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Genetic Counselling and Risk Assessment Management of High Risk Patients

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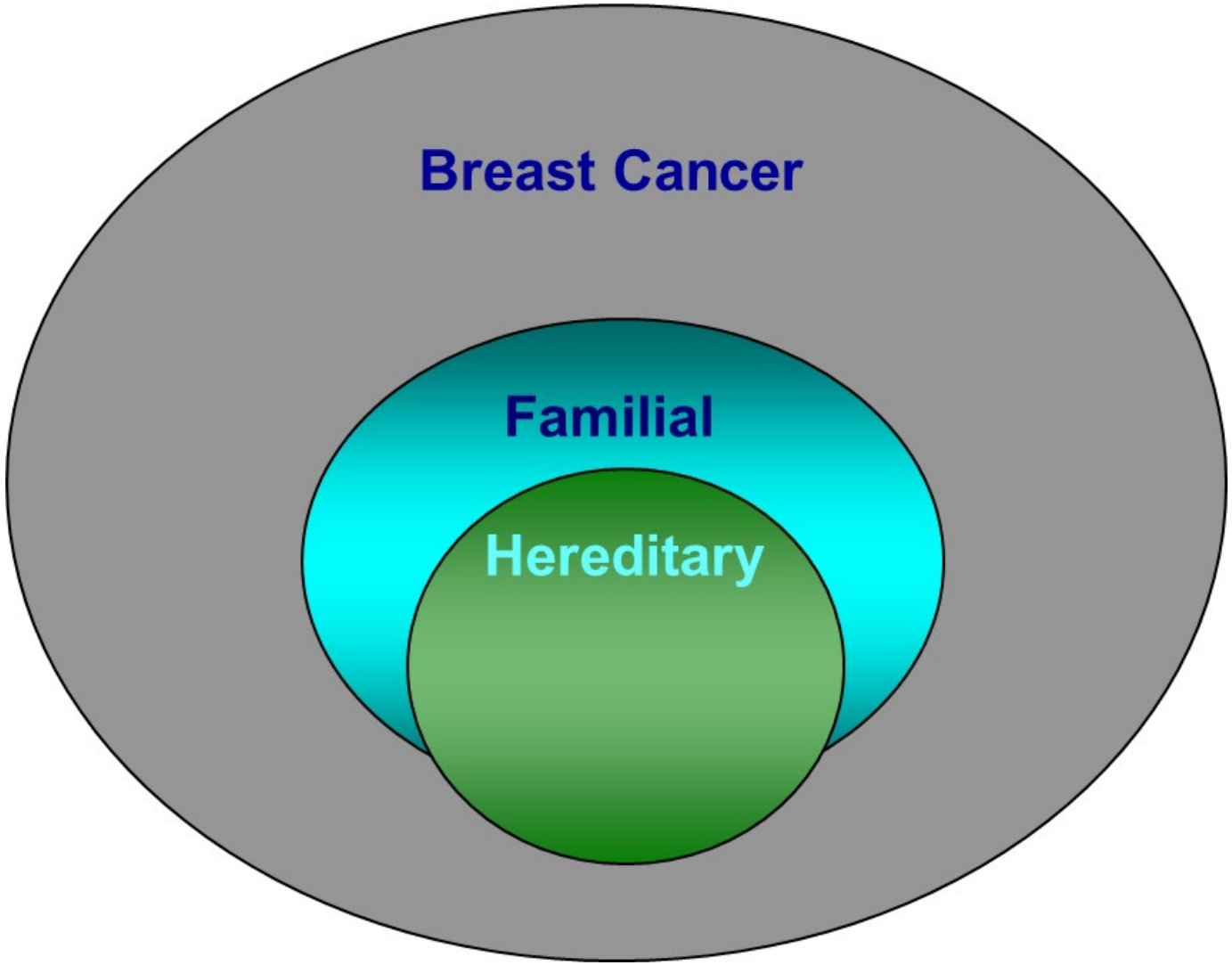
Conflict of Interest Disclosure

No financial relationships to disclose

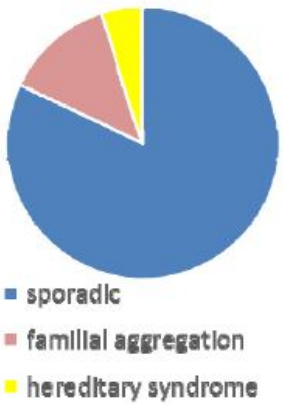
Comunicating risk – a difficult task

Numeracy includes minimal statistical literacy

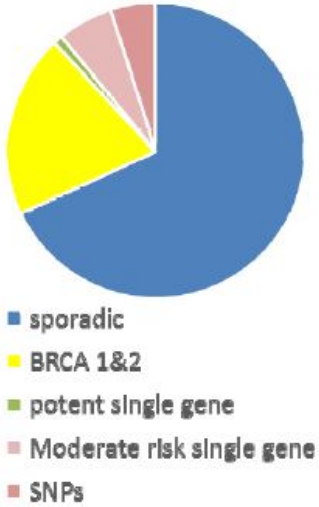
Health numeracy is a person's ability to access, interpret, and use numeric information to make health decisions.


