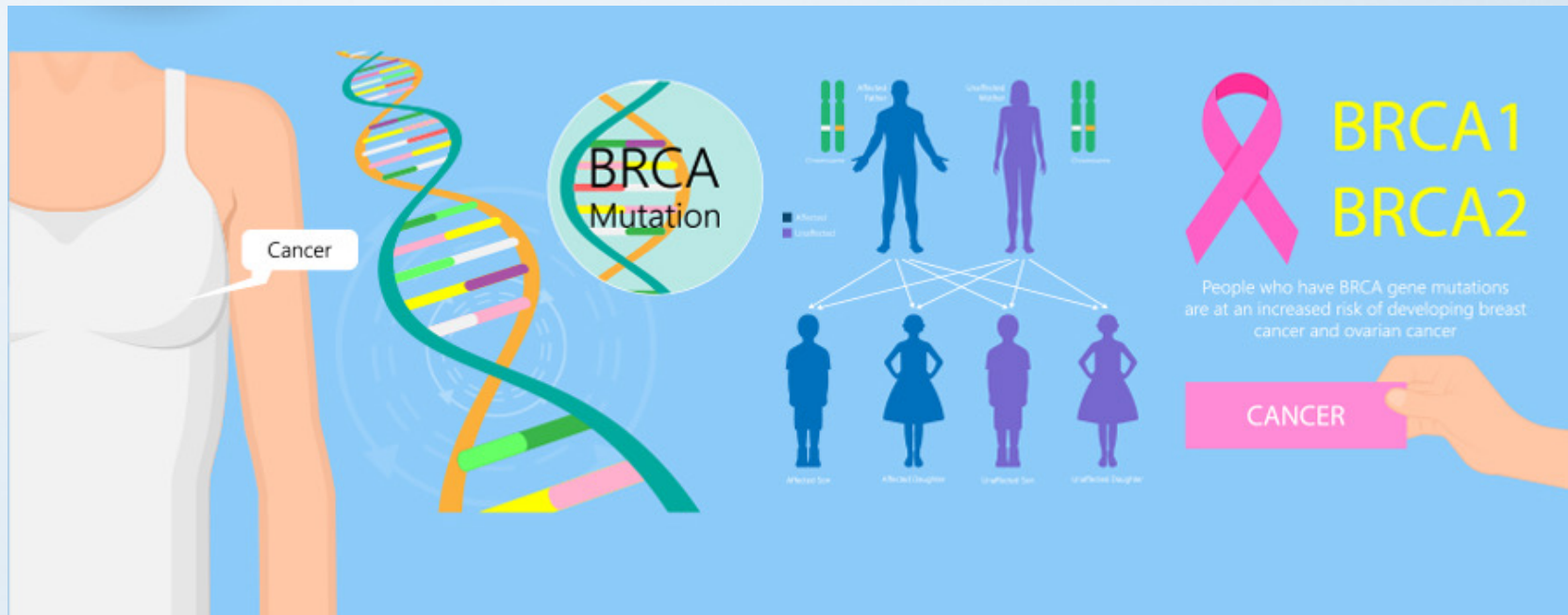


Screening For high familial risk women

Risk-Reducing Breast and Ovarian Surgery for Women at High Familial Risk



Hamda Alzarooni

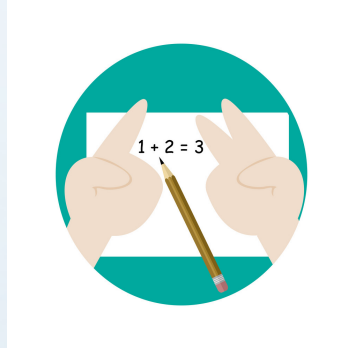
Objective:

- Identify your high risk patient
- How can we reduce the risk?
- Surveillance
 - Imaging Modalities:
 - Breast MRI
 - Mammography
 - Breast US
 - Current Screening recommendation
- Risk-Reducing Surgery
 - Risk-Reducing Mastectomy
 - Risk-Reducing Salpingo-Oophorectomy

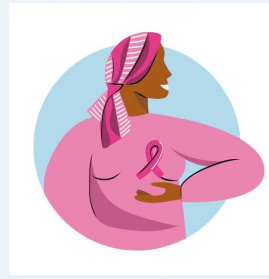
Patient
W/O
Breast
Cancer



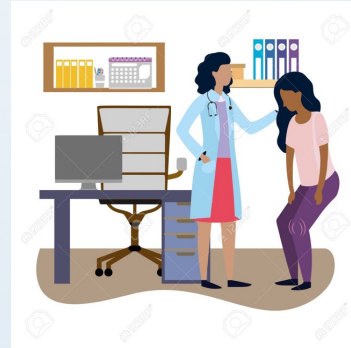
History
CBE
Risk
assessment



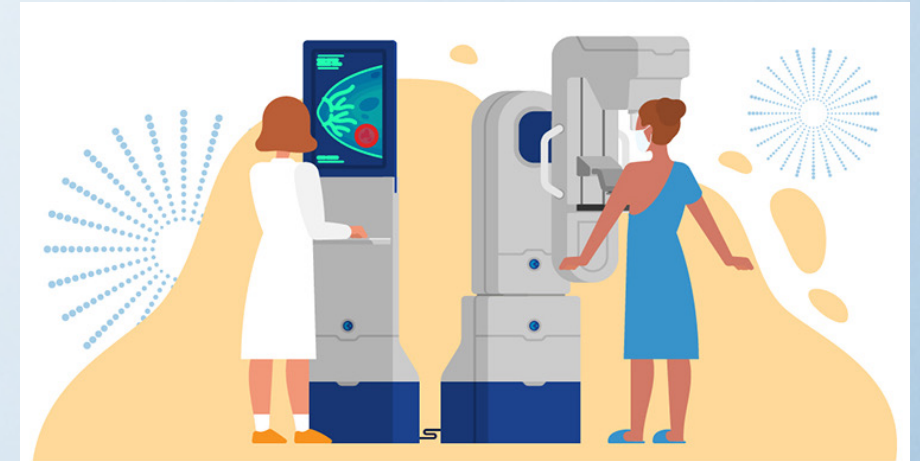
Is she a high
risk patient?



