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ESMO Clinical Practice Guidelines

Management of *BRCA* mutation carriers

Clinical Case Presentation

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DISCLOSURES

Nothing to disclose

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

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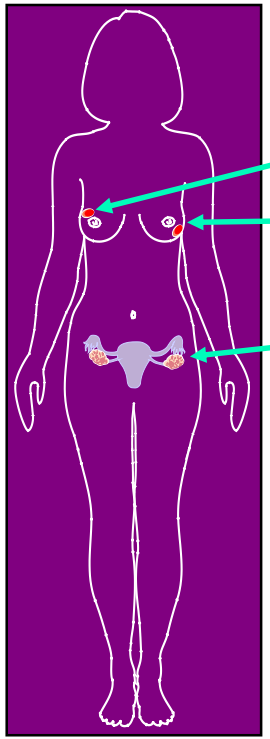
- **Breast cancer screening**
- **Breast cancer risk-reduction** and prevention
- **Ovarian cancer screening**
- **Ovarian cancer risk-reduction** and prevention
- Screening recommendations after risk-reducing surgery
- **Reproductive considerations in *BRCA* mutation carriers**
- Prevention & screening of other *BRCA*-associated cancers and approach to male carriers
- Prevention & screening of cancers in the presence of other moderate-high risk genetic mutation syndromes
- **Personalised medicine & future directions**

Background

- > 90% of hereditary breast and ovarian cancer syndromes arise because of a mutation in *BRCA1/2*
- Mutation in *BRCA1/2* associated with significantly increased lifetime risk of breast and ovarian cancer
- *BRCA2* associated with increased risk of other malignancies

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

Breast Cancer Risk

Table 2. Breast and Ovarian Cancer Incidence Rates Per 1000 Person-Years, Kaplan-Meier Estimates of the Cumulative Risks, and Standardized Incidence Rates by 10-Year Age Groups

Age, During Follow-up, y[a]	No. of Women Contributing in Age Category[a]	No. of Person-Years	No. of Events	Incidence per 1000 Person-Years (95% CI)	Cumulative Risk, % (95% CI)[b]	Standardized Incidence Rate (95% CI)[c]
Breast Cancer						
BRCA1 mutation carriers						
≤20	53	74.0	0	0		
21-30	605	2222.5	13	5.9 (3.4-10.1)	4 (2-7)	73.7 (42.9-126.8)
31-40	1048	3831.6	90	23.5 (19.1-28.9)	24 (21-29)	46.2 (37.3-57.1)
41-50	870	3317.8	94	28.3 (23.1-34.7)	43 (39-48)	17.2 (14.0-21.2)
51-60	479	1905.9	49	25.7 (19.4-34.0)	56 (51-61)	9.7 (7.2-12.9)
61-70	201	761.3	19	25.0 (15.9-39.1)	66 (61-72)	7.0 (4.5-11.0)
71-80	55	243.0	4	16.5 (6.2-43.9)	72 (65-79)	4.8 (1.8-12.8)
Total	2276[d]	12356.1	269	21.8 (19.3-24.5)		16.6 (14.7-18.7)
BRCA2 mutation carriers						
≤20	30	44.0	0	0		
21-30	329	1046.0	5	4.8 (2.0-11.5)	4 (2-9)	60.8 (25.5-144.9)
31-40	625	2136.1	23	10.8 (7.2-16.2)	13 (9-19)	20.3 (13.5-30.5)
41-50	669	2365.0	65	27.5 (21.6-35.1)	35 (29-41)	16.4 (12.9-20.9)
51-60	384	1437.2	44	30.6 (22.8-41.1)	53 (46-59)	11.4 (8.4-15.5)
61-70	174	610.2	14	22.9 (13.6-38.7)	61 (55-68)	6.4 (3.8-10.7)
71-80	68	274.6	6	21.9 (9.8-48.6)	69 (61-77)	6.6 (3.0-14.7)
Total	1610[d]	7913.1	157	19.8 (17.0-23.2)		12.9 (11.1-15.1)

