Modulo 007_RES - LOCANDINA
Revisione n. 4
Data di emissione: 26 marzo 2018
Approvato ed emesso in originale

S.S. FORMAZIONE PERMANENTE E AGGIORNAMENTO

12 novembre 2019

Ruolo della chirurgia nelle portatrici di mutazione

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Ruolo della chirurgia nelle portatrici di mutazione

BRCA mutated patients have to consider **surgery** in **different stages of their lives**

Before cancer

⇩

Surgical <u>Prevention</u>

Breast Cancer
→ Bilateral Prophylactic Mastectomy (BPM)

Ovarian Cancer
→ Bilateral Salpingo Oophorectomy (BSO)

Surgical <u>Treatment</u>

Breast Cancer
→ Breast Conservative Treatment (BCT)
→ Mastectomy (M)

⇧

After cancer

Strategies for Cancer prevention

- SURVEILLANCE
- CHEMOPREVENTION
- PROPHYLACTIC SURGERY

  Prophylactic bilateral Mastectomy

  Prophylactic bilateral salpingo-oophorectomy

Risk reduction mastectomy (RRM)

Efficacy of Bilateral prophylactic mastectomy in high risk women

Author	FU yrs	Design	N° of breast cancers		
			Surgery	Surveillance	Protection
Hartmann	13.4	retrospective	0/1	-	89.5-100%
Rebbeck	6.5	retrospective + prospective	2	184	90-95%
Mejers-Heijboer	2.9	prospective	0	8	100%
Kiljn	4.1	prospective	1	23	96%
Isern	4.3	retrospective	0	-	100%

Retrospective analyses with median follow-up periods of 13 to 14 years have indicated that **bilateral risk–reducing mastectomy (RRM) decreased the risk of developing breast cancer by at least 90% in moderate- and high-risk women and in known BRCA1/2 mutation carriers.**

NCCN Guidelines 2017, BC Risk Reduction

Risk reduction mastectomy (RRM)

International trends in the uptake of cancer risk reduction strategies in women with a *BRCA1* or *BRCA2* mutation

6223 women were identified from an **international database of female BRCA mutation carriers** and included women from **59 centres from ten countries.**

The **mean age** at prophylactic mastectomy was **41.8 years**

The mean age at mastectomy was **40.7 years for BRCA1** carriers and

42.4 years for BRCA2 carriers

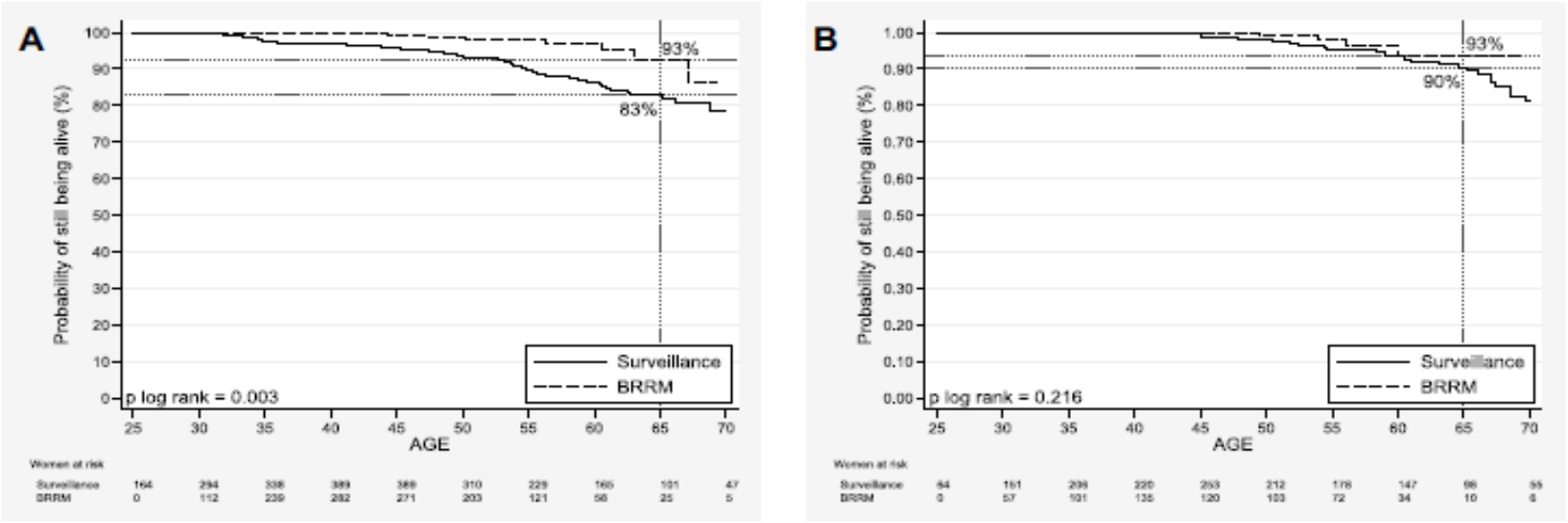
Only **3.4%** of the mastectomies were done at **age 60 and above**

Kelly Metcalfe et al. British Journal of Cancer ***(2019)***

Risk reduction mastectomy (RRM)

Survival after bilateral risk-reducing mastectomy in healthy *BRCA1* and *BRCA2* mutation carriers

A **multicenter cohort study**, to estimate the associations between BRRM and the overall and BC-specific mortality rates, separately for BRCA1 and BRCA2 mutation carriers → During a **mean follow-up of 10.3 years**, 722 out of 1712 BRCA1 (42%) and 406 out of 1145 BRCA2 (35%) mutation carriers underwent BRRM.