Breast cancer awareness
CBE
Genetic counselor
Psychologist
Risk reducing strategies



High risk clinic
Check your Hospital
Protocol



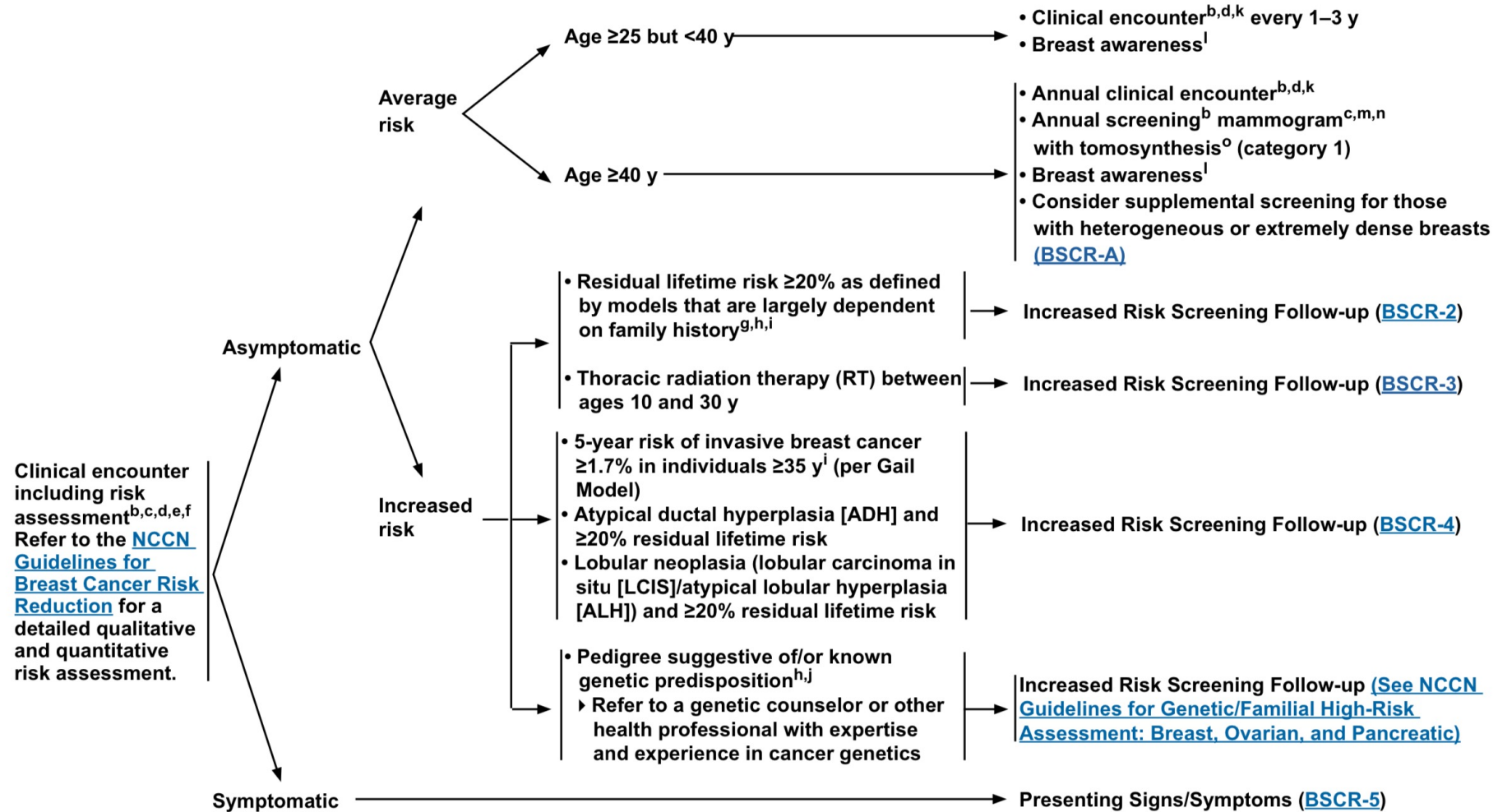
Active Surveillance

Who is at risk?

- Hereditary Breast Cancer = 7-10%
 - BRCA1 = 52%
 - BRCA2 = 32%
 - PTEN, TP53, STK11, CDH1, other... = 16%
- Greater than 30% carrier probability of BRCA1, 2 or TP53 (BOADICEA)
- Familial Breast Cancer (negative gene mutation testing)=15-20%
- Women with life time risk of IBC >20% (NICE >30%) (IBISII, BOADICEA)
- Thoracic Radiation 10 - 30 y/o

SCREENING OR SYMPTOM CATEGORY^a

SCREENING/FOLLOW-UP^b



Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

How can we reduce the risk?