CI, confidence interval

Kuchenbacker, JAMA 2017

Ovarian Cancer Risk

Ovarian Cancer						
BRCA1 mutation carriers						
≤20	53	74.0	0	0		
21-30	667	2493.0	0	0		
31-40	1464	5506.6	10	1.8 (1.0-3.4)	2 (1-3)	41.4 (22.27-76.8)
41-50	1061	3558.2	25	7.0 (4.7-10.4)	8 (6-12)	56.7 (38.05-84.5)
51-60	501	1744.7	24	13.8 (9.2-20.5)	20 (16-26)	53.3 (35.78-79.5)
61-70	230	817.3	24	29.4 (19.7-43.8)	41 (33-50)	69.1 (45.17-105.7)
71-80	88	351.0	2	5.7 (1.4-22.8)	44 (36-53)	11.8 (2.94-47.0)
Total	2905[d]	14544.8	85	5.8 (4.7-7.2)		49.6 (40.0-61.5)
BRCA2 mutation carriers						
≤20	30	44.0	0	0		
21-30	353	1134.0	0	0		
31-40	831	2953.0	1	0.3 (0.1-2.4)	0 (0-2)	7.3 (1.03-51.9)
41-50	862	2961.0	0	0	0 (0-2)[e]	
51-60	534	1836.5	12	6.5 (3.7-11.5)	7 (4-11)	24.5 (13.91-43.1)
61-70	267	974.0	10	10.3 (5.5-19.1)	15 (10-23)	21.5 (11.20-41.3)
71-80	108	435.0	1	2.3 (0.3-16.3)	17 (11-25)	4.4 (0.62-31.0)
Total	2161[d]	10337.5	24	2.3 (1.6-3.5)		13.7 (9.1-20.7)

Kuchenbacker, JAMA 2017

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Breast Cancer Screening

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

Breast cancer screening

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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

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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

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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

CRRM in women who had breast cancer?

	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

CRRM in women who had breast cancer?

No in study

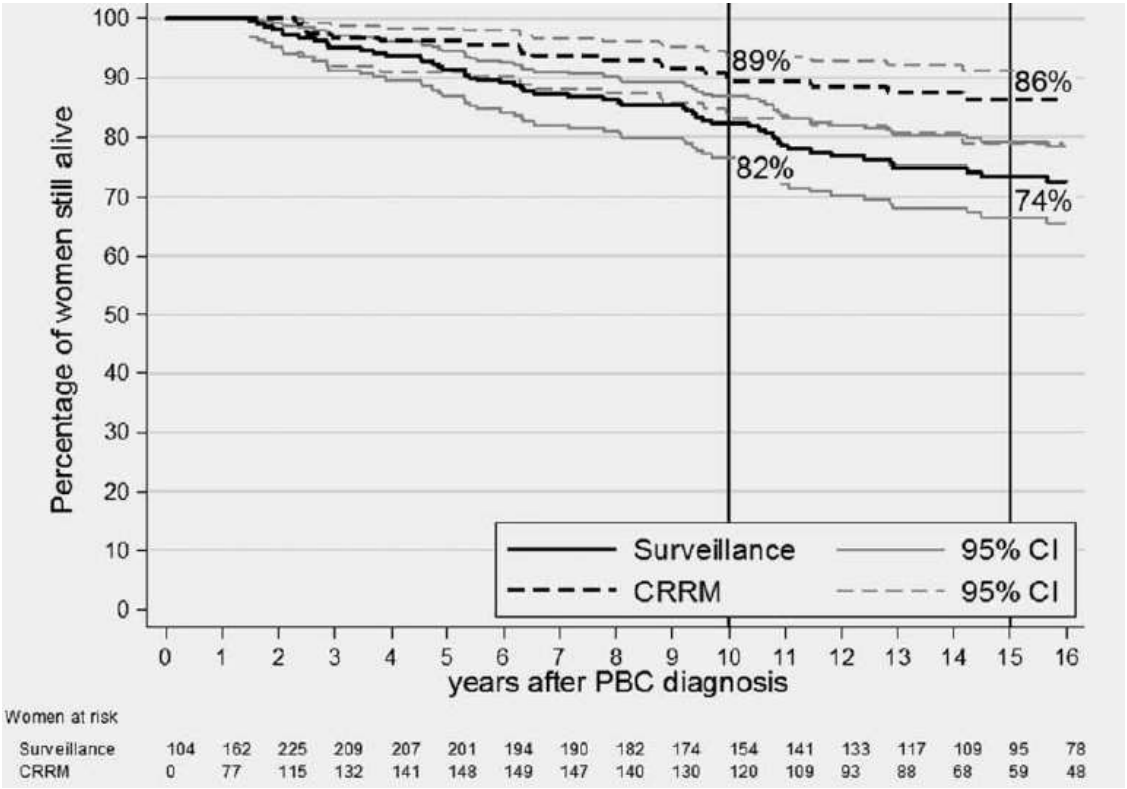
Contralateral mastectomy	110	104	95	92	83	71	61	58	45	42	39
No contralateral mastectomy	141	134	127	122	116	108	101	94	87	83	72