***Overall survival curves** for **BRCA1** (a) and **BRCA2** (b) mutation carriers*

Conclusion: BRRM was associated with **lower mortality than surveillance for BRCA1 mutation carriers**, but for BRCA2 mutation carriers, BRRM may lead to similar BC-specific survival as surveillance.

Our findings support a **more individualized counseling based on BRCA mutation type**

*Bernadette et al. Breast Cancer Research and Treatment (**2019**)*

Risk reduction mastectomy 2018 NCCN Indications

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Breast Cancer Risk Reduction

The 2018 **NCCN Breast Cancer Risk Reduction Panel** supports the use of **BPM for carefully selected women** at high risk for breast cancer who desire this intervention, exclusively **considering BRCA1/2 and other genetic mutations** or previous history of **CLIS**

The recommendation for undergoing a BPM is that it has the greatest benefit in risk reduction for
women before age 40 years

Risk reduction mastectomy 2018 NCCN Indications

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018 Breast Cancer Risk Reduction

- Women considering BPM, should first have **appropriate multidisciplinary consultations** and a **clinical breast examination** and **bilateral mammogram** if not performed within the past 6 months.
- Women who choose RRM may undergo the procedure **with or without immediate breast reconstruction**.

- **Axillary node assessment has limited utility** at the time of BPM. Women undergoing RRM do not require an axillary lymph node dissection unless breast cancer is identified on pathologic evaluation of the mastectomy specimen.

Following BPM, for monitoring breast health, women should **continue with annual exams** of the chest or reconstructed breast as there is still a small risk of developing breast cancer. **Mammograms are not recommended** in this situation.

ARTICLE IN PRESS

Original Study

Satisfaction and Impact on Quality of Life of Clinical and Instrumental Surveillance and Prophylactic Surgery in BRCA-mutation Carriers

Marta D'Alonzo,[1] Eleonora Piva,[2] Silvia Pecchio,[1] Viola Liberale,[1] Paola Modaffari,[1] Riccardo Ponzone,[3] Nicoletta Biglia[1]

An **anonymous questionnaire** was administered to ***174 BRCA1-2*** *mutation carriers.*

Table 1 Patient Characteristics

Characteristic	No. Patients = 79 (%)
BRCA status	
BRCA1	47 (59.5)
BRCA2	29 (36.7)
BRCA1 and BRCA2	3 (3.8)
History of cancer	
Unilateral breast cancer	32 (40.5)
Bilateral breast cancer	7 (8.8)
Ovarian cancer	4 (5)
Concomitant breast and ovarian cancer	2 (2.6)
Other cancer	1 (1.3)
No cancer	33 (41.8)

Table 2 Preventive Strategies Adopted by the Patients

Preventive Strategy	No. Patients = 79 (%)
Surveillance only	32 (40.5)
Prophylactic oophorectomy	27 (34.2)
Prophylactic mastectomy	5 (6.3)
Prophylactic oophorectomy and mastectomy	15 (19)

Table 4 Risk-reducing Mastectomy

	Full	Partial	Absent
Breast sensitivity, %	5	55	40
	High	Moderate	Low
Satisfaction for cosmesis, %	65	30	5
	Unchanged	Partially Worse	Worse
Body image, %	25	40	35

D'alonzo et al. Clinical Breast Cancer ***2018***

Journal of *Clinical Medicine*

MDPI

Article

Concerns and Expectations of Risk-Reducing Surgery in Women with Hereditary Breast and Ovarian Cancer Syndrome

Paola Modaffari [1], Riccardo Ponzone [2], Alberta Ferrari [3], Isabella Cipullo [1], Viola Liberale [1], Marta D'Alonzo [1], Furio Maggiorotto [2] and Nicoletta Biglia [1,*]

PROGETTO Ab.BRAC.cio

aBRCAdaBRA
TUMORE EREDITARIO AL SENO E OVAIO

An anonymous 40-items **questionnaire** was designed to **investigate expectations and concerns about RR Surgery**

the questionnaire included:

- knowledge and concerns about RRS, postoperative complications and late effects;
- knowledge and concerns about screening procedures for BC and OC;
- role of their partner in the decision-making on RRS;

For RR Mastectomy

- satisfaction on given information on RRM surgical procedure, cosmetic and tactile sensation of reconstructed breasts;
- influence of RRM on body appearance and sexual intimacy.

123 completed the questionnaire, with a participation rate of 84.8%

Table 1. Details on Risk-Reducing Surgery and medical history of women with Hereditary Breast and Ovarian Cancer (HBCO) syndrome included in the study.

