THE SCIENTIFIC LANDSCAPE OF BREAST CANCER:

RAMATHIBODI SCHOOL OF NURSING
AND THAINAKARIN HOSPITAL BREAST CANCER CONFERENCE

March 7th, 2024

Genomics of Breast Cancer

Basic Knowledge of Hereditary Cancer, Genetic Determinants of Breast Cancer & Genetic Counseling

Kanin Sriudomporn, MD
Division of Medical Genetic and Molecular Biology,
Department of Internal Medicine

Mahidol University
Faculty of Medicine Ramathibodi Hospital

Disclosure

- Division of Medical Genetics and Molecular Biology, Department of Internal Medicine, Faculaty of Medicine, Ramathibodi Hospital
- Thailand Medical Genetics and Genomics Association (TMGGA)
- Ramathibodi School of Nursing
- Thainakarin Hospital

MGGA สมาคมเวชพันธุศาสตร์และจีโนมิกส์ทางการแพทย์
MEDICAL GENETICS AND GENOMICS ASSOCIATION

โรงเรียนพยาบาลรามาธิบดี
คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล

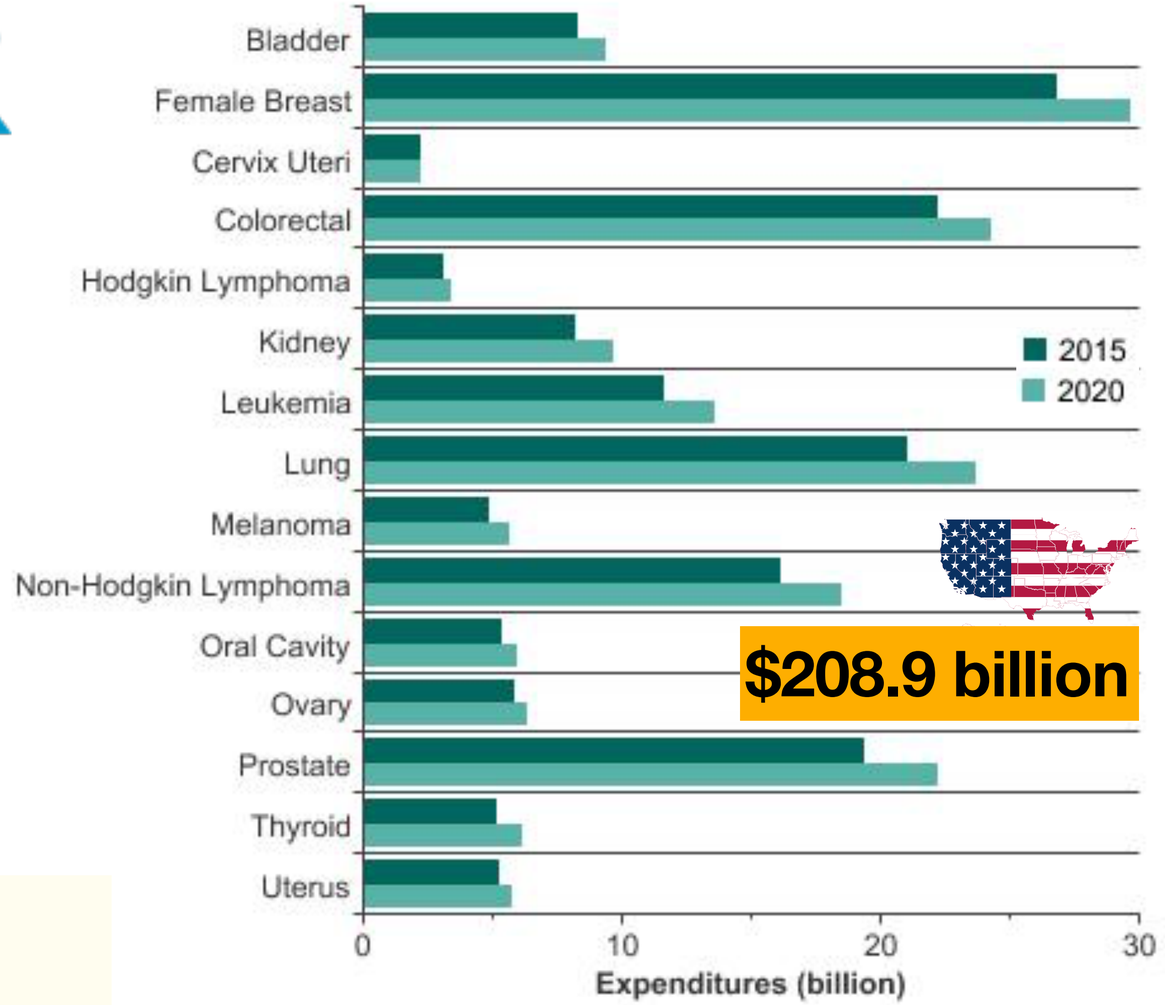
โรงพยาบาล ไทยนครินทร์
THAINAKARIN HOSPITAL

CANCER TODAY

World Health Organization

19 million new cases
of cancer diagnosed

Over 10 million deaths
worldwide in 2020



KEY in genetics research:
Identification of persons at increased risk for cancer **before** its development

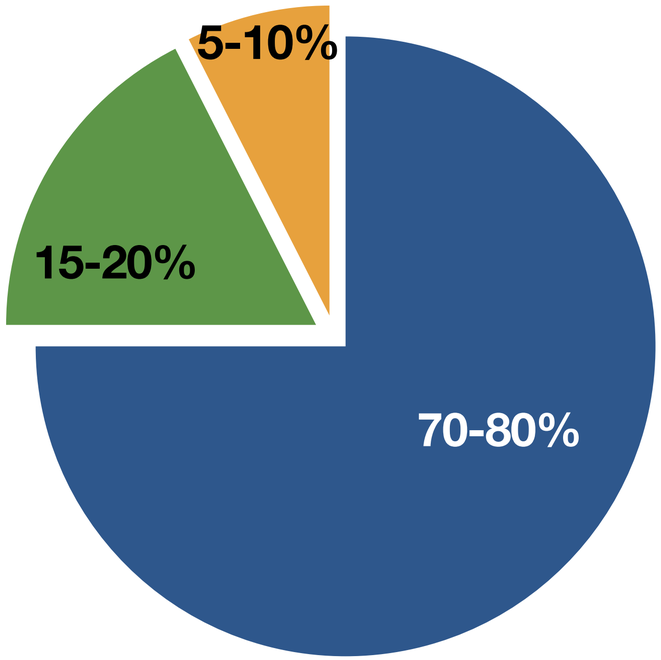
Total estimated national expenditures for cancer care around **$208.9 billion in 2020**

Cancer Epidemic Biomarkers Prev. 2020;29(7):1304-12.

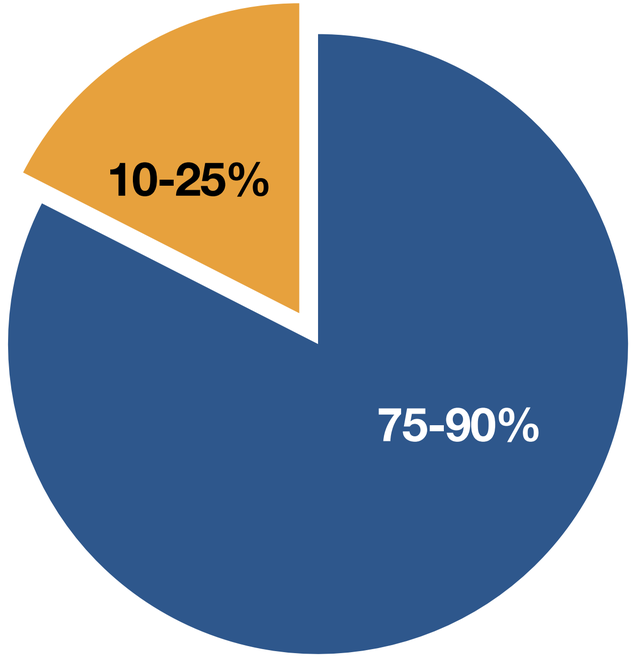
Proportion of Inherited Cancer

Sporadic VS Familial VS Inherited Cancer

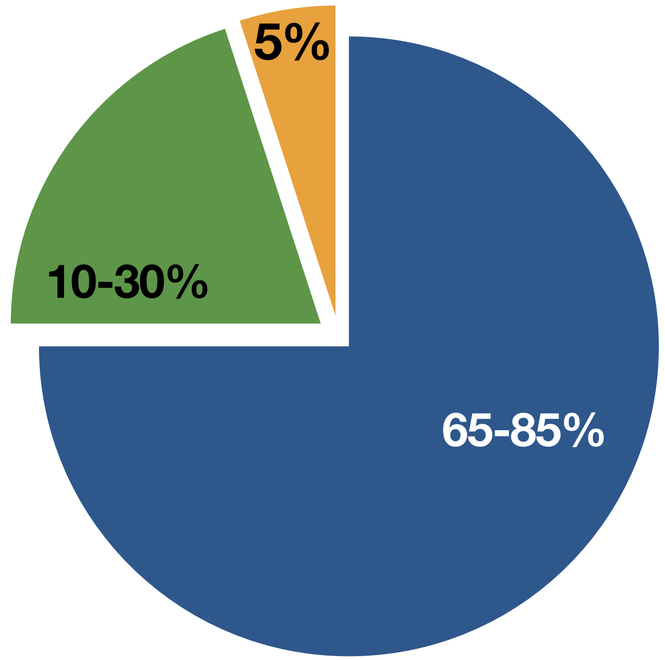
Breast Cancer



Ovarian Cancer



Colorectal Cancer



Sporadic Cancer Familial Cancer Inherited Cancer

Adapted from NIH NATIONAL CANCER INSTITUTE

Common Cancer

Common Hereditary & Non-Hereditary Cancer

Common Hereditary Cancer

Breast Cancer

Ovarian Cancer

Endometrial Cancer

Colorectal Cancer

Thyroid Cancer

Common Non-Hereditary Cancer

Hepatobilliary Cancer

Lung Cancer

Cervical Cancer

Head & Neck Cancer

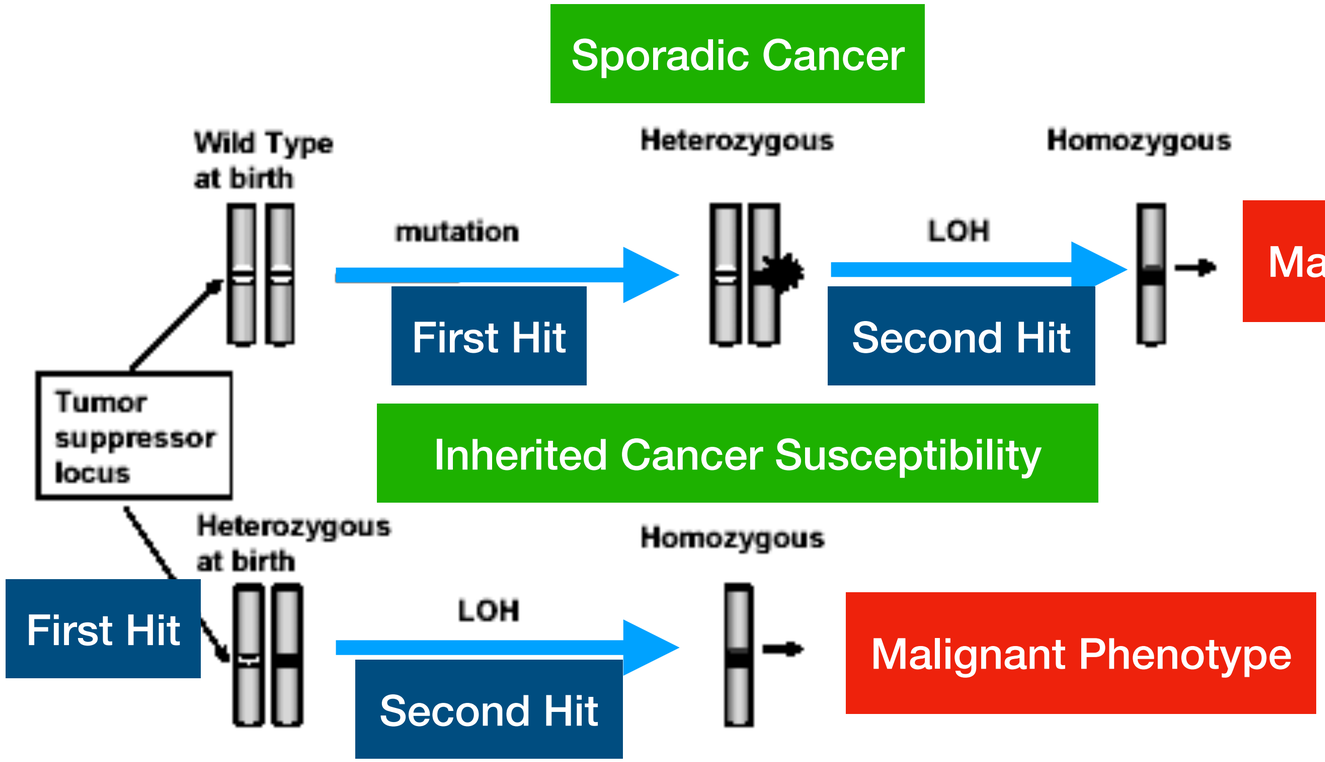
Germ Cell Tumor

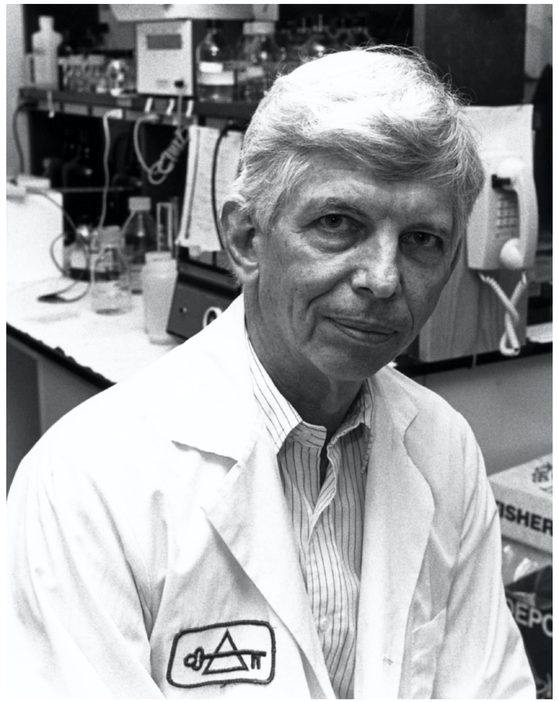
Leukemia

Initiation of Cancer Development

Two-hit Hypothesis

Two-hit hypothesis



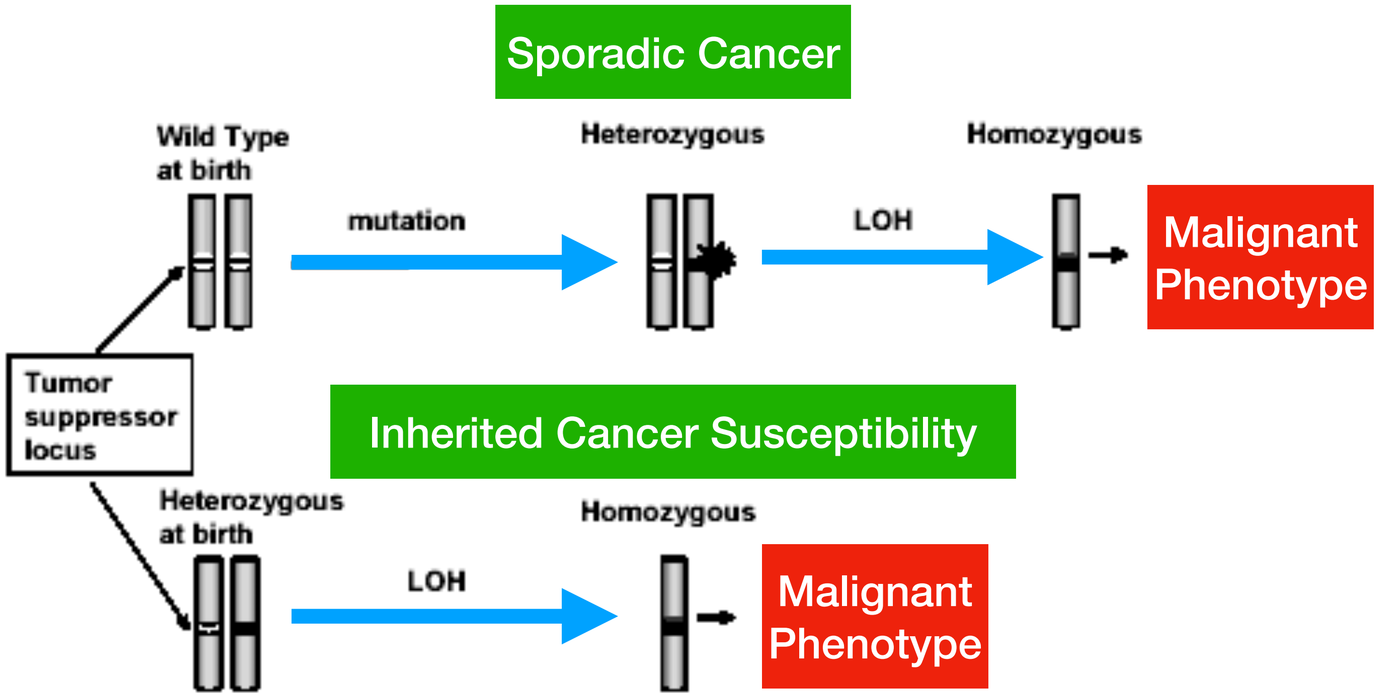


Alfred G. Knudson
(1922-2016)

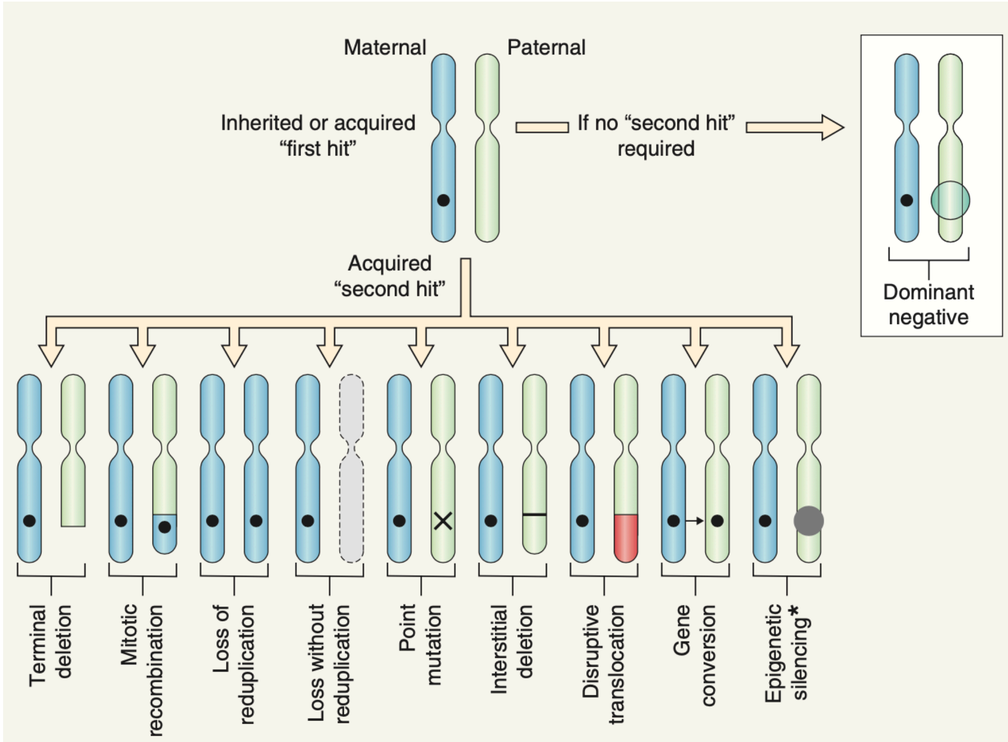
Initiation of Cancer Development

Two-hit Hypothesis

Two-hit hypothesis



Loss of Heterozygosity



The Role of Cyclin E in Cell Cycle Regulation and Genomic Instability ;Sep 17, 2020, Jean L. Bolognia Dermatology 4th Edition

General Considerations

Terminology

Mutation ≠ **Polymorphism**

A **permanent change** in the nucleotide sequence

A variant with a frequency **above 1%**

Replace both terms by

Variant

Genet Med 17, 405–423 (2015).

General Considerations

Variant Modifiers; 5-tier System of Classification

1. Pathogenic	> 95% certainty of pathogenicity
2. Likely Pathogenic	> 90% certainty of pathogenicity
3. Uncertain Significance	
4. Likely Benign	> 90% certainty of benign
5. Benign	> 95% certainty of benign

Clinicians and patients were willing to tolerate a slightly higher chance of error, leading to the 90-95% decision

Genet Med 17, 405–423 (2015).

Review Guideline

Mahidol University
Faculty of Medicine Ramathibodi Hospital

Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®)
Version 1.2024

Kanin Sriudomporn, MD
Division of Medical Genetic and Molecular Biology,
Department of Internal Medicine

NCCN National Comprehensive Cancer Network®

Breast Cancer

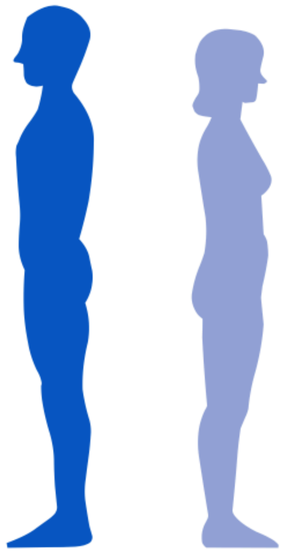
Overview

American Cancer Society® Cancer Facts & Figures 2023

Estimated New Cases

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

Male		
Prostate	288,300	29%
Lung & bronchus	117,550	12%
Colon & rectum	81,860	8%
Urinary bladder	62,420	6%
Melanoma of the skin	58,120	6%
Kidney & renal pelvis	52,360	5%
Non-Hodgkin lymphoma	44,880	4%
Oral cavity & pharynx	39,290	4%
Leukemia	35,670	4%
Pancreas	33,130	3%
All sites	**1,010,310**	



Female		
Breast	297,790	31%
Lung & bronchus	120,790	13%
Colon & rectum	71,160	8%
Uterine corpus	66,200	7%
Melanoma of the skin	39,490	4%
Non-Hodgkin lymphoma	35,670	4%
Thyroid	31,180	3%
Pancreas	30,920	3%
Kidney & renal pelvis	29,440	3%
Leukemia	23,940	3%
All sites	**948,000**	

American Cancer Society. Cancer Facts & Figures 2023.

Breast Cancer

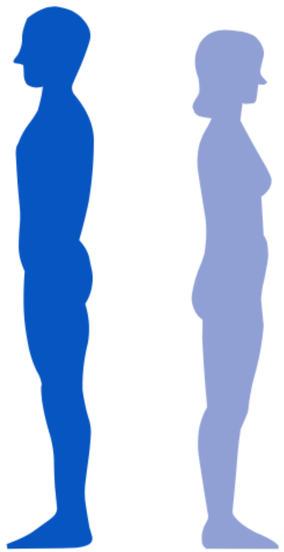
Overview

American Cancer Society® Cancer Facts & Figures 2023

Estimated Deaths

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

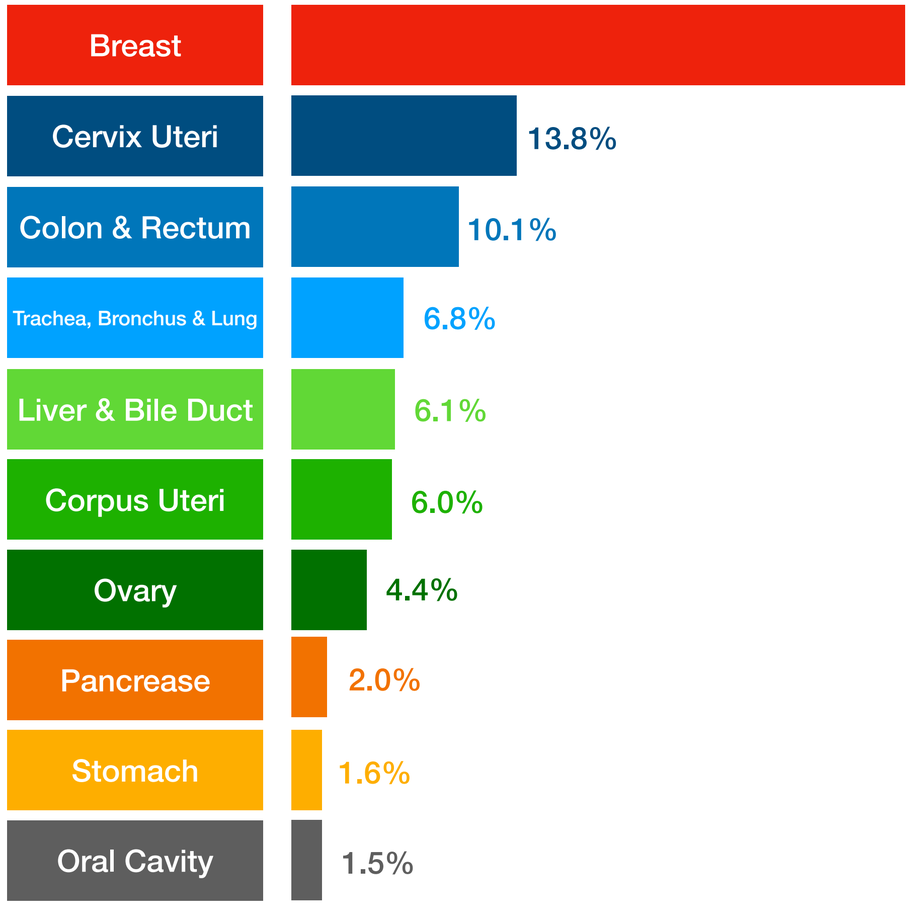
Male			Female		
Lung & bronchus	67,160	21%	Lung & bronchus	59,910	21%
Prostate	34,700	11%	Breast	43,170	15%
Colon & rectum	28,470	9%	Colon & rectum	24,080	8%
Pancreas	26,620	8%	Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%	Ovary	13,270	5%
Leukemia	13,900	4%	Uterine corpus	13,030	5%
Esophagus	12,920	4%	Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%	Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%	Brain & other nervous system	7,970	3%
All sites	**322,080**		**All sites**	**287,740**	

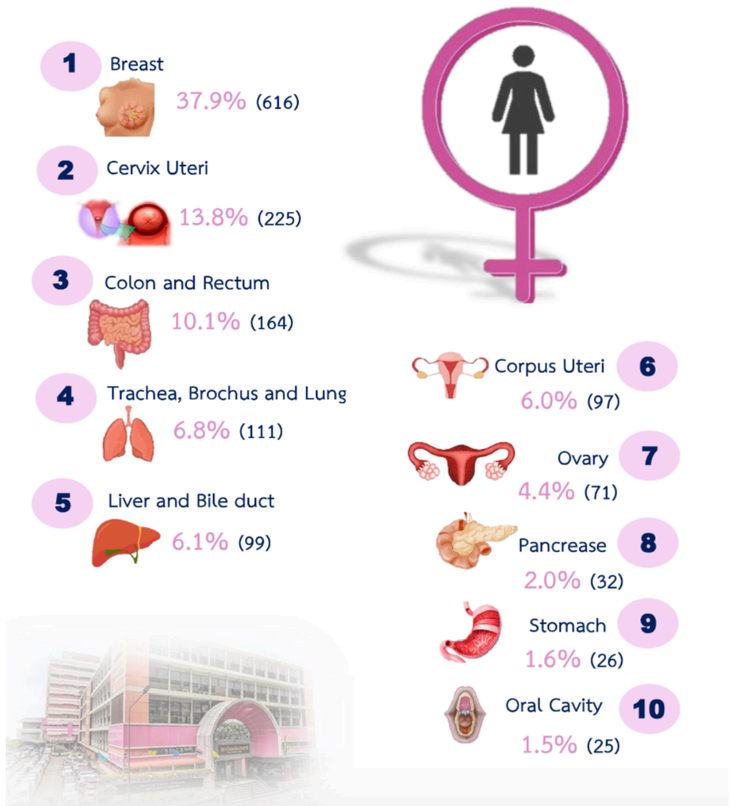


American Cancer Society. Cancer Facts & Figures 2023.

Breast Cancer in Thailand

The Most Common Top 10 Cancer of Thai Women





Hospital-Based Cancer Registry 2021

Breast Cancer in Thailand

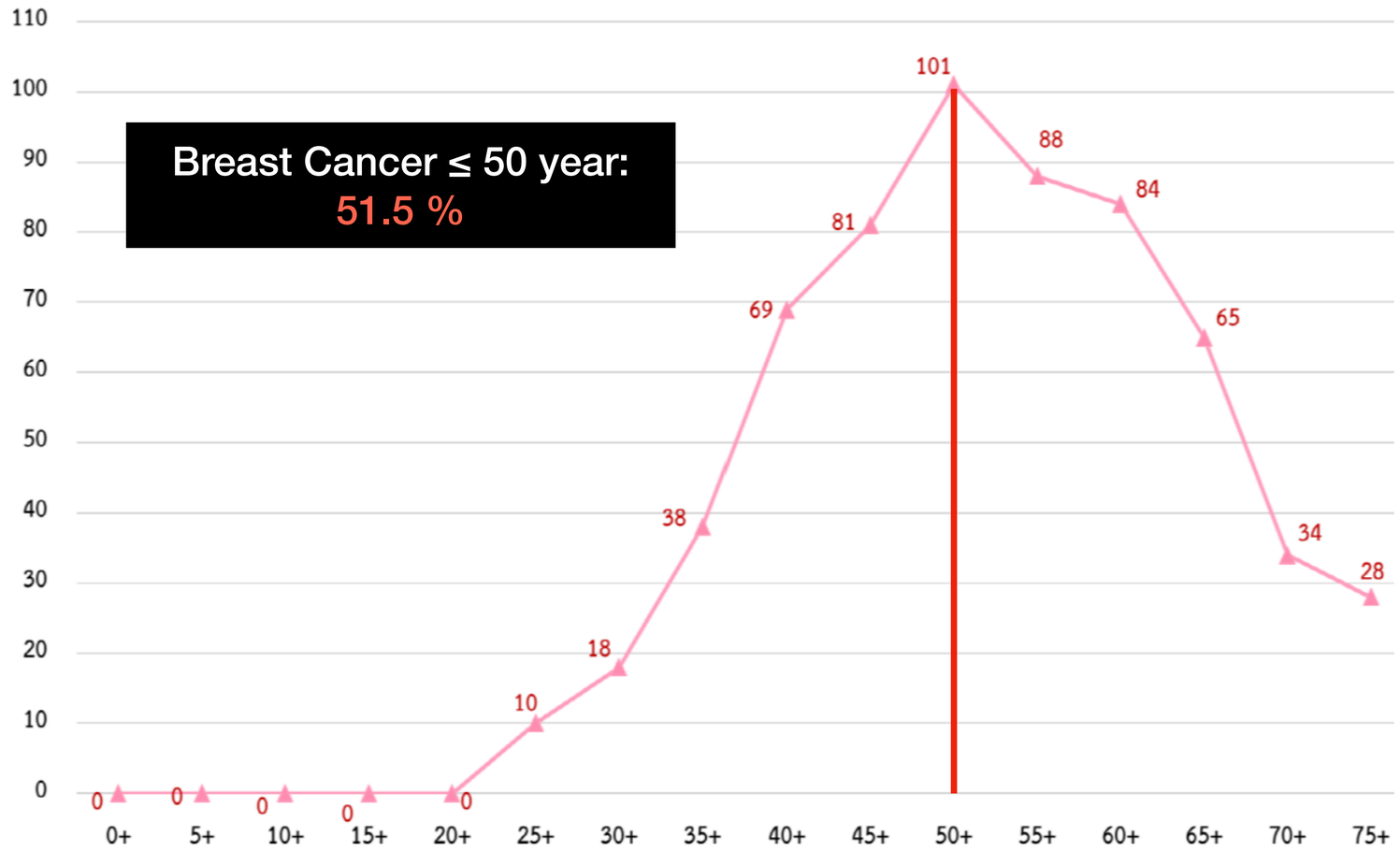
Number of New Breast Cancer Patients by Staging

Stage	Female	
	Number	%
Stage 1	144	23.4
Stage 2	175	28.4
Stage 3	143	23.2
Stage 4	146	23.7
Unknow Stage	8	1.3
Total	616	100.0

Hospital-Based Cancer Registry 2021

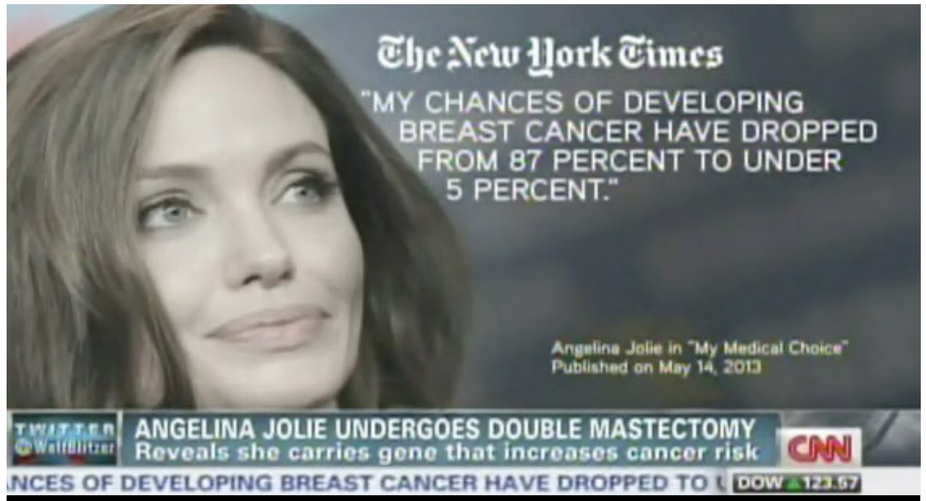
Breast Cancer in Thailand

Number of New Breast Cancer Patients by Age-group



Hospital-Based Cancer Registry 2021


THE
ANGELINA
EFFECT
Angelina Jolie's double mastectomy puts genetic testing in the spotlight. What her choice reveals about calculating risk, cost and peace of mind
BY JEFFREY KLUGER & ALICE PARK


The New York Times
"MY CHANCES OF DEVELOPING BREAST CANCER HAVE DROPPED FROM 87 PERCENT TO UNDER 5 PERCENT."
Angelina Jolie in "My Medical Choice"
Published on May 14, 2013
TWITTER
@WolfBlitzer
ANGELINA JOLIE UNDERGOES DOUBLE MASTECTOMY
Reveals she carries gene that increases cancer risk
CNN
NCES OF DEVELOPING BREAST CANCER HAVE DROPPED TO
DOW 123.67

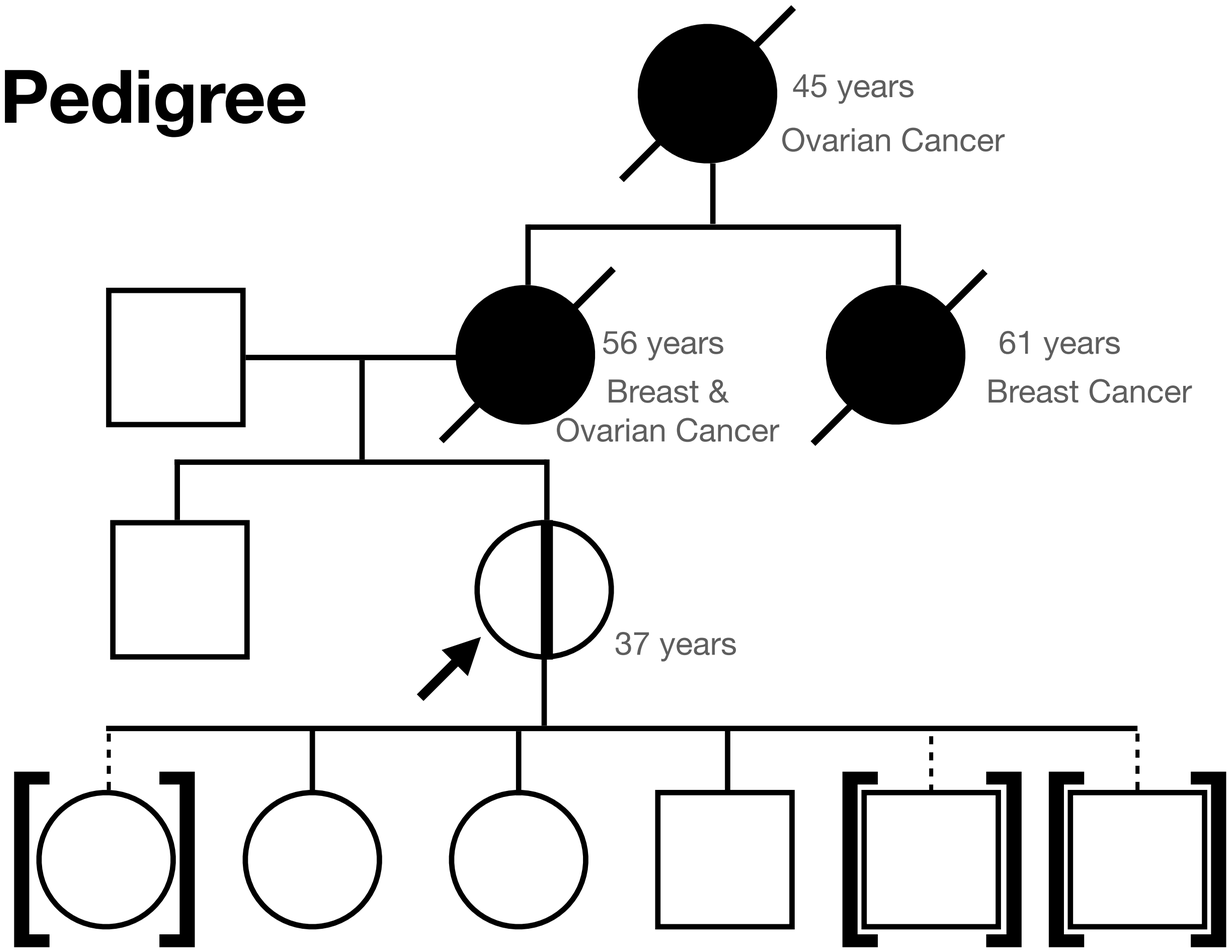

"THE ANGELINA EFFECT"
BRCA GENE TESTING IN AMERICA
BEFORE ANGELINA'S 2013 ANNOUNCEMENT:
350 PER WEEK
AFTER ANGELINA'S 2013 ANNOUNCEMENT:
500 PER WEEK
40%
AARP
CNN
7:44 AM ET
TODAY
ATLANTA 73°
CHARLOTTE 64°
WASHINGTON 57°
NEW DAY


Angelina's
DOUBLE MASTECTOMY
Inside
HER BRAVE CHOICE
'THIS WAS THE RIGHT THING TO DO'
Details of her emotional decision and how Brad helped her heal: 'All I want is for her to have a long and healthy life'

The Angelina Effect

Family History of Hereditary Breast and Ovarian Cancer

Pedigree



On May 14th **2013**, Angelina Jolie shared with the world her experience of **bilateral risk reducing mastectomy** [11] based on her inheriting a maternally derived pathogenic variant mutation in the *BRCA1* gene.

In **2015**, Angelina Jolie wrote about her experience with **risk reducing salpingo-oophorectomy**.

Sci Rep ***11****, 2847 (2021).*

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

BRCA1 gene:

- Chromosome 17q21.31
- Triple-negative predisposing

BRCA2 gene:

- Chromosome 13q13.1
- ER+ predisposing

Repair of replication-mediated dsDNA breaks (**Homologous Recombination**)

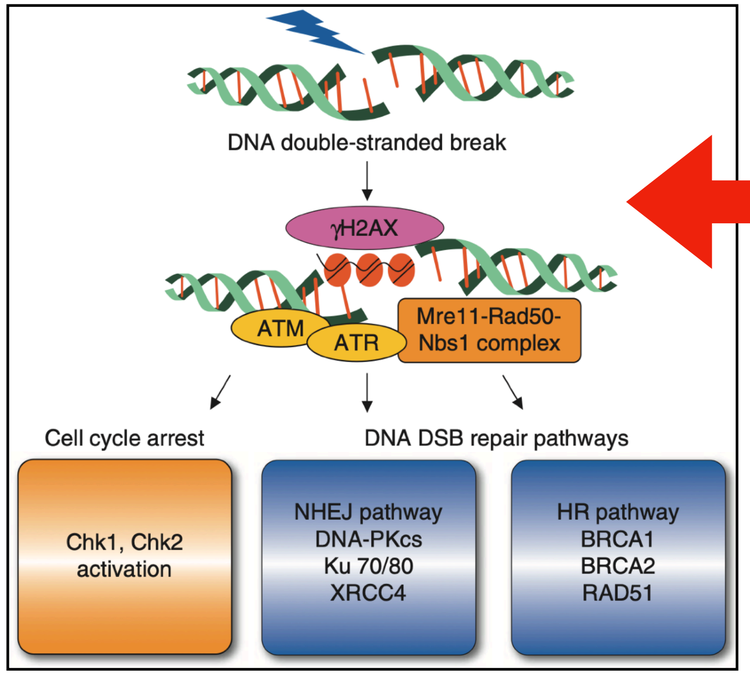
Overall prevalence:

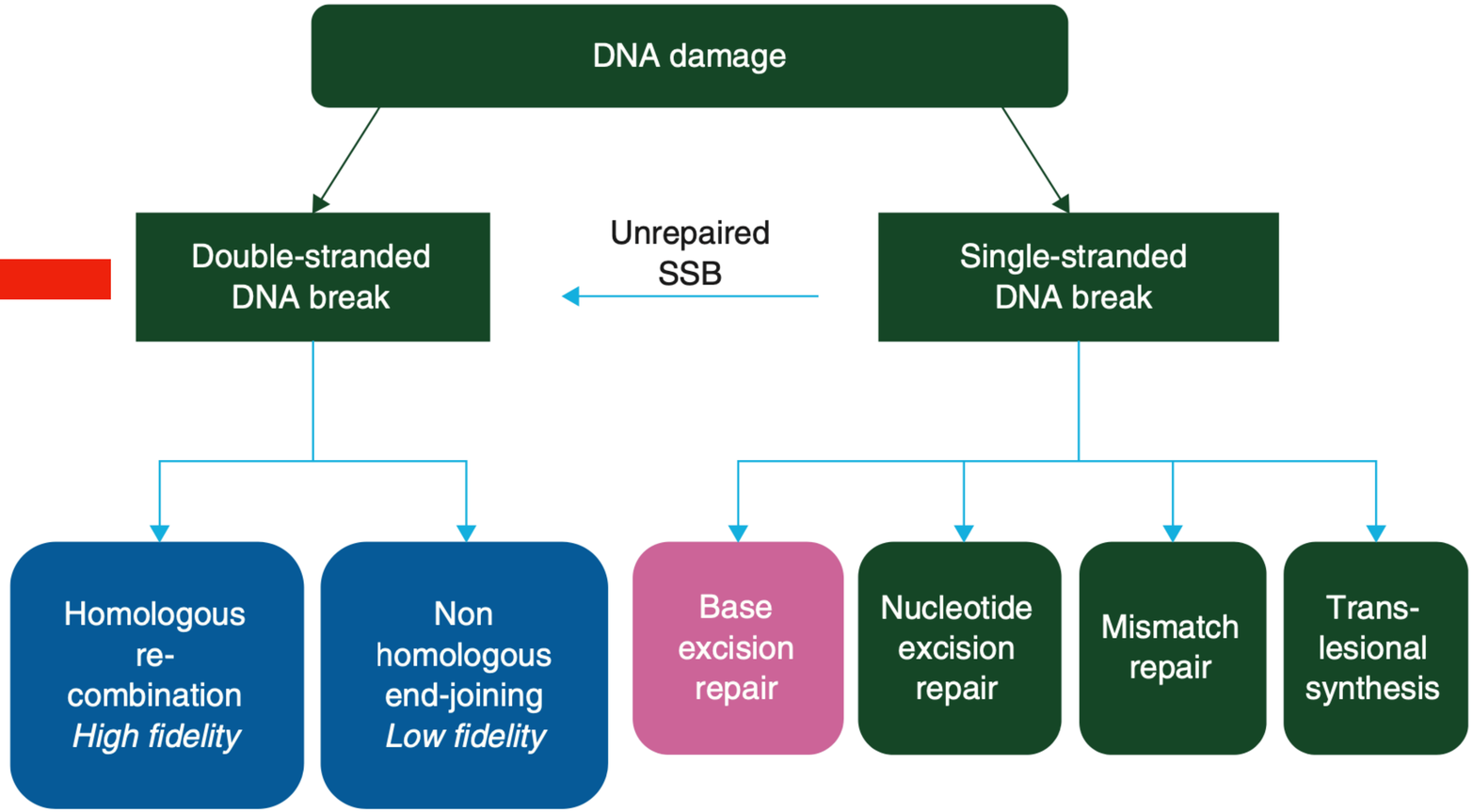
BRCA1 & BRCA2 = 1:400 to 1:500

Obstet Gynecol 2009;113:957-966.

DNA Repair Mechanism

PARP inhibitor

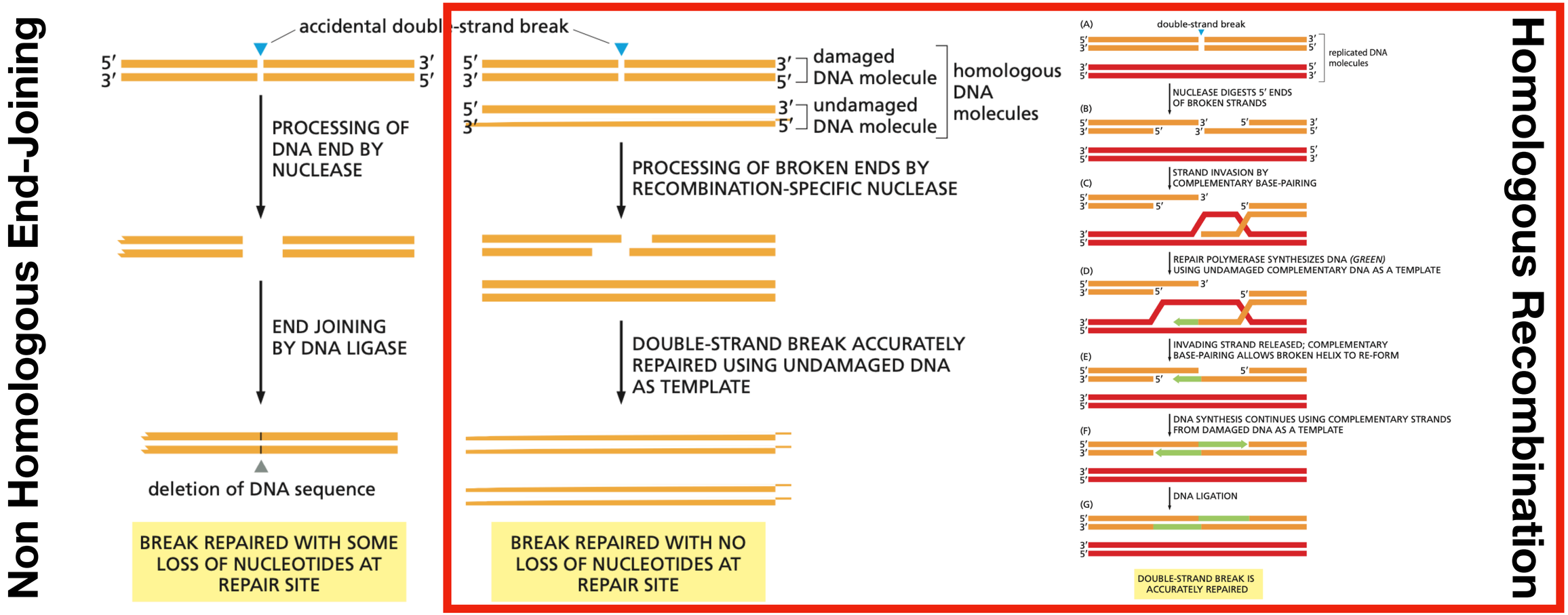




Annals of Oncology 25: 32–40, 2014

DNA Repair Mechanism

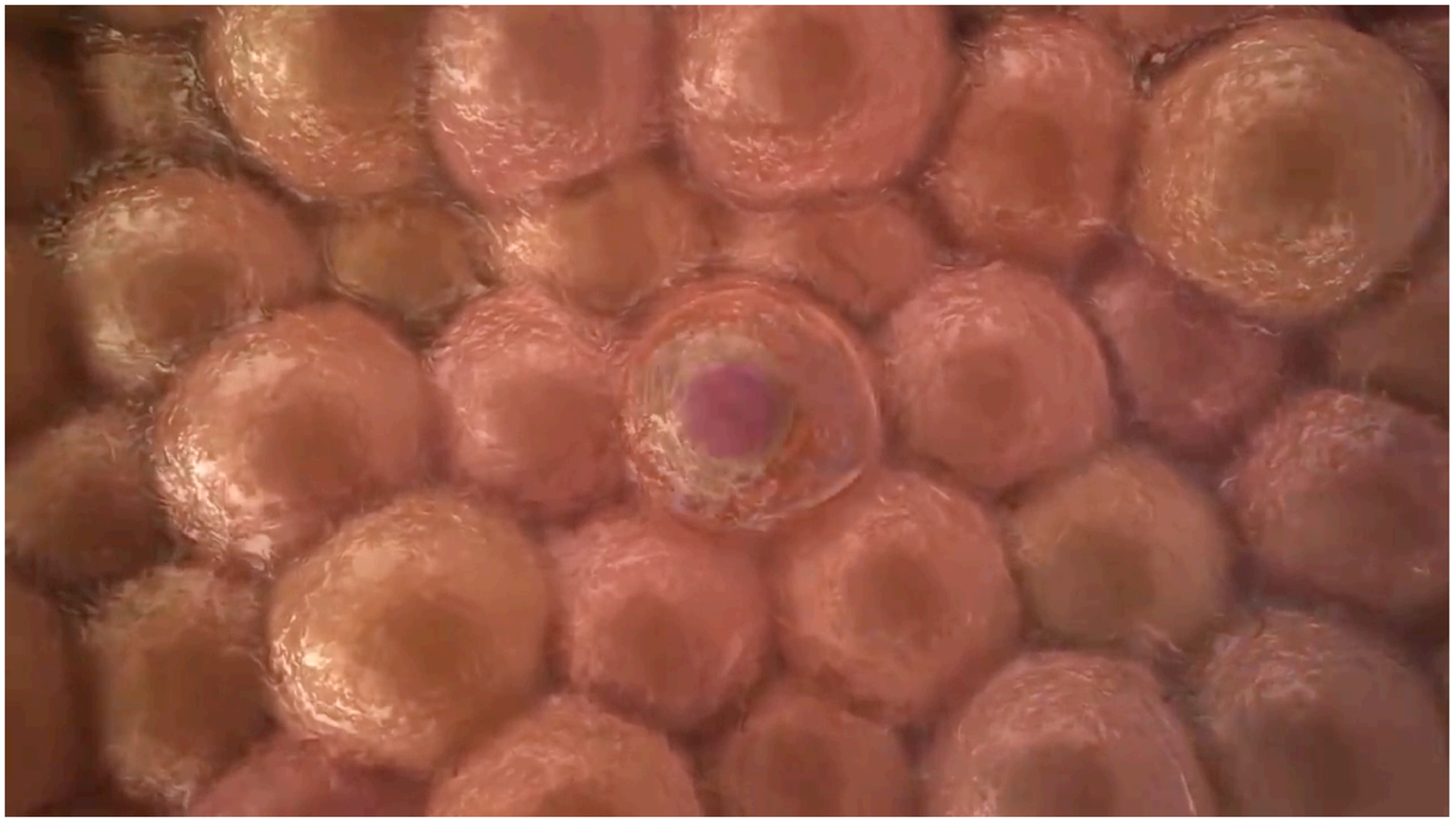
Double Strand Break Repair



Essential Cell Biology 5th Edition (2018).

DNA Repair Mechanism

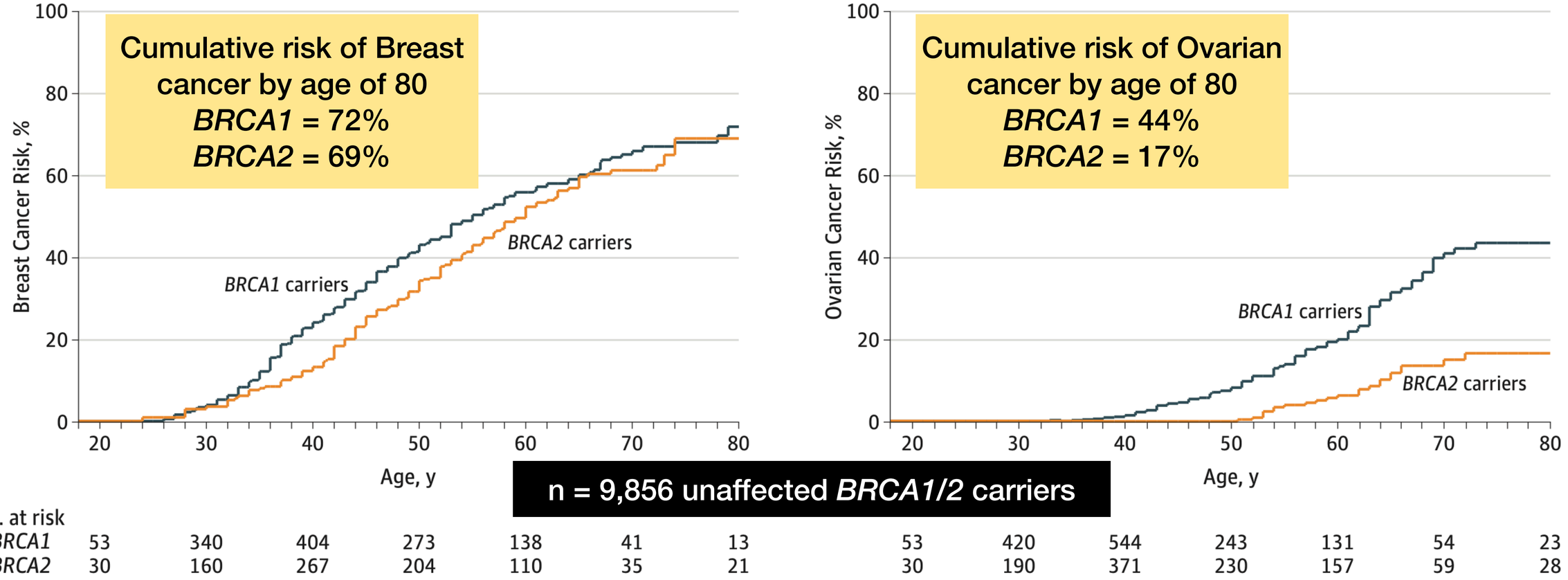
Double Strand Break Repair and Normal PARP Function



***Nymus 3D**: https://www.youtube.com/watch?v=2yl_SoOWFMU*

Hereditary Breast and Ovarian Cancer

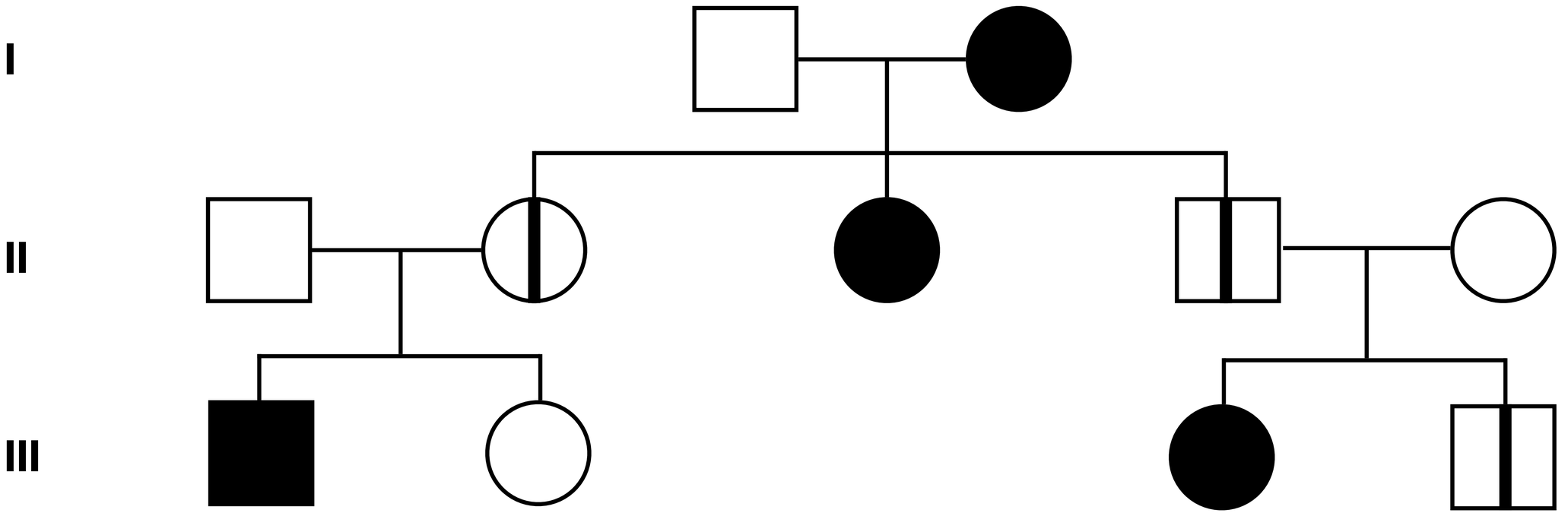
Kaplan-Meier of Cumulative Risks of Breast and Ovarian Cancers

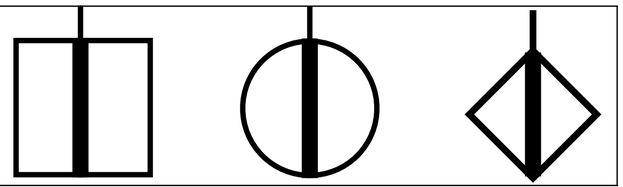


J Natl Cancer Inst 2006;98:1694-1706.

Penetrance

Asymptomatic/Presymptomatic Carrier

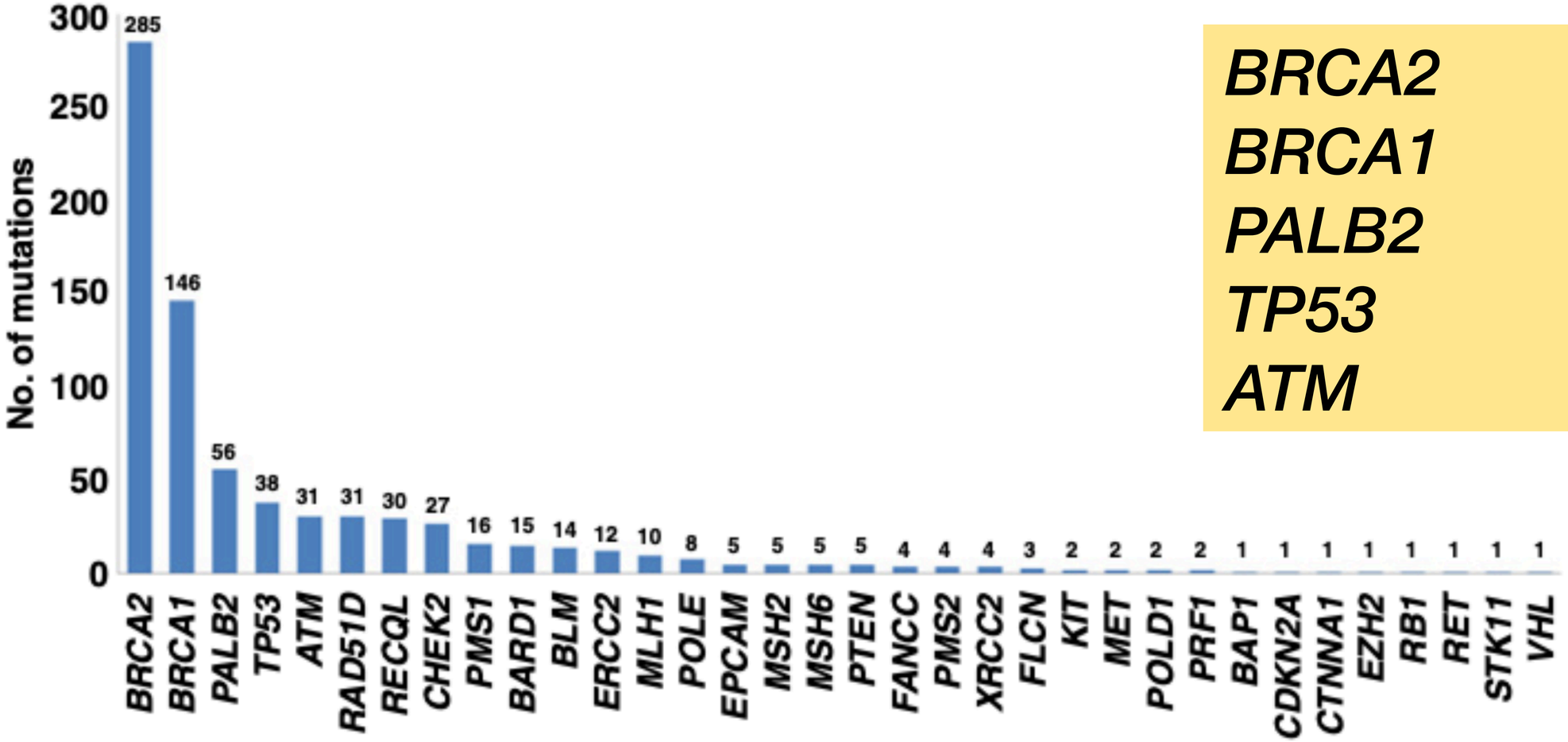


Asymptomatic/presymptomatic carrier :no clinical symptoms now, but could later exhibit symptoms	

Oxford Desk Reference: Clinical Genetics and Genomics 2nd Edition

Hereditary Breast and Ovarian Cancer

Proportion of Predisposing Genes



BRCA2	37 %
BRCA1	19 %
PALB2	7 %
TP53	5 %
ATM	4 %

Clin Cancer Res 2017;15;23(20):6113-6119.

Genetic Risk Assessment & Counselling

Formal Risk Assessment

Evaluation of Patient's Needs and Concerns

- Assess the patient's concerns and reasons for seeking counselling
- Address their personal needs and priorities in the counselling process
- Highly exaggerated perception of risk among women with family history who seek cancer risk counselling
- Assess patients knowledge about benefits, risks, and limitations of genetic testing
- Positive supportive interaction

Journal of Clinical Oncology, Vol 17, No 3 (March), 1999: pp 1040-1046

Genetic Risk Assessment & Counselling

Formal Risk Assessment

		Model				
	Quartiles	1	2	3	4	Total
Women	1	14	1	1	1	17
	2	37	6	6	8	57
	3	20	9	1	10	40
	4	45	7	2	32	86
	Total	116	23	10	51	200

overestimation | agreement | underestimation

Fig 1. Women's estimates versus model estimates of mutation risk.

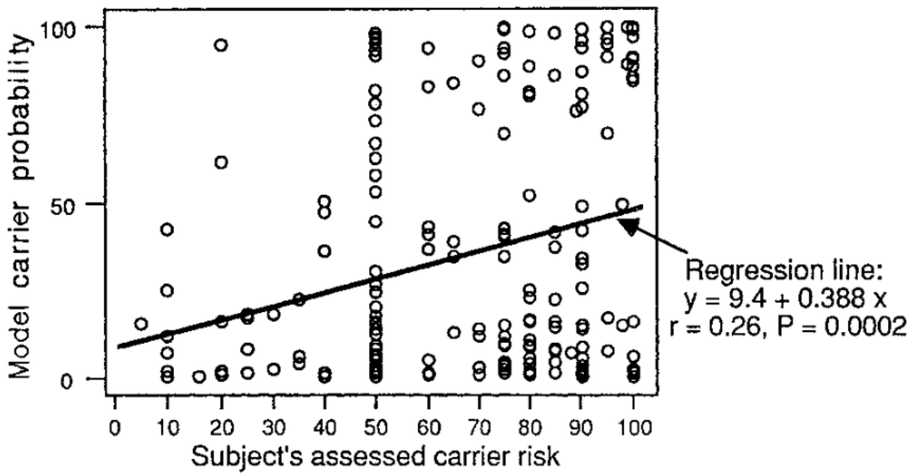
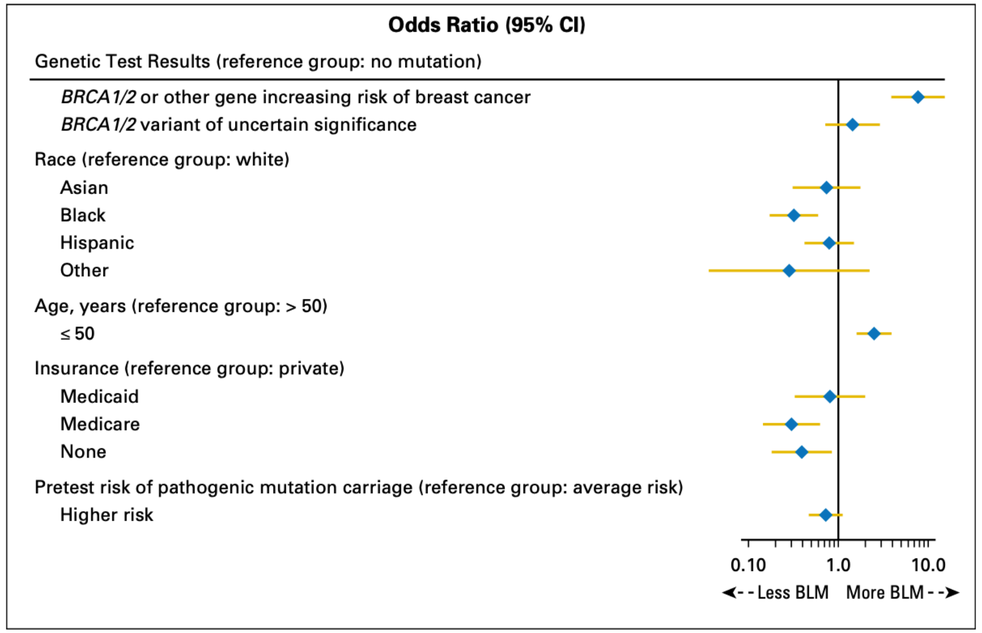


Fig 3. Comparison of women's own estimates of having a *BRCA1* and *BRCA2* mutation with the BRCAPRO model.

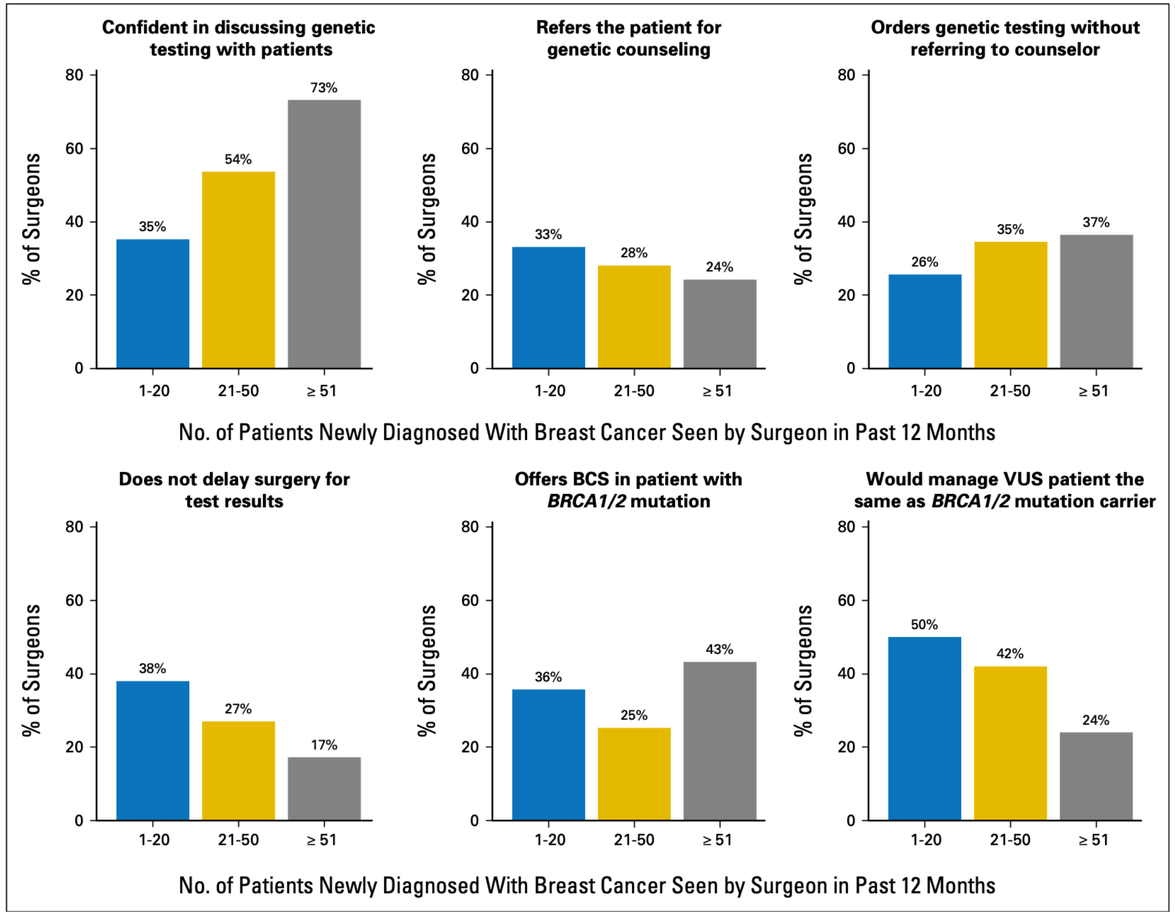
Journal of Clinical Oncology, Vol 17, No 3 (March), 1999: pp 1040-1046

Genetic Risk Assessment & Counselling

Genetic Counselling



Many patients undergoing genetic testing do not receive proper counselling



J Clin Oncol 2017. 35:2232-2239.

Genetic Risk Assessment & Counseling

Principles of Genetic Risk Assessment and Counseling

The decision to offer genetic testing involves **3 related stages**:

It is recommended that a **genetic counselor**, clinical **geneticist**, **oncologist**, **surgeon**, oncology **nurse**, or other health professional with expertise and experience in cancer genetics be involved at each stage whenever possible.

NCCN Guideline Version 1.2024

Genetic Risk Assessment & Counseling

Principles of Genetic Risk Assessment and Counseling

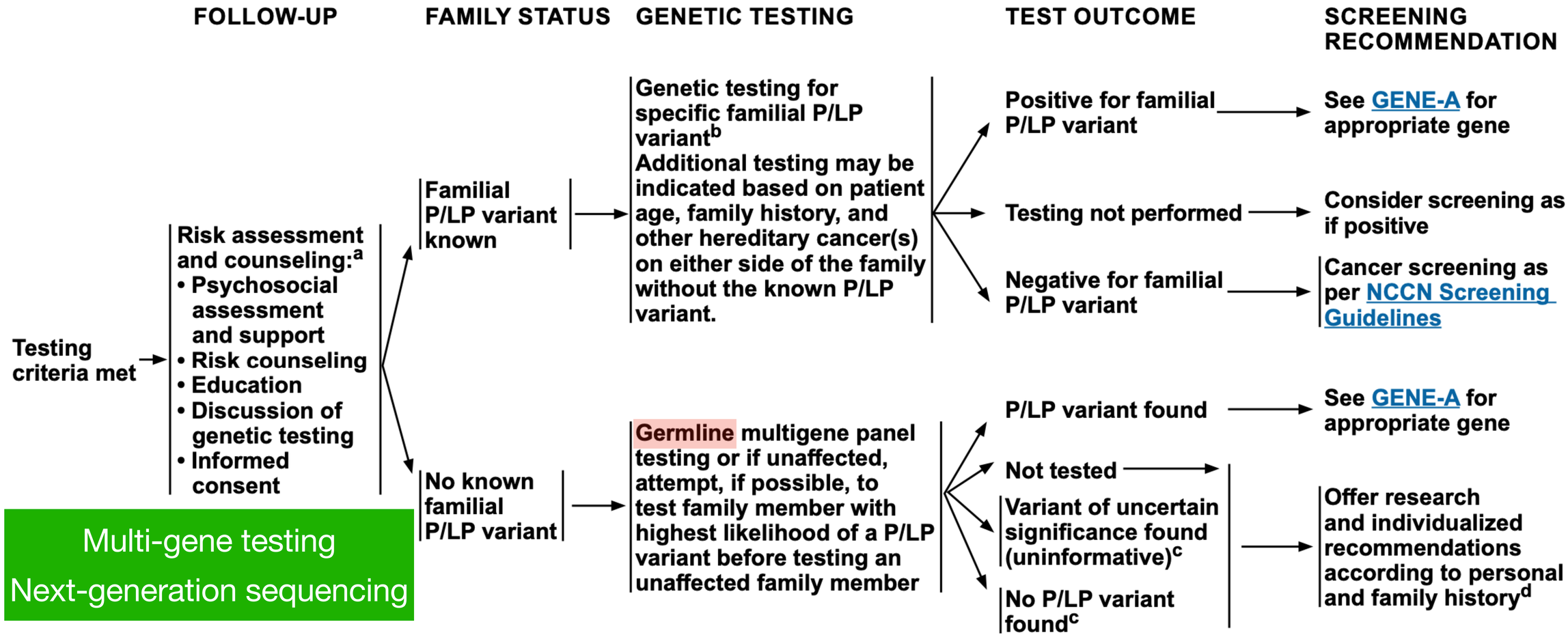
The decision to offer genetic testing involves **3 related stages**:

Testing should be considered in **appropriate individuals** where it is likely to impact the risk management and/or treatment of the tested individuals and/or their at-risk family members who also have increased risk.

NCCN Guideline Version 1.2024

Hereditary Breast and Ovarian Cancer

Genetic Testing Process



NCCN Guideline Version 1.2024

Hereditary Cancer Testing Criteria

General Testing Criteria: Clinically Indicated

- Individuals with any **blood relative with a known pathogenic/likely pathogenic variant** in cancer susceptibility gene
- Individuals meeting the criteria but tested negative with **previous limited testing** (eg, single gene and/or absent deletion duplication analysis) pursuing multi-gene testing
- A pathogenic/likely pathogenic variant identified on **tumor genomic testing** that has clinical implications if also identified in the germline
- To **aid in systemic therapy** and **surgical decision-making**
- Individual who meets **Li-Fraumeni** syndrome testing criteria or **PTEN** hamartoma tumor syndrome testing criteria or **Lynch** syndrome

NCCN Guideline Version 1.2024

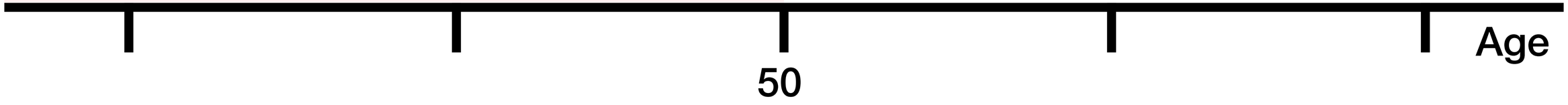
Hereditary Cancer Testing Criteria

General Testing Criteria: Clinically Indicated

- For Personal or Family History of **Breast Cancer** with specific features:

Age ≤ 50 years

Breast cancer diagnosed at age ≤ 50 years



NCCN Guideline Version 1.2024

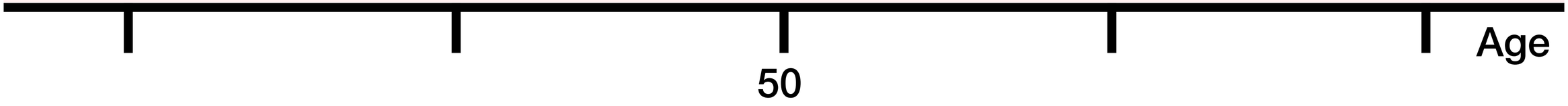
Hereditary Cancer Testing Criteria

General Testing Criteria: Clinically Indicated

- For Personal or Family History of **Breast Cancer** with specific features:

Any Age

- Ashkenazi Jewish
- Male Breast Cancer



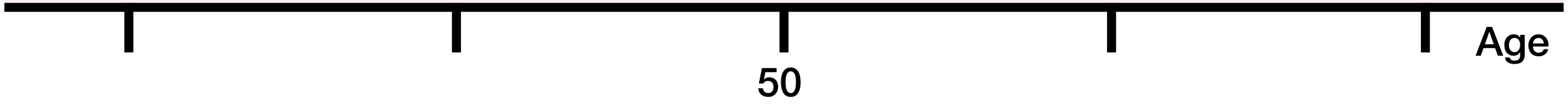
NCCN Guideline Version 1.2024

Hereditary Cancer Testing Criteria

General Testing Criteria: Clinically Indicated

- For Personal or Family History of **Breast Cancer** with specific features:

Any Age
Pathology/Histology • Triple-negative Breast Cancer • Multiple Primary Breast Cancer (Synchronous or Metachronous) • Lobular Breast cancer with family history of diffuse gastric cancer



NCCN Guideline Version 1.2024

Hereditary Cancer Testing Criteria

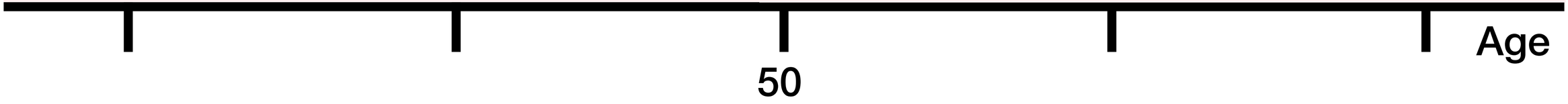
General Testing Criteria: Clinically Indicated

- For Personal or Family History of **Breast Cancer** with specific features:

Any Age

Family History ≥ 1 close blood relative with

- Breast Cancer at age ≤ 50 years
- Male Breast Cancer
- Ovarian Cancer (include fallopian tube or peritoneal cancer)
- Pancreatic Cancer
- Prostate Cancer with metastatic, or high- or very-high-risk group



NCCN Guideline Version 1.2024

Hereditary Cancer Testing Criteria

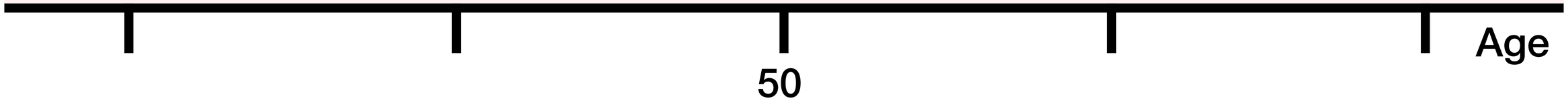
General Testing Criteria: Clinically Indicated

- For Personal or Family History of **Breast Cancer** with specific features:

Any Age

Family History

- ≥ 3 total diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer



NCCN Guideline Version 1.2024

Hereditary Cancer Testing Criteria

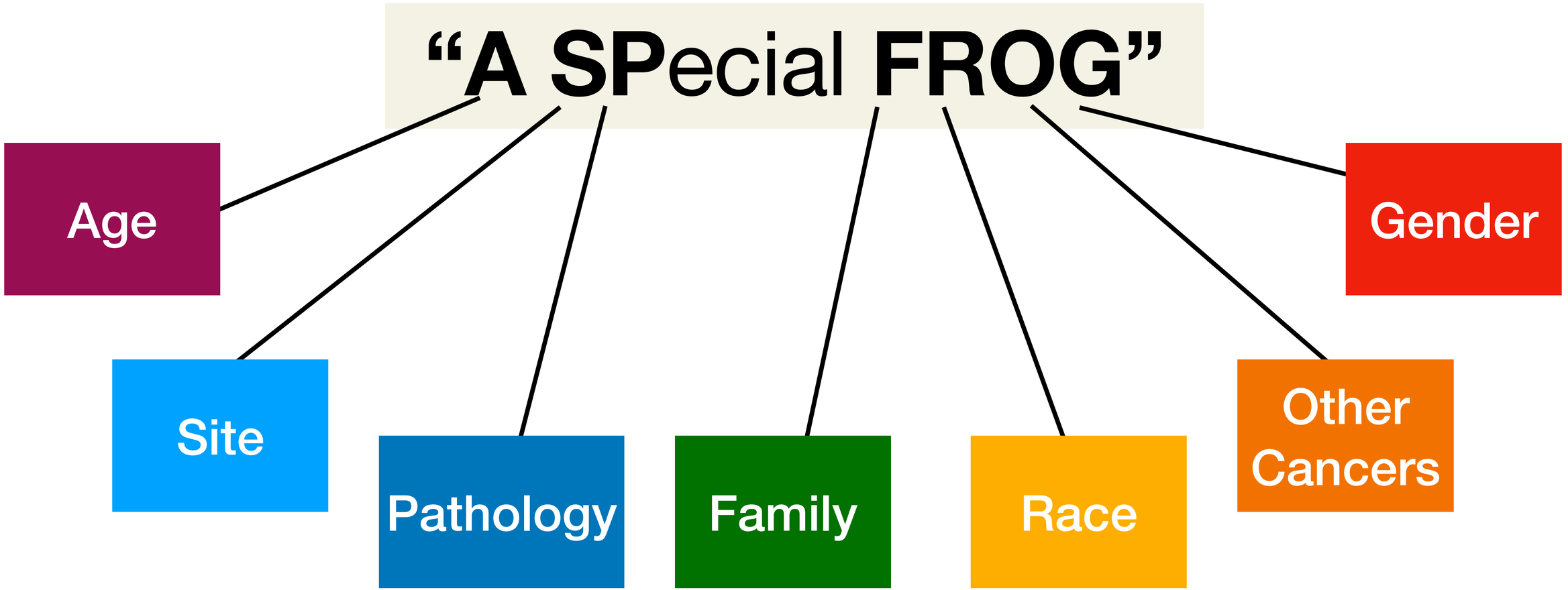
General Testing Criteria: Clinically Indicated

- An individual affected with breast cancer (not meeting testing criteria) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making)
- An affected or unaffected individual who otherwise does not meet the criteria above but has a **probability >5%** of a BRCA 1/2 pathogenic variant based on prior probability models (eg, **Tyrer-Cuzick, BRCAPro, CanRisk**)

NCCN Guideline Version 1.2024

Hereditary Cancer Testing Criteria

General Testing Criteria: Mnemonic



Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Risk Assessment, Counselling, and Management:

- Breast awareness; starting at 18 years

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

POLICY STATEMENT

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

Ethical and Policy Issues in Genetic Testing and Screening of Children

Adult Onset

No impacted medical management

Outside of newborn screening, genetic testing of children is less commonly performed. Diagnostic genetic testing may be performed on a child with signs or symptoms of a potential genetic condition or for treatment decisions made on the basis of results of pharmacogenetic assays. Genetic testing may also be performed on an asymptomatic child with a positive family history for a specific genetic condition, particularly if early treatment may affect morbidity or mortality. The American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG) provide the following recommendations regarding genetic testing and screening of minors. An accompanying technical report pro-

Pediatrics 2013;131:620-622

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Woman Screening Recommendation:

- Clinical breast exam every 6 - 12 months; starting at 25 years
- Breast Cancer Screening **Individualized based on family history if CA breast diagnosed before age of 30**
  - Age 25-29 years: Annual breast **MRI with contrast** Days 7-15 of menstrual cycle

(or **Mammogram** only if MRI unavailable)

High-quality Breast MRI Screening

- Dedicated breast coil
- Ability to perform biopsy under MRI guidance
- Experienced radiologist in breast MRI
- Regional availability

NCCN Guideline Version 1.2024

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

529 asymptomatic women suspected or proven to carry BRCA

Mean follow-up time = 5.3 years

University of Bonn, Germany

Sensitivity

	Mammography		Ultrasound		Mammography + Ultrasound		MRI		Mammography + MRI	
	Sensitivity (%)	TP/TP + FN	Sensitivity (%)	TP/TP + FN	Sensitivity (%)	TP/TP + FN	Sensitivity (%)	TP/TP + FN	Sensitivity (%)	TP/TP + FN
All women	32.6	14/43	39.5	17/43	48.8	21/43	90.7	39/43	93.0	40/43
With personal history of breast cancer	33.3	4/12	41.7	5/12	41.7	5/12	66.6	8/12	75.0	9/12
Without personal history of breast cancer	32.3	10/31	38.7	12/31	51.6	16/31	100.0	31/31	100.0	31/31
Risk 20%	50.0	3/6	67.7	4/6	83.3	5/6	100.0	6/6	100.0	6/6
Risk 21%-40%	25.0	5/20	30.0	6/20	45.0	9/20	100.0	20/20	100.0	20/20
Mutation carriers	25.0	2/8	25.0	2/8	37.5	3/8	100.0	8/8	100.0	8/8

Specificity

	Mammography		Ultrasound		Mammography + Ultrasound		MRI		Mammography + MRI	
	Specificity (%)	TN/TN + FP	Specificity (%)	TN/TN + FP	Specificity (%)	TN/TN + FP	Specificity (%)	TN/TN + FP	Specificity (%)	TN/TN + FP
All women	96.8	1,364/1,409	90.5	1,275/1,409	89.0	1,254/1,409	97.2	1,370/1,409	96.1	1,354/1,409
With personal history of breast cancer	95.5	252/264	88.3	233/264	87.1	230/264	96.2	254/264	95.1	251/264
Without personal history of breast cancer	97.1	1,112/1,145	91.0	1,042/1,145	89.4	1,024/1,145	97.5	1,116/1,145	96.3	1,103/1,145
Risk 20%	96.5	302/313	90.4	283/313	88.2	276/313	97.4	305/313	95.5	299/313
Risk 21-40%	97.4	676/694	91.2	633/694	89.9	624/694	97.7	678/694	97.0	673/694
Mutation carriers	96.9	154/159	91.2	145/159	88.7	141/159	97.5	155/159	94.4	150/159

False negative mammogram correlate with high breast tissue density.

J Clin Oncol 2005;23:8469-8476

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

GENE-RAD-RISK study

GENEPSO (France)
EMBRANCE (UK)
HEBON (Netherland)

1,993 female carriers of BRCA1/2 mutation (2006-2009)

	Until diagnosis of breast cancer			During 5-year period		
	Entire cohort (n=1,993; 747 cases)			Subcohort (n=955; 144 cases)		
	Person-years	Cases	HR (95%CI)[a]	Person-years	Cases	HR (95%CI)[b]
Before age 30						
Never	27,160	263	1.00	1,679	57	1.00
Ever	28,110	333	1.33 (1.12-1.57)	1,412	58	1.65 (1.11-2.46)
Dose category						
<0·0020	14,442	164	1.29 (1.06-1.57)	874	33	1.48 (0.94-2.33)
0·0020-0·0066	6,031	73	1.35 (1.04-1.77)	280	12	1.55 (0.81-2.98)
0·0066-0·0174	3,965	45	1.22 (0.89-1.67)	147	6	1.90 (0.69-5.21)
≥0·0174	3,671	51	1.56 (1.15-2.11)	109	7	4.16 (2.01-8.62)

Exposure to diagnostic radiation prior to 30 years was associated with increased risk of breast cancer in women with BRCA1/2 mutation

MRI reduces radiation exposure

BMJ 2012;345:e5660

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Woman Screening Recommendation:

- Clinical breast exam every 6 - 12 months; starting at 25 years
- Breast Cancer Screening **Individualized based on family history if CA breast diagnosed before age of 30**
  - Age 25-29 years: Annual breast **MRI with contrast** **Days 7-15 of menstrual cycle**

    (or **Mammogram** only if MRI unavailable)
  - Age 30-75 years: Annual Mammogram & Breast MRI with contrast
  - Age > 75 years: consider on individual basis
  - BRCA P/LP variant: annual mammogram & Breast MRI with contrast

NCCN Guideline Version 1.2024

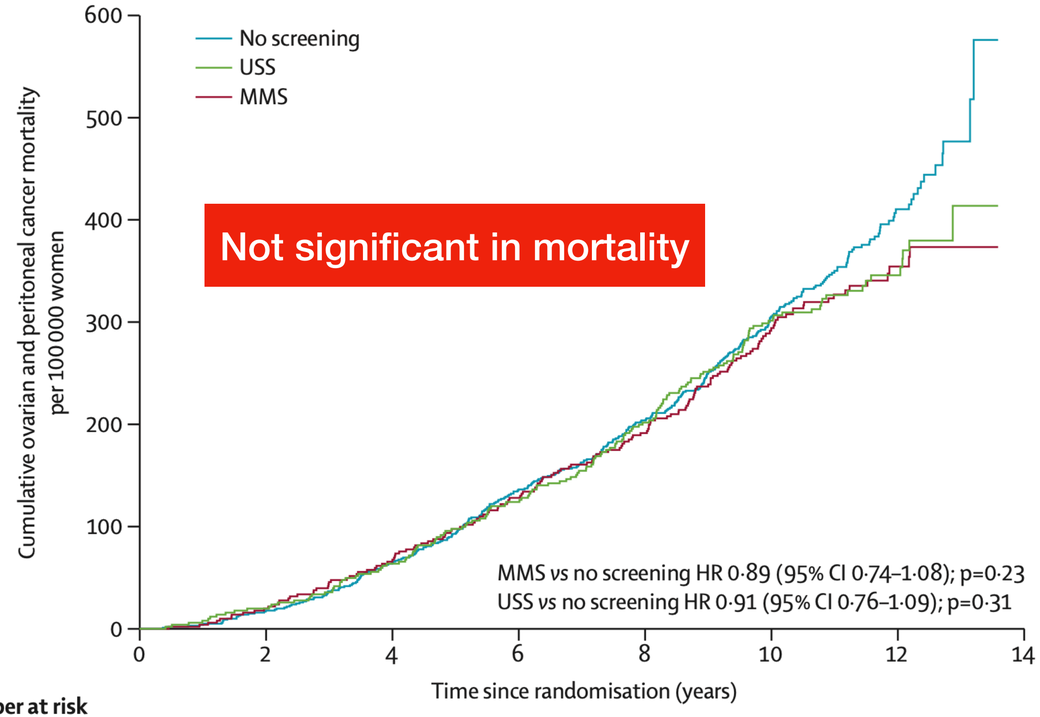
Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Woman Screening Recommendation:

- Ovarian & Peritoneal Cancer Screening
  - Annual Transvaginal Ultrasound
  - CA-125 every 3-4 months
  - ROCA (risk of ovarian cancer algorithm) score
- Starting at 30-35 years of age

UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)



Number at risk

No screening	101299	100720	99662	98238	96632	75582	25252
MMS	50624	50343	49846	49176	48345	37758	12592
USS	50623	50623	49838	49192	48363	37768	12689

NCCN Guideline Version 1.2024

Hereditary Breast and Ovarian Cancer

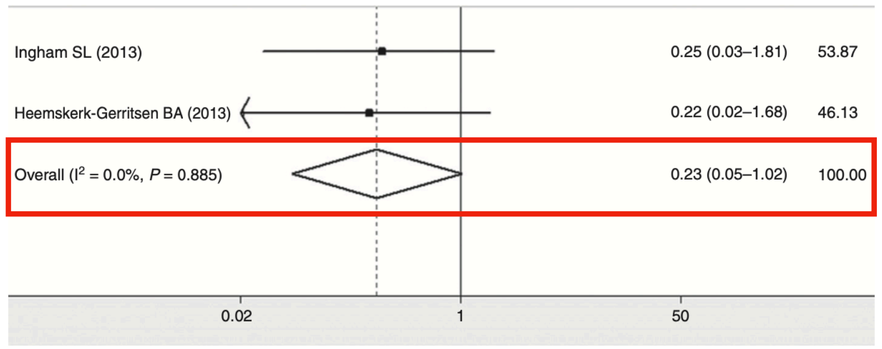
BRCA-Related Cancer Syndrome

Risk Reduction Surgery:

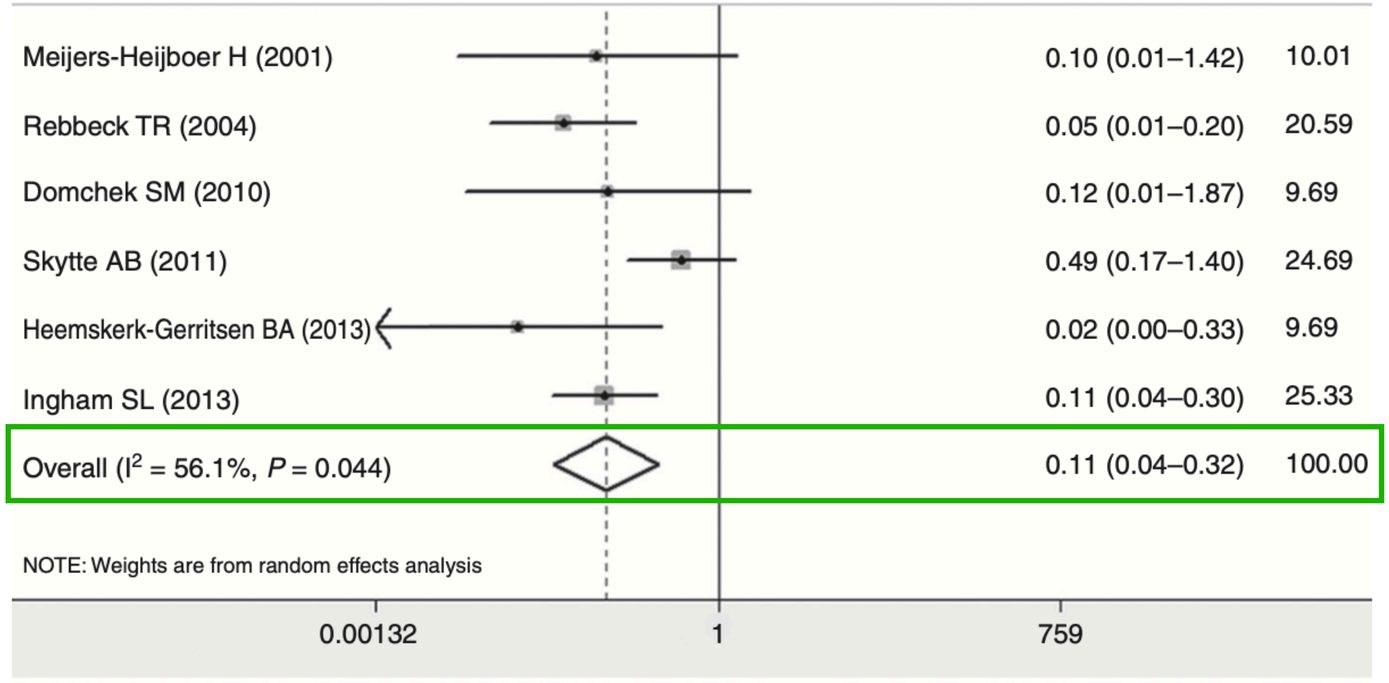
- **Bilateral Total Mastectomy**

  Meta-analysis (n = 2,555)

All-Cause Mortality



Breast Cancer Risk



Clin Cancer Res 2016;22:3971-3981.

Hereditary Breast and Ovarian Cancer

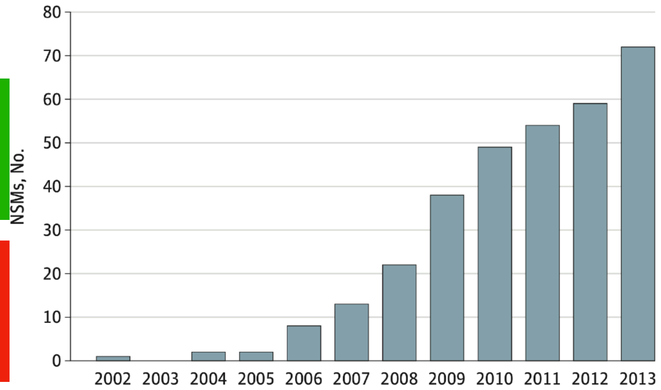
BRCA-Related Cancer Syndrome

Risk Reduction Surgery:

- **Nipple-sparing Mastectomy**
  - 346 patients with 548 procedures with 56-month mean follow-up: No breast cancer developed in the study ($p<0.001$)

SAFE & EFFECTIVE

MORE DATA NEEDED



Prediction Model	Group	Women, No.	Expected New Primary Breast Cancers, No.							
			0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00
BOADICEA[12]	*BRCA1* mutation carriers	201	10.6	11.7	12.8	13.9	15.0	16.1	17.2	18.3
	BRCA2 mutation carriers	145	5.7	6.4	8.2	7.9	8.7	9.5	10.2	11.0
Chen and Parmigiani[13]	Women aged 20-70 y at NSM	343	16.4	18.3	20.2	22.1	24.0	25.9	27.8	29.7
van den Broek et al[14]	Women aged <50 y with primary breast cancer and contralateral NSM	103	NA	NA	NA	9.7	NA	NA	NA	NA

JAMA Surg 2018;153:123-129.

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Risk Reduction Surgery:

- **Bilateral Salpingo-oophorectomy**

Association between Oophorectomy and All-cause mortality

Variable	No. of Patients	*BRCA1*			*BRCA2*			All Patients		
		HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age group at study entry, years										
≤ 40	2,104	0.27	0.15 to 0.48	< .001	0.44	0.17 to 1.09	.08	0.30	0.19 to 0.49	< .001
41-50	1,906	0.23	0.16 to 0.33	< .001	0.29	0.14 to 0.59	< .001	0.24	0.17 to 0.33	< .001
51-60	1,189	0.28	0.19 to 0.43	< .001	0.19	0.08 to 0.43	< .001	0.27	0.18 to 0.38	< .001
≥ 61	584	0.43	0.25 to 0.71	.001	0.89	0.33 to 2.43	.84	0.49	0.31 to 0.76	.002
Total	5,783	0.30	0.24 to 0.38	< .001	0.33	0.22 to 0.50	< .001	0.31	0.26 to 0.38	< .001
Previous breast cancer										
Yes	2,561	0.31	0.24 to 0.39	< .001	0.34	0.22 to 0.52	< .001	0.32	0.26 to 0.39	< .001
No	2,633	0.21	0.12 to 0.37	< .001	0.67	0.08 to 5.35	.70	0.23	0.13 to 0.39	< .001

J Clin Oncol 2014;32:1547-1553.

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Risk Reduction Surgery:

- **Bilateral Salpingo-oophorectomy**

Association between Oophorectomy and Breast Cancer

Mutation	Unadjusted			Adjusted		
	OR	*P*	95% CI	OR	*P*	95% CI
BRCA1 or *BRCA2*	0.46	.00001	0.32 to 0.65	0.46	.00001	0.32 to 0.65
BRCA1	0.43	.00006	0.29 to 0.65	0.44	.00006	0.29 to 0.66
BRCA2	0.57	.11	0.28 to 1.15	0.57	.11	0.28 to 1.15

Decrease hormonal exposure ??

J Clin Oncol 2005;23:7491-7496.

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Risk Reduction Surgery:

- **Bilateral Salpingo-oophorectomy**

Association between Oophorectomy and Breast Cancer

Age at Oophorectomy, Years	No. With Oophorectomy		Unadjusted			Adjusted*		
	Patient Case	Patient Control	OR	*P*	95% CI	OR	*P*	95% CI
BRCA1/2								
No oophorectomy	1,388	1,751	1.0	—	—	1.0	—	—
≤ 40	23	59	0.41	.0004	0.25 to 0.68	0.41	.0005	0.25 to 0.68
41-50	21	47	0.47	.005	0.28 to 0.79	0.47	.005	0.28 to 0.80
51+	7	9	0.71	.53	0.25 to 2.06	0.70	.51	0.24 to 2.03
BRCA1								
No oophorectomy	1,021	1,320	1.0	—	—	1.0	—	—
≤ 40	17	50	0.36	.0004	0.20 to 0.63	0.36	.0005	0.20 to 0.64
41-50	16	34	0.49	.02	0.27 to 0.91	0.50	.02	0.27 to 0.92
51+	5	7	0.67	.50	0.21 to 2.13	0.66	.48	0.21 to 2.09
BRCA2								
No oophorectomy	360	426	1.0	—	—	1.0	—	—
≤ 40	6	9	0.70	.49	0.25 to 1.96	0.69	.49	0.25 to 1.95
41-50	5	12	0.43	.12	0.15 to 1.23	0.44	.12	0.15 to 1.24
51+	2	2	1.00	1.00	0.06 to 16.0	1.00	1.00	0.06 to 16.1

BRCA1 age < 40

J Clin Oncol 2005;23:7491-7496.

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Risk Reduction Surgery:

- **Bilateral Salpingo-oophorectomy**

Variable	Age-adjusted HR (95% CI)	P	Multivariable* HR (95% CI)	P
Oophorectomy†				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.91 (0.71 to 1.16)	.43	0.89 (0.69 to 1.14)	.35
Family history of breast cancer‡				
0 family members	1.00 (Referent)		1.00 (Referent)	
1 family member	1.38 (1.06 to 1.76)	.01	1.36 (1.06 to 1.75)	.02
≥2 family members	1.34 (0.93 to 1.94)	.12	1.38 (0.95 to 2.00)	.09
Oral contraceptive use				
Never	1.00 (Referent)		1.00 (Referent)	
Ever	1.08 (0.87 to 1.35)	.48	1.38 (0.95 to 2.00)	.16
BRCA mutation				
BRCA1§	1.00 (Referent)		1.00 (Referent)	
BRCA2§	0.81 (0.62 to 1.08)	.15	0.86 (0.62 to 1.20)	.38
Country of residence				
Poland	1.00 (Referent)		1.00 (Referent)	
Canada	0.78 (0.59 to 1.03)	.08	0.77 (0.54 to 1.08)	.13
Other	1.00 (0.73 to 1.36)	.98	0.80 (0.48 to 1.34)	.41
United States	0.99 (0.74 to 1.34)	.96	0.97 (0.69 to 1.38)	.88

J Natl Cancer Inst 2017;109

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Risk Reduction Surgery:

- **Bilateral Salpingo-oophorectomy**

Variable	Age-adjusted HR (95% CI)	P	Multivariable* HR (95% CI)	P
All women				
BRCA1† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.96 (0.73 to 1.26)	.76	0.97 (0.73 to 1.29)	.85
BRCA2† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.65 (0.37 to 1.16)	.14	0.68 (0.38 to 1.21)	.19
Breast cancer diagnosed prior to age 50 y§				
BRCA1† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.79 (0.55 to 1.13)	.51	0.84 (0.58 to 1.21)	.34
BRCA2† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.18 (0.05 to 0.63)	.007	0.17 (0.05 to 0.61)	.006

BRCA2 age < 50

J Natl Cancer Inst 2017;109

Hereditary Breast and Ovarian Cancer

BRCA-Related Cancer Syndrome

Risk Reduction Surgery:

- **Bilateral Salpingo-oophorectomy**

NCCN Guidelines Panel Recommendation for women with known BRCA1/2 pathogenic/likely pathogenic variant

- Age 35-40 years for BRCA1
- Age 40-45 years for BRCA2
- Unless age of diagnosis in family

Salpingectomy alone is not the standard of care for risk reduction.

Clinical Significance of **Concurrent Hysterectomy** at the time of RRSO is unclear. (Limited data about serous uterine cancer in *BRCA1*)

NCCN Guideline Version 1.2024

Summary of Cancer Risk Management

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
ATM	• **Absolute risk:** 20%–30%[3,4,5,6] • **Management:**[b] ▸ Screening: Annual mammogram at age 40 y and consider breast MRI with and without contrast starting at age 30–35 y[c,d,e] ▸ Risk reduction: Evidence insufficient for risk-reducing mastectomy (RRM); manage based on family history • **Strength of evidence of association with cancer:** Strong	• **Absolute risk:** 2%–3%[10-12] • **Management:**[f] ▸ Risk reduction: Evidence insufficient for risk-reducing salpingo oophorectomy (RRSO); manage based on family history • **Strength of evidence of association with cancer:** Strong	**Pancreatic cancer** • **Absolute risk:** ~5%–10%[g,23] • **Management:** Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A. • **Strength of evidence of association with cancer:** Strong **Prostate cancer** • Emerging evidence for association with increased risk.[24] Consider prostate cancer screening starting at age 40 years (Guidelines for Prostate Cancer Early Detection)
	Comments: Heterozygous *ATM* P/LP variants should not lead to a recommendation to avoid RT at this time. See Discussion for information regarding the c.7271T>G variant, which is associated with greater risk of breast cancer. See GENE-B for reproductive implications/recessive disease.		
BARD1	• **Absolute risk:** 17%–30%[7] • **Management:** ▸ Screening: Annual mammogram and consider breast MRI with and without contrast starting at age 40 y[c,d,e] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history • **Strength of evidence of association with cancer:** Strong[7-9]	**Evidence of increased risk:** No established association	**Other cancers** • Unknown or insufficient evidence

Summary of Cancer Risk Management

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
BRCA1	• **Absolute risk:** >60%[5,25-29] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence of association with cancer:** Very strong **Male breast cancer** • **Absolute risk:** 0.2%–1.2% by age 70 y[30,31] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence of association with cancer:** Strong	• **Absolute risk:** 39%–58%[33] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence of association with cancer:** Very strong	**Pancreatic cancer** • **Absolute risk:** ≤5%[31] • **Management:** Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A. • **Strength of evidence of association with cancer:** Strong **Prostate cancer** • **Absolute risk:** 7%–26%[34] • **Management:** See *BRCA* Pathogenic Variant-Positive Management
	Comment: See GENE-B for reproductive implications/recessive disease.		
BRCA2	• **Absolute risk:** >60%[5,21-25] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence of association with cancer:** Very strong **Male breast cancer** • **Absolute risk:** 1.8%–7.1% by age 70 y[30,31,32] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence of association with cancer:** Strong	• **Absolute risk:** 13%–29%[33] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence of association with cancer:** Very strong	**Pancreatic cancer** • **Absolute risk:** 5%–10%[31] • **Management:** Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A. • **Strength of evidence of association with cancer:** Very strong **Prostate cancer** • **Absolute risk:** 19%–61%[34,35] • **Management:** See *BRCA* Pathogenic Variant-Positive Management **Melanoma** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: See GENE-B for reproductive implications/ recessive disease.		

Summary of Cancer Risk Management

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
BRIP1	• **Absolute risk:** Insufficient data to define • **Management:** Insufficient data; managed based on family history • **Strength of evidence of association with cancer:** Limited; potential increase in female breast cancer[8]	• **Absolute risk:** 5%–15%[10-12,39] • **Management:** ▸ Risk reduction: Recommend RRSO starting at age 45–50 y[h] • **Strength of evidence of association with cancer:** Strong	**Other cancers** • Unknown or insufficient evidence
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of P/LP variants in *BRIP1* justifies RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset of ovarian cancer. See GENE-B for reproductive implications/recessive disease.		
CDH1	• **Absolute risk:** 41%–60%[36-38] • **Management:**[b] ▸ Screening: Annual mammogram and consider breast MRI with and without contrast starting at age 30 y[c,d] ▸ Risk reduction: Discuss option of RRM • **Strength of evidence of association with cancer:** Strong	**Evidence of increased risk:** No established association	**Hereditary diffuse gastric cancer (HDGC)** • **Strength of evidence of association with cancer:** Strong • See NCCN Guidelines for Gastric Cancer: Principles of Genetic Risk Assessment for Gastric Cancer
	Comments: There is controversy over how to manage gastric cancer risk in individuals with P/LP variants in *CDH1* in the absence of a family history of gastric cancer. However, one small study found that >50% of such individuals had gastric cancer identified at the time of risk-reducing total gastrectomy (Jacobs MF, et al. Gastroenterology 2019;157:87-96), and penetrance for lifetime risk is increased with a positive family history of HDGC (Roberts ME, et al. JAMA Oncol 2019;5:1325-1331). Cleft lip with or without cleft palate has been associated with *CDH1* P/LP variants (Frebourg T, et al. J Med Genet 2006;43:138-142).		

Summary of Cancer Risk Management

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
CDKN2A	**Evidence of increased risk:** No established association	**Evidence of increased risk:** No established association	**Pancreatic cancer** • **Absolute risk:** >15% • **Management:** Screening, see PANC-A. • **Strength of evidence of association with cancer:** Very strong **Melanoma** • **Absolute risk:** 28%–76% depending on other risk factors, including family history, geographic location, and other genetic modifiers[40,41] • **Strength of evidence of association with cancer:** Strong • **Management:** See comment **Other cancers** • See comment
	Comments: Comprehensive skin examination by a dermatologist, supplemented with total body photography and dermoscopy is recommended biannually for individuals with P/LP variants affecting biologically relevant *CDKN2A* isoforms (ie, p16INK4A and p14ARF). Because P/LP variants that specifically disrupt the p14ARF protein cause a unique predisposition to nerve sheath tumors, sarcomas, melanoma, and other cancers, increased multidisciplinary cancer surveillance beyond pancreatic and dermatologic management has been recommended, which may include annual full-body and brain MRI based on the presentation in individuals/families (Sargen M, et al. Br J Dermatol 2016;175:785-789; Chan et al. Hered Cancer Clin Pract 2021;19:21).		
CHEK2	• **Absolute risk:** 20%–40%[5,6,7,42,43,44] • **Management:**[b] ▸ Screening: Annual mammogram at age 40 y and consider breast MRI with and without contrast starting at age 30–35 y[c,d,e] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history • **Strength of evidence of association with cancer:** Strong[45]	**Evidence of increased risk:** No established association	**Colorectal cancer** • NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (GENE-1) **Prostate cancer** • Emerging evidence for association with increased risk.[54] Consider prostate cancer screening starting at age 40 years (NCCN Guidelines for Prostate Cancer Early Detection)
	Comments: Risk data are based only on frameshift P/LP variants. The risks for most missense variants are unclear but for some P/LP variants, such as Ile157Thr, the risk for breast cancer appears to be lower. Additional cancer risk management based on this variant (Ile157Thr) is not recommended. Management should be based on best estimates of cancer risk for the specific P/LP variant.		

Summary of Cancer Risk Management

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
MSH2, MLH1, MSH6, PMS2, EPCAM [f]	***MLH1, MSH2, MSH6, PMS2,* and *EPCAM*** • **Absolute risk:** <15%[46,47,48] • **Management:** Insufficient data; managed based on family history • **Strength of evidence of association with cancer:** Limited	***MLH1*** • **Absolute risk:** 4%–20%[49,50] • **Strength of evidence:** Strong ***MSH2 /EPCAM*** • **Absolute risk:** 8%–38%[49,50,52,53] • **Strength of evidence:** Strong ***MSH6*** • **Absolute risk:** ≤1%–13%[51,52] • **Strength of evidence:** Strong ***PMS2*** • **Absolute risk:** 1.3%–3%[53] • **Strength of evidence:** Limited • **Management for all genes:** NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	**Pancreatic cancer** • **Absolute risk:** <5%–10% (excluding *PMS2*) • **Management:** Screen P/LP variant carriers with a family history of pancreatic cancer (insufficient evidence for *PMS2*), see PANC-A. • **Strength of evidence of association with cancer:** Strong **Colorectal, uterine, others** • NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comments: Counsel for biallelic risk of P/LP variants that lead to CMMRD. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.		
NF1	• **Absolute risk:** 20%–40%[55,56] • **Management:**[b] ▸ Screening: Annual mammogram starting at age 30 y and consider breast MRI with and without contrast from ages 30–50 y[c,d] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history • **Strength of evidence of association with cancer:** Strong	**Evidence of increased risk:** No established association	**Malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors (GIST), others** • Recommend referral to *NF1* specialist for evaluation and management
	Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.		

Summary of Cancer Risk Management

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
PALB2	• **Absolute risk:** 41%–60%[5,8,22,57] • **Management:**[b] ▸ Screening: Annual mammogram and breast MRI with and without contrast at 30 y[c,d] ▸ Risk reduction: Discuss option of RRM • **Strength of evidence of association with cancer:** Strong **Male breast cancer** • **Absolute risk:** 0.9% by age 70 y[22] • **Management:** See comment • **Strength of evidence of association with cancer:** Strong	• **Absolute risk:** 3%–5%[10-12,22,65,66] • **Management:**[f] ▸ Risk reduction: Consider RRSO at age starting at 45–50 y[h,67,68] • **Strength of evidence of association with cancer:** Strong	**Pancreatic cancer** • **Absolute risk:** 2%–5% • **Management:** Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A • **Strength of evidence of association with cancer:** Limited **Other cancers** • Unknown or insufficient evidence
	Comments: See GENE-B for reproductive implications/recessive disease. For males, it is reasonable to consider breast cancer screening similar to that for carriers of a *BRCA1* P/LP variant. See BRCA-A.		
PTEN	• **Absolute risk:** 40%–60% (historical cohort data), >60% (projected estimates)[58-62] • **Management:**[b] See Cowden Syndrome Management • **Strength of evidence of association with cancer:** Strong[63,64]	**Evidence of increased risk:** No established association	**Thyroid, colorectal, endometrial, renal cancers** • See Cowden Syndrome Management

Summary of Cancer Risk Management

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
RAD51C	• **Absolute risk:** 17%–30%[5,7,45] • **Management:** Annual mammogram and consider breast MRI with and without contrast starting at age 40 y • **Strength of evidence of association with cancer:** Strong	• **Absolute risk:** 10%–15%[10-12,69,70] • **Management:** ▸ Risk reduction: Recommend RRSO starting at 45–50 y[h] • **Strength of evidence of association with cancer:** Strong	**Other cancers** • Unknown or insufficient evidence
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of P/LP variants in RAD51C justifies RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer. See GENE-B for reproductive implications/ recessive disease.		
RAD51D	• **Absolute risk:** 17%–30%[5,7,45] • **Management:** Annual mammogram and consider breast MRI with and without contrast starting at age 40 y • **Strength of evidence of association with cancer:** Strong	• **Absolute risk:** 10%–20%[10-12,69,70] • **Management:** ▸ Risk reduction: Recommend RRSO at starting at 45–50 y[h] • **Strength of evidence of association with cancer:** Strong	**Other cancers** • Unknown or insufficient evidence
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of P/LP variants in RAD51D justifies RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		

Summary of Cancer Risk Management

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
STK11	**Absolute risk:** 32%–54%[71,72] • **Management:** ▸ Screening: Annual mammogram and breast MRI with and without contrast starting at age 30 y NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome (PJS) ▸ Risk reduction: Discuss option of RRM • **Strength of evidence of association with cancer:** Strong	**Evidence of increased risk:** No established association	**Pancreatic cancer** • **Absolute risk:** >15% • **Management:** Screening, see PANC-A • **Strength of evidence of association with cancer:** Strong **Non-Epithelial Ovarian Cancer (Sex cord with annular tubules)** • **Absolute risk:** >10%[65] • **Management:** NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - (PJS) • **Strength of evidence of association with cancer:** Strong **Other cancers** • NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - (PJS)
	Comments: Case-control studies have consistently demonstrated germline *STK11* PVs to be associated with high lifetime risks of pancreatic cancer. However, these variants are rare, and the risk estimates have wide confidence intervals.		
TP53	• **Absolute risk:** >60%[5,73,74,75] • **Management:** Li-Fraumeni Syndrome Management • **Strength of evidence of association with cancer:** Very strong[76]	**Evidence of increased risk:** No established association	**Pancreatic cancer** • **Absolute risk:** ~5%[74] • **Management:** Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A. • **Strength of evidence of association with cancer:** Limited **Other cancers**[i] • Classical LFS spectrum cancers (in addition to breast): soft tissue sarcoma, osteosarcoma, CNS tumor, ACC • Many other cancers have been associated with LFS, especially melanoma, colorectal, gastric, and prostate. • Li-Fraumeni Syndrome Management
	Comment: See Discussion for information on hypomorphic variants.		

Disclosure

- Division of Medical Genetics and Molecular Biology, Department of Internal Medicine, Faculaty of Medicine, Ramathibodi Hospital
- Thailand Medical Genetics and Genomics Association (TMGGA)
- Ramathibodi School of Nursing
- Thainakarin Hospital

MGGA สมาคมเวชพันธุศาสตร์และจีโนมิกส์ทางการแพทย์
MEDICAL GENETICS AND GENOMICS ASSOCIATION

โรงเรียนพยาบาลรามาธิบดี
คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล

โรงพยาบาล ไทยนครินทร์
THAINAKARIN HOSPITAL