Breast Cancer
Familial
Hereditary

Genetic Aetiology of Breast/Ovarian Cancer



1984

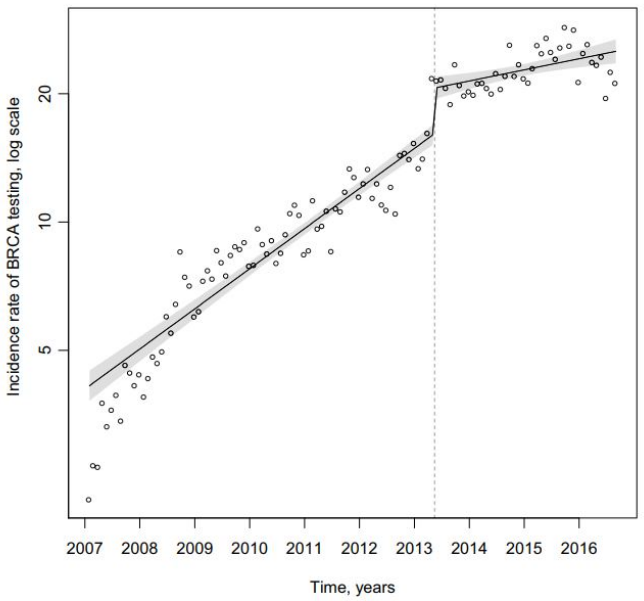


2007

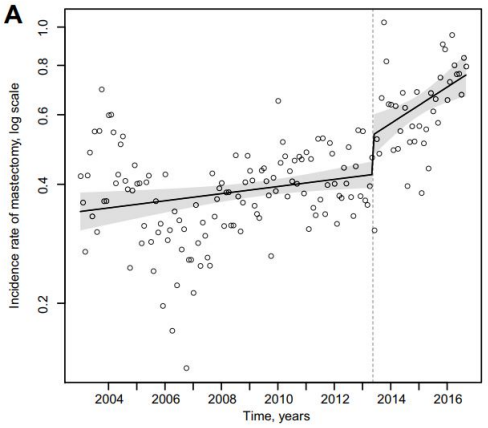
2014

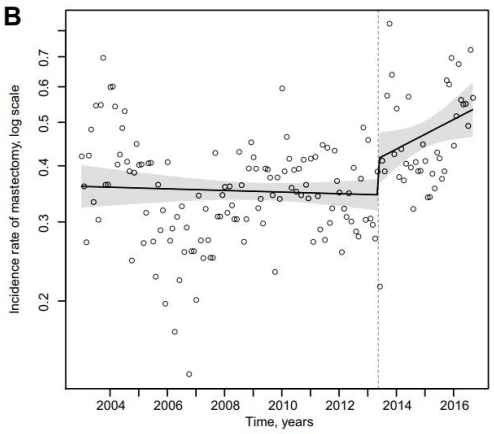
Lynda Wyld's courtesy

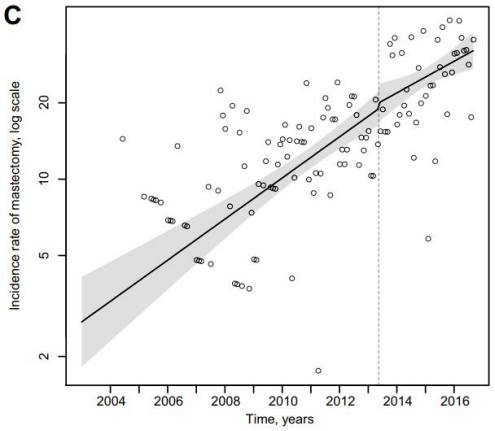
Overall, the **Angelina Jolie Effect** represents a long-lasting impact of a celebrity on public health awareness with significant increases in genetic testing and mastectomy rates