Characteristics	Results
Median age at survey filling-out	47 (26–76) years
Median age at the HBOC* syndrome diagnosis	41 (18–68) years
The indication of the genetic test:	
At least one relative with a proven genetic mutation	44 (21.6%)
Previous Breast Cancer	87 (42.6%)
Previous Ovarian Cancer	11 (5.4%)
Previous Breast and Ovarian Cancer	2 (1.0%)
Multiple cases of Breast and Ovarian Cancer in the patient's family	60 (29.4%)
Genetic mutation	
BRCA1	106 (51.9%)
BRCA2	84 (41.2%)
BRCA1 + BRCA2	2 (1.0%)
High Familial risk	12 (5.9%)
Risk-Reducing Mastectomy (115 women, excluding 89 women with a previous BC°)	
RRM	39 (33.9%)
Intentioned for RRM	35 (30.4%)
RRM Declined	34 (29.6%)
Not reported	7 (6.1%)
Risk-Reducing Salpingo-Oophorectomy (191 women, excluding 13 women with a previous OC^)	
RRSO	128 (67.0%)
Intentioned for RRSO	47 (24.6%)
RRSO Declined	10 (5.2%)
Not reported	6 (3.1%)
Carriers who declined both RR Mastectomy and Salpingo-Oophorectomy	8 (3.9%)

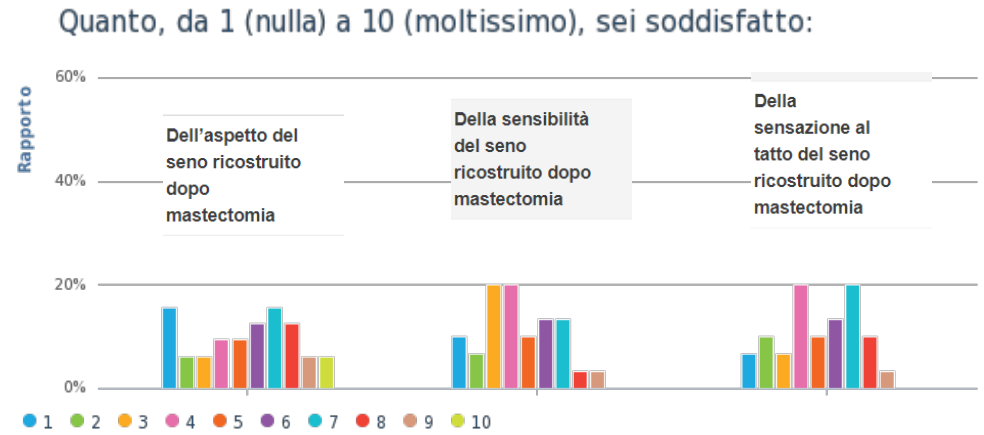
* HBOC = Hereditary Breast and Ovarian Cancer syndrome; ° BC = Breast Cancer; ^ OC = Ovarian Cancer.

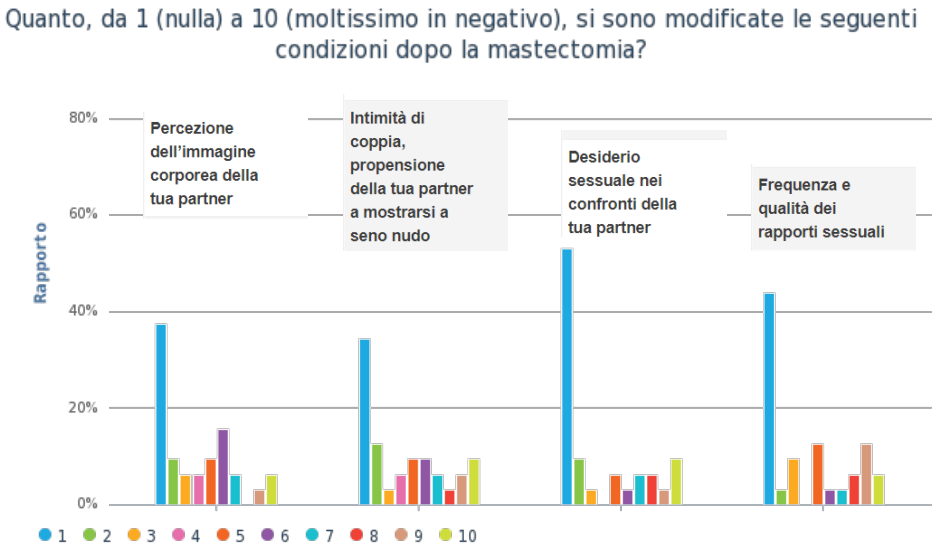
J. Clin. Med. ***2019***

Article

Concerns and Expectations of Risk-Reducing Surgery in Women with Hereditary Breast and Ovarian Cancer Syndrome

Paola Modaffari [1], Riccardo Ponzone [2], Alberta Ferrari [3], Isabella Cipullo [1], Viola Liberale [1], Marta D'Alonzo [1], Furio Maggiorotto [2] and Nicoletta Biglia [1,*]





- Participants are **well-informed about the options to manage cancer risk**, and women with previous cancer are more concerned with screening failure.
- **Satisfaction with RR Mastectomy is high**, even if <u>many carriers are unsatisfied with reconstructed breast feel and nipple-areola complex tactile sensation</u> and those with previous breast cancer report a change in their sexual habits

J. Clin. Med. ***2019***

Risk reduction mastectomy (RRM)

International trends in the uptake of cancer risk reduction strategies in women with a *BRCA1* or *BRCA2* mutation

6223 women were identified from an **international database of female BRCA mutation carriers** and included women from **59 centres from 10 countries.**