N=390
< 65 years (78% < 50 years) at diagnosis
Stage 1-2

CRRM, contralateral risk-reducing mastectomy

Metcalfe et al, BMJ, 2014

CRRM in women who had breast cancer?



N=583

Greatest benefit?
< 40 years
Grade 1-2
HR+ disease
No chemotherapy

CI, confidence interval; CRRM, contralateral risk-reducing mastectomy; HR, hormone receptor; PBC, primary breast cancer

Heemskerk-Gerritsen et al. IJC 2015

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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

Risk-reducing salpingo-oophorectomy

Table 2. Trials of Risk-Reducing Salpingo-Oophorectomy (RRSO) in *BRCA1* and *BRCA2* Carriers.

Study and Focus	Design	Patients		Follow-up	Ovarian Cancers		Hazard Ratio (95% CI)		
		RRSO	No RRSO		RRSO	No RRSO	*BRCA1* and *BRCA2*	*BRCA1* Only	*BRCA2* Only
		number			*number*				
Ovarian-cancer risk reduction									
Kauff et al.[45]	Prospective unmatched cohort	98	72	Mean, 24.2 mo	1	5	0.15 (0.02–1.31)	NR	NR
Rebbeck et al.[46]	Retrospective cohort, prospective follow-up	259	292	Mean, RRSO, 8.2 yr, no RRSO, 8.9 yr	2*	58	0.04 (0.01–0.16)	NR	NR
Finch et al.[47]	Retrospective cohort	1041	779	Mean, 3.5 yr	7†	32	0.20 (0.07–0.58)	NR	NR
Domchek et al.[48]	Prospective matched cohort	155	271	Mean, RRSO, 3.1 yr, no RRSO, 2.1 yr	2	16	0.11 (0.03–0.47)	NR	NR
Kauff et al.[49]	Prospective unmatched cohort	509	283	Median, RRSO, 34–40 mo, no RRSO, 38 mo	3	12	0.12 (0.03–0.41)	0.15 (0.04–0.56)	NA‡
Rebbeck et al.[50]	Meta-analysis	1555	1285	NR	NR	NR	0.21 (0.12–0.39)	NR	NR
Domchek et al.[27]§	Prospective unmatched cohort	465	1092	3 yr	6¶	63	0.28 (0.12–0.69)	0.31 (0.12–0.82)	NA‡
Finch et al.[51]§	Prospective unmatched cohort	1602	1334	Mean, 5.6 yr	32‖	108	0.20 (0.13–0.30)	NR	NR