Time, years







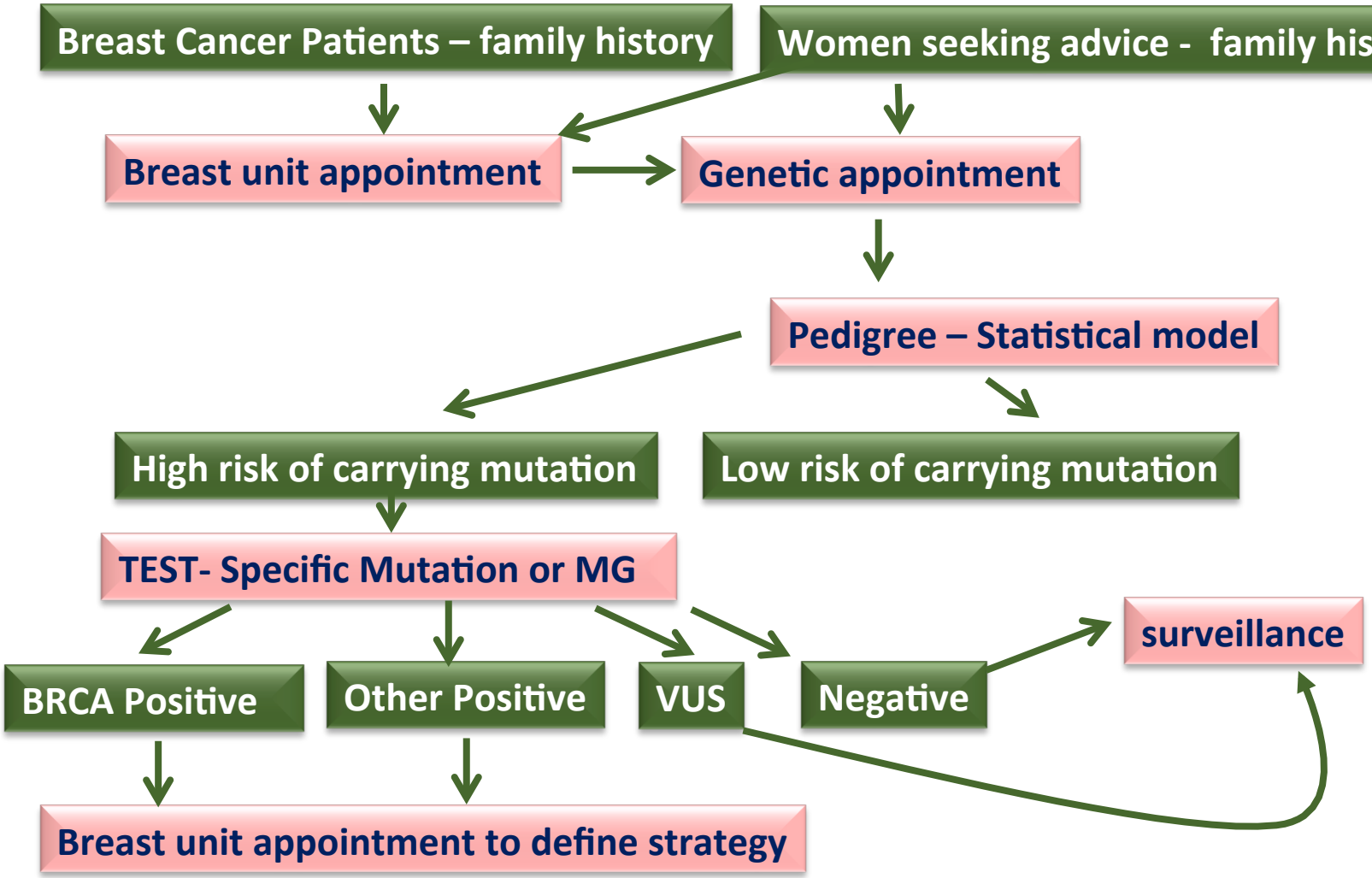
Criteria for genetic risk evaluation

Without a personal history of cancer
Known mutation in the family
A first degree relative with breast cancer < 45 years old
Two or more relatives with breast cancer at the same side of the family and at least one < 45 years old
Two or more breast cancer primaries in a first degree relative at any age
A first or second degree relative with ovarian cancer at any age
Male breast cancer at any age
Family history of 3 or more of the following: breast,pancreatic, prostate (Gleason score ≥7 or metastatic), melanoma, sarcoma, adrenocortical carcinoma, brain tumours, leukemia, diffuse gastric cancer, colon, endometrial, thyroid, kidney, dermatologic alterations and/or macrocephaly, hamartomatous polyps of GI tract

Criteria for genetic risk evaluation

Breast Cancer diagnosis with any of the following
Known mutation in the family
Breast cancer diagnosed before 35 years old
Triple negative breast cancer before 50 years old
Two breast cancer primaries
Breast cancer at any age and more than 1 first or second degree relatives with breast cancer < 50 years old and 1 or more first or second degree relatives with ovarian cancer at any age
Two or more first or second degree relatives with breast, prostate (Gleason score ≥7 or metastatic) and pancreatic cancer at any age
Personal history of pancreatic cancer at any age
Ashkenazi Jewish descent with breast, ovarian or pancreatic cancer at any age
Male breast cancer
An individual wit a personal or family history of 3 or more of the following (especially if diagnosed at or before 50 years) breast, pancreatic, prostate (Gleason score ≥7 or metastatic), melanoma, sarcoma, adrenocortical carcinoma, brain tumours, leukemia, diffuse gastric cancer, colon, endometrial, thyroid, kidney, dermatologic alterations and/or macrocephaly, hamartomatous polyps of GI tract

RISK PATHWAY



WHICH TEST

- Clear suggestion of specific syndrome – Teste Specific Gene
- No suggestion other than age, family aggregation without a clear direction – MGP

✓HIGH RISK GENE ≥ 50% or greater lifetime risk of breast cancer

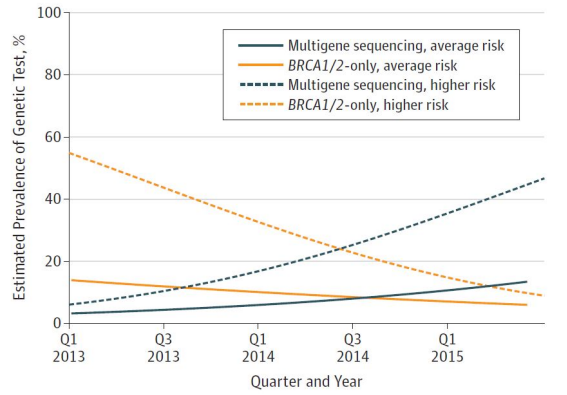
✓MODERATE RISK GENE 20-49% lifetime risk of breast cancer

Uptake, Results, and Outcomes of Germline Multiple-Gene Sequencing After Diagnosis of Breast Cancer

Allison W Kurian, Kevin C Ward, Ann S Hamilton, Dennis M Deapen, Paul Abrahamse, Irina Bondarenko, Yun Li, Sarah T Hawley, Monica Morrow, Reshma Jagsi, Steven J Katz

JAMA Oncology 2018 May 10

Figure. Trends in Genetic Test Type



BRCA1 and *BRCA2* (*BRCA1/2*)-only vs multiple-gene sequencing for 5026 patients with complete information on all variables. Blue lines represent

Key Points

Question What are the results and outcomes of more comprehensive genetic sequencing after diagnosis of breast cancer?

Findings In this population-based study, multiple-gene sequencing markedly replaced *BRCA1*- and *BRCA2*-only tests and enabled 2-fold higher detection of clinically relevant pathogenic variants without an associated increase in prophylactic mastectomy. Multiple-gene sequencing was more often delayed postsurgery and yielded much higher rates of variants of uncertain significance, particularly in racial/ethnic minorities.

Meaning Multiple-gene sequencing rapidly replaced more limited testing and enabled 2-fold higher detection of clinically relevant findings, but important targets for improvement include postsurgical delay and racial/ethnic disparity in variants of uncertain significance.

Table 3. Impact of Test Results on Prophylactic Mastectomy Outcomes

Genetic Test Result	Patient Strongly Considered Prophylactic Mastectomy[a]	Surgeon Recommended Prophylactic Mastectomy[a]	Patient Received Prophylactic Mastectomy[a]
BRCA1/2 pathogenic variant (n = 64)	80.3	51.4	79.0
Other pathogenic variant[b] (n = 24)	39.8	10.3	37.6
VUS only (n = 198)	38.8	14.4	30.2
Negative (n = 1030)	43.7	14.1	35.3

Abbreviation: VUS, variant of unknown significance.

[a] Weighted percent consideration, recommendation, and receipt of prophylactic mastectomy: all $P < .001$.