- Multidisciplinary Team
 - Oncologist, Breast Surgeon, Plastic Surgeon, Psychologist, Genetic Counselor.
 - Risk assessment for patient and family.
 - Counseling on the benefit, risk and consequences of risk reducing strategies.
 - Address psychosocial and quality-of-life aspects
- Risk Reducing Strategies:
 - Surveillance
 - Chemoprevention
 - Risk-reducing surgery of the breasts, ovaries and fallopian tubes.

Surveillance

- Breast MRI
- Mammography
- Breast US



Breast MRI

- Higher sensitivity 71 – 100%
- Lower specificity compared to Mammogram
- Cant detect microcalcifications

Sensitivity of:
MRI + Mammo = 94%
MRI only= 77%
Mammo only= 39%

Annals of Internal Medicine

REVIEW

Systematic Review: Using Magnetic Resonance Imaging to Screen Women at High Risk for Breast Cancer

Ellen Warner, MD, MSc; Hans Messersmith, MPH; Petrina Causer, MD; Andrea Eisen, MD; Rene Shumak, MD; and Donald Plewes, PhD

Background: A sensitive and acceptable screening regimen for women at high risk for breast cancer is essential. Contrast-enhanced magnetic resonance imaging (MRI) of the breast is highly sensitive for diagnosis of breast cancer but has variable specificity.

Purpose: To summarize the sensitivity, specificity, likelihood ratios, and posttest probability associated with adding MRI to annual

of patient screening to large multicenter studies with repeated rounds of annual screening were identified. Characteristics of women that varied across study samples included age range, history of breast cancer, and *BRCA1* or *BRCA2* mutation status. Studies used dynamic contrast-enhanced MRI with axial or coronal plane images (European studies) or sagittal images (North American studies). The most common findings were that the addition of MRI to annual mammography increased the detection of breast cancer, but also increased the detection of false-positive findings.

Mammography, Breast Ultrasound, and Magnetic Resonance Imaging for Surveillance of Women at High Familial Risk for Breast Cancer

Christiane K. Kuhl, Simone Schrading, Claudia C. Leutner, Nuschin Morakkabati-Spitz, Eva Wardelmann, Rolf Fimmers, Walther Kuhn, and Hans H. Schild

A B S T R A C T

Purpose

To compare the effectiveness of mammography, breast ultrasound, and magnetic resonance imaging (MRI) for surveillance of women at increased familial risk for breast cancer (lifetime risk of 20% or more).

Patients and Methods

We conducted a surveillance cohort study of 529 asymptomatic women who, based on their family history and/or mutational analysis, were suspected or proven to carry a breast cancer susceptibility gene (*BRCA*). A total of 1,542 annual surveillance rounds were completed with a mean follow-up of 5.3 years. Diagnostic accuracies of the three imaging modalities used alone or in different combinations were compared.

Results

Forty-three breast cancers were identified in the total cohort (34 invasive, nine ductal carcinoma-in-situ). Overall sensitivity of diagnostic imaging was 93% (40 of 43 breast cancers); overall node-positive rate was 16%, and one interval cancer occurred (one of 43 cancers, or 2%). In the analysis by modality, sensitivity was low for mammography (33%) and ultrasound (40%) or the

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Submitted November 14, 2004; accepted August 9, 2005.

Supported by a grant from the Förderverein für Radiologie an der Universität Bonn. The High Risk Clinics at the Department of Gynecology was supported by the German Cancer Aid (Deutsche Krebshilfe).

Presented in part at the Plenary Session of the 39th Annual Meeting of the American Society of Clinical Oncology, May 31-June 3, 2003, Chicago, IL.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Asymptomatic women with high risk of breast Ca = 529

Annual MRI + US +
Mammogram
(max gap of 8 weeks)
X5 years

N of Ca= 43 in 41 pts
40 detected by imaging
MRI= 39
MRI + Mammo= 40
Mammo= 14
US= 17
2 presented with palpable
mass

Breast Cancer Awareness and CBE

- Higher proliferation rate
- The reported doubling time for carriers was 45 days compared to 84 days for non-carriers
 - (Tilanus-Linthorst MM, Krieger M, Boetes C, Hop WC, Obdeijn IM, Oosterwijk JC, et al. Hereditary breast cancer growth rates and its impact on screening policy. Eur J Cancer. 2005;41(11):1610-7)

Survival of patients with *BRCA1*-associated breast cancer diagnosed in an MRI-based surveillance program

Pål Møller · Astrid Stormorken · Christoffer Jonsrud · Marit Muri Holmen · Anne Irene Hagen · Neal Clark · Anita Vabø · Ping Sun · Steven A. Narod · Lovise Mæhle

Received: 16 April 2013 / Accepted: 17 April 2013 / Published online: 25 April 2013
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Abstract We report the 5- and 10-year survival rate of women diagnosed with breast cancer in the context of an annual MRI-based surveillance program. In 2001, as part of a national initiative, women in Norway with a *BRCA1* mutation were offered annual screening with breast MRI in addition to mammography. 802 women with a *BRCA1* mutation were screened one or more times and followed for a mean of 4.2 years. As of December 2011, 68 of 802 women in the screening program were diagnosed with DCIS or invasive breast cancer (8.5 %), including eight prevalent, 50 incident screen-detected and eight interval cancers. Two latent cancers were detected at prophylactic

mastectomy. Sixty-three of the cancers were invasive and five were in situ. The mean tumour size was 1.4 cm (range 0.2–4.5 cm), and 85 % of the patients were node-negative. Ten of the 68 patients died of cancer in the follow-up period. The 5-year breast cancer-specific survival for women with cancer was 75 % (95 % CI 56–86 %) and the 10-year survival was 69 % (95 % CI: 48–83 %). The 5-year survival for women with Stage 1 breast cancer was 82 % compared to 98 % in the population. The 5- and 10-year survival of women with a *BRCA1*-associated breast cancer detected in a national MRI-based screening program in *BRCA1* mutation carriers Norway was less than anticipated. The benefit of annual MRI surveillance on reducing