RRSO, risk-reducing salpingo-oophorectomy

Hartmann et al, NEJM, 2016

Risk-reducing salpingo-oophorectomy

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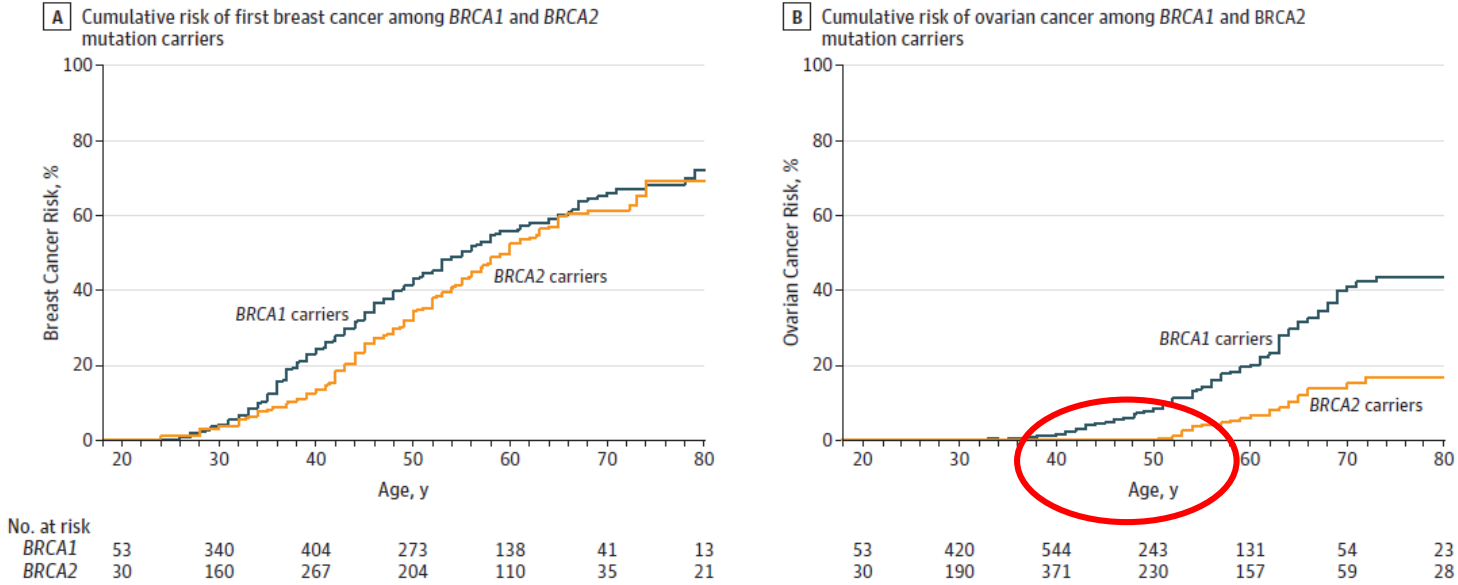
Study and Focus	Design	Patients		Follow-up	Ovarian Cancers		Hazard Ratio (95% CI)		
		RRSO	No RRSO		RRSO	No RRSO	*BRCA1* and *BRCA2*	*BRCA1* Only	*BRCA2* Only
		number			*number*				
Mortality ††									
Domchek et al.[48]	Two cohorts, one age-matched and one un-matched	155 matched; 183 un-matched	271 matched; 460 un-matched	Mean, RRSO, 3.1 yr, no RRSO, 2.1 yr			0.24 (0.08–71); 0.47 (0.15–1.46)	NR	NR
Finch et al.[51]	Prospective unmatched cohort	905	1334§	Mean, 5.6 yr; mean age at start of follow-up, RRSO, 50.5 yr (range, 30–88), no RRSO, 42.4 yr (range, 30–86)			0.23 (0.13–0.39)	0.21 (0.12–0.37)	0.67 (0.08–5.35)
Domchek et al.[27]	Prospective unmatched cohort	336	1034	3 yr; mean age at start of follow-up, RRSO, 44 yr (range, 21–79), no RRSO, 36 yr (range, 18–90)			0.40 (0.26–0.61)	0.38 (0.24–0.62)	0.52 (0.22–1.23)
Rocca et al.[56]	Cohort of women in Olmsted County, MN (not selected for BRCA-positive status); case:control	1091	2383	Median, RRSO, 25 yr, no RRSO, 26 yr			1.67 (1.16–2.40)	NR	NR

CI, confidence interval; RRSO, risk-reducing salpingo-oophorectomy

Hartmann et al, NEJM, 2016

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

VUS, variant of unknown significance

THANK YOU