[b] The other genes in which patients had pathogenic variants were *APC* (2), *ATM* (3), *BARD1* (1), *BRIP1* (2), *CHEK2* (4), *MLH1* (1), *MSH6* (1), *NBN* (1), *NF1* (1), *PALB2* (3), *PMS2* (2), *RAD50* (1), *RAD51C* (2), and *RAD51D* (1). The total number of pathogenic variants is 25 because 1 patient had 2 pathogenic variants.

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v103–v110, 2016
doi:10.1093/annonc/mdw327

Prevention and screening in *BRCA* mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening†

S. Paluch-Shimon[1], F. Cardoso[2], C. Sessa[3], J. Balmana[4], M. J. Cardoso[2], F. Gilbert[5] & E. Senkus[6], on behalf of the ESMO Guidelines Committee*

Also

- NCCN Guidelines
- NICE Guidelines

FACTS

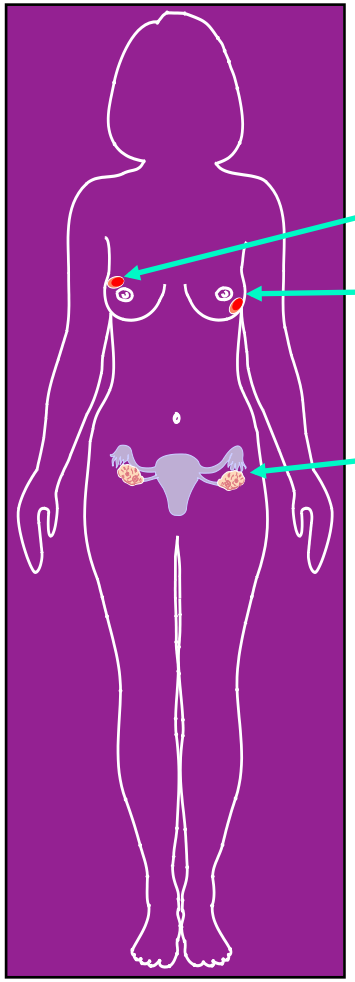
- **Lifetime estimates of Breast Cancer risk in BRCA carriers vary from 36-90%**
- **BRCA mutation status has definite associations with breast cancer subtype (BRCA1 70-90% triple negative and BRCA2 80% ER positive)**
- **BRCA 2 associated cancers occur usually later than BRCA1 cancers**
- **All events and outcomes in other breast cancer–related genes, such as p53, ATM, CHEK2, PALB2, and PTEN are poorly documented because of the paucity of data.**

Gene	Breast Cancer	Other Cancers	Lifetime BC Risk In carriers
BRCA1	HBOC syndrome	Breast, ovarian, primary peritoneal malignancies	50-85%
BRCA2	HBOC syndrome	Breast, ovarian, pancreatic, melanoma, prostate,	50-85%
PALB2	Familial Breast Cancer	Similar to BRCA2	40-60%
TP53	Li-Fraumeni syndrome	Multiple primary cancers, sarcomas, brain, premenopausal breast cancers, leukimas, adrenocorticocarcinomas	50-90%
PTEN	Cowden syndrome	Breast, thyroid, endometrial, renal cell, melanoma, colorectal cancer	25-50 (up 85)%
STK11	Peutz-Jeghers syndrome	Breast, colorectal, gastric, pancreatic, lung, ovarian and testicular cancers	45-50%
CDH1	HDGC	Diffuse gastric cancer, lobular breast cancer	39-52%
CHEK2	Familial Breast Cancer	Breast, possibly colorectal cancer	20-40% (c.1100delC)
ATM	Familial Breast Cancer	Breast cancer	20%
NBN	Familial Breast Cancer	Breast cancer	20-30% (c.1100delC)
MRE11A	Familial Breast Cancer	Breast cancer	Undetermined
RAD50	Familial Breast Cancer	Breast cancer	Undetermined
BRIP1	Familial Breast Cancer	Breast cancer	20%

FACTS

- The likelihood that breast or ovarian cancer will develop in a mutation carrier is influenced by multiple factors.
- (genetic and nongenetic - lifestyle - modifiers of risk)
- Ex: Age
- Unaffected 30 years old BRCA2 carrier
- 66% CR of BC by 80 and 12,2% CR of OC by 80
- Unaffected 60 years old BRCA2 carrier
- 35% CR of BC by 80 and 3,9 % CR of OC by 80

BRCA1/2-associated cancers: lifetime risk
Significant variability in penetrance



Breast cancer: 50%-70%

Second primary breast cancer: 40%-50%

Ovarian cancer: 15-45% *BRCA1* > *BRCA2*

Increased risk of other cancers:
Male breast cancer *BRCA2* > *BRCA1*
Pancreatic cancer *BRCA2*
Prostate cancer *BRCA2*
Melanoma *BRCA2*

Different definitions of "lifetime" yield different outcomes
"Remaining lifetime risk" higher for younger patients

SCENARIOS

1 - Mutation carrier

2 – Breast Cancer and mutation carrier

Mutation carrier - Breast cancer screening

Clinical breast examination every 6-12 months is recommended from age 25 or 10 years prior to the youngest breast cancer diagnosis in the family, whichever is earlier	V, B
All carriers should be encouraged to "breast-aware" and to seek immediate medical attention if they perceive any changes in their breast or lumps in the axilla	V, B
Annual screening MRI should be commenced from age 25 with the addition of annual mammography from age 30	II, A
If MRI screening is not available, annual mammography should be utilised from age 30	III, B
Breast ultra-sonography can be considered if MRI is unavailable and may also be used as an adjunct to mammography.	IV, B

MRI, magnetic resonance imaging

Mutation carrier - Breast cancer screening

Cancer Detection Rate and Recall Rate according to Modality

Variable	Mammography (n = 1957)	MR Imaging (n = 1977)
CDR per 1000 examinations	7.2	21.8
No. of cancers	14	43
95% CI	3.92, 11.97	15.78, 29.19
Median size of invasive cancer (mm)	15	9
Abnormal interpretation recall rate*	11.1	23.3
No. of studies BI-RADS 0, 3, 4, 5	217	461
95% CI	9.73, 12.56	21.47, 25.25

Note.—$P < .001$ comparing CDR between mammography and MR imaging.