BRCA1 carrier= 802

Annual MRI + Mammo
10 years Follow up

68 BC diagnosed
8 interval Ca

10 year survival rate:
<1cm tumor = 93%
1-2cm tumor = 58%
>2cm tumor= 23%

Mammography:

- Low sensitivity, high specificity
- Sensitivity varies depends on breast density, age, tumor pathology 30 – 98%
- Rate of interval cancer 29 – 50%
- Digital mammography > screen-film mammography in <50 y/o
- Digital Breast Tomosynthesis + Digital mammography:
 - Improves cancer detection
 - Reduces false-positive call-back rates
 - Double radiation exposure, but does not exceed dose limit approved by FDA

Research

Original Investigation

Breast Cancer Screening Using Tomosynthesis in Combination With Digital Mammography

Sarah M. Friedewald, MD; Elizabeth A. Rafferty, MD; Stephen L. Rose, MD; Melissa A. Durand, MD; Donna M. Plecha, MD; Julianne S. Greenberg, MD; Mary K. Hayes, MD; Debra S. Copit, MD; Kara L. Carlson, MD; Thomas M. Cink, MD; Lora D. Barke, DO; Linda N. Greer, MD; Dave P. Miller, MS; Emily F. Conant, MD

IMPORTANCE Mammography plays a key role in early breast cancer detection. Single-institution studies have shown that adding tomosynthesis to mammography increases cancer detection and reduces false-positive results.

OBJECTIVE To determine if mammography combined with tomosynthesis is associated with better performance of breast screening programs in the United States.

DESIGN, SETTING, AND PARTICIPANTS Retrospective analysis of screening performance metrics from 13 academic and nonacademic breast centers using mixed models adjusting for site as a random effect.

EXPOSURES Period 1: digital mammography screening examinations 1 year before tomosynthesis implementation (start dates ranged from March 2010 to October 2011 through the date of tomosynthesis implementation); period 2: digital mammography plus tomosynthesis examinations from initiation of tomosynthesis screening (March 2011 to October 2012) through December 31, 2012.

MAIN OUTCOMES AND MEASURES Recall rate for additional imaging, cancer detection rate, and positive predictive values for recall and for biopsy.

RESULTS A total of 454 850 examinations (n=281 187 digital mammography; n=173 663 digital mammography + tomosynthesis) were evaluated. With digital mammography, 29 726 patients were recalled and 5056 biopsies resulted in cancer diagnosis in 1207 patients (n=815 invasive; n=392 in situ). With digital mammography + tomosynthesis, 15 541 patients were

← Editorial page 2488

+ Author Video Interview at jama.com

Normal risk population
454,850 examination

Digital Mammo= 281,187
Digital Mammo + Tomo=
173,663

Digital Mammo
Recall= 29,726
Biopsy= 5,056
Cancer= 1,207

Digital Mammo + Tomo
Recall= 15,541
Biopsy= 3,285
Cancer= 950

Breast US:

- Good adjunct to MRI and Mammography
- Not a good screening modality
 - Operator dependent
 - Time consuming
 - Risk of not scanning the whole breast
 - Limited field view
 - High false positive



- Automated Breast US (ABUS): not operator dependent, takes 15 minutes, provide reconstructed coronal slices.

Screening in pregnancy and lactation

- Pregnancy:
 - Mammography – recommended at routine interval. Lower sensitivity and specificity.
 - MRI contrast, Not recommended due to gadolinium toxicity risk
 - US alone - not recommended
- Lactation:
 - Mammography – recommended at routine interval. To be done 3 months after stopping lactation
 - MRI – Recommended. Difficult interpretation due to high vascularity.
 - US alone - not recommended

MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING PREGNANCY

Condition	Recommendation				Rationale for Recommendation/Other Considerations
	CBE	Mammogram with Tomosynthesis ^b	Ultrasound	MRI	
Average Risk Screening in Individuals ≥40 Years	R	R	NR ^c	NR	<ul style="list-style-type: none"> • There is no contraindication to screening mammography during pregnancy. • While ionizing radiation exposure with mammography is many-fold below the threshold of fetal teratogenesis (see comments below), due to the infrequency of pregnancy-associated breast cancers (PABC) and the decreased sensitivity and specificity of mammography during pregnancy, providers and patients may implement a short delay in routine breast imaging based on prior imaging and date of delivery in individuals who are at average risk until after pregnancy. • There are no data evaluating the use of ultrasound alone as an alternative screening method in individuals who are at average risk during pregnancy; therefore, this is not recommended as an alternative to screening mammography.
Increased Risk Screening <ul style="list-style-type: none"> • Individuals with a genetic mutation, or a first-degree relative of gene mutation carrier who remains untested • Individuals who received thoracic RT between ages 10 and 30 years • Individuals with a residual lifetime risk ≥20% as defined by models that are largely dependent on family history^a • Individuals with ADH or lobular neoplasia (LCIS/ ALH) and ≥20% residual lifetime risk. 	R	R	O	NR	<ul style="list-style-type: none"> • In individuals who are at increased risk for breast cancer, it is appropriate to recommend screening mammography at routine intervals (see BSCR-2 and BSCR-3). • The use of screening ultrasound alone has not been evaluated as a method to reduce breast cancer mortality in individuals who are at increased risk for breast cancer and pregnant. • Contrast-enhanced breast MRI is not recommended during pregnancy due to the trans-placental passage of gadolinium, and potential concerns of exposure of gadolinium to the fetus. Non-contrast MRI is not recommended due to lack of sensitivity.