18 → **27.8% had a prophylactic bilateral mastectomy**

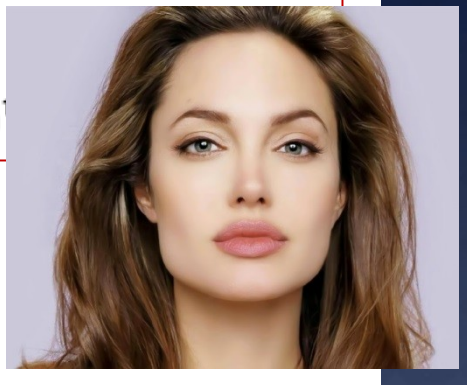
The mastectomy rate was highest in the **United States** (36 → **49.9%)** and lowest in **Poland** (2.7 → **4.5%).** In Italy the rate is **10%.**

Women who received **genetic testing in 2009 or later** were **more likely to elect for prophylactic mastectomy** compared to women who received testing prior to 2009 (30.3% versus 26.9%) (P = 0.04)

Kelly Metcalfe et al. British Journal of Cancer ***(2019)***

Risk-reducing mastectomy rates in the US: a closer examination of the Angelina Jolie effect

Alexander Liede[1] · Mona Cai[1] · Tamara Fidler Crouter[1,2] · Daniela Niepel[3] · Fiona Callaghan



The *Angelina Effect*—a term coined by *Time* magazine to describe the **rise in internet searches related to breast cancer genetics and counseling**—represents a long-lasting impact of celebrity on public health awareness as **significant increases in genetic testing and mastectomy rates** were observed and sustained in subsequent years.

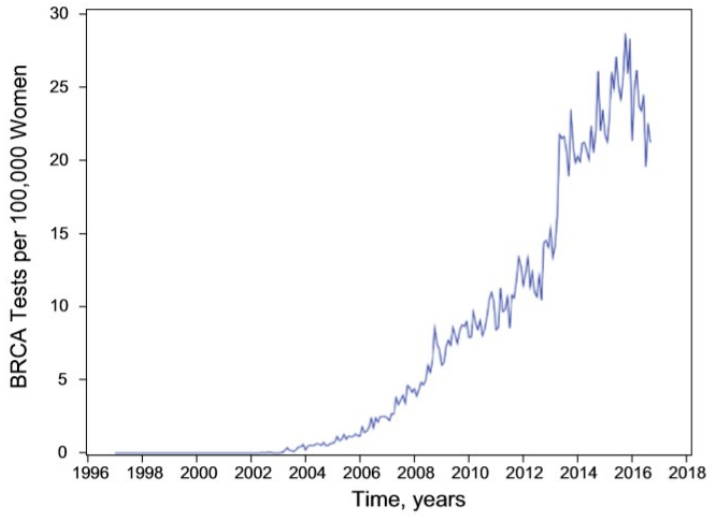


Fig. 1 Monthly incidence rates of *BRCA* genetic testing among adult female enrollees in MarketScan database (1997–2006)

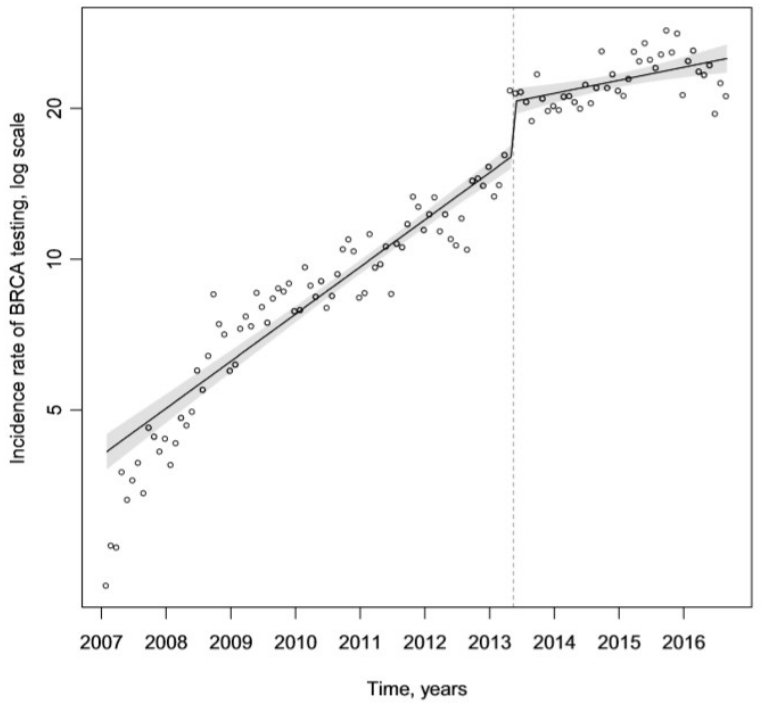


Fig. 2 Interrupted time series analyses of *BRCA* testing monthly incidence rates per 100,000 among adult female enrollees in MarketScan database (2007–2016) before and after Jolie op-ed on May 14, 2013 (shading depicts 95% CIs)

Breast Cancer Research and Treatment (***2018***)

Strategies for ovarian Cancer prevention

- SURVEILLANCE
- CHEMOPREVENTION
- PROPHYLACTIC SURGERY
  - Prophylactic bilateral mastectomy
  - **Prophylactic bilateral salpingo-oophorectomy**

The effectiveness of RRSO **in reducing risk**

85-95% reduction in the risk of **ovarian and fallopian cancer**

50-68% reduction in the risk of **breast cancer**

Rebbeck TR et al J Natl Cancer Inst **2009**

All-causes **mortality reduction** of **70%**

*Eleje GU et al. Cochrane Reviews **2018***

RRSO performed **before age 50**

!