* BI-RADS 0, 3, 4, 5.

BI-RADS, Breast Imaging Reporting and Data System; CDR, cancer detection rate; CI, confidence interval; MR, magnetic resonance

Lo G et al. Radiology, 2017

Breast cancer screening

Screening Performance Measures according to Modality (BI-RADS 3 a Positive Screening)

Variable	Mammography	MR imaging
Sensitivity (%)*	31.0 (14/45) [18.17, 46.65]	95.6 (43/45) [84.85, 99.46]
Specificity (%)†	89.4 (1709/1912) [87.92, 90.73]	78.4 (1514/1932) [76.46, 80.18]
PPV1	6.5 (14/217) [3.57, 10.59]	9.3 (43/461) [6.83, 12.36]
PPV2	26.9 (14/52) [15.57, 41.02]	26.1 (43/165) [19.55, 33.46]
PPV3	29.2 (14/48) [16.95, 44.06]	36.1 (43/119) [27.53, 45.44]

Note.—PPV1= abnormal findings at screening, defined as the percentage of all positive screening examinations resulting in a true-positive case. PPV2 = biopsy recommended, defined as the percentage of screening examinations recommended for biopsy. PPV3 = biopsy performed, defined as the percentage of biopsies performed that yielded true-positive cases.

* Sensitivity of mammography versus MR imaging, $P < .001$.

† Specificity of mammography versus MR imaging, $P < .001$.

BI-RADS, Breast Imaging Reporting and Data System; MR, magnetic resonance; PPV, positive predictive value

Lo G et al. Radiology, 2017

Breast Cancer
risk-reducing surgery

Risk-reducing surgery	
Bilateral RRM is the most effective method for reducing breast cancer risk amongst *BRCA1/2* mutation carriers	III, B
SSM and NSM are accepted alternatives to total mastectomy	III, C
Immediate breast reconstruction should be offered	V, C

NSM, nipple-sparing mastectomy; RRM, risk-reducing mastectomy; SSM, skin-sparing mastectomy

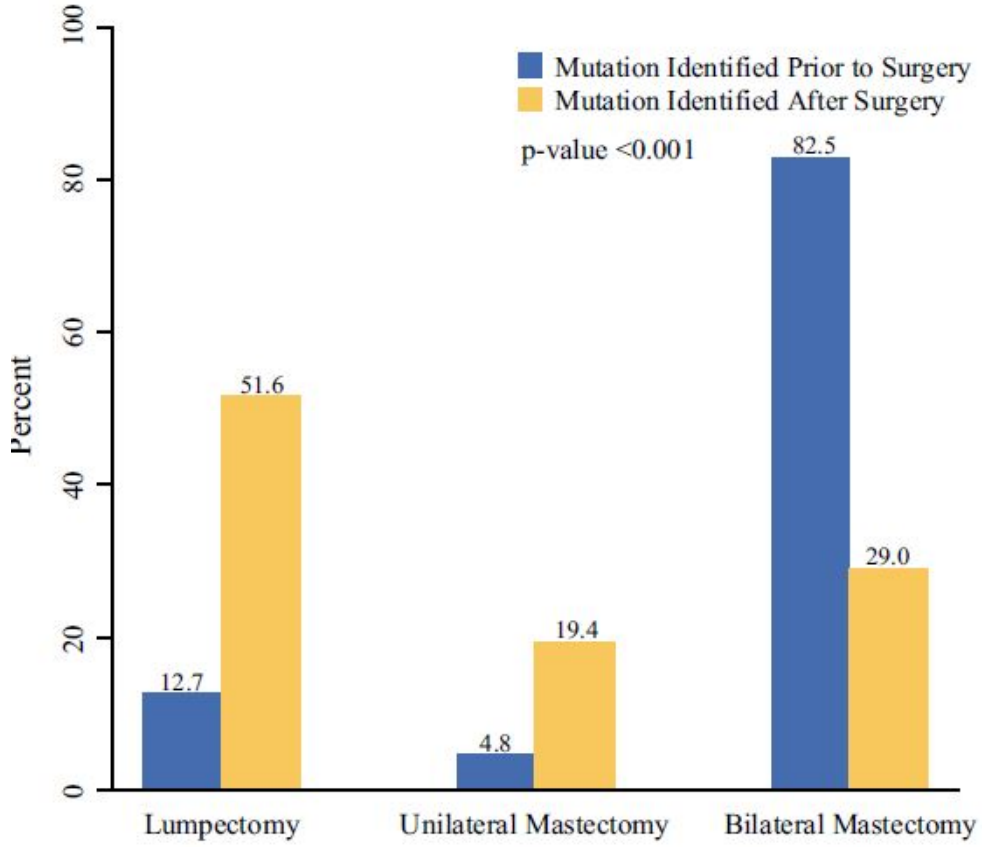
2 – Breast Cancer and mutation carrier

Choices:

- ❑ **BCS**
- ❑ **Unilateral mastectomy**
- ❑ **Unilateral therapeutic mastectomy with CPM**

Decision-making process

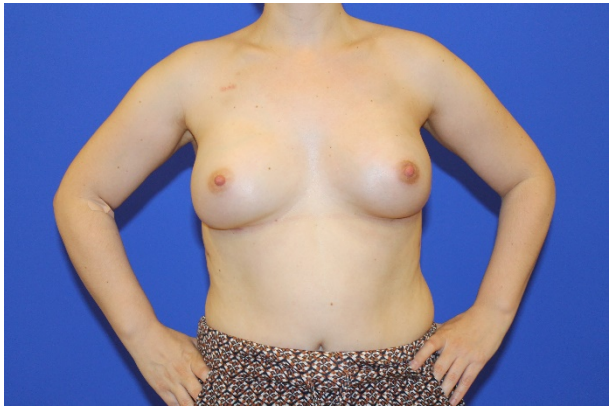
- Risk of ipsilateral breast recurrence (IBR)
- Risk of contra-lateral breast cancer (CBC)
- Potential survival benefit of contralateral prophylactic mastectomy (CPM)
- Factors with impact in IBR or CBC