R = Recommended, NR = Not recommended, O = Optional, depending on individual circumstances.

^a There are significant limitations in interpretation of PRS. PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including diverse populations.

^b Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

^c Consider supplemental screening for those with heterogeneous or extremely dense breasts.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MANAGEMENT OF BREAST CANCER SCREENING AND BREAST SYMPTOMS DURING LACTATION

Condition	Recommendation				Rationale for Recommendation/Other Considerations
	CBE	Mammogram with Tomosynthesis ^b	Ultrasound	MRI	
Average Risk Screening in Individuals ≥40 Years	R	R	NR ^c	NR	<ul style="list-style-type: none"> While there is both decreased sensitivity and specificity of screening mammography during lactation, there is no contraindication to screening mammography during lactation. A short delay in routine breast imaging may be implemented until after lactation, in those with average risk of getting breast cancer based on prior imaging results particularly if they are not planning prolonged breastfeeding It is recommended to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination
Increased Risk <ul style="list-style-type: none"> Individuals with a genetic mutation, or a first-degree relative of gene mutation carrier who remains untested Individuals who received thoracic RT between ages 10 and 30 years Individuals with a residual lifetime risk ≥20% as defined by models that are largely dependent on family history.^a Individuals with ADH or lobular neoplasia (LCIS/ ALH) and ≥20% residual lifetime risk. 	R	R	NR	R	<ul style="list-style-type: none"> In individuals who are at increased risk for breast cancer, it is appropriate to recommend screening mammography at routine intervals (see BSCR-2 and BSCR-3). The use of screening ultrasound alone has not been evaluated as a method to reduce breast cancer mortality in individuals who are at increased risk for breast cancer and lactating. In individuals who are at increased risk for breast cancer, it is appropriate to recommend screening breast MRI at routine intervals (see BSCR-2 and BSCR-3). <ul style="list-style-type: none"> There is minimal excretion of gadolinium into human breast milk, with less than 1% of permitted neonatal dose of contrast over the first 24 hours after maternal administration. Breast MRI appears to be highly sensitive for the detection of known PABC and may proceed if due during lactation in individuals who are at increased risk for breast cancer. It is recommended to either pump the milk or breastfeed just prior to imaging to improve sensitivity and comfort of the examination.

R = Recommended, NR = Not recommended.

^a There are significant limitations in interpretation of PRS. PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including diverse populations.

^b Tomosynthesis can decrease call back rates and improve cancer detection compared with 2D mammography alone.

^c Consider supplemental screening for those with heterogeneous or extremely dense breasts.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Screening recommendation

- Life time risk >20%:
 - Annual mammogram with Tomosynthesis
 - Start 10 years before first relative diagnosed (not before 30), or begin at 40 years
 - Annual breast MRI with contrast
 - Start 10 years before first relative diagnosed (not before 25), or begin at 40 years
- BRCA carrier:
 - Annual mammogram with Tomosynthesis
 - Start age 30 (40 NICE)
 - Annual breast MRI with contrast
 - Start age 25
- Can stop high risk screening by the age of 75 (70 NICE)

NICE guidelines

equivalent risks

This group of women at very high genetic risk of developing breast cancer includes:

- BRCA1 carriers
- BRCA2 carriers
- risk equivalent to BRCA carriers not tested [\[footnote 1\]](#), but have a first degree relative who has a BRCA1 or BRCA2 genetic mutation
- women who have a mutation in another high-risk gene including [\[footnote 2\]](#):
 - PALB2
 - PTEN
 - STK11
 - CDH1 (E-Cadherin)

Age	Test	Frequency of testing
25 to 29 (see note)	Magnetic resonance imaging (MRI)	Annual
30 to 39	MRI	Annual
40 to 50	MRI and mammography	Annual
51 to under 71	Mammography with or without MRI (based on review of background density from 50 years)	Annual

- <https://www.gov.uk/government/publications/breast-screening-higher-risk-women-surveillance-protocols/tests-and-frequency-of-testing-for-women-at-very-high-risk--2>

Risk Reducing Surgery

- Risk Reducing Mastectomy (RRM)
- Risk-Reducing Salpingo-Oophorectomy (RRSPO)

Risk Reduction Mastectomy (RRM)

- Risk-reducing mastectomy can be considered in:
 - BRCA mutation carrier or women having other susceptibility genes.
 - Women who had Chest radiation therapy <30 years.
 - Women with strong family history without genetic mutation
 - Women with histological risk factor; extensive atypical ductal hyperplasia (ADH) and lobular carcinoma in situ (LCIS)



RISK-REDUCING INTERVENTION

Risk-reducing surgery

- Risk-reducing mastectomy desired^{bb}

→ [See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#)

^{bb} Risk-reducing mastectomy should generally be considered only in individuals with a pathogenic/likely pathogenic genetic mutation (not variants of undetermined significance) conferring a high risk for breast cancer ([See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#)), compelling family history, or 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 2-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 a risk-reducing endocrine agent.