Published studies of **risk-reducing** salpingo-oophorectomy and **cancer risk** in ***BRCA1/2*** *mutation carriers*

Study, first author, and year (reference)	Ovarian and/or fallopian tube cancer by mutation status			Breast cancer by mutation status		
	BRCA1/2	*BRCA1*	*BRCA2*	*BRCA1/2*	*BRCA1*	*BRCA2*
Rebbeck et al., 1999 (9)	NA	NA	NA	NA	HR = 0.53 (0.33 to 0.84), N = 122†	NA
Kauff et al., 2002 (10)	HR = 0.15 (0.02 to 1.31), N = 170†	NA	NA	HR = 0.32 (0.08 to 1.20), N = 131†	NA	NA
Rebbeck et al., 2002 (8)	HR = 0.04 (0.01 to 0.16), N = 551†	NA	NA	HR = 0.47 (0.29 to 0.77), N = 241†	NA	NA
Rutter et al., 2003 (17)	OR = 0.29 (0.12 to 0.73), N = 251	NA	NA	NA	NA	NA
Eisen et al., 2005 (15)	NA	NA	NA	OR = 0.46 (0.32 to 0.65), N = 3305	OR = 0.44 (0.29 to 0.66), N = 2432	OR = 0.57 (0.28 to 1.15), N = 873
Kramer et al., 2005 (12)	NA	NA	NA	NA	HR = 0.38 (0.15 to 0.97), N = 98	NA
Domchek et al., 2006 (13)	HR = 0.11 (0.03 to 0.47), N = 426†	NA	NA	HR = 0.36 (0.20 to 0.67), N = 426†	NA	NA
Finch et al., 2006 (11)	HR = 0.20 (0.07 to 0.58), N = 1828	NA	NA	NA	NA	NA
Chang-Claude et al., 2007 (14)	NA	NA	NA	HR = 0.56 (0.29 to 1.09), N = 1601	HR = 0.50 (0.24 to 1.04), N = 1187	HR = 0.40 (0.07 to 2.44), N = 414
Kauff et al., 2008 (16)	HR = 0.12 (0.03 to 0.41), N = 792	HR = 0.15 (0.04 to 0.56), N = 498	HR = 0.00,‡ N = 294	HR = 0.53 (0.29 to 0.96), N = 597	HR = 0.61 (0.30 to 1.22), N = 368	HR = 0.28 (0.08 to 0.92), N = 229

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85-95% reduction in the risk of **ovarian and fallopian cancer**

50-68% reduction in the risk of **breast cancer**

Rebbeck et al J Natl Cancer Inst ***2009***

Risk Reduction Salpingo-Oophorectomy (RRSO)

NCCN National Comprehensive Cancer Network®

The NCCN Guidelines panel recommends limiting RRSO for women **with a known BRCA1/2 pathogenic or likely pathogenic variant**

Natl Compr Canc Netw NCCN, Genetic/Familial High-Risk Assessment, ***2019***

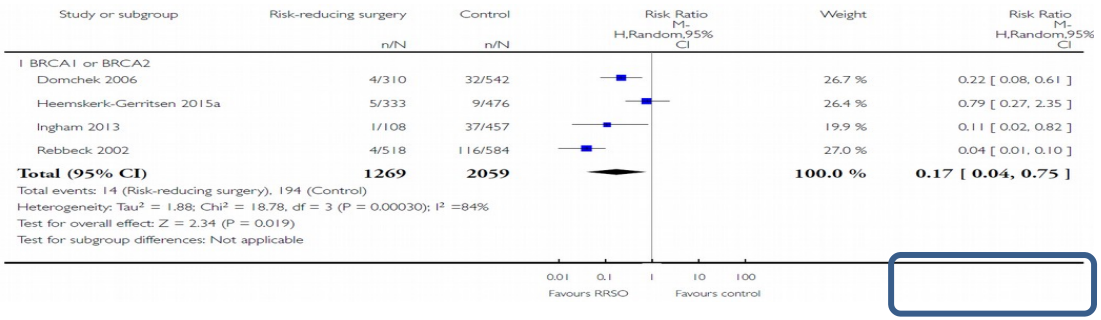
Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations (Review)

Cochrane Library

Cochrane Database of Systematic Reviews

Eleje GU et al. Cochrane Database of Systematic Reviews ***2019***

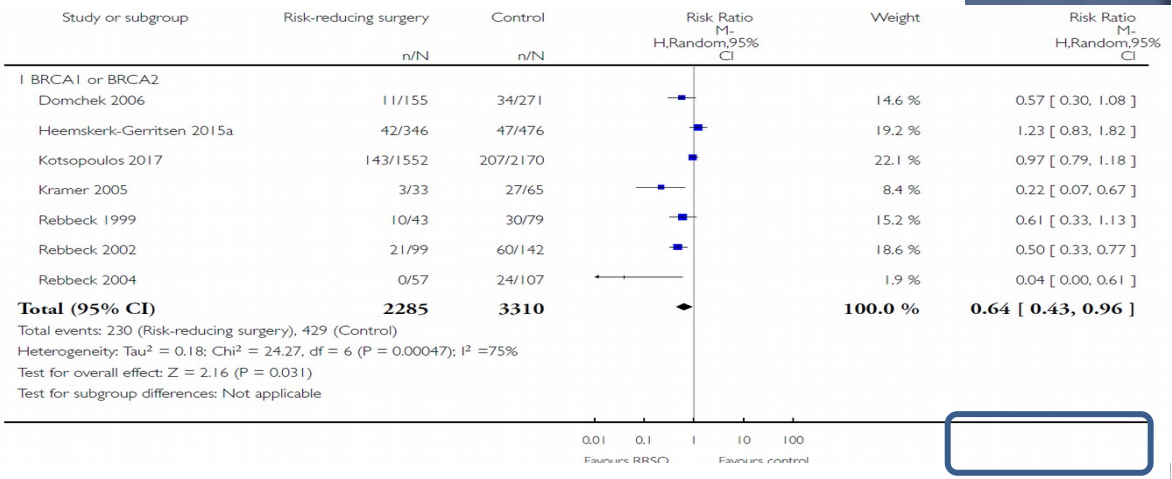
Comparison 1 Risk-reducing salpingo-oophorectomy (RRSO) versus no RRSO in BRCA1 or BRCA2 mutation carriers, Outcome 4 HGSC incidence.