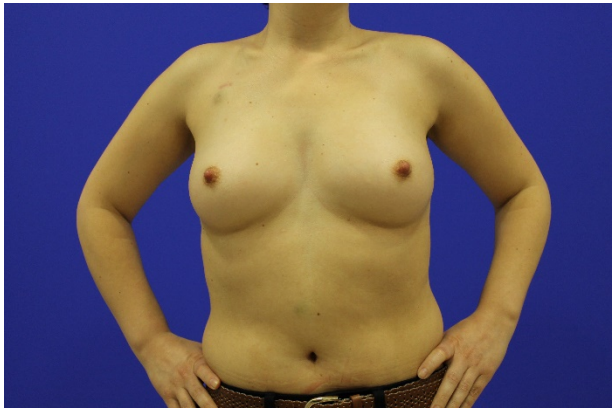


Impact that Timing of Genetic Mutation Diagnosis has on Surgical Decision Making and Outcome for BRCA1/BRCA2 Mutation Carriers with Breast Cancer
Akiko Chiba et al 2016, Ann Surg Oncology

INTERNATIONAL NIPPLE SPARING MASTECTOMY REGISTRY

PI:
Riccardo Audisio
Isabela Rubio





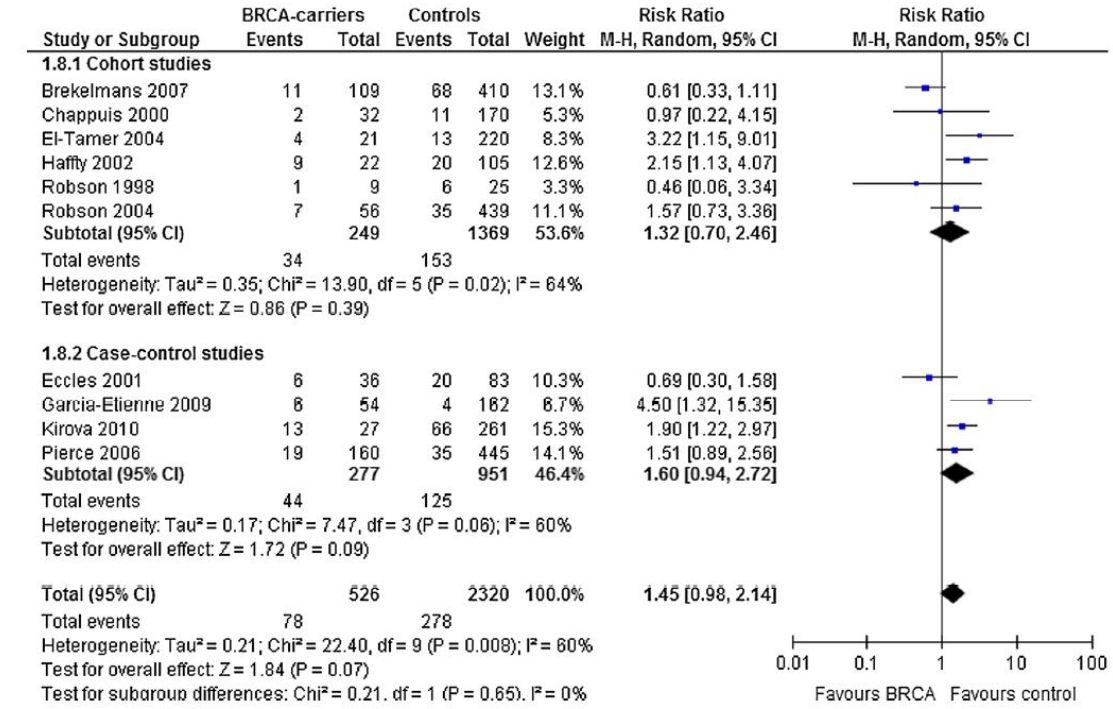
Nipple Sparing Mastectomy - safety

Ann Surg Oncol. 2011 Oct;18(11):3102-9
Prophylactic and therapeutic mastectomy in BRCA mutation carriers: can the nipple be preserved? *Reynolds C1, Davidson JA, Lindor NM, Glazebrook KN, Jakub JW, Degnim AC, Sandhu NP, Walsh MF, Hartmann LC, Boughey JC.*

Ann Surg Oncol. 2015 Feb;22(2):370-6.
Nipple-sparing mastectomy in BRCA1/2 mutation carriers: an interim analysis and review of the literature*. Yao K1, Liederbach E, Tang R, Lei L, Czechura T, Sisco M, Howard M, Hulick PJ, Weissman S, Winchester DJ, Coopey SB, Smith BL.*

Decision-making process

❑ Risk of ipsilateral breast recurrence (IBR)