^{bb} Risk-reducing mastectomy should generally be considered only in individuals with a pathogenic/likely pathogenic genetic mutation (not variants of undetermined significance) conferring a high risk for breast cancer ([See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#)), compelling family history, or 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 2-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 a risk-reducing endocrine agent.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

RRM:

- RRM reduces breast cancer incidence = >90%
- Women who choose risk-reducing surgery= 18–51%
- 35 – 40 years old / 10 years before the first relative diagnosed with breast cancer.
- Unanticipated breast malignancies have been found in 5–10% of breast specimens from RRM. MRI recommend within 3 months from surgery
- Risk of recurrent breast cancer in the Ipsilateral and contralateral breast in BRCA gene mutation patients is higher compared to general population.

RRM– *BRAN*:

- Benefit
 - Reduce risk of breast cancer >90%
- Risk
 - Surgery related complications
 - Psychological impact
- Alternative
 - Chemoprevention 60%
- Do Nothing
 - Surveillance

Prospective multicenter Cohort study - JAMA 2010

ORIGINAL CONTRIBUTION

Association of Risk-Reducing Surgery in *BRCA1* or *BRCA2* Mutation Carriers With Cancer Risk and Mortality

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Wendy S. Rubinstein, MD, PhD

Context Mastectomy and salpingo-oophorectomy are widely used by carriers of *BRCA1* or *BRCA2* mutations to reduce their risks of breast and ovarian cancer.

Objective To estimate risk and mortality reduction stratified by mutation and prior cancer status.

Design, Setting, and Participants Prospective, multicenter cohort study of 2482 women with *BRCA1* or *BRCA2* mutations ascertained between 1974 and 2008. The study was conducted at 22 clinical and research genetics centers in Europe and North America to assess the relationship of risk-reducing mastectomy or salpingo-oophorectomy with cancer outcomes. The women were followed up until the end of 2009.

Main Outcomes Measures Breast and ovarian cancer risk, cancer-specific mortality, and overall mortality.

Results No breast cancers were diagnosed in the 247 women with risk-reducing mastectomy compared with 98 women of 1372 diagnosed with breast cancer who did not have risk-reducing mastectomy. Compared with women who did not undergo risk-reducing salpingo-oophorectomy, women who underwent salpingo-oophorectomy had a lower risk of ovarian cancer, including those with prior breast cancer (6% vs 1%, respectively; hazard ratio [HR], 0.14; 95% confidence interval [CI], 0.04-0.59) and those without prior breast cancer (6% vs 2%; HR, 0.28 [95% CI, 0.12-0.69]), and a lower risk of first diagnosis of breast cancer in *BRCA1* mutation carriers (20% vs 14%; HR, 0.63 [95% CI, 0.41-0.96]) and *BRCA2* mutation carriers (23% vs 7%; HR, 0.36 [95% CI, 0.16-0.82]) compared with women who did not undergo risk-reducing sal-

Women w/ *BRCA1* and *BRCA2* mutation= 2482

Breast Cancer

RRM= 0

No RRM= 7%

RRSO= 14% (*BRCA1*), 7% (*BRCA2*)

No RRSO= 20% (*BRCA1*), 23% (*BRCA2*)

Ovarian cancer

RRSO

History of BC= 1%

No History of BC= 2%

No RRSO= 6%

All-cause Mortality

RRSO= 3%

No RRSO= 10%

Contralateral RRM

- The Society of Surgical Oncology in 2007 suggested the following three potential indications for CRRM: risk reduction, problems in surveillance due to dense breasts and symmetry issues
- The effect of contralateral surgery is complex as the biology and stage of the ipsilateral cancer will have a strong impact on prognosis.
- CRRM is associated with a decreased metachronous breast cancer incidence but not improved survival among patients with elevated familial/genetic risk.
 - (Fayanju, O. M., Stoll, C. R., Fowler, S., Colditz, G. A., & Margenthaler, J. A. (2014). Contralateral prophylactic mastectomy after unilateral breast cancer: a systematic review and meta-analysis. *Annals of surgery*, 260(6), 1000–1010)



RESEARCH

Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis



OPEN ACCESS

Kelly Metcalfe *professor¹ adjunct scientist²*, Shelley Gershman *registered nurse^{1,2}*, Parviz Ghadirian *professor³*, Henry T Lynch *professor⁴*, Carrie Snyder *registered nurse⁴*, Nadine Tung *associate professor⁵*, Charmaine Kim-Sing *professor⁶*, Andrea Eisen *medical oncologist⁷*, William D Foulkes *professor⁸*, Barry Rosen *associate professor⁹*, Ping Sun *statistician²*, Steven A Narod *professor²*

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Women w/ BRCA1 and BRCA2 mutation + stage 1 or 2 BC= 390

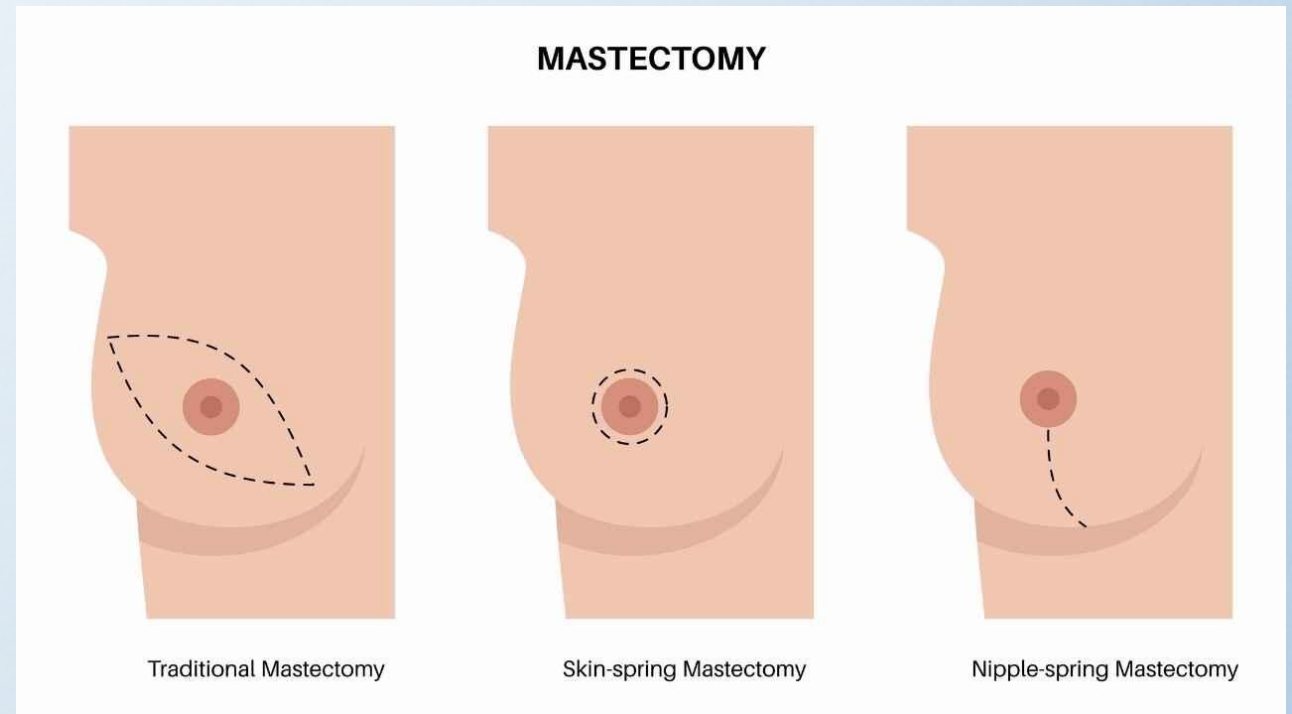
Bilateral Mastectomy= 181
Unilateral Mastectomy= 209

Survival rate at 20 years
Bilateral Mastectomy= 88%
Unilateral Mastectomy= 66%

After adjusted analysis,
association was not significant

Surgical Options of RRM:

- Simple Mastectomy
- Skin Sparing Mastectomy
- Nipple Sparing Mastectomy



Nipple Sparing Mastectomy (NSM):

- Patient selection criteria for NSM:
 - Early stage IBC
 - DCIS <5cm
 - Tumor located >2cm away from the NAC
 - Tumor biology: Luminal, HER2 negative
 - No lymphovascular invasion
 - No evidence of Multifocal or Multicentric disease

Retrospective Cohort - JAMA 2018

Research

JAMA Surgery | **Original Investigation**

Oncologic Safety of Prophylactic Nipple-Sparing Mastectomy in a Population With *BRCA* Mutations

A Multi-institutional Study

James W. Jakub, MD; Anne Warren Peled, MD; Richard J. Gray, MD; Rachel A. Greenup, MD; John V. Kiluk, MD; Virgilio Sacchini, MD; Sarah A. McLaughlin, MD; Julia C. Tchou, MD, PhD; Robert A. Vierkant, MS; Amy C. Degnim, MD; Shawna Willey, MD

IMPORTANCE Nipple-sparing mastectomy (NSM) offers superior cosmetic outcomes and has been gaining wide acceptance; however, its role among patients with *BRCA* mutations remains controversial.

OBJECTIVE To report on the oncologic safety of NSM and provide evidence-based data to patients and health care professionals regarding preservation of the nipple-areolar complex during a risk-reducing mastectomy in a population with *BRCA* mutations.

DESIGN, SETTING, AND PARTICIPANTS We retrospectively reviewed the outcomes of 9 institutions' experience with prophylactic NSM from 1968 to 2013 in a cohort of patients with *BRCA* mutations. Patients with breast cancer were included if they underwent contralateral risk-reducing mastectomy; however, only the prophylactic side was considered in the analysis. Patients found to have an occult primary breast cancer at the time of risk-reducing mastectomy, those having variant(s) of unknown significance, and those undergoing free nipple grafts were excluded.

MAIN OUTCOMES AND MEASURES The primary outcome measure was development of a new breast cancer after risk-reducing NSM. Three reference data sources were used to model the expected number of events, and this was compared with our observed number of events.

[← Invited Commentary page 129](#)

Women w/ BRCA1 and BRCA2
mutation + prophylactic NSM=
346

Breast cancer incident= 0 in 4.6
years follow up

TABLE 3. CHARACTERISTICS OF THE 639 MODERATE-RISK AND HIGH-RISK WOMEN WHO UNDERWENT BILATERAL PROPHYLACTIC MASTECTOMY.

CHARACTERISTIC	MODERATE RISK (N=425)	HIGH RISK (N=214)
Age at mastectomy (yr)		
Median	42	42
Range	18–79	20–75
Age at menarche (yr)		
Median	13	13
Range	7–17	9–17
Nulliparous (%)	12	13
Age at first live birth (yr)		
Median	21	21
Range	15–43	15–41
Mean no. of breast biopsies before mastectomy	2.4	1.9
Type of mastectomy (%)		
Subcutaneous	90	89
Total	10	11

TABLE 4. CHARACTERISTICS OF SEVEN WOMEN WITH BREAST CANCER AFTER BILATERAL PROPHYLACTIC SUBCUTANEOUS MASTECTOMY.

PATIENT No.	LOCATION	YEARS AFTER MASTECTOMY	FAMILY HISTORY
1	Left breast	15	Moderate risk
2	Chest wall	2	Moderate risk
3	Left breast, “above areola”	5	Moderate risk
4	Chest wall	25	Moderate risk
5	Bone marrow	12	High risk
6	Left lateral side of chest wall	3	High risk
7	Left nipple	6	High risk

*14 years follow up

Hartmann, L. C., Schaid, D. J., Woods, J. E., Crotty, T. P., Myers, J. L., Arnold, P. G., Petty, P. M., Sellers, T. A., Johnson, J. L., McDonnell, S. K., Frost, M. H., & Jenkins, R. B. (1999). Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *The New England journal of medicine*, 340(2), 77–84. <https://doi.org/10.1056/NEJM199901143400201>

Techniques in NAC- Sparing Mastectomy

- Ensure complete clearance of ductal tissue by dissecting the breast tissue from the NAC at the dermal level.
- NAC Blood supply. Major source of blood supply is from the second perforator branch from the internal mammary artery.
- Frozen section of the nipple can be considered in selected cases.
- Discuss option of Skin sparing mastectomy with patient in case frozen section is positive for malignancy.

Breast Reconstruction:

- Autologous reconstruction
 - More stable aesthetic result, softer breast mound.
 - Less complications in patients with previous chest radiation.
 - Extensive surgery. Increased operative times. involved microsurgical techniques and potential for surgical morbidity at two separate sites.
 - Options:
 - TRAM Flap
 - Double DIEP (for bilateral mastectomy)
 - LD Flap (w or w/o implant)
 - Perforator flaps from from superior/inferior gluteal artery region

Breast Reconstruction in High Risk Patients

- Implant based breast reconstruction
 - Less morbid surgery.
 - Implant loss rate 10-15% within 1 year.
 - Options:
 - Permanent implants
 - Expander followed by implant
- Smoking, high body mass index and preoperative irradiation are well-known predictors of complications

Role of SLNB in RRM

- Current recommendation that SLN biopsy is not indicated in patients undergoing RRM.

Bilateral Risk-Reducing Salpingo-Oophorectomy

- Recommended by the age of 35 – 40, or individualized based on age of onset of ovarian cancer in the family
- Reduces the risk of Ovarian cancer by 80%
- Decreases the risk of IBC in BRCA1 by 56% and 46% in BRCA2. Greater risk reduction if BSO performed <40 years.
 - (Breast Cancer Risk Following Bilateral Oophorectomy in BRCA1 and BRCA2 Mutation Carriers: An International Case-Control Study, J Clin Oncol, 2005)
 - Complications: Premature Menopause, cardiovascular disease, osteopenia, osteoporosis, and non-cancer mortality when it was performed before the age of 45 years and without HRT.

Can I take HRT after BPO?

VOLUME 23 · NUMBER 31 · NOVEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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Submitted January 10, 2005; accepted August 3, 2005.

Supported by grants from the Public Health Service (R01-CA83855 to T.R.R.; CA74415 to S.L.N.), the University of Pennsylvania Cancer Center (to T.R.R.

Effect of Short-Term Hormone Replacement Therapy on Breast Cancer Risk Reduction After Bilateral Prophylactic Oophorectomy in *BRCA1* and *BRCA2* Mutation Carriers: The PROSE Study Group

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A B S T R A C T

Purpose

Bilateral prophylactic oophorectomy (BPO) is widely used for cancer risk reduction in women with *BRCA1/2* mutations. Many premenopausal women choose to take hormone replacement therapy (HRT) after undergoing BPO to abrogate immediate symptoms of surgically-induced menopause. Thus, we evaluated whether the breast cancer risk reduction conferred by BPO in *BRCA1/2* mutation carriers is altered by use of post-BPO HRT.

Methods

We identified a prospective cohort of 462 women with disease-associated germline *BRCA1/2* mutations at 13 medical centers to evaluate breast cancer risk after BPO with and without HRT. We determined the incidence of breast cancer in 155 women who had

BRCA1,2 =
462

RRSO =
155

No RRSO =
286

Risk of IBC
(HR)

+HRT =
0.37

No HRT =
0.38

No HRT = 1

Bilateral Salpingectomy with ovarian retention (BSOR)

- TP53 mutations seen in the ovaries cancer match the specific mutations seen in the precursor lesions found in the fallopian tubes; this suggests a clonal origin.
- Serous tubal intraepithelial carcinomas (STICs) and early invasive tubal carcinomas in 50% to 60% of women with sporadic ovarian cancer
- STICs Found in 10% to 15% of the fallopian tubes examined from women with BRCA1/2 mutations who undergo RRSO
 - (Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: evidence for a causal relationship. Am J Surg Pathol. 2007; 31: 161-169.)
 - (Bowtell DDL. The genesis and evolution of high-grade serous ovarian cancer. Nat Rev Cancer. 2010; 10: 803-808)
- There are no actual data on risk reduction for ovarian cancer by salpingectomy, and there are clear data that RRSO reduces the risk of both breast and ovarian cancer and improves survival in women with BRCA1 and BRCA2 mutations.

Thank you