Ovarian cancer incidence in ***BRCA1/2*** *mutation carriers*

Comparison 1 Risk-reducing salpingo-oophorectomy (RRSO) versus no RRSO in BRCA1 or BRCA2 mutation carriers, Outcome 5 Breast cancer incidence.

Breast cancer incidence in ***BRCA1/2*** *mutation carriers*



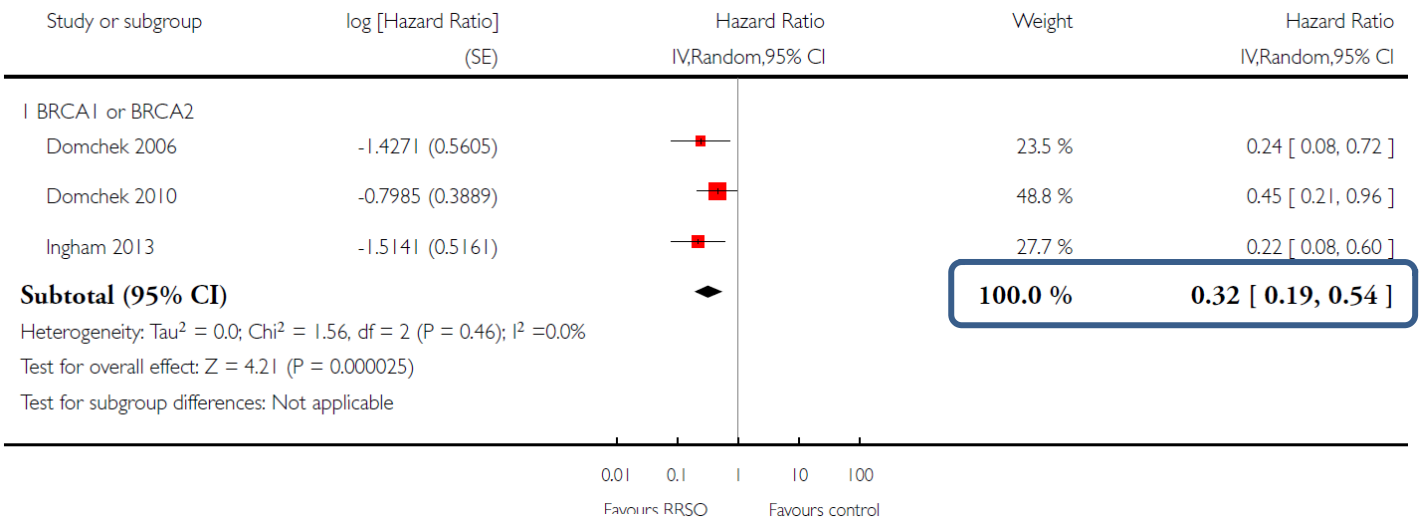
Risk-reducing salpingo-oophorectomy and **overall survival** in ***BRCA1/2*** *mutation carriers*

Cochrane Library

Cochrane Database of Systematic Reviews

Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations (Review)

Comparison 1 Risk-reducing salpingo-oophorectomy (RRSO) versus no RRSO in BRCA1 or BRCA2 mutation carriers, Outcome 1 Overall survival.