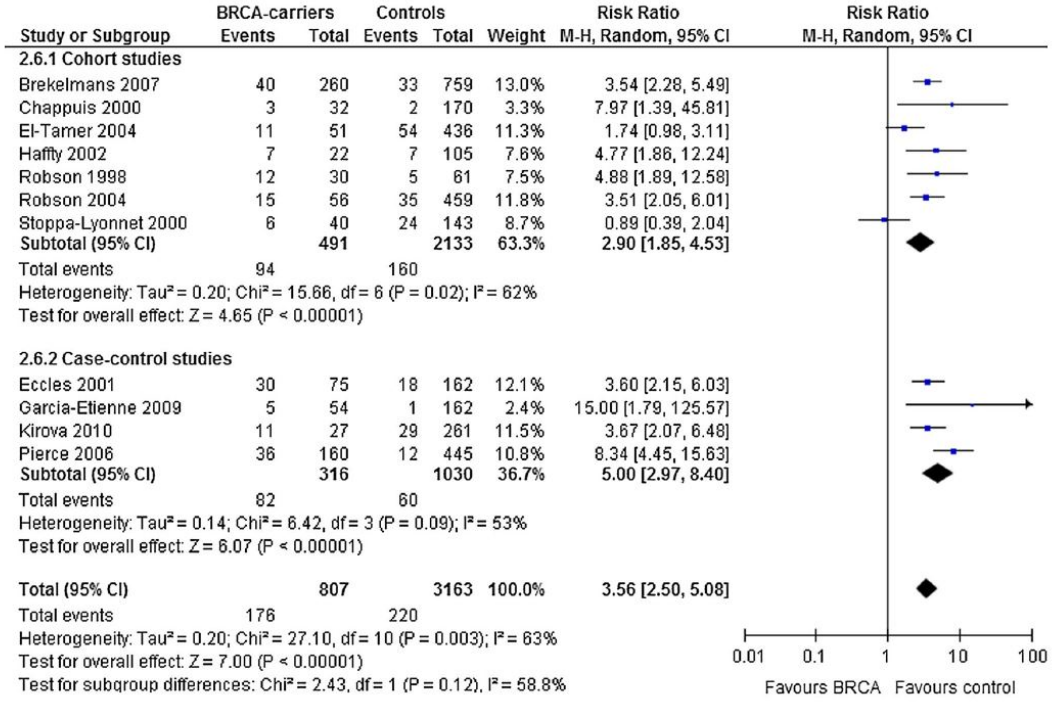
Forest plot of risk for ipsilateral breast recurrence: BRCA mutation carriers versus non-carriers

- Studies > 7 years f-up Increase in IBR 23,7%-15,9% p<0.003 Later events new cancers?
- BRCA1=BRCA2 IBR
- Adjuvant/Neo Chemo and ooforectomy reduce IBR

Valachis, Nearchou, Lind BREA 2014
Surgical management of BC in BRCA mutation carriers - SR and MA

Decision-making process

❑ Risk of contra-lateral breast cancer (CBC)



Study or Subgroup	BRCA-carriers Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Cohort studies						
Brekelmans 2007	40	260	33	759	13.0%	3.54 [2.28, 5.49]
Chappuis 2000	3	32	2	170	3.3%	7.97 [1.39, 45.81]
El-Tamer 2004	11	51	54	436	11.3%	1.74 [0.98, 3.11]
Haffty 2002	7	22	7	105	7.6%	4.77 [1.86, 12.24]
Robson 1998	12	30	5	61	7.5%	4.88 [1.89, 12.58]
Robson 2004	15	56	35	459	11.8%	3.51 [2.05, 6.01]
Stoppa-Lyonnet 2000	6	40	24	143	8.7%	0.89 [0.39, 2.04]
Subtotal (95% CI)		**491**		**2133**	**63.3%**	**2.90 [1.85, 4.53]**
Total events	94		160			
Heterogeneity: Tau² = 0.20; Chi² = 15.66, df = 6 (P = 0.02); I² = 62%						
Test for overall effect: Z = 4.65 (P < 0.00001)						
2.6.2 Case-control studies						
Eccles 2001	30	75	18	162	12.1%	3.60 [2.15, 6.03]
Garcia-Etienne 2009	5	54	1	162	2.4%	15.00 [1.79, 125.57]
Kirova 2010	11	27	29	261	11.5%	3.67 [2.07, 6.48]
Pierce 2006	36	160	12	445	10.8%	8.34 [4.45, 15.63]
Subtotal (95% CI)		**316**		**1030**	**36.7%**	**5.00 [2.97, 8.40]**
Total events	82		60			
Heterogeneity: Tau² = 0.14; Chi² = 6.42, df = 3 (P = 0.09); I² = 53%						
Test for overall effect: Z = 6.07 (P < 0.00001)						
Total (95% CI)		**807**		**3163**	**100.0%**	**3.56 [2.50, 5.08]**
Total events	176		220			
Heterogeneity: Tau² = 0.20; Chi² = 27.10, df = 10 (P = 0.003); I² = 63%						
Test for overall effect: Z = 7.00 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.43, df = 1 (P = 0.12), I² = 58.8%						

Forest plot of risk for contralateral breast cancer: BRCA-mutation carriers versus non-carriers

- **> CBC in BRCA**
- **BRCA1>BRCA2 CBC**
- **Adjuvant HT reduces CBC**
- **Increasing age reduces CBC**

Valachis, Nearchou, Lind BREA 2014
Surgical management of BC in BRCA mutation carriers - SR and MA

Decision-making process

❑ Potential survival benefit of contralateral prophylactic mastectomy (CPM)

	CRRM	No CRRM	Adjusted HR for OS	Comments
UK	105	593	0.37(0.17,0.80)	Median age at Dx -40, mostly Stage I-II, BRCA1+2
North American	181	209	0.52(0.29,0.93)	Mean age at Dx - 42 Stage I-II, BRCA1+2
Dutch	242	341	0.49(0.29,0.82)	Median age at Dx 38, Greatest benefit in <40, Grade1-2, HR+ BRCA1>>BRCA2, No BC-specific mortality

Evans et al, BCRT, 2013
Metcalfe et al, BMJ, 2014
Heemskerk, Int Journal of Cancer, 2015

Decision-making process

❑ Factors with impact in IBR or CBC

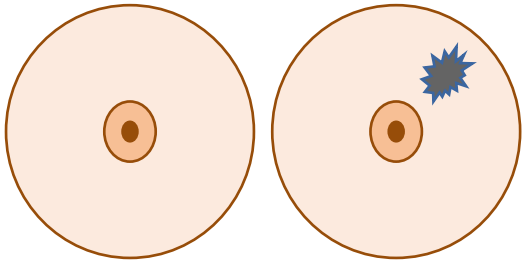
IBR

- Neo or adjuvant Chemotherapy
- Oophorectomy
- (Age – longer follow-up (new primaries))

CBC

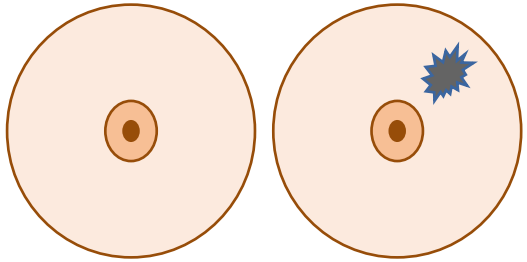
- ER status
- Adjuvant Tamoxifen
- Ooforectomy
- Older age at diagnosis

BRCA Positive



- IBR – 1-2% year <7 Y
  IBR – doubles >7 Y
- CBC – 3% year BRCA1 - 2% year BRCA2

BRCA Negative



- IBR – 1-2% year
- CBC -0.5% year

NO OVERALL SURVIVAL DIFFERENCES

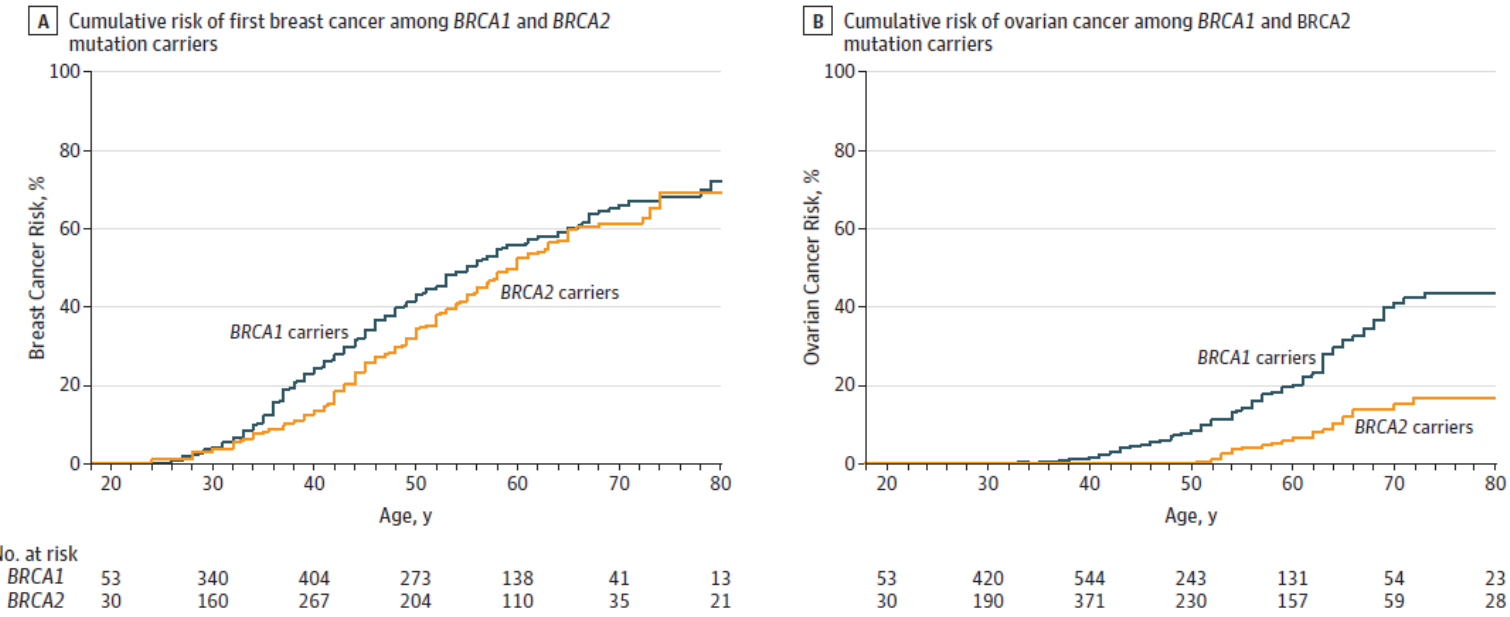
Ovarian Cancer risk-reducing surgery

Screening	
Prior to RRSO, 6 monthly trans-vaginal ultrasound and measures of serum Ca125 may be considered from the age of 30, however the limited value of these tools as an effective screening measure should be communicated to individuals	V, C
Risk-reducing surgery	
The most effective measure for reducing the risk of ovarian cancer is RRSO (combined removal of ovaries AND the fallopian tubes)	I, A
RRSO should be performed at age 35-40	II, B
Risk-reducing salpingectomy alone is not recommended, outside the setting of a clinical trial	V, C

RRSO, risk-reducing salpingo-oophorectomy

Timing of RRSO?

Figure 2. Estimated Cumulative Risks of Breast and Ovarian Cancer in Mutation Carriers



RRSO, risk-reducing salpingo-oophorectomy

Kuchenbacker, JAMA 2017

Reproductive considerations

- **Encourage completion of child-bearing prior to RRSO**
- **Options for pre-natal diagnosis and pre-implantation genetic diagnosis**
  - **however, PGD requires IVF**
- **Fertility preservation prior to treatment in those diagnosed with cancer**
- **Critical to manage menopausal symptoms following RRSO**

IVF, *in vitro* fertilisation; PGD, pre-implantation genetic diagnosis; RRSO, risk-reducing salpingo-oophorectomy

Future Directions

- **Ongoing collaborative efforts to ensure publicly available data on VUS**
- **Tailoring risk assessment by evaluation of candidate genes that effect penetrance**
- **Collaborative efforts to help determine optimal risk-reduction approaches for moderate-risk genes**
- **Clinical trials for risk-reduction & prevention**

VUS, variant of unknown significance

AND don't forget about non genetic modifiers of risk

Lifestyle changes

"Lose some weight, quit smoking, move around more, and eat the carrot."

Champalimaud Foundation Breast Unit

THANK YOU