Surgical Risk Reduction for Genetic Indications and High-Risk Status

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NCCN Guidelines

- Risk-reducing mastectomy should generally be considered only in individuals with:
  - a pathogenic/likely pathogenic genetic mutation (not for variants of undetermined significance) conferring a high risk for breast
  - compelling personal or family history
  - possibly with prior thoracic RT at <30 years of age.
- The value of risk-reducing mastectomy in individuals with pathogenic/likely pathogenic mutations in other genes associated with a two-fold or greater risk for breast cancer(based on large epidemiologic studies) in the absence of a compelling family history of breast cancer is unknown.
- While this approach has been previously considered for LCIS, the currently preferred approach is risk reducing endocrine agents.

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Mutation	Absolute BC Risk	RRM?
ATM	20-40%	Evidence insufficient, manage based on family history
BARD1	20-40%	Evidence insufficient, manage based on family history
BRCA1	>60%	Discuss option of RRM
BRCA2	>60%	Discuss option of RRM
BRIP1	Insufficient Data	Evidence insufficient, manage based on family history
CDH1	41-60%	Discuss option of RRM
CHEK2	20-40%	Evidence insufficient, manage based on family history
MSH2, MLH1, MSH6, PMS2, EPCAM	<15%	Evidence insufficient, manage based on family history
NF1	20-40%	Evidence insufficient, manage based on family history
PALB2	41-60%	Discuss option of RRM
PTEN (Cowden)	40-60% (historic), >60% (projected)	P/LP variant: Discuss option of RRM Clinical CS/PHTS syndrome: manage based on family history.
RAD51C, RAD51D	20-40%	Evidence insufficient, manage based on family history
STK11	32-54%	Discuss option of RRM
TP53 (Li-Fraumeni)	>60%	Discuss option of RRM

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NCCN 2022

High risk mutations

- BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, TP53

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BRCA penetrance

Table 2. Predicted Mean Cancer Risk to Currently Unaffected *BRCA1/2* Mutation Carriers

	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 34	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
60 years	—		—		—		—		9.8	7.8 to 11

NOTE. The CI is provided for the mean risk, not the risk itself.

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ASK2ME™ | All Syndromes Known to Man Evaluator

Chen 2007

Other indications

- Compelling family history
- Prior thoracic RT at <30 years of age
  - Hodgkin lymphoma treated with high dose radiation to mantle field.
  - Recently lower doses and smaller field have decreased the risk.

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Not routine indications

- LCIS and other high-risk lesions

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Benefit of Risk Reducing Mastectomy

- Reduces the risk of breast cancer by 90-95%.
  - Most data in the BRCA mutation populations.
- No improvement in mortality.

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Ludwig 2016

Options for Surgery

- Total mastectomy
- Skin sparing mastectomy
- Nipple sparing mastectomy

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Nipple Sparing Mastectomy

- 346 patients with BRCA1 or 2 mutations who underwent either bilateral risk reducing mastectomy (202) or contralateral risk reducing mastectomy (144).
- No new cancers identified with median follow up of 34 months.
- In cancer patients, recurrence rate in the nipple areolar complex after NSM is between 0-3.7%.
- Early data shows safe option however longer follow up and larger patient series would be ideal

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Jakub 2018, Galimberti 2016

Sentinel lymph node biopsy

- Can be done selectively.
- Risk of occult cancer at time of mastectomy is about 5%.
- One study of 409 patients found an increased risk of invasive cancer in postmenopausal patients (3.7%), patients age >60 years (7.5%), and patients with history of LCIS (7.7%).
- Breast MRI can help to identify breast cancer occult to mammogram and concerns on imaging can prompt sentinel lymph node biopsy.

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Boughey 2006, McLaughlin 2008

Risks of Surgery

- Bleeding, infection, numbness, prolonged fluid collections, chronic pain, skin necrosis, shoulder pain or stiffness, scarring ect
- Changes to body image and sexual relationships.

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Psychosocial and quality of life

- Most studies report a high level of satisfaction with decision to undergo risk reducing mastectomy.
- Changes in body image are variable
- Many studies report an adverse effect on sexual relationships and satisfaction.

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