BRCA 1 only **0.30 [0.17, 0.52]**

BRCA 2 only **0.44 [0.23, 0.85]**

All-causes mortality reduction of 70%

Eleje GU et al. Cochrane Database of Systematic Reviews ***2019***

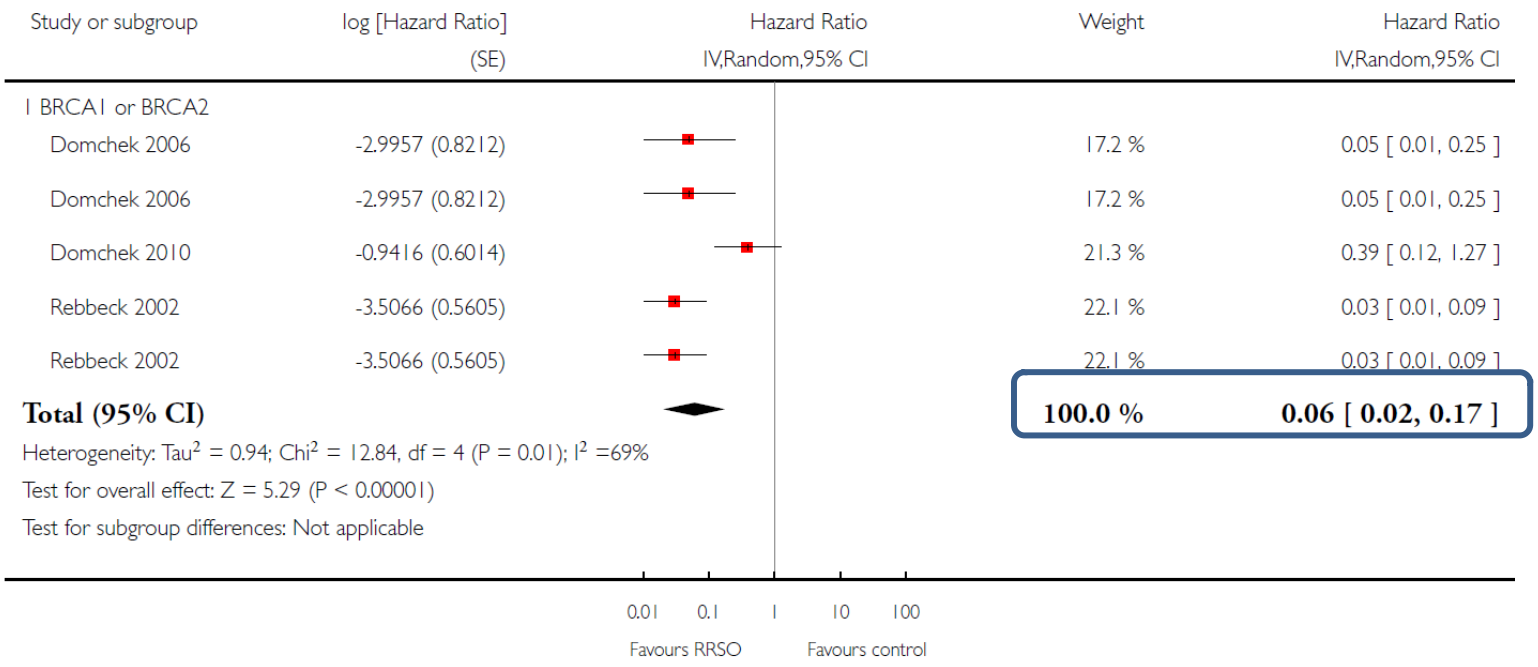
Cochrane Library

Cochrane Database of Systematic Reviews

Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations (Review)

Analysis 1.2. Comparison 1 Risk-reducing salpingo-oophorectomy (RRSO) versus no RRSO in BRCA1 or BRCA2 mutation carriers, Outcome 2 High-grade serous cancer (HGSC) mortality.

Ovarian cancer related mortality
in ***BRCA1/2*** *mutation carriers*



Eleje GU et al. Cochrane Database of Systematic Reviews ***2019***

The **optimal Age** for RRSO

- An optimal age for RRSO **is difficut to find**

- Mean age at diagnosis of **ovarian cancer was 50.8 year** for BRCA1/2

Rebbeck et al J Natl Cancer Inst 2009

- At present, the guidelines for ovarian cancer risk management **recommed bilateral salpingo-oophorectomy at the completion of childbearing or by age 35 to 40**

Natl Compr Canc Netw NCCN 2019

Risk-reducing bilateral salpingo-oophorectomy is routinely recommended to women at high risk **after completion of their family**.

In **BRCA1** mutation carriers, this is usually **from the age of 35 years and definitely by 40 years**, because below the age of 40 years, the risk of ovarian cancer is only 2%.

In those with **BRCA2** gene mutations, there is growing acceptance that women have **until the age of 45 years** to undergo surgery because their cumulative risk of ovarian cancer by age 50 years is only 0–1%.

Menon et al. Obstet Gynecol, 2018

RRSO and **residual risk for peritoneal cancer**

There is a **4.3% at 20 years residual risk for peritoneal cancer** in BRCA1 and BRCA2 mutation carriers following prophylactic salpingo-oophorectomy

*Natl Compr Canc Netw NCCN **2019***

But…

It is possible that these are actually **metastases of sub-clinical disease that was present at the time of surgery (occult carcinomas)**

Undiagnosed cancers at the time of surgery will be considered primary peritoneal cancer when they become clinically apparent

It is possible that **fewer peritoneal cancers will be diagnosed** after oophorectomy if the **comprehensive pathology review** of the salpingo-oophorectomy specimens is conducted on all patients

