

Mutazione BRCA e Chirurgia Profilattica

Francesco RASPAGLIESI, M.D.

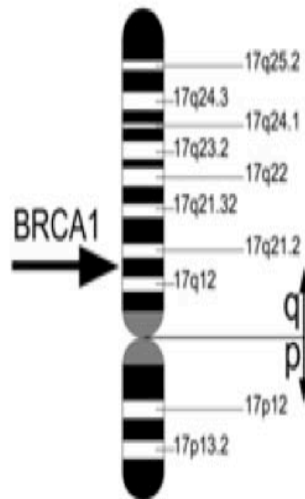
*Direttore Unità di Oncologia Ginecologica
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano*



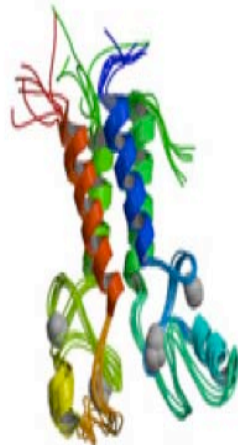
BRCA1 and BRCA2 Cancer Genes



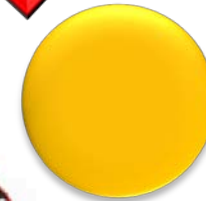
Chromosome 17



BRCA1

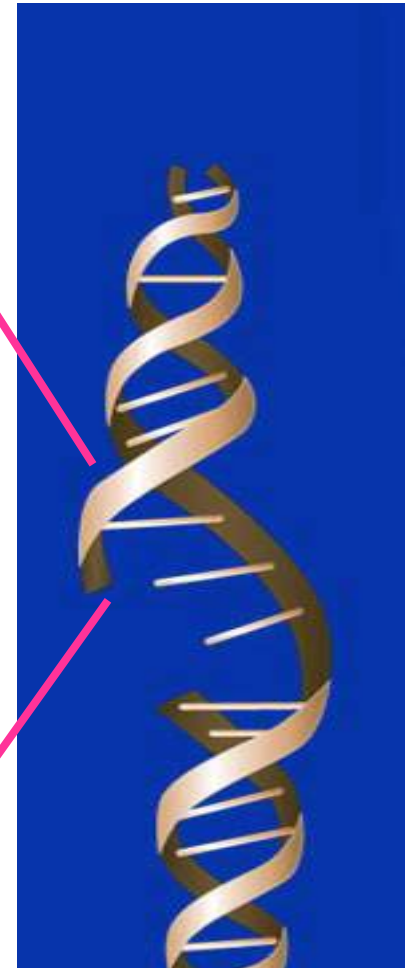


BRCA2



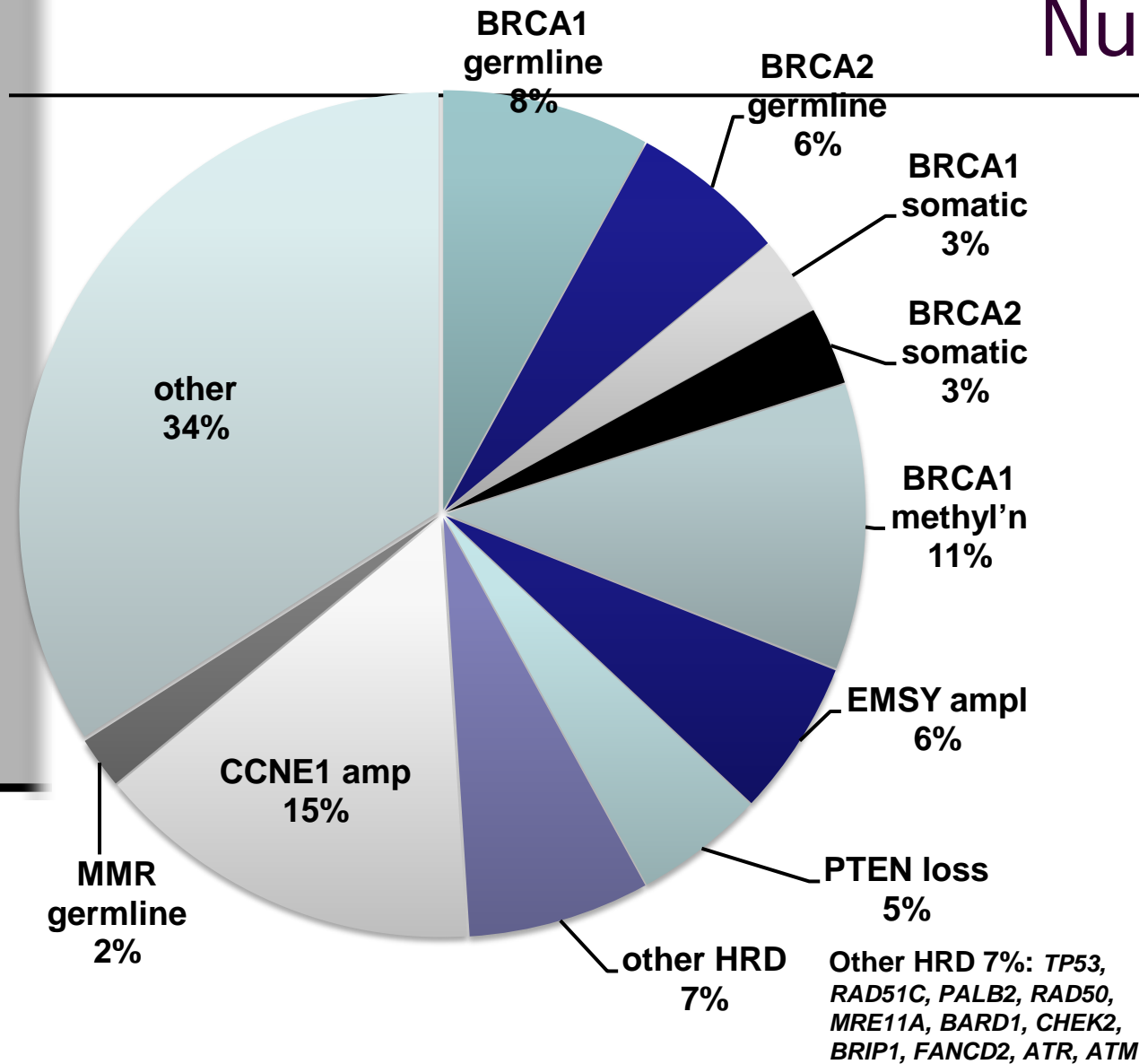
BRCA1

BRCA2



BRCA:

Nuove Evidenze



TCGA, *Nature* 2011; Tan et al, JCO 2008; Mendes-Pereira et al, EMBO Mol. Med. 2009



TEST GENETICO

- **Multipli casi di tumore mammario (in premenopausa) o ovarico nella stessa famiglia**
- **Paziente con tumore mammario e ovarico**
- **Tumore della tuba**
- **Tumore mammario bilaterale**
- **Tumore mammario nel maschio**
- **Un consanguineo con documentata mutazione BRCA**
- **Multipli casi di tumore mammario nelle diverse generazioni della stessa famiglia**



BRCA Risk Calculator

Available at: www.brcacalculator.com

BRCA

Please answer the following questions to evaluate your patient's risk for a *BRCA1* or *BRCA2* mutation.

Is the patient male or female?

☐

Male

☒

Female

Is the patient of Ashkenazi Jewish decent?

☐

Yes

☒

No

Has the patient ever been diagnosed with breast cancer?

☐

Yes

☒

No

Has the patient ever been diagnosed with ovarian cancer?

☐

Yes

☒

No

Family History

(Includes at least one first or second degree relative.)

Has anyone in your patient's family been diagnosed with breast cancer under the age of 50?

☒

Yes

☐

No

More than 1 relative?

☐

Yes

☒

No

Has anyone in your patient's family been diagnosed with ovarian cancer?

☒

Yes

☐

No

More than 1 relative?

☐

Yes

☒

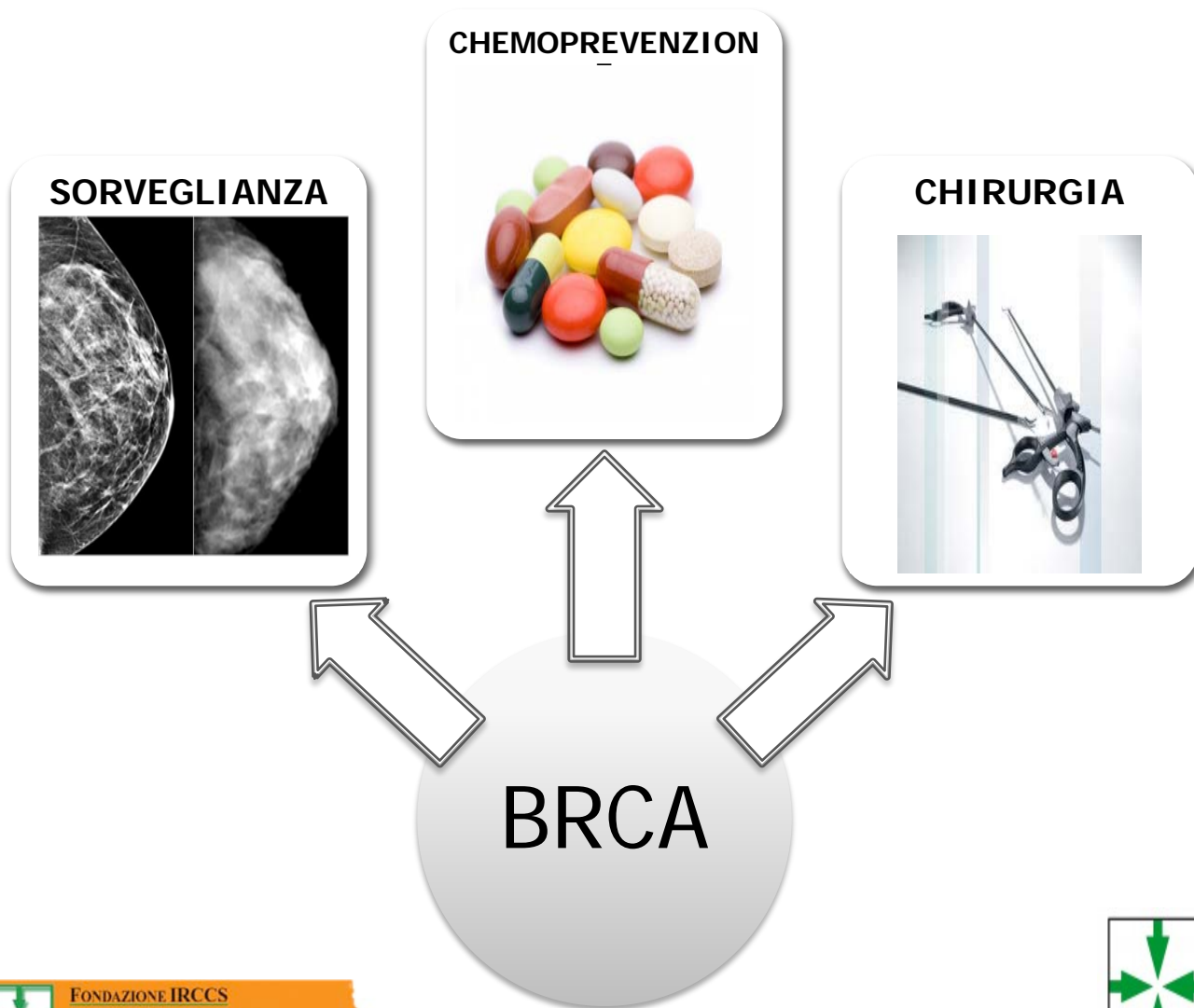
No

Calculated BRCA Mutation Risk:

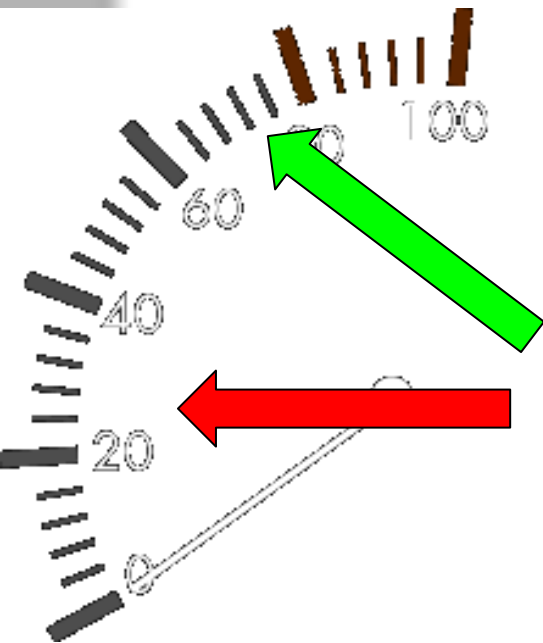
7.2%

[Reset](#)

BRCA



BRCA: SORVEGLIANZA



MAMMELLA

- Autopalpazione mensile
- Esame clinico ogni sei mesi
- Mammografia, ecografia e RMN

OVAIO

- Valutazione clinica ogni 6 mesi
- Ecografia pelvica trans-vaginale ogni 6 mesi
- Dosaggio CA125 ogni 6 mesi

BRCA: SORVEGLIANZA

Multicenter Surveillance of Women at High Genetic Breast Cancer Risk Using Mammography, Ultrasonography, and Contrast-Enhanced Magnetic Resonance Imaging (the High Breast Cancer Risk Italian 1 Study)

501 DONNE CON MUTAZIONE BRCA1/2 O RISCHIO ALTO
52 TUMORI MAMMARI DIAGNOSTICATI
94% ALLO SCREENING
6% CANCRI D'INTERVALLO

Esame	Sensitività	P Value
Palpazione	18%	
Rx mammografia	55%	
Ecografia	52%	
RMI con mdc	91%	<0.001
RX mammo + eco	63%	

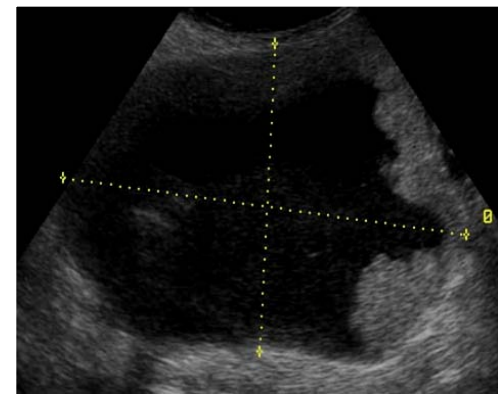
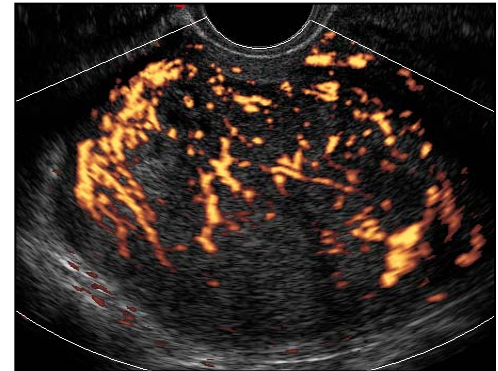
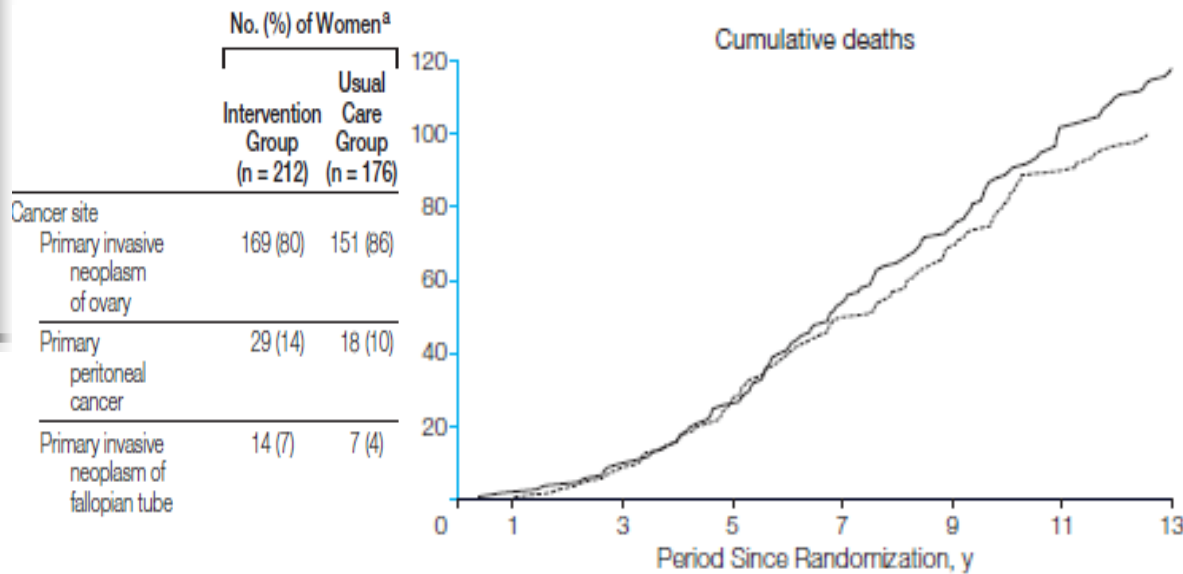
BRCA: SORVEGLIANZA PER TUMORE OVAIO

ONLINE FIRST

JAMA 2011 Jun; 305(22): 2295-2303

Effect of Screening on Ovarian Cancer Mortality

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial



BRCA: CHEMOPREVENZIONE

CHEMOPREVENZION



MAMMELLA

- Tamoxifene
- Raloxifene
- Vitamina A e Retinoidi

OVAIO

- Contraccettivi orali
- Vitamina A e Retinoidi

Fisher et al., J Natl Canc Inst 2005

Vogel et al, JAMA 2006

King et al, JAMA 2001

Gronwald J, et al., IJC 2006

BRCA: CHIRURGIA PROFILATTICA

CHIRURGIA



BRCA: CHIRURGIA PROFILATTICA

CHIRURGIA



- Mastectomia
- Annessiectomia

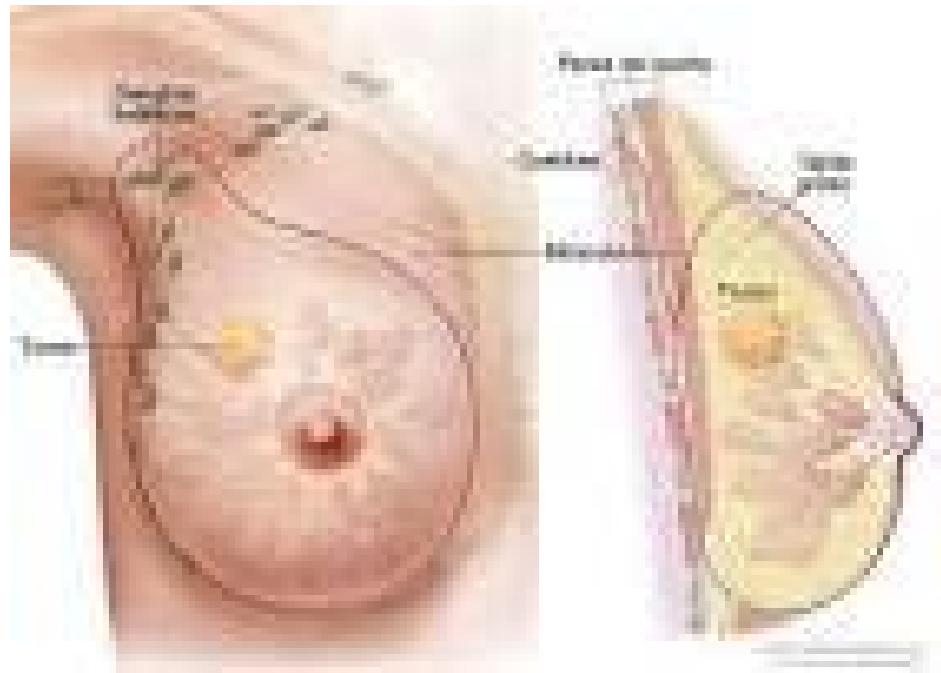
BRCA: CHIRURGIA PROFILATTICA MAMMARIA

CHIRURGIA



Mastectomia profilattica contro-laterale

Mastectomia profilattica bilaterale



BRCA: CHIRURGIA PROFILATTICA MAMMARIA

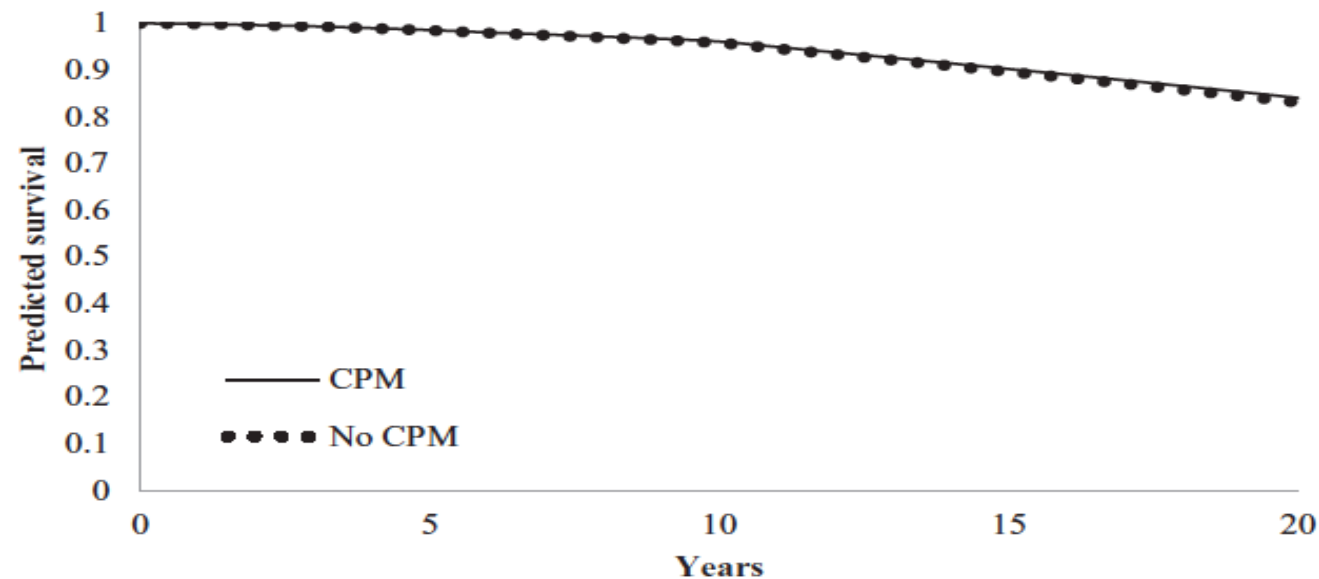
CHIRURGIA



Mastectomia profilattica contro-laterale – **Popolazione generale**

Survival Outcomes After Contralateral Prophylactic Mastectomy: A Decision Analysis

Pamela R. Portschy, Karen M. Kuntz, Todd M. Tuttle



FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

BRCA: CHIRURGIA PROFILATTICA MAMMARIA

CHIRURGIA



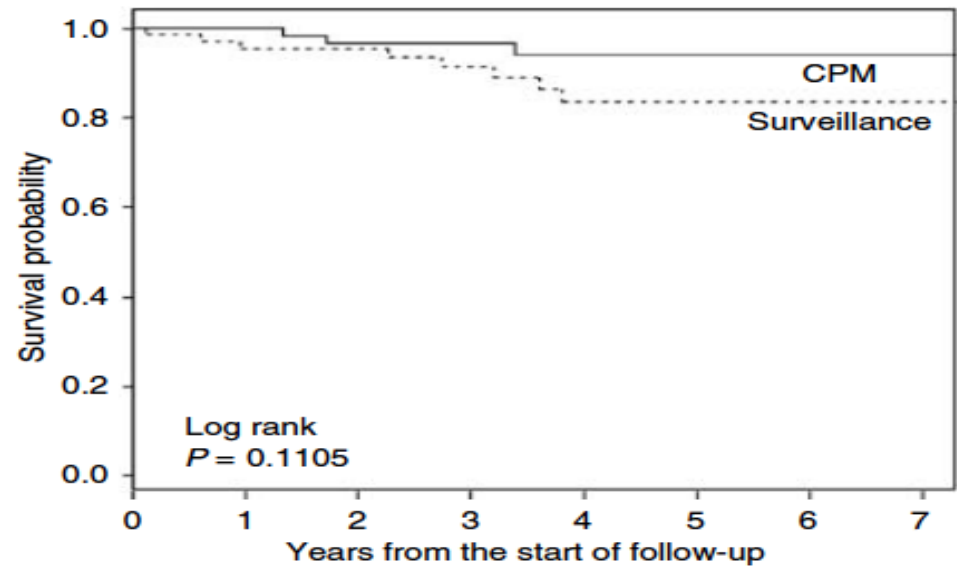
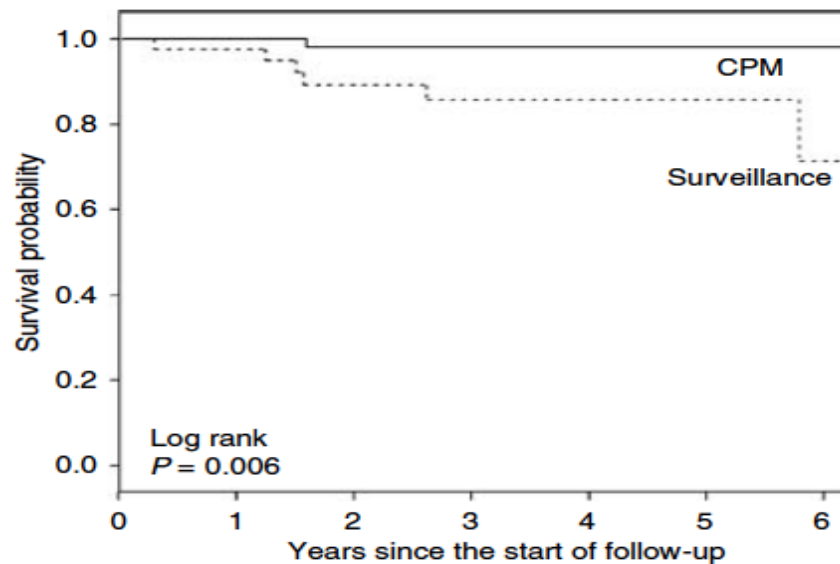
Risk reduction of contralateral breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers

Van Sprundel et al, BJC. 2005



TUMORE CONTROLATERALE

SOPRAVVIVENZA



BRCA: CHIRURGIA PROFILATTICA

CHIRURGIA



Mastectomia profilattica bilaterale Pazienti con mutazione BRCA 1-2



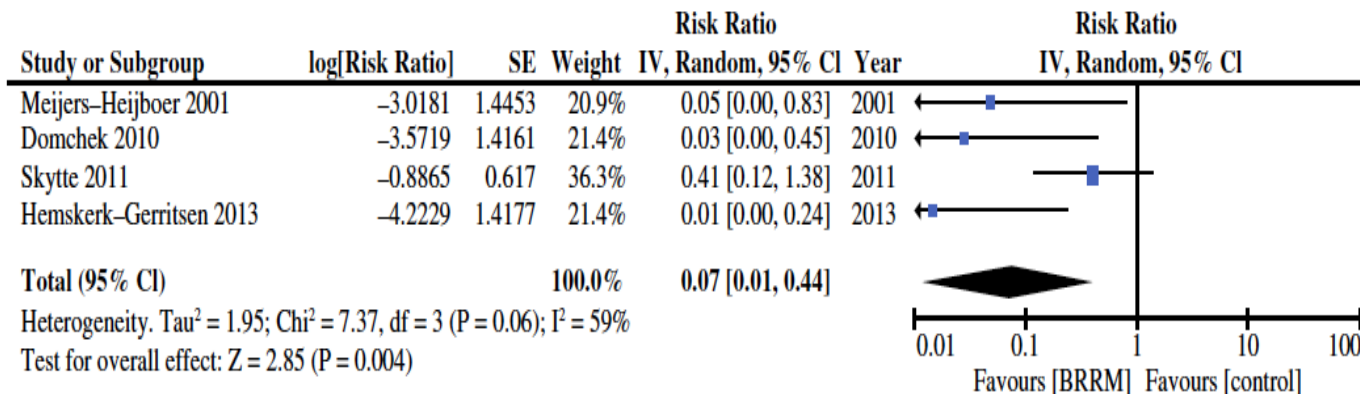
Pazienti con mutazione BRCA1-2 : CHIRURGIA PROFILATTICA – PRO

CHIRURGIA



Bilateral Risk-Reduction Mastectomy in BRCA1 and BRCA2 Mutation Carriers: A Meta-analysis

Francesca De Felice, MD¹, Claudia Marchetti, MD², Angela Musella, MD², Innocenza Palaia, PhD², Giorgia Perniola, PhD², Daniela Musio, MD¹, Ludovico Muzii, PhD², Vincenzo Tombolini, MD¹, and Pierluigi Benedetti Panici, MD²



De Felice et al, Ann Surg Oncol. 2015

Pazienti con mutazione BRCA1-2 : CHIRURGIA PROFILATTICA – CONTRA

CHIRURGIA



- Non azzeramento del rischio
- Aspetti chirurgici (degenza / complicanze / cicatrici)
- Impatto psicologico
- Alterata immagine di se
- Allattamento

Pazienti con mutazione BRCA1-2

CHIRURGIA PROFILATTICA

Mastectomia profilattica bilaterale



Pazienti con mutazione BRCA1-2

CHIRURGIA PROFILATTICA ANNESSIALE

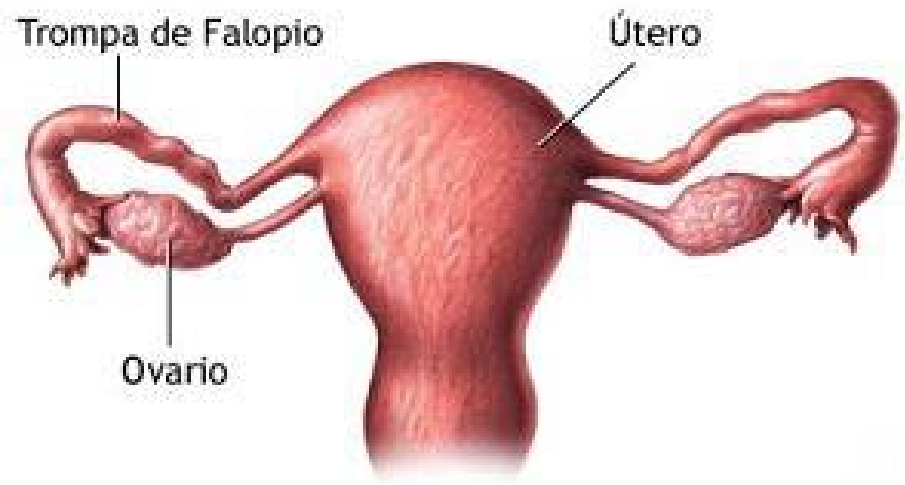
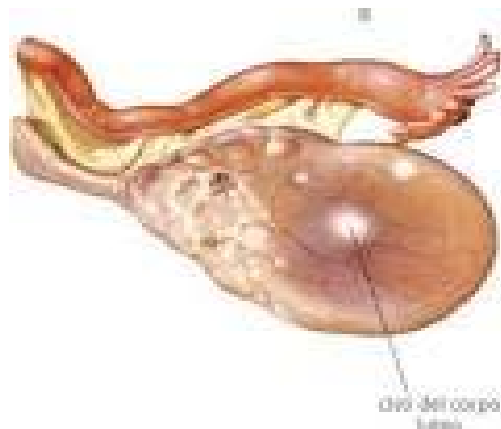
CHIRURGIA



Annessiectomia

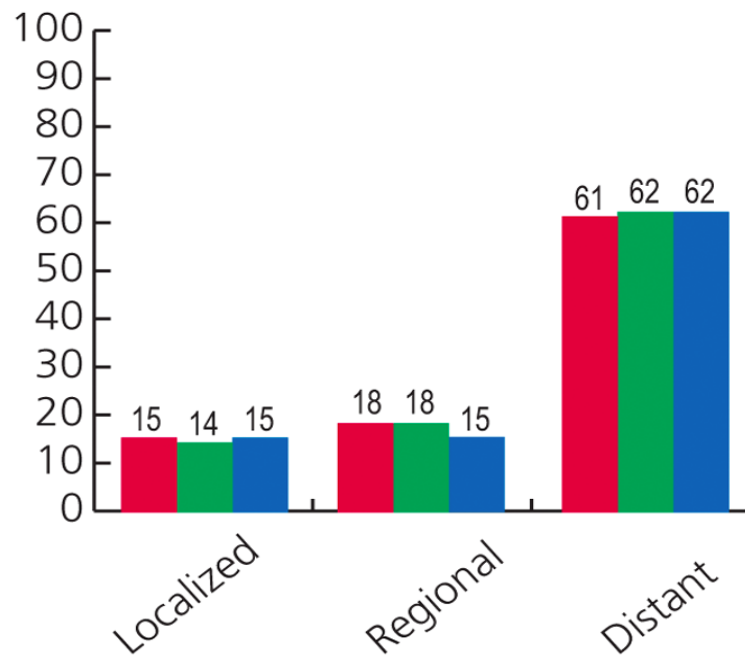


Salpingectomia / Fimbriectomia

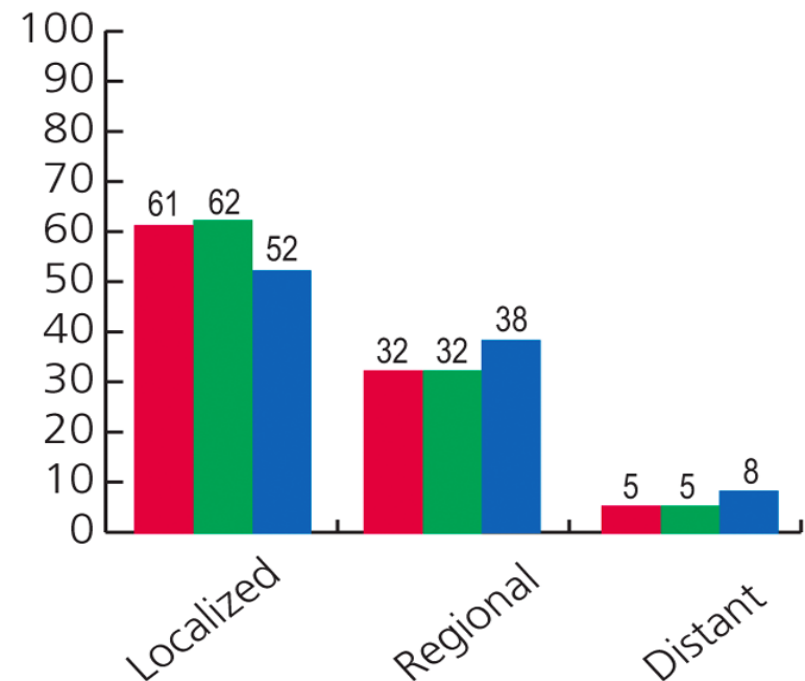


Il Cancro Ovarico: Una Malattia Aggressiva

Ovary



Female breast



BRCA: CHIRURGIA PROFILATTICA ANNESSIALE



Annessiectomia Laparoscopica

BRCA: CHIRURGIA PROFILATTICA ANNESSIALE

Risk-Reducing Salpingo-Oophorectomy for the Prevention of *BRCA1*- and *BRCA2*-Associated Breast and Gynecologic Cancer: A Multicenter, Prospective Study

Noah D. Kauff, Susan M. Domchek, Tara M. Friebe, Mark E. Robson, Johanna Lee, Judy E. Garber, Claudine Isaacs, D. Gareth Evans, Henry Lynch, Rosalind A. Eeles, Susan L. Neuhausen, Mary B. Daly, Ellen Matloff, Joanne L. Blum, Paul Sabbatini, Richard R. Barakat, Clifford Hudis, Kenneth Offit, and Timothy R. Rebbeck



Kauff et al, JCO. 2008

BRCA: CHIRURGIA PROFILATTICA ANNESSIALE

Table 3. Hazard Ratio for the Development of BRCA-Associated Gynecologic Cancer After RRSO

Mutation	No. of Patients	No. of Women Electing RRSO	Mean FU (months)	No. of Gynecologic Cancers After RRSO	No. of Women Under Surveillance	Mean FU (months)	No. of Gynecologic Cancers	Hazard Ratio	95% CI	P
<i>BRCA1</i> and <i>BRCA2</i>	792	509	40.3	3	283	40.1	10	0.03	0.03 to 0.41	.001
<i>BRCA1</i>	498	325	41.1	3	173	40.1	10	0.15	0.03 to 0.56	.005
<i>BRCA2</i>	294	184	39.0	0	110	33.7	2	0.00	Not estimable	

Riduzione del Rischio di Tumore Ginecologico 90%

Table 4. Hazard Ratio for the Development of BRCA-Associated Breast Cancer After RRSO

