP53, *PTEN*, *etc*

"Somatic" or "Driver" or "Tumor" changes that lead to cancer progression and may be targetable
e.g.
Gain of *HER2*
BRCA1/2 mutation

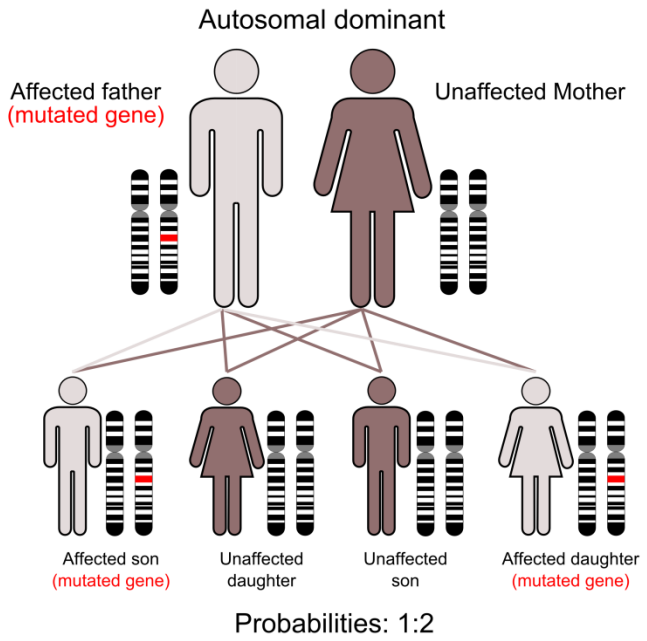
Can be passed on to family members

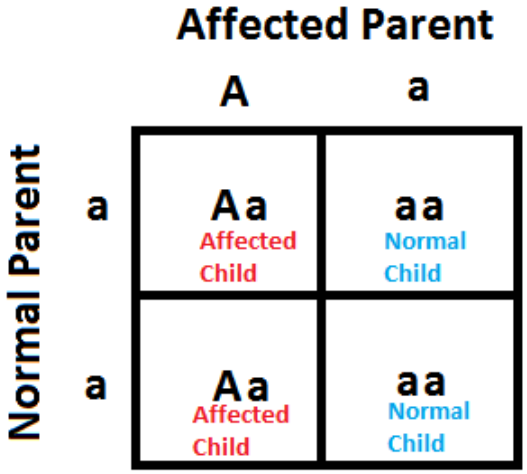
Cannot be passed on to family members

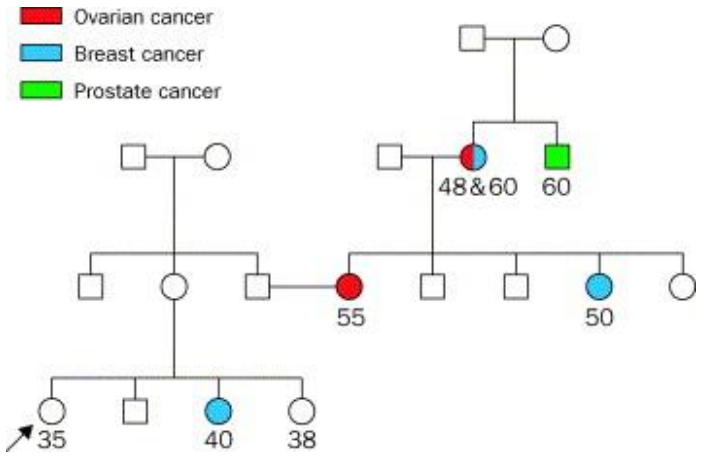
Ways cancer genetic mutations can be inherited (passed down through families)

	Monogenic Autosomal Dominant	Monogenic Autosomal Recessive	Polygenic
Examples in breast cancer	*BRCA1, BRCA2*, many others	None (?*GEN1*)	~100
Number of genes involved	One	One	Many
Number of mutations inherited	One	Two	Many
Clinical testing available	Yes	n/a yet	No

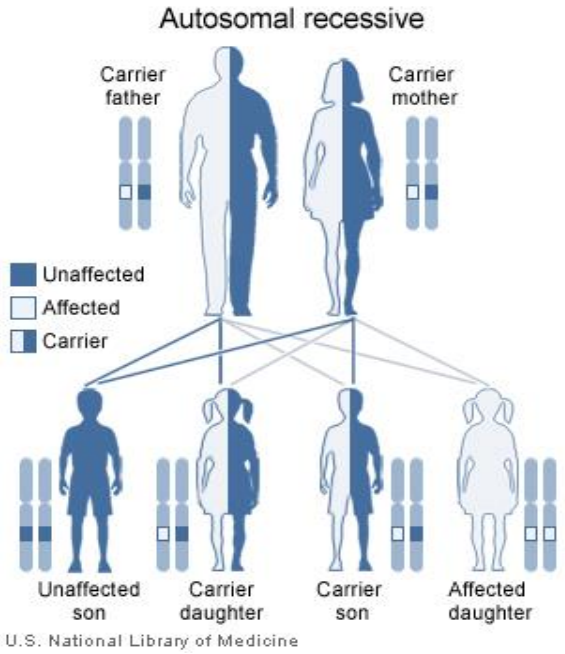
Monogenic Autosomal Dominant Inheritance

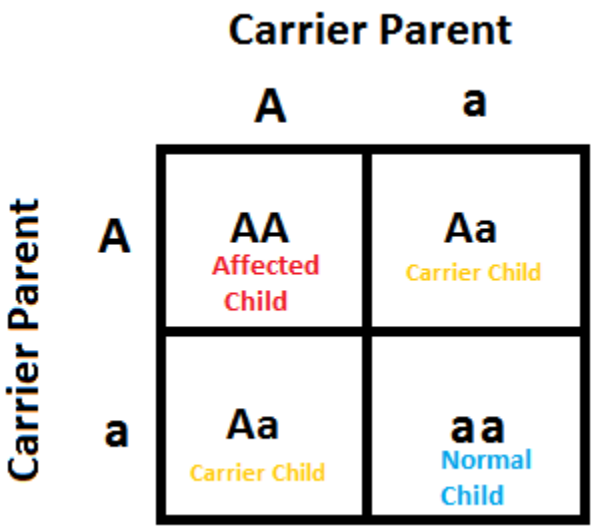


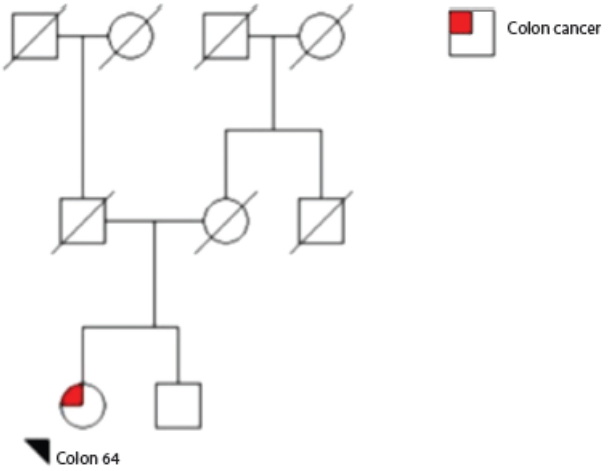




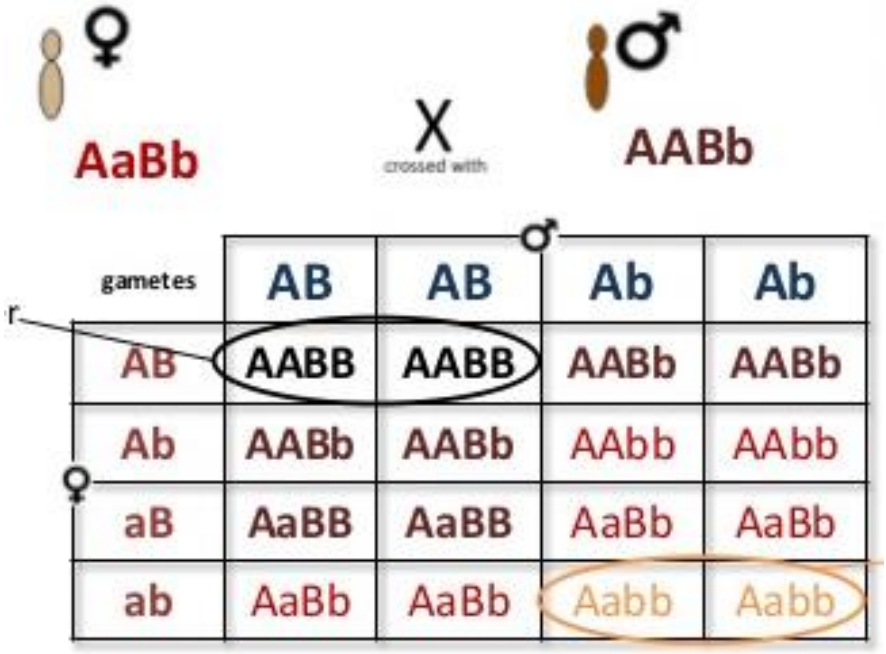
Monogenic Autosomal Recessive Inheritance





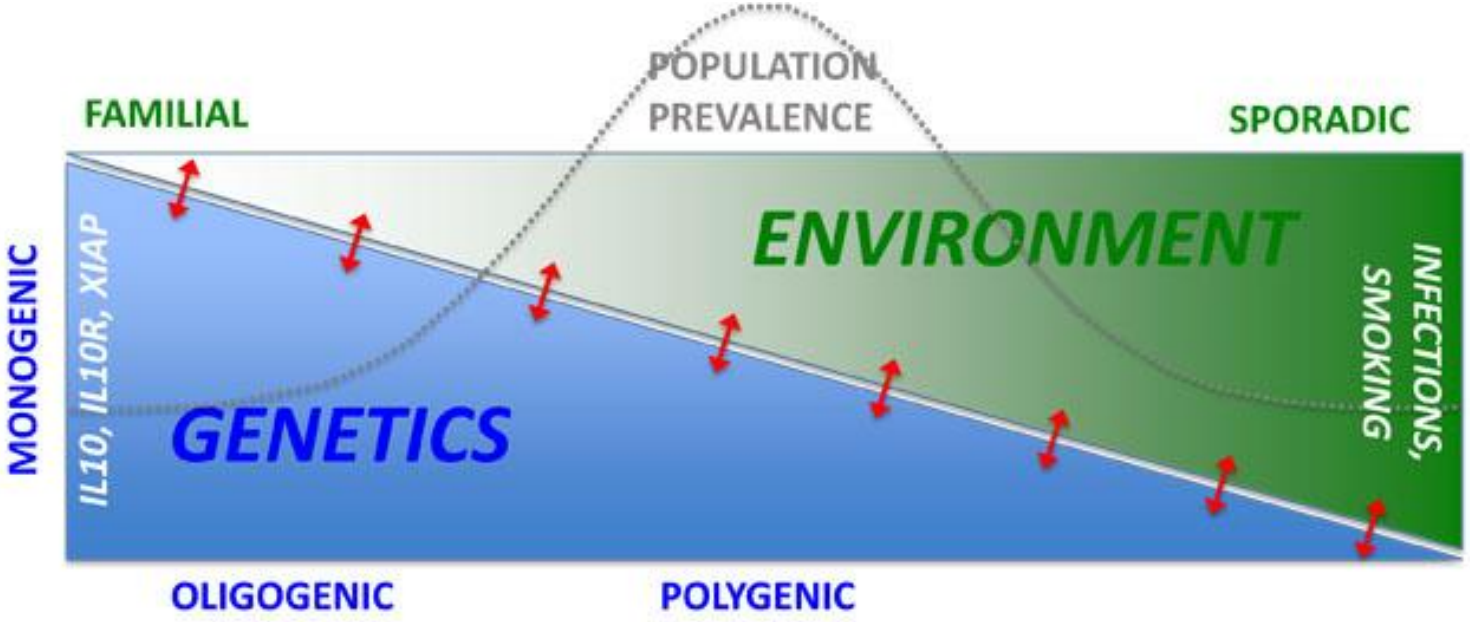


Polygenic Inheritance



But this is only two common SNPs
For breast cancer now there over 100 SNPs -> depending on how they combine could lead to 10000 possible genotypes!

And it's not even really that simple



PART 1B:

OVERVIEW OF CANCER RISK EVALUATION

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What is cancer risk evaluation?

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- **Unaffected (cancer-free) individuals**
  - to estimate your personal risk of developing cancer based on your family history

- **Affected (have had cancer) individuals**
  - to estimate your personal risk of developing another cancer based on your personal and family history
  - to help family members estimate their cancer risk

What happens when you do cancer risk evaluation?

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- Meet with a genetic counselor (GC) to review your personal and family cancer history
- Possibly undergo genetic testing
- Meet with the GC and an MD specializing in cancer risk to determine a medical management plan

Why should I do genetic testing?

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1. **Personal benefit to the breast cancer patient**
   a) Early stage breast: surgical options, ?adjuvant chemotherapy
   b) Advanced cancers: PARP inhibitors for treatment of metastatic BRCA1/2 related cancers – approved for ovarian, trials for breast, pancreatic cancer, and other advanced solid tumors

2. **Benefit to family**
   a) Early screening
   b) Preventive surgery
   c) Preventive medicaitons

Should a breast cancer patient undergo cancer risk evaluation? - NCCN

- Diagnosed at age<50
- Have triple negative breast cancer
- All Men
- All individuals of Ashkenazi Jewish ancestry
- Personal history of prior breast cancer
- Personal history of prior ovarian cancer
- Close relative(s) with any of following:
  - -breast cancer under age 50
  - - ovarian cancer
  - - pancreatic cancer
  - - aggressive or early onset prostate cancer
  - - other rare cancers such as sarcoma, adrenal cancer, brain tumor, leukemia*

  *(possibly also in some cases with other family members with endometrial cancer, thyroid cancer, stomach cancer)

Should an unaffected person undergo cancer risk evaluation? - NCCN

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<u>One close relative with:</u>
- 2 breast cancers
- breast cancer under age 45
- ovarian cancer
- male breast cancer

OR

<u>Two or more close relatives with any combination of:</u>
- breast cancer
- ovarian cancer
- pancreatic cancer
- aggressive prostate cancer

The family member with cancer is the best person to test
This applies if affected relatives are either deceased or unwilling to undergo testing

Medicare Testing Guidelines

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Personal history of breast cancer and one or more of the following indications:

- Diagnosed ≤45 y;
- Diagnosed ≤50 y with:
  - An additional breast cancer primary;
  - ≥ close blood relative* with breast cancer at any age;
  - ≥1 close relative with pancreatic cancer;
  - ≥1 relative with prostate cancer (Gleason score ≥7);
  - An unknown or limited family history;

- Diagnosed ≤ 60y with a:
  - Triple negative breast cancer (estrogen receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (HER2) negative);

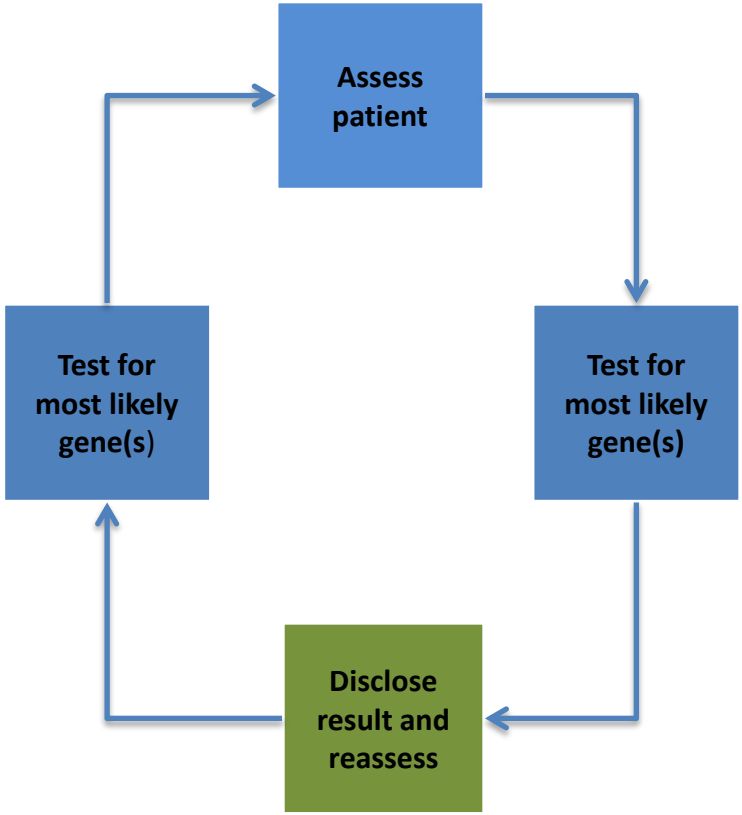
- Diagnosed at any age with:
  - ≥1 close blood relatives* with breast cancer diagnosed ≤ 50y;
  - ≥2 close blood relative* with breast cancer at any age;
  - ≥1 close blood relative* with invasive ovarian cancer (includes fallopian tube and primary peritoneal cancer);
  - ≥2 close blood relatives* with pancreatic cancer or prostate cancer (Gleason score ≥7) at any age;
  - Close male blood relative* with breast cancer;
  - Individual of ethnicity associated with higher mutation frequency (e.g. Ashkenazi Jewish);

*NCCN defines blood relative as first- (parents, siblings and children), second- (grandparents, aunts, uncles, nieces and nephews, grandchildren and half-siblings), and third degree-relatives (great-grandparents, great-aunts, great uncles, great grandchildren and first cousins) on same side of family.

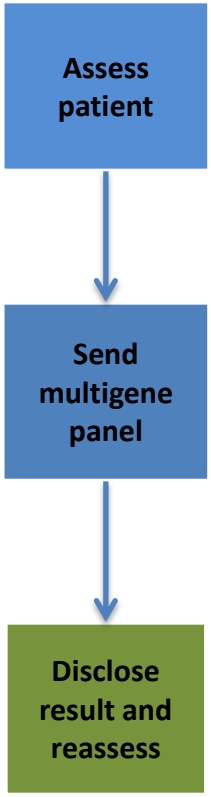
**Includes fallopian tube, and primary peritoneal cancers. BRCA-related ovarian cancers are associated with epithelial non-mucinous histology.

How is testing done?

Before



Today



So, what's different?

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- **More types of mutations in *BRCA1/2* can now be easily tested**
  - Myriad genetics (sole tester of *BRCA1/2* from 1996 to 2013) only tested for single base pair changes and small frameshifts until 2006 (BRAC*Analysis*) when it introduced a test for large deletions/insertions, also called LGRs or large genomic rearrangements (BART) test
  - However, many insurance companies did not cover BART for many years
  - Since 2014, Myriad's Comprehensive BRAC*Analysis* tests for both, as does Myriad MyRisk and current genetic testing panels from other companies
- **More genes beside *BRCA1/2* can now be tested**
- **There are more companies than Myriad testing for *BRCA1/2* now**
- **Insurance coverage has significantly expanded**

So, what should I do?

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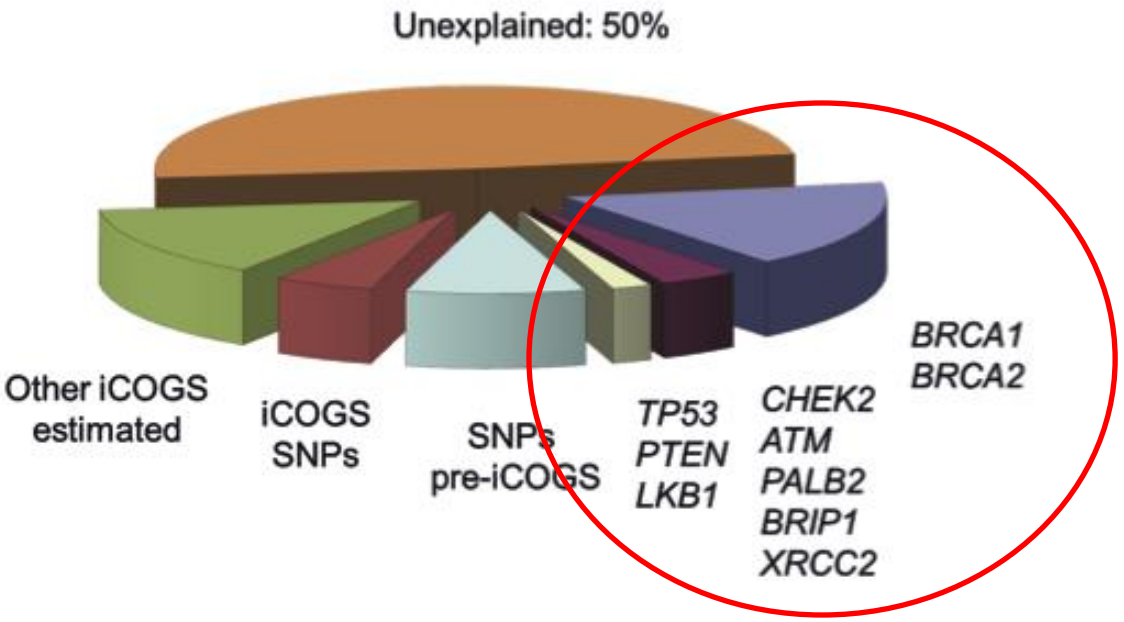
- **If you had an ER positive breast cancer over age 50 and you have no family history of breast or ovarian cancer, you probably don't need genetic testing**
- **If you had genetic testing within the last 2 years, you are probably up to date, but you can always check back with your genetics provider**
- **For other women, genetic testing or new genetic testing may be warranted -> ask your oncologist or visit our website**

https://www.pennmedicine.org/cancer/navigating-cancer-care/programs-and-centers/basser-center-for-brca

What could I be tested for in 2016?



Some breast cancer panels as of 2016

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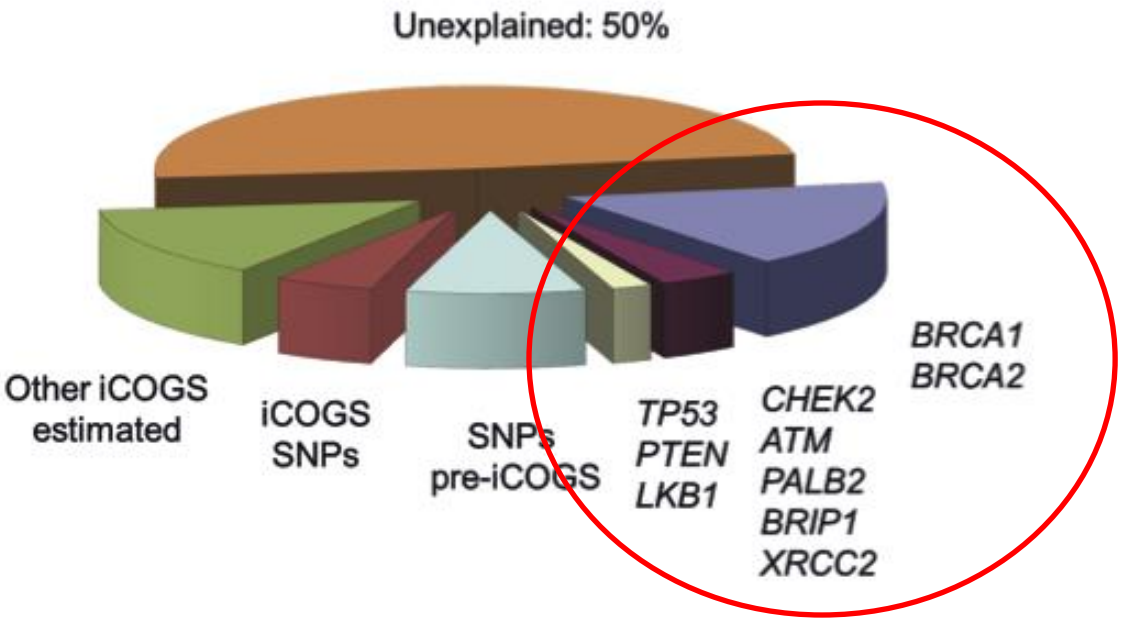
Gene	Myriad MyRisk	Ambry Breast Next	GeneDx Breast	Invitae Breast
# of genes	25	17	9	14
BRCA1	X	X	X	X
BRCA2	X	X	X	X
CDH1	X	X	X	X
PTEN	X	X	X	X
TP53	X	X	X	X
ATM	X	X	X	X
BARD1	X	X		X
BRIP1	X	X		X
CHEK2	X	X	X	X
PALB2	X	X	X	X
MRE11A	X	X		
NBN	X	X		X
NF1		X		X
RAD50	X	X		
RAD51C	X	X		
RAD51D	X	X		
MUTYH	X	X		
Other Genes	+9 more on this panel	On other panels	On other panels	Can customize additions

What could I be tested for?



PART 2:

BRCA1 AND BRCA2

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What are BRCA1 and BRCA2?

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***BRCA1* and *BRCA2* genes are "tumor suppressors" that are involved in the response to DNA damage**

Toxins
Carcinogens
UV Light
Smoking
Normal growth
Etc..

Cancer Risks in female *BRCA1* and *BRCA2* mutation carriers

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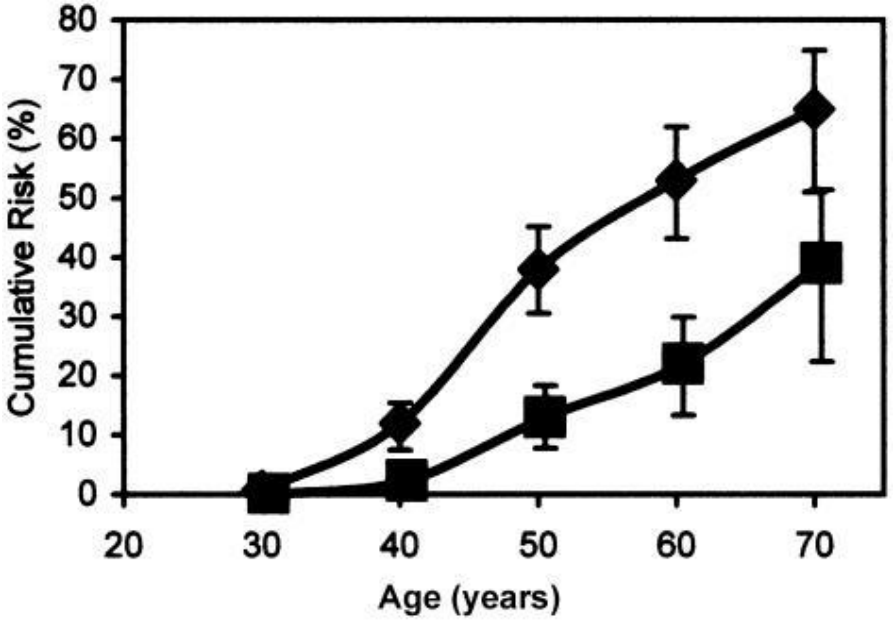
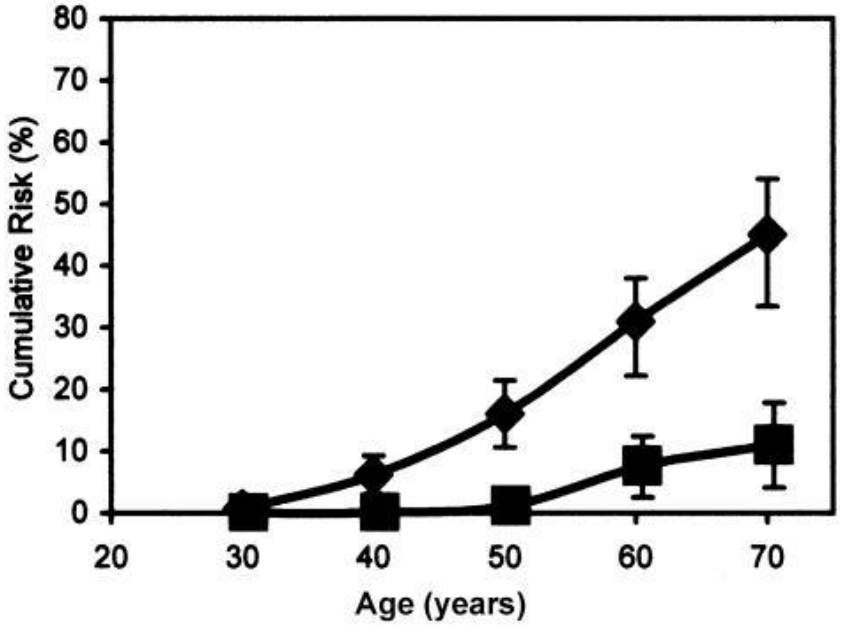
	Women with *BRCA1* Mutation	Women with *BRCA2* mutation	Average woman in US without mutation
Breast	60-80%	50-70%	13%
Ovarian	30-45%	10-20%	1-2%
Pancreatic	2-3%	3-5%	1%
Melanoma	-	3-5%	1-2%

Cancer risks in male *BRCA1* and *BRCA2* mutation carriers

	Men with *BRCA1* Mutation	Men with *BRCA2* mutation	Average man in US without mutation
Breast	1-5%	5-10%	0.1%
Prostate	*	15-25%*	16%
Pancreatic	2-3%	3-5%	1%
Melanoma	-	3-5%	1-2%

Age Specific Risks of Cancer for *BRCA1/2* carriers

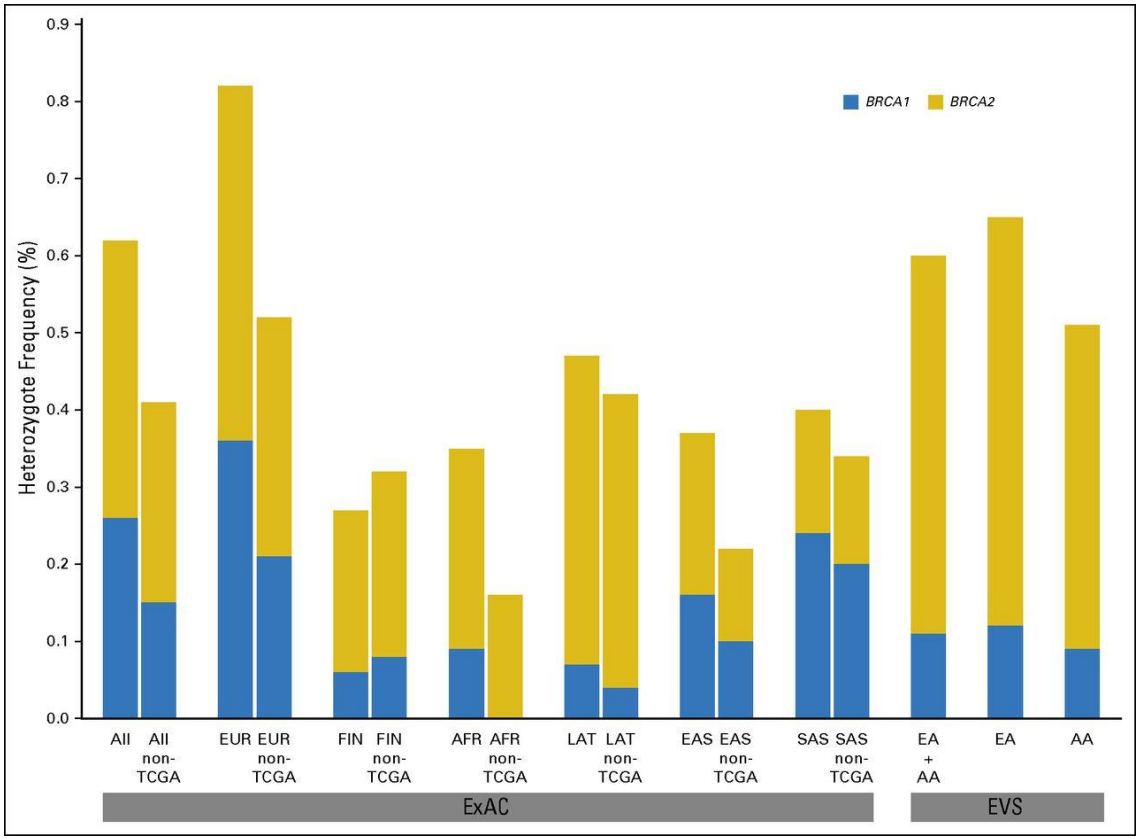




◆ **Breast cancer**

■ **Ovarian cancer**

How common are *BRCA1/2* mutations?



IN THE GENERAL POPULATION:
~ 1 in 250 people

All ethnic populations probably about the same, including African Americans, Latinos, Asians

How common are *BRCA1/2* mutations in breast cancer patients?

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1. The Prevalence of Deleterious Mutations in *BRCA1* and *BRCA2* (Excludes Individuals of Ashkenazi Ancestry)

	Family History (Includes at least one first- or second-degree relative)					
Patient's History	No breast cancer <50, or ovarian cancer in any relative†	Breast cancer <50 in one relative; no ovarian cancer in any relative	Breast cancer <50 in more than one relative; no ovarian cancer in any relative	Ovarian cancer at any age in one relative; no breast cancer <50 in any relative	Ovarian cancer in more than one relative; no breast cancer <50 in any relative	Breast cancer <50 and ovarian cancer at any age††
No breast cancer or ovarian cancer at any age	1.5%	2.6%	5.6%	3.0%	5.3%	7.2%
Breast cancer ≥50	2.2%	3.8%	8.0%	4.9%	9.5%	10.6%
Breast cancer <50	4.7%	10.4%	21.2%	10.3%	21.9%	26.6%
Male breast cancer	6.9%	17.4%	36.6%	15.9%	*33.3%	28.3%
Ovarian cancer at any age, no breast cancer	7.7%	14.3%	27.4%	14.7%	22.7%	34.4%
Breast cancer ≥50 and ovarian cancer at any age	12.1%	23.6%	50.0%	23.6%	44.2%	39.4%
Breast cancer <50 and ovarian cancer at any age	26.3%	40.0%	64.5%	41.2%	45.5%	57.4%

BRCA1/2 in the Ashkenazi Jewish population

Women AND men of Ashkenazi Jewish ancestry have a 1 in 40 chance of carrying a *BRCA1/2* mutation

How common are *BRCA1/2* mutations in breast cancer patients?

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2. The Prevalence of Deleterious Mutations in *BRCA1* and *BRCA2* in Individuals of Ashkenazi Ancestry

	Family History (Includes at least one first- or second-degree relative)					
Patient's History	No breast cancer <50, or ovarian cancer, in any relative†	Breast cancer <50 in one relative; no ovarian cancer in any relative	Breast cancer <50 in more than one relative; no ovarian cancer in any relative	Ovarian cancer at any age in one relative; no breast cancer <50 in any relative	Ovarian cancer in more than one relative; no breast cancer <50 in any relative	Breast cancer <50 and ovarian cancer at any age††
No breast cancer or ovarian cancer at any age	8.2%	13.0%	16.4%	12.7%	22.3%	22.9%
Breast cancer ≥50	3.3%	7.1%	10.8%	13.2%	13.6%	16.7%
Breast cancer <50	7.9%	17.5%	26.9%	18.1%	20.0%	33.0%
Male breast cancer	13.5%	26.8%	*46.2%	*21.1%	*66.7%	*55.6%
Ovarian cancer at any age, no breast cancer	16.2%	26.4%	47.4%	26.2%	57.1%	57.8%
Breast cancer ≥50 and ovarian cancer at any age	20.5%	18.2%	*30.0%	*31.3%	*100.0%	*55.6%
Breast cancer <50 and ovarian cancer at any age	42.1%	*63.2%	*85.7%	*62.5%	*100.0%	*36.4%

What we can do for *BRCA1/2* carriers

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1. Cancer

	Cancer screening	Cancer prevention	Cancer treatment
Ovarian	Transvaginal ultrasound + CA125 blood test	Oophorectomy Oral contraceptives	PARP inhibitors (Lynparza) FDA approved
Breast	Mammogram + MRI	Bilateral mastectomy Tamoxifen Raloxifene	?PARP inhibitors or platinums (currently in clinical trials)
Prostate	PSA + digital rectal exam	Unknown	
Pancreatic	Endoscopic ultrasound	Unknown	

2. Reproductive counselling

- PGD
- Risk of Fanconi Anemia

Ovarian Cancer Risk Reduction - Oophorectomy

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Table 4. Risk-Reducing Salpingo-oophorectomy and All-Cause Mortality[a]

	All Eligible Women			No Prior Breast Cancer[b]			Prior Breast Cancer[c]		
	Total (n = 2482)	*BRCA1* (n = 1587)	*BRCA2* (n = 895)	Total (n = 1458)	*BRCA1* (n = 935)	*BRCA2* (n = 523)	Total (n = 1027)	*BRCA1* (n = 654)	*BRCA2* (n = 373)
Risk-reducing salpingo-oophorectomy									
Yes	993 (40.0)	706 (44.5)	287 (32.1)	447 (30.7)	327 (35.0)	120 (22.9)	451 (43.9)	317 (48.5)	134 (35.9)
Deaths	31 (3.1)	25 (3.5)	6 (2.1)	8 (1.8)	8 (2.4)	0	19 (4.2)	14 (4.4)	5 (3.7)
No	1489 (60.0)	881 (55.5)	608 (67.9)	1011 (69.3)	608 (65.0)	403 (77.1)	576 (56.1)	337 (51.5)	239 (64.1)
Deaths	146 (9.8)	93 (10.6)	53 (8.7)	60 (5.9)	43 (7.1)	17 (4.2)	92 (16.0)	54 (16.0)	38 (15.9)
Age, mean (range), y									
At time of risk-reducing oophorectomy	45.4 (20.5-79.0)	44.5 (20.5-79.0)	47.6 (30.4-72.9)	43.2 (20.5-79.0)	42.1 (20.5-79.0)	46.4 (33.0-68.5)	47.6 (29.7-75.2)	47.0 (29.7-75.2)	49.1 (30.4-72.9)
At start of follow-up for those without oophorectomy	39.8 (18.1-90.4)	38.5 (18.2-90.4)	41.6 (18.1-82.7)	36.3 (18.1-90.4)	35.1 (18.2-90.4)	38.2 (18.1-82.7)	45.3 (21.9-86.2)	44.2 (21.9-86.2)	46.9 (26.1-77.7)
Follow-up, mean (range), y									
To death	6.0 (0.5-23.5)	5.9 (0.6-22.3)	6.2 (0.5-23.5)	9.0 (0.96-23.5)	8.5 (1.0-22.3)	10.3 (2.8-23.5)	4.6 (0.5-20.3)	4.3 (0.6-20.3)	5.1 (0.5-13.3)
To censoring	5.0 (0.5-27.9)	5.0 (0.5-27.7)	4.9 (0.5-27.9)	5.8 (0.5-27.9)	5.7 (0.5-27.7)	5.9 (0.5-27.9)	4.5 (0.5-24.6)	4.8 (0.5-24.6)	4.1 (0.5-15.4)
All-cause mortality after risk-reducing salpingo-oophorectomy, HR (95% CI)[d]	0.40 (0.26-0.61)	0.38 (0.24-0.62)	0.52 (0.22-1.23)	0.45 (0.21-0.95)	0.52 (0.24-1.14)	No deaths	0.30 (0.17-0.52)	0.26 (0.13-0.52)	0.45 (0.17-1.16)
Age <50 y	0.41 (0.25-0.67)	0.40 (0.24-0.68)	0.16 (0.02-1.30)	0.70 (0.31-1.57)	0.50 (0.21-1.20)	No deaths	0.28 (0.14-0.55)	0.30 (0.14-0.64)	0.19 (0.02-1.59)
Age ≥50 y	0.37 (0.15-0.94)	0.22 (0.06-0.85)	0.47 (0.12-1.80)	0.28 (0.03-2.42)	0.93 (0.11-8.12)	No deaths	0.37 (0.13-1.03)	0.12 (0.02-0.73)	0.46 (0.10-2.13)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Values are expressed as number (percentage) unless otherwise indicated. Participants were censored at last contact.
[b] There were no breast cancer cases prior to risk-reducing salpingo-oophorectomy or in those who did not undergo salpingo-oophorectomy prior to the start of follow-up.
[c] Breast cancer allowed prior to risk-reducing salpingo-oophorectomy or start of follow-up.
[d] Adjusted for year of birth and stratified by center.

Oophorectomy reduces the risk of death by ~60-80% in both *BRCA1* and *BRCA2* carriers

-> there is a decrease in risk of death due to any cause, including ovarian cancer

Ovarian Cancer Risk Reduction - Screening

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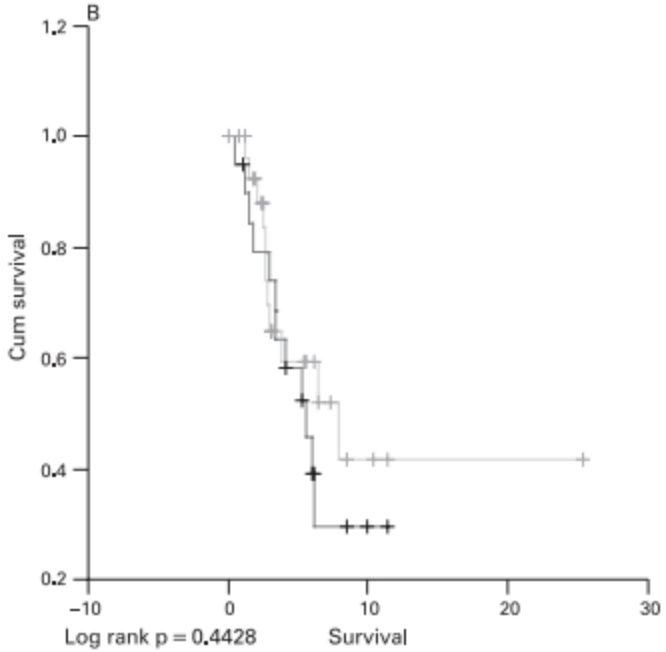
- We offer transvaginal ultrasound and CA125 blood testing starting at age 30 until the time of oophorectomy

- However, there is no evidence that screening improves survival, although it *might* identify ovarian cancer at an earlier stage

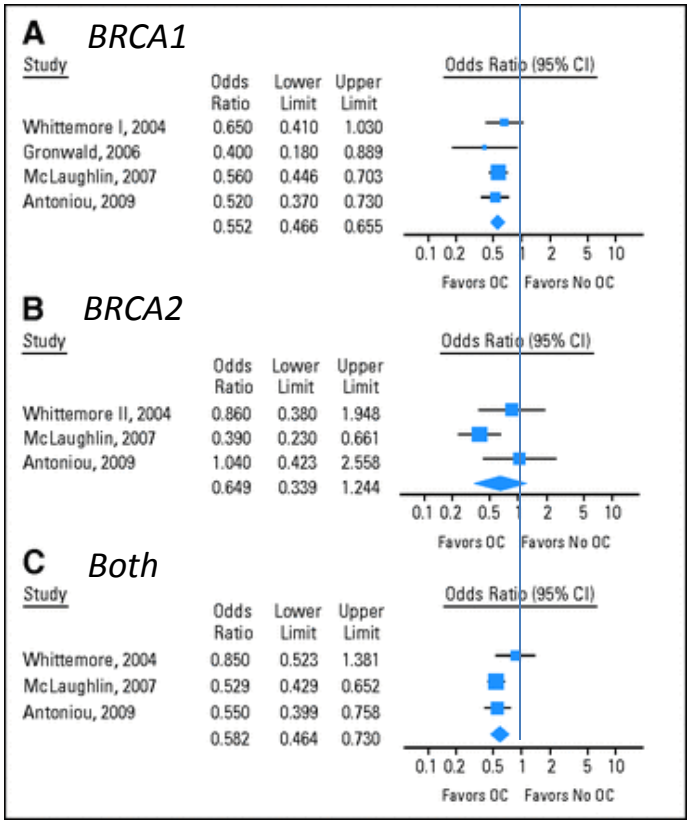
We need better screening tests!



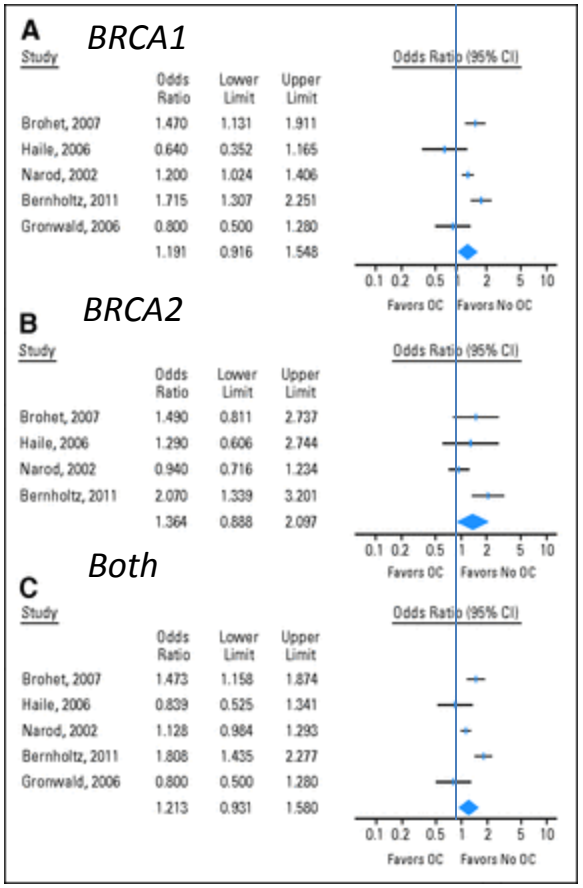
Ovarian Cancer Risk Reduction – Oral Contraceptives

BASSER CENTER FOR BRCA

Ovarian Cancer

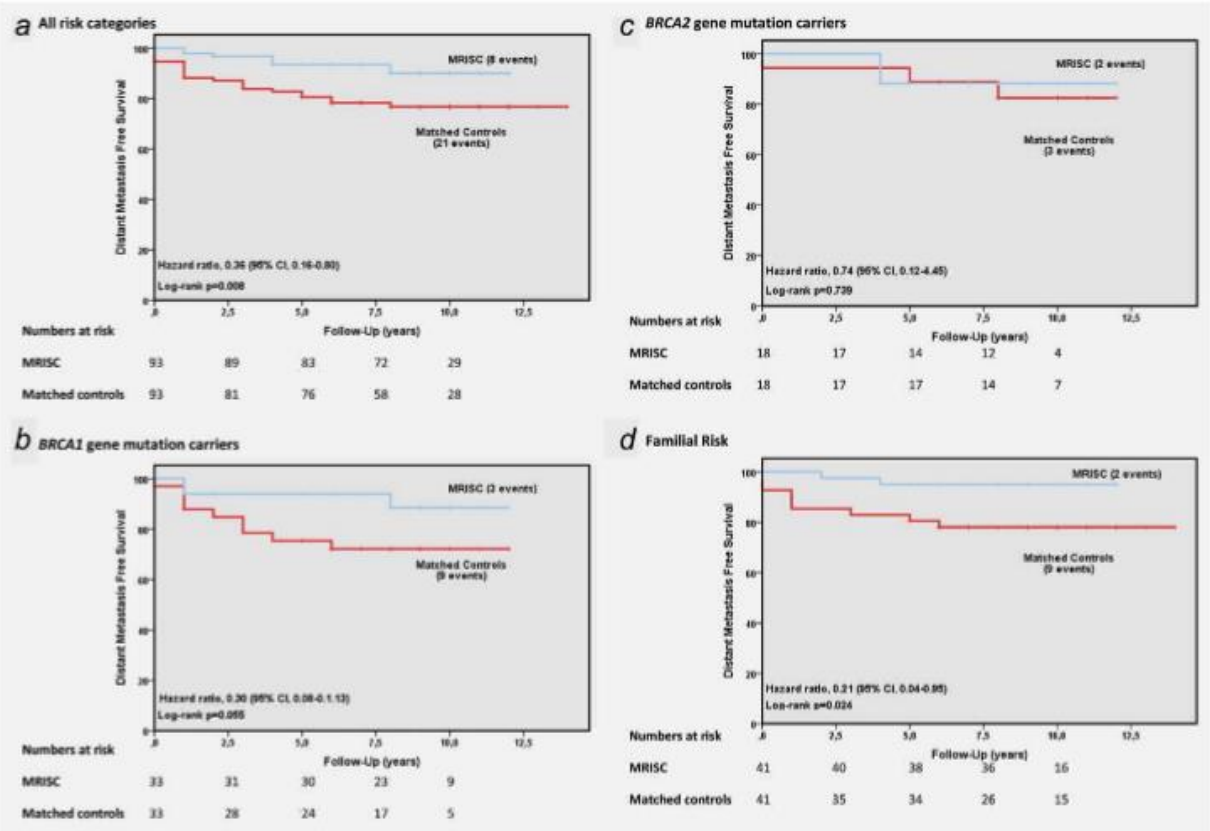


Breast Cancer



Oral Contraceptives reduce the risk of ovarian cancer by ~50% in *BRCA1* carriers, less so in *BRCA2*. There is no evidence of an increase in breast cancer risk

Breast Cancer Risk Reduction - Screening



Breast MRIs not only find breast cancers in *BRCA1* and *BRCA2* carriers but they may actually improve survival in *BRCA1* carriers

Breast Cancer Risk Reduction - Screening

BASSER CENTER FOR BRCA

Table 2. Sensitivity and specificity of screening modalities[a]

Previous table | Figures and tables index | Next table

		Mammography			MRI			Combination		
Age group (years)	Mutation status	No. of BC detected	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	No. of BC detected	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	No. of BC detected	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
All ages	*BRCA1* (n=112)	39	35.7 (25.9–46.9)	93.8 (89.3–96.5)	92	88.6 (73.4–95.6)	84.4 (78.7–88.8)	98	92.5 (80.1–97.4)	80.4 (72.8–86.2)
	BRCA2 (n=72)	31	44.6 (31.9–58)	93.4 (88.4–96.3)	53	80.1 (58.9–91.9)	85.3 (79.6–89.6)	64	92.7 (79.3–97.7)	80.5 (72.8–86.4)
≤40	*BRCA1* (n=46)	18	39.1 (26.2–53.9)	94.9 (91.2–97.1)	34	77.5 (57–90)	84.3 (78.7–88.7)	38	86.8 (63.1–96.2)	81 (73.9–86.5)
	BRCA2 (n=18)	10	55.6 (32.9–76.1)	92.3 (86.6–95.7)	9	52.7 (27.2–76.8)	80.2 (72.9–85.8)	15	87.2 (56.1–97.3)	75.3 (66.6–82.4)
41–50	*BRCA1* (n=38)	13	34.2 (21–50.5)	91.5 (86.7–94.6)	34	93.1 (70.8–98.7)	82.9 (77.9–87)	35	94.1 (74.5–98.9)	77.2 (70.5–82.8)
	BRCA2 (n=38)	14	37.8 (22.7–55.5)	92 (87–95.2)	30	86.4 (58.2–96.7)	86 (81.1–89.8)	33	91.2 (70.4–97.9)	80 (73.3–85.3)
>50	*BRCA1* (n=28)	8	29.4 (12.8–54.2)	96.8 (91.9–98.8)	24	89.1 (54.8–98.2)	89.9 (82.6–94.3)	25	89.3 (71.3–96.6)	87.4 (79.3–92.6)
	BRCA2 (n=17)	7	45.5 (19.3–74.4)	97.4(92.8–99.1)	14	85 (43.7–97.7)	91.1 (84–95.2)	16	94.1 (67.5–99.2)	88.6 (80.7–93.6)

Abbreviations: BC=breast cancer; CI=confidence interval; MRI=magnetic resonance imaging.

[a] Stratified by age at screening and by *BRCA1* or *BRCA2* mutation status.

Mammograms may not add significantly to breast MRI screening in *BRCA1* carriers and older *BRCA2* carriers but clearly add benefit in younger *BRCA2* carriers

Breast Cancer Risk Reduction - Mastectomy

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Table 1. Risk-Reducing Mastectomy and Risk of First Occurrence of Breast Cancer[a]

	Prior or Concurrent Risk-Reducing Salpingo-oophorectomy					
	Yes			No		
	Total (n = 959)	*BRCA1* (n = 617)	*BRCA2* (n = 342)	Total (n = 660)	*BRCA1* (n = 415)	*BRCA2* (n = 245)
Risk-reducing mastectomy						
Yes	172 (17.9)	116 (18.8)	56 (16.4)	75 (11.4)	43 (10.4)	32 (13.1)
Breast cancer diagnosis	0	0	0	0	0	0
No	787 (82.1)	501 (81.2)	286 (83.6)	585 (88.6)	372 (89.6)	213 (86.9)
Breast cancer diagnosis	64 (8.1)	44 (8.8)	20 (7.0)	34 (5.8)	19 (5.1)	15 (7.0)
Age, mean (range), y						
At time of risk-reducing mastectomy	40.7 (22.4-64.6)	40.1 (24.8-62.5)	42.0 (22.4-64.6)	37.9 (22.4-64.6)	36.7 (24.8-52.1)	39.4 (22.4-64.6)
At start of follow-up for those without mastectomy	40.5 (18.3-87.8)	39.5 (18.3-87.8)	42.2 (18.9-79.7)	37.6 (18.3-87.8)	36.7 (18.3-87.8)	39.1 (18.9-79.7)
Follow-up, mean (range), y						
To breast cancer diagnosis	3.1 (0.5-9.3)	3.3 (0.5-9.3)	2.6 (0.6-6.8)	3.1 (0.6-8.7)	3.6 (0.6-8.7)	2.5 (0.6-6.8)
To censoring	3.5 (0.5-13.0)	3.7 (0.5-13.0)	3.0 (0.5-11.5)	2.7 (0.5-13.0)	2.7 (0.5-13.0)	2.5 (0.5-11.5)
Occult breast cancer diagnosis[b]	4 (<1)	3 (<1)	1 (<1)	3 (<1)	2 (<1)	1 (<1)
Breast cancer after risk-reducing mastectomy, HR (95% CI)[c]	NA	NA	NA	NA	NA	NA

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, data cannot be estimated.
[a] Values are expressed as number (percentage) unless otherwise indicated. There were no cases of breast cancer prior to ascertainment or risk-reducing salpingo-oophorectomy. Participants were censored at occurrence of ovarian cancer, death, or last contact.
[b] Cancer was found incidentally at the time of prophylactic mastectomy and excluded from analysis.
[c] There were no cancer events in those with risk-reducing mastectomy so HRs cannot be estimated.

Mastectomy reduces the risk of breast cancer by almost 100% but the evidence for an overall benefit on survival is controversial

Breast Cancer Risk Reduction - Oophorectomy

BASSER CENTER FOR BRCA

Table 5. Risk-Reducing Salpingo-oophorectomy and Breast Cancer–Specific Mortality[a]

	All Eligible Women			No Prior Breast Cancer[b]			Prior Breast Cancer[c]		
	Total (n = 2407)	*BRCA1* (n = 1536)	*BRCA2* (n = 871)	Total (n = 1414)	*BRCA1* (n = 902)	*BRCA2* (n = 512)	Total (n = 995)	*BRCA1* (n = 636)	*BRCA2* (n = 359)
Risk-reducing salpingo-oophorectomy									
Yes	983 (40.8)	697 (45.4)	286 (32.8)	441 (31.2)	321 (35.6)	120 (23.4)	448 (45.0)	314 (49.4)	134 (37.3)
Deaths	21 (2.1)	16 (2.3)	5 (1.7)	2 (0.5)	2 (1.0)	0	16 (3.6)	11 (3.5)	5 (3.7)
No	1424 (59.2)	839 (54.6)	585 (67.2)	973 (68.8)	581 (64.4)	392 (76.6)	547 (55.0)	322 (50.6)	225 (62.7)
Deaths	81 (5.7)	51 (6.1)	30 (5.1)	22 (2.3)	16 (2.8)	6 (1.5)	63 (11.5)	39 (12.1)	34 (15.1)
Age, mean (range), y									
At time of oophorectomy	45.3 (20.5-75.2)	44.4 (20.5-75.2)	47.5 (30.4-72.9)	43.2 (20.5-73.9)	42.0 (20.5-73.9)	46.4 (32.9-68.5)	47.6 (29.7-75.2)	47.0 (29.7-75.2)	49.1 (30.4-72.9)
At start of follow-up for those without oophorectomy	39.3 (18.1-87.6)	38.0 (18.2-87.6)	41.2 (18.1-82.7)	35.8 (18.1-87.6)	34.5 (18.2-87.6)	37.8 (18.1-82.7)	45.1 (21.9-86.2)	43.9 (21.9-86.2)	46.7 (26.1-77.7)
Follow-up, mean (range), y									
To death	4.6 (0.5-21.4)	4.1 (0.6-21.4)	5.4 (0.5-27.9)	8.6 (1.6-21.4)	8.5 (1.6-21.4)	8.8 (2.8-18.3)	3.6 (0.5-13.3)	2.9 (0.6-10.2)	4.7 (0.5-13.3)
To censoring	5.0 (0.5-27.9)	5.0 (0.5-27.7)	4.9 (0.5-27.9)	5.8 (0.5-27.9)	5.7 (0.5-27.7)	5.9 (0.5-27.9)	4.5 (0.5-24.6)	4.8 (0.5-24.6)	4.1 (0.5-15.4)
Breast cancer–specific mortality after risk-reducing salpingo-oophorectomy, HR (95% CI)[d]	0.44 (0.26-0.76)	0.38 (0.20-0.72)	0.82 (0.30-2.20)	0.27 (0.05-1.33)	0.30 (0.06-1.53)	No deaths	0.35 (0.19-0.67)	0.27 (0.12-0.58)	0.87 (0.32-2.37)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Values are expressed as number (percentage) unless otherwise indicated. Participants were censored at last contact.
[b] There were no cases of breast cancer prior to risk-reducing salpingo-oophorectomy or in those who did not undergo salpingo-oophorectomy prior to the start of follow-up.
[c] Breast cancer allowed prior to risk-reducing salpingo-oophorectomy or start of follow-up.
[d] Adjusted for year of birth and stratified by center.

Oophorectomy reduces the risk of death due to ovarian cancer AND breast cancer -> ~60-70% in *BRCA1* carriers although less so in *BRCA2* (~20%)

Breast Cancer Risk Reduction – Tamoxifen

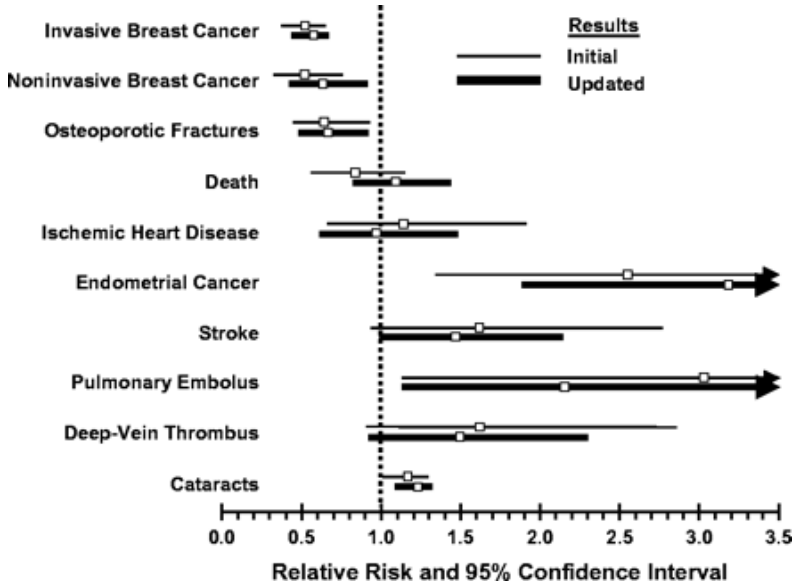


Table 3. Study Participants Who Developed Breast Cancer

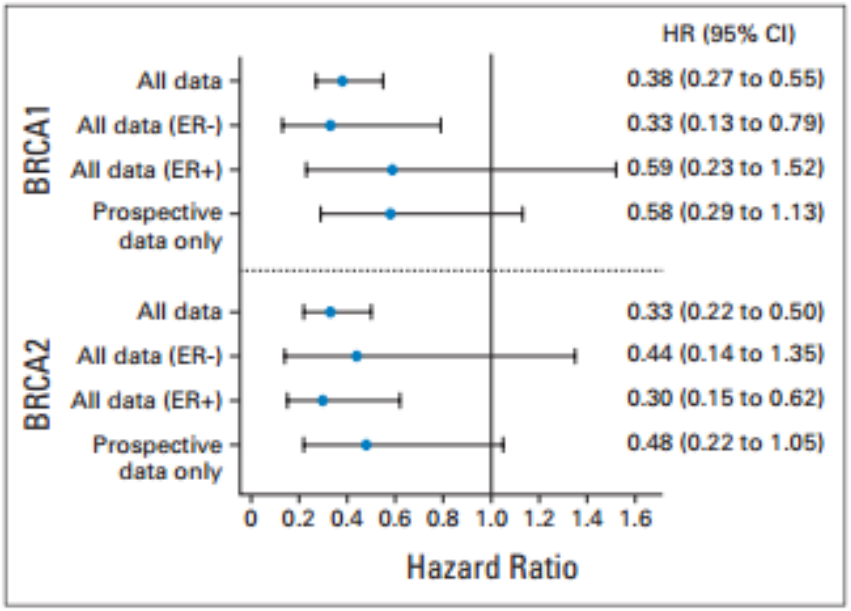
	Placebo	Tamoxifen	Risk Ratio (95% Confidence Interval)
BRCA1 mutation	3	5	1.67 (0.32-10.70)
BRCA2 mutation	8	3	0.38 (0.06-1.56)
Wild type	182	87	0.48 (0.37-0.61)
All participants*	211	109	0.52 (0.41-0.65)

*Includes 288 genotyped cases and 32 cases without DNA available.

Tamoxifen reduces the risk of breast cancer in high risk patients by at least 50% including *BRCA2* carriers, although possibly there is little to no effect in *BRCA1* carriers

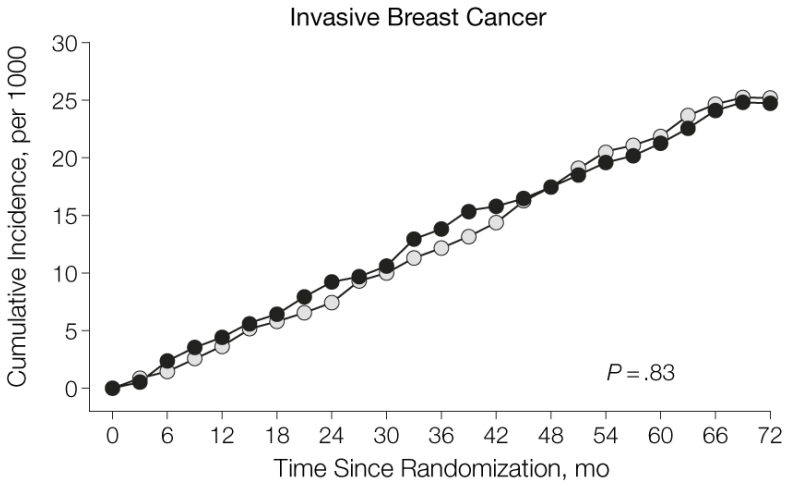
Tamoxifen does increase the risk of cardioembolic events and endometrial cancer

Contralateral Breast Cancer Risk Reduction – Tamoxifen after one breast cancer diagnosis



Tamoxifen reduces the risk of a 2nd breast cancer by at least 50%

Breast Cancer Risk Reduction – Raloxifene



No. at Risk					
Raloxifene	9745	8916	6701	4323	833
Tamoxifen	9726	8931	6653	4254	809

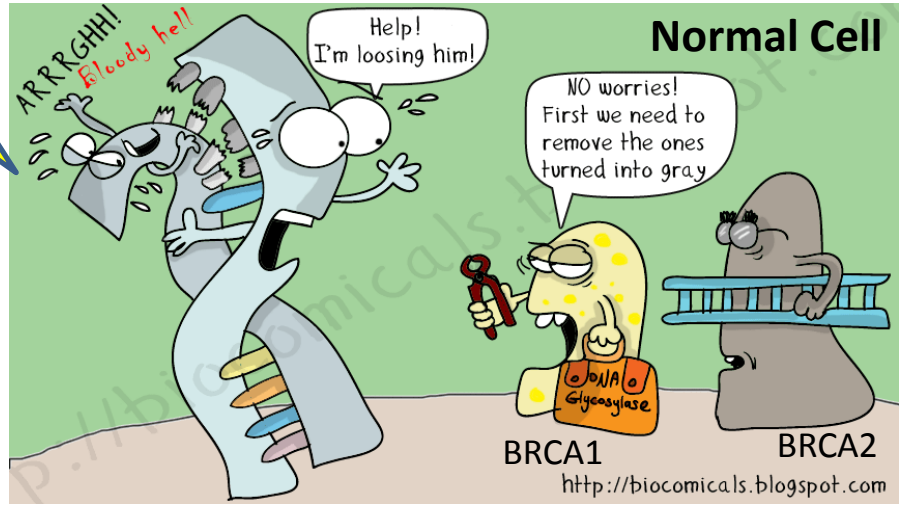
Raloxifene is equivalent to tamoxifen in breast cancer risk reduction (all high risk patients, not just *BRCA1/2*)

Raloxifene has less side effects and has a benefit for osteoporosis prevention

Synthetic lethality and PARP inhibitors

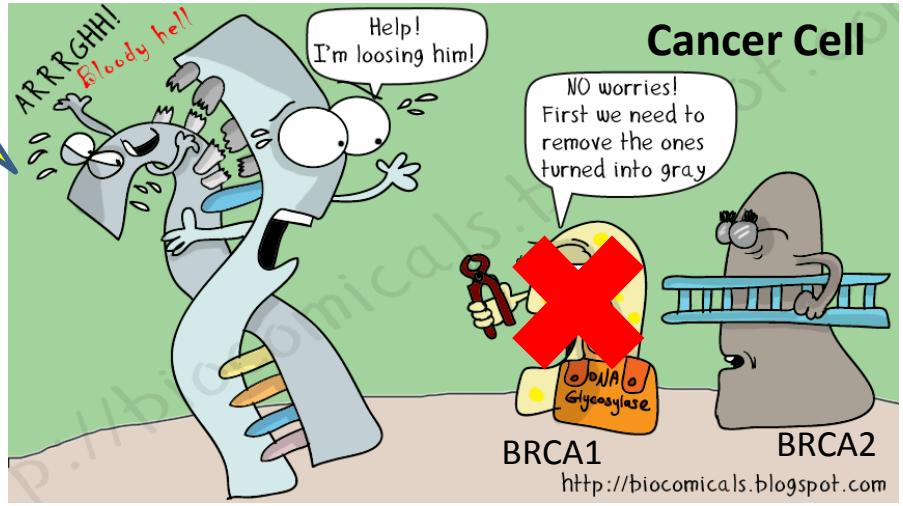
BASSER CENTER FOR BRCA

PARP inhibitor



Cell survives

PARP inhibitor



Cell death

PARP inhibitors 2016

BASSER CENTER FOR BRCA

- **There are 5 PARP inhibitors**
  - Olaparib (AZD2281) by AstraZeneca = Lynparza *FDA approved
  - Niraparib (MK4827) by Tesaro
  - Rucaparib (AG014699) by Clovis
  - Veliparib (ABT-888) by AbbVie
  - Talazoparib (BMN-673) by BioMarin

- **Iniparib is NOT a PARP inhibitor – cytotoxic and antineoplastic but mechanism unknown**

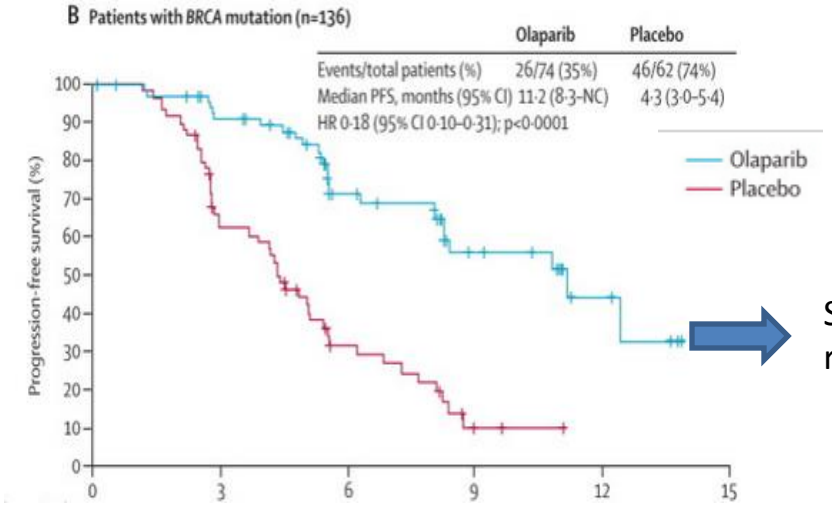
What led to FDA approval for olaparib for 4th line therapy in metastatic ovarian cancer patients?

BASSER CENTER FOR BRCA

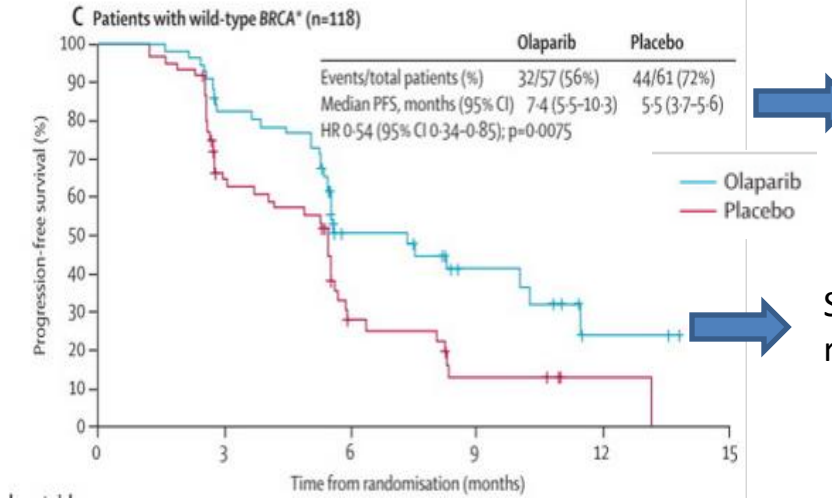
Audeh et al. *(2010)*
Lancet 376:245–251.

Ledermann et al. *(2012)*
N Engl J Med 366:1382–1392.

Ledermann et al. *(2014)*
Lancet Oncol 15:852–861.



Subset of long-term responders (>3 years)



Subset of non *BRCA* carriers that had benefit

Subset of long-term responders (>3 years)

Penn Medicine

the cure is within
ABRAMSON CANCER CENTER

Taking a PARP inhibitor

- **More common but less concerning side effects of the PARPi: Fatigue, nausea, diarrhea, loss of appetite and myelosuppression**

- **Less common but more concerning side ffects of the PARPi:**
  - 1) Myelodysplastic syndrome and AML have developed in 22 of 2618 patients (<1%) patients treated with Lynparza
  - 2) pneumontitis

- **Cannot be used in pregnancy**

- **Drug interactions**
  - Need to decreased dose of PARP inhibitor with CYP3A inhibitors (azole anti-fungals, clarithromycin, erythromycin, cimetidine, grapefruit juice)
  - CYP3A inducers will decreased PARP inhibitor efficacy (rifampin, carbamazepine, ritonavir, St. John's wort)

Active research areas with use of PARP inhibitors

BASSER CENTER FOR BRCA

- **Assays to determine PARPi sensitivity**
  - Response rates in TNBC similar to *BRCA* mutated BC in some studies
  - Myriad HR Deficiency "HRD" assay

- **Combining PARPi with other drugs?**
  - EGFR inhibitors -> decrease BRCA1 in nucleus -> induce HRD
  - CDK inhibitors-> decrease BRCA1 in nucleus -> induce HRD
    - NCT01434316: Phase I veliparib + dinaciclib (inhibits CDK1, CDK2, CDK5, and CDK9) in BRCAmut advanced solid tumors
  - PI3K inhibitors -> downregulate BRCA1/2 -> induce HRD

- **Overcoming resistance mechanisms**

Survivorship issues for *BRCA1/2* breast cancer patients

BASSER CENTER FOR BRCA

- **Managing the effects of cancer treatment**
  - Neuropathy
  - Lymphedema
  - Body image
- **Managing the concern for recurrence**
- **Managing the risk of another cancer**
  - Ovaries
  - Breast
  - Skin
  - Pancreas
- **Pregnancy**
- **Premature Menopause**
  - Symptoms
  - Cardiovascular Health
  - Bone health

Survivorship - Risk of 2nd primary cancer by age

BASSER CENTER FOR BRCA

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

Survivorship – Managing the risk of another cancer

BASSER CENTER FOR BRCA

Site	What to do
Another breast cancer (risk is 1-3% per year)	1. Contralateral mastectomy 2. Screening with breast MRI and mammogram 3. Tamoxifen
Ovarian cancer	Oophorectomy
Skin cancer (melanoma)	Dermatology exams early
Pancreatic cancer (*BRCA2*)	If family history of pancreatic cancer, consider screening
Other cancers	Follow population guidelines (i.e. don't forget about your colonoscopy and Pap smear!)

Pancreatic cancer in *BRCA1/2* carriers

Pancreatic Cancer - ~10% familial, 2% due to already known genes such as *BRCA2* and *PALB2*

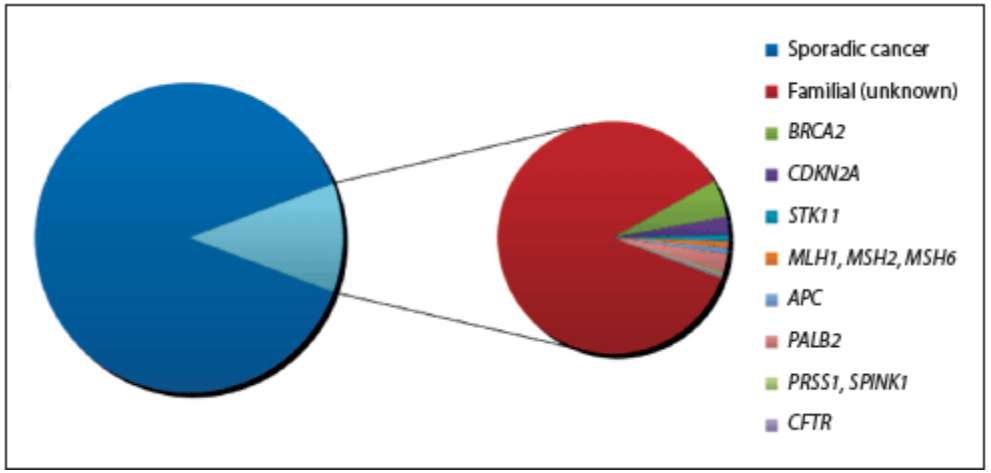


Table 1: Selected Genetic Syndromes with Associated Pancreatic Cancer Risk

Syndrome	Gene	Estimated cumulative risk of pancreatic cancer	Estimated increased risk compared to general population
Peutz-Jeghers Syndrome	*STK11*	11% to 36% by age 65–70 years[54]	132-fold[53]
Familial Pancreatitis	*PRSS1, SPINK1, CFTR*	40% to 53% by age 70–75 years[58-60]	26-fold to 87-fold[28,58-60]
Melanoma-Pancreatic Cancer Syndrome	*CDKN2A*	17% by age 75 years[63]	20-fold to 47-fold[62,63]
Lynch Syndrome	*MLH1, MSH2 (MSH6)*	4% by age 70 years[72]	9-fold to 11-fold[72,73]
Hereditary Breast-Ovarian Cancer Syndrome	*BRCA1, BRCA2*	1.4%–1.5% (women) and 2.1%–4.1% (men) by age 70[74,79]	2.4-fold to 6-fold[74,78,79]
Familial Pancreatic Cancer	Unknown in most families (family X is an exception)*	≥3 first-degree relatives with pancreatic cancer: 7%–16% by age 70[47] 2 first-degree relatives with pancreatic cancer: 3% by age 70[47]	≥3 first-degree relatives with pancreatic cancer: 32-fold[85] 2 first-degree relatives with pancreatic cancer: 6.4-fold[85] 1 first-degree relative with pancreatic cancer: 4.6-fold[85]

*One family (family X) with a mutation in the *palladin* (*PALLD*) gene has been identified.[506]

Prostate cancer in *BRCA1/2* carriers

BASSER CENTER FOR BRCA

- **Rare high risk gene mutations increase PrCa risk**
  - *BRCA2* mutations 2-6x increase risk; *BRCA1* less clear
  - *HOXB13* G84E increases risk ~2-3x
  - Lynch syndrome possibly associated with increased risk (1 study 5x)

- ***BRCA1/2* PrCa is more aggressive**
  - more commonly Gleason $\geq$8, nodal involvement, distant metastases
  - survival worse for *BRCA2* (and maybe *BRCA1*) carriers
    - 8.6 vs 15.7 years (p=0.015) for *BRCA1/2* carriers
    - 2 vs 12 years (p<0.001) for *BRCA2*

- ***BRCA1/2* carriers w/prostate cancer respond to PARP inhibitors**

Summary – *BRCA1/2*

BASSER CENTER FOR BRCA

- ***BRCA1/2*** **mutations can be found in between 2-30% of breast cancer patients depending on breast cancer type, age of diagnosis, family history and ethnicity**

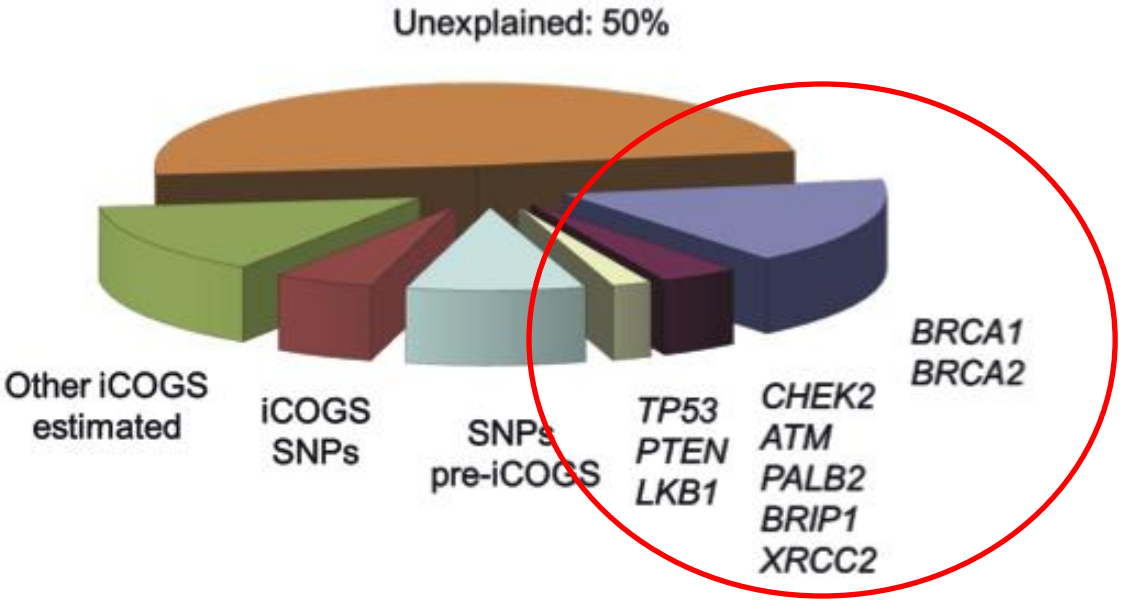
- ***BRCA1/2*** **mutations increase a breast cancer patient's risk of a second breast cancer, ovarian cancer, pancreatic cancer and melanoma**

- **Knowledge of a *BRCA1/2* mutation allows a breast cancer patient to better manage her future cancer risks and those of her family**

PART 3:

OTHER BREAST CANCER GENES

Other Breast cancer genes



Some breast cancer panels as of 2016

BASSER CENTER FOR BRCA

Gene	Myriad MyRisk	Ambry Breast Next	GeneDx Breast	Invitae Breast
# of genes	25	17	9	14
BRCA1	X	X	X	X
BRCA2	X	X	X	X
CDH1	X	X	X	X
PTEN	X	X	X	X
TP53	X	X	X	X
ATM	X	X	X	X
BARD1	X	X		X
BRIP1	X	X		X
CHEK2	X	X	X	X
PALB2	X	X	X	X
MRE11A	X	X		
NBN	X	X		X
NF1		X		X
RAD50	X	X		
RAD51C	X	X		
RAD51D	X	X		
MUTYH	X	X		
Other Genes	+9 more on this panel	On other panels	On other panels	Can customize additions

Hereditary Breast Cancer – Beyond *BRCA1/2*

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Table 3. Genes for Which an Association between Protein-Truncating Variants and Breast-Cancer Risk Has Been Established.

Gene	Magnitude of Relative Risk Associated with Truncating Variants*		Risk Associated with Missense Variants†	Estimated Relative Risk (90% CI)‡	P Value	Absolute Risk by 80 Yr of Age§	Comments	Other Associated Cancers	References
	Moderate	High				%			
BRCA1	Yes	Yes	Yes	11.4		75	Estimates are based on the BOADICEA model for a woman born in 1960	Ovary	Antoniou et al.,[10] Lee et al.,[11] Chen and Parmigiani,[12] Mavaddat et al.[13]
BRCA2	Yes	Yes	Yes	11.7		76	Estimates are based on the BOADICEA model for a woman born in 1960; p.Lys3326Ter in the carboxyl terminus is associated with a lower increase in risk	Ovary, prostate, pancreas	Antoniou et al.,[10] Lee et al.,[11] Chen and Parmigiani,[12] Mavaddat et al.[13]
TP53¶	Yes	Yes	Yes	105 (62–165)			Most published risk estimates are subject to ascertainment bias	Childhood sarcoma, adrenocortical carcinoma, brain tumors	Hisada et al.,[14] Hwang et al.[15]
PTEN	Unknown	Unknown	Yes	No reliable estimate‖			Published risk estimates are subject to ascertainment bias	Thyroid, endometrial cancer	Bubien et al.,[16] Tan et al.[17]
CDH1	Likely	Unknown	Unknown	6.6 (2.2–19.9)	0.004	53	Specific to lobular breast cancer	Diffuse gastric cancer	Pharoah et al.[18]
STK11	Unknown	Unknown	Unknown	No reliable estimate**			Published risk estimates are subject to ascertainment bias	Colon, pancreas, ovarian sex cord–stromal tumors	Hearle et al.[19]
NF1	Likely	Unlikely	Unknown	2.6 (2.1–3.2)	2.3×10^{-13}	26	Estimates are based on cohort studies of patients with neurofibromatosis type 1††	Malignant tumors of peripheral nerve sheath, brain, central nervous system	Madanikia et al.,[20] Seminog and Goldacre[21]
PALB2	Likely	Unknown	Unknown	5.3 (3.0–9.4)	4×10^{-10}	45	Estimates are based on a meta-analysis of published case–control and family studies	Pancreas	Antoniou et al.,[22] Heikkinen et al.,[23] Rahman et al.,[24] Erkko et al.[25]

Hereditary Breast Cancer – Beyond *BRCA1/2*

BASSER CENTER FOR BRCA

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	Moderate	High				%			
ATM	Likely	Unlikely	Yes	2.8 (2.2–3.7)	5×10^{-11}	27	The p.Val2424Gly variant is associated with higher risk than truncating variants	Pancreas	Renwick et al.,[26] Thompson et al.,[27] Janin et al.,[28] Olsen et al.[29]
CHEK2	Likely	Unlikely	Yes	3.0 (2.6–3.5)	8×10^{-37}	29	Most data for truncating variants are limited to the variant c.1100delC; p.Ile157Thr is associated with an increase in risk that is 1.3 times as high as in the general population	Lung, although p.Ile157Thr is associated with reduced risk	Meijers-Heijboer et al.,[30] CHEK2 Breast Cancer Case–Control Consortium,[31] Weischer et al.,[32] Kilpivaara et al.[33]
NBN	Likely	Unlikely	Unknown	2.7 (1.9–3.7)	5×10^{-7}	23	Almost all data pertain to the c.657del5 variant in Slavic populations	Unknown	Zhang et al.[34]

What are the other breast cancer genes?

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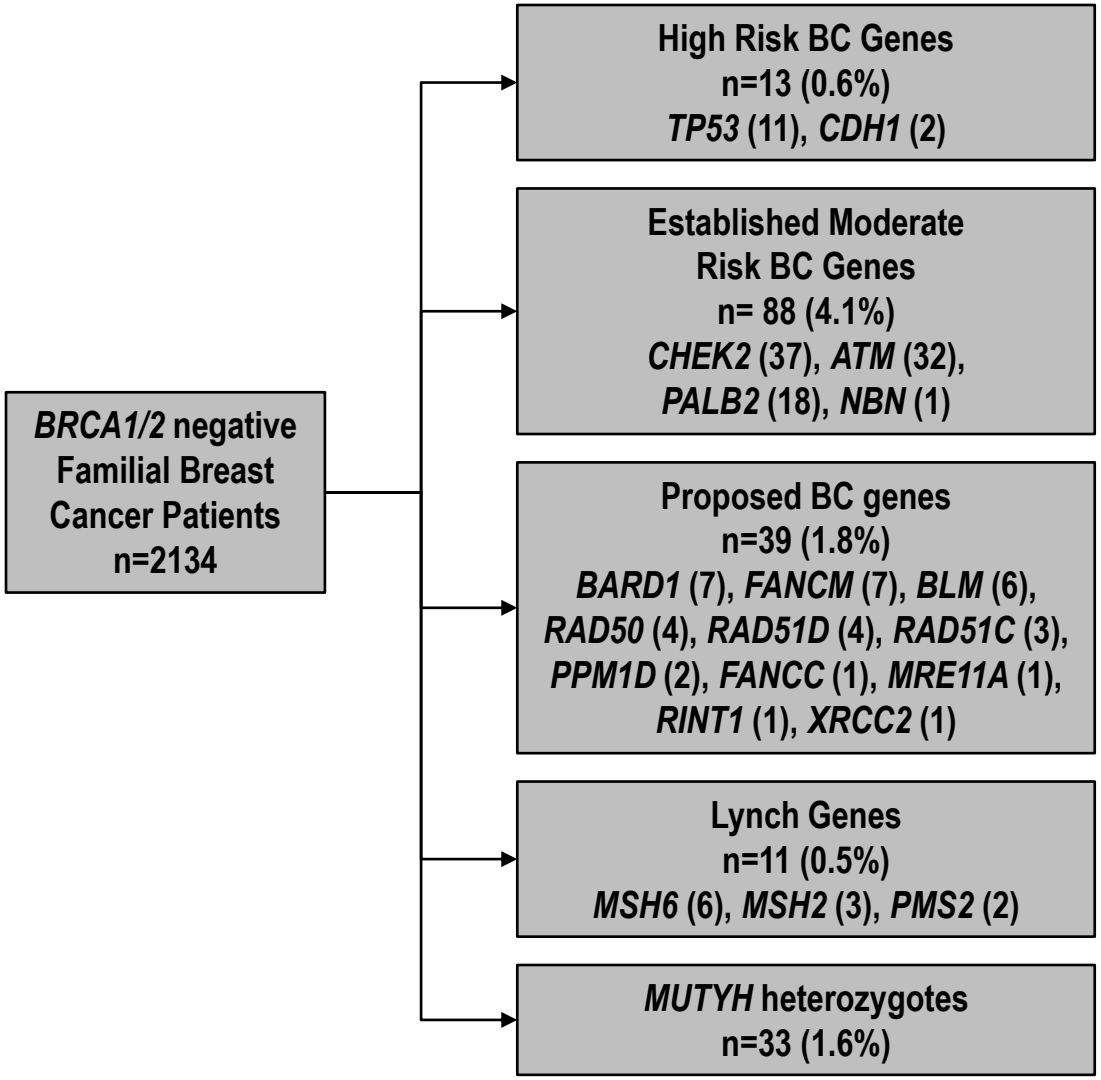
- **Other high risk genes**
  - Extremely high risks of breast and other cancers (lifetime ~80-95%)
  - Extremely rare (altogether <1% of breast cancer patients)
  - *TP53* – Li Fraumeni syndrome ; *CDH1* – Hereditary diffuse gastric cancer syndrome; *PTEN* – Cowden syndrome; *STK11* – Peutz Jeghers syndrome

- **Moderate risk genes**
  - Moderately increased risks of breast cancer (lifetime ~20-30%)
  - Other cancer risks unclear
  - Probably ~4-5% of breast cancer patients
  - *ATM, CHEK2, NBN,* maybe others

- ***PALB2***
  - somewhere in the middle, maybe lifetime risks 30-50%
  - Other cancer risks being studied
  - Maybe 1% of breast cancer patients

How common are mutations in other breast cancer genes?



But do the other genes cause breast cancer?

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Gene (p-value <0.5)	OR	p-value	95% CI	Case AC	Case Freq	Control AC	Control AN	Control Freq
TP53	8.141	2.29E-06	3.444-18.44	11	0.26%	17	53579	0.03%
PALB2	7.337	4.83E-09	3.861-13.547	18	0.42%	31	53738	0.06%
ATM	3.681	1.39E-07	2.301-5.713	27	0.63%	92	53288	0.17%
*MUTYH**	3.485	0.0081	1.272-8.294	7	0.16%	25	53063	0.05%
*ATM**	3.446	4.69E-06	2.044-5.588	22	0.52%	80	53288	0.15%
BARD1	3.172	0.0123	1.165-7.473	7	0.16%	27	52157	0.05%
*CHEK2**	1.894	0.0045	1.211-2.859	27	0.63%	169	50448	0.33%
CHEK2 (not low risk)	1.546	0.0357	1.018-2.271	30	0.70%	230	50448	0.46%
Gene (p-value >0.5 or <5 cases)								
BLM	1.233	0.636	0.435-2.843	6	0.14%	61	53468	0.11%
BRIP1	0.599	0.77	0.07-2.303	2	0.05%	42	53681	0.08%
CDH1	8.113	0.0494	0.677-70.814	2	0.05%	3	51922	0.01%
CHEK2 (p.I157T,S428F)	1.328	0.0537	0.985-1.761	55	1.29%	491	50448	0.97%
FANCC	0.253	0.181	0.006-1.476	1	0.02%	49	52870	0.09%
FANCM	0.472	0.0514	0.187-0.994	7	0.16%	184	53071	0.35%
MRE11A	0.545	1	0.013-3.36	1	0.02%	23	53534	0.04%
MSH2	4.707	0.0989	0.448-28.768	2	0.05%	5	50210	0.01%
MSH6	2.299	0.0633	0.786-5.579	6	0.14%	32	52301	0.06%
MUTYH	1.036	0.853	0.703-1.482	33	0.77%	396	53063	0.75%
NBN	0.3	0.371	0.007-1.769	1	0.02%	41	52529	0.08%
PMS2	0.452	0.44	0.053-1.72	2	0.05%	51	49235	0.10%
*PMS2**	0.699	1	0.081-2.735	2	0.05%	33	49235	0.07%
PPM1D	0.891	1	0.102-3.575	2	0.05%	25	47537	0.05%
RAD50	0.627	0.528	0.167-1.672	4	0.09%	79	52897	0.15%
RAD51C	0.78	1	0.091-3.06	2	0.05%	32	53293	0.06%
RAD51D	8.302	0.00446	1.722-35.035	4	0.09%	6	53110	0.01%
RINT1	0.34	0.526	0.008-2.015	1	0.02%	37	53662	0.07%
XRCC2	1.265	0.567	0.029-8.896	1	0.02%	10	53987	0.02%

But do the other genes cause breast cancer?

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Table 4. Frequency of genetic mutations in study cases versus ExAC controls

Gene	Case Allele Count[1]	Case Allele Number	Control Allele Count[2]	Control Allele Number	Case Frequency	Control Frequency	Odds Ratio (95% CI)[3]	P-value
PALB2	116	22166	31	53600	0.52%	0.06%	9.05 (6.09 - 13.45)	0.000
CDH1	11	22562	3	47815	0.05%	0.01%	7.77 (2.17 - 27.86)	0.003
PTEN	8	21084	1	54198	0.04%	0.00%	20.56 (2.57 - 164.44)	0.001
TP53	36	22816	17	53110	0.16%	0.03%	4.93 (2.77 - 8.78)	0.000
ATM	111	22816	92	53832	0.49%	0.17%	2.85 (2.16 - 3.75)	0.000
BARD1	32	21084	27	53147	0.15%	0.05%	2.99 (1.79 - 4.99)	0.000
BRIP1	48	22816	42	52913	0.21%	0.08%	2.65 (1.75 - 4.01)	0.000
RAD51D	18	15082	6	53616	0.12%	0.01%	10.66 (4.23 - 26.87)	0.000
CHEK2	138	22816	230	48886	0.60%	0.47%	1.29 (1.04 - 1.59)	0.142
NBN	12	20830	41	52759	0.06%	0.08%	0.74 (0.39 - 1.41)	0.841
MLH1	1	12254	10	54298	0.01%	0.02%	0.44 (0.06 - 3.46)	0.888
MSH2	7	12254	5	49080	0.06%	0.01%	5.61 (1.78 - 17.67)	0.012
MSH6	11	12254	32	52724	0.09%	0.06%	1.48 (0.75 - 2.93)	0.737
PMS2	12	12254	51	48567	0.10%	0.11%	0.93 (0.5 - 1.75)	0.997
MRE11A	14	15928	23	54077	0.09%	0.04%	2.07 (1.06 - 4.02)	0.188
RAD51C	19	18562	32	53485	0.10%	0.06%	1.71 (0.97 - 3.02)	0.318
RAD50	23	15928	79	53036	0.14%	0.15%	0.97 (0.61 - 1.54)	0.999
XRCC2	7	14226	10	53873	0.05%	0.02%	2.65 (1.01 - 6.97)	0.238

Summary – Other breast cancer genes

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- Many other genes increase a risk of breast cancer, and more are being discovered
- We still do not know the genetic underpinnings of breast cancer in up to 90% of cases
- Whether you should have further genetic testing for other genes besides *BRCA1/2* should be discussed with your oncologist or a cancer genetics provider

FINAL SUMMARY - So, what should I do?

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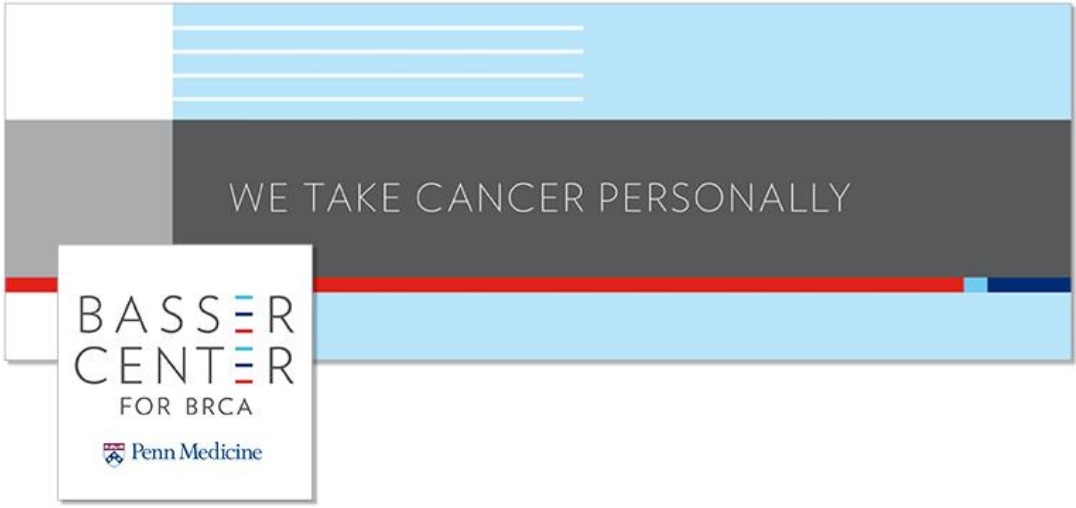
- **If you had an ER positive breast cancer over age 50 and you have no family history of breast or ovarian cancer, you probably don't need genetic testing**

- **If you had genetic testing within the last 2 years, you are probably up to date, but you can always check back with your genetics provider**

- **For all other breast cancer patients, genetic testing or new genetic testing may be warranted -> ask your oncologist or visit our website**

https://www.pennmedicine.org/cancer/navigating-cancer-care/programs-and-centers/basser-center-for-brca



THANK YOU FOR YOUR ATTENTION!