*Levine DA et al J Clin Oncol **2003***

Detection rate of occult cancer 5-10%

*Hideko Yamauchi, Int JCO **2018***

RRSO **rigorous operative and pathologic protocol and peritoneal lavage**

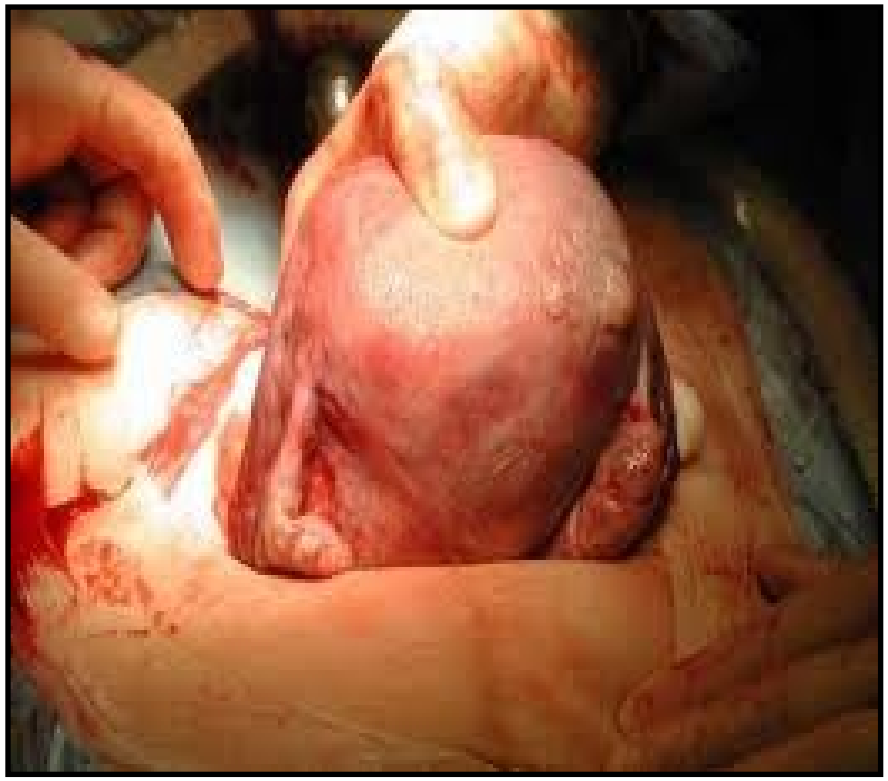
Peritoneal washing should be perfermed at surgery

and

pathologic assessment should include fine sectioning of the ovaries and fallopian tubes.

Natl Compr Canc Netw NCCN 2019

RRSO and **Concurrent Hysterectomy**



There is controversy as to whether this requires removal of the uterus.

Even if careful ligation of the fallopian tube at the uterine origin is performed, **a small portion of interstitial fallopian tube in the cornua of the uterus is left** in situ if hysterectomy is not performed

However, in the largest study on fallopian tube cancer to date, **92% of cancers originated in the distal or midportion of the tube**

Cass I et al Gynecol Oncol 2010

RRSO and **Concurrent hysterectomy**: **advantages**

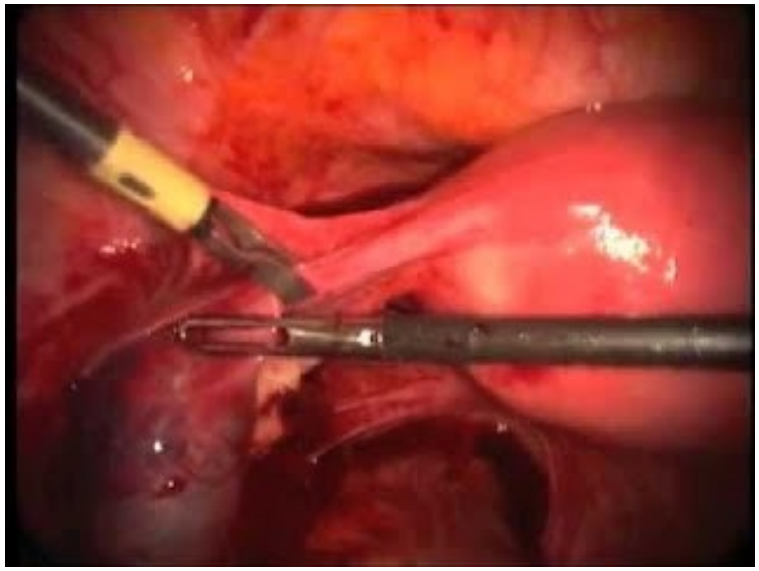
The additional benefit of concurrent hysterectomy is not clear at the time.

More data are needed to determine the magnitude of the association between BRCA pathogenic/likely pathogenic variants and development of serous uterine cancer.

For patients who choose to undergo RRSO, the provider may discuss the risks and benefits of concurrent hysterectomy

Natl Compr Canc Netw NCCN ***2019***

Prophylactic Salpingectomy



The majority of BRCA-associated ovarian cancers appear to **arise in the fallopian tube.**

Several studies have reported the identification of either invasive high-grade serous carcinomas of the fallopian tube or serous tubal intraepithelial carcinomas of BRCA1/2 carriers undergoing preventive bilateral salpingo-oophorectomy

Crum; Curr Opin Obstet Gynecol 2007

The wide acceptance that a large proportion of **highgrade serous cancers originates in the fallopian tube and involves the ovary secondarily** has led to the exploration of **salpingectomy as a means of reducing risk** while maintaining ovarian function in premenopausal women.

Menon et al. Obstet Gynecol, 2018

Prophylactic Salpingectomy and delayed Oophorectomy

- **More data are needed** regarding its efficacy in reducing the risk for ovarian cancer.
- Further, *BRCA1/2* carriers who undergo salpingectomy without oophorectomy **may not get the 50% reduction in breast cancer risk** that *BRCA1/2* carriers who undergo oophorectomy receive.

Therefore, at this time, the panel does not recommend risk-reducing salpingectomy alone as the standard of care in *BRCA1/2* carriers.

… Clinical trials of interval salpingectomy with delayed oophorectomy are ongoing…….

Natl Compr Canc Netw NCCN ***2019***

Grazie per l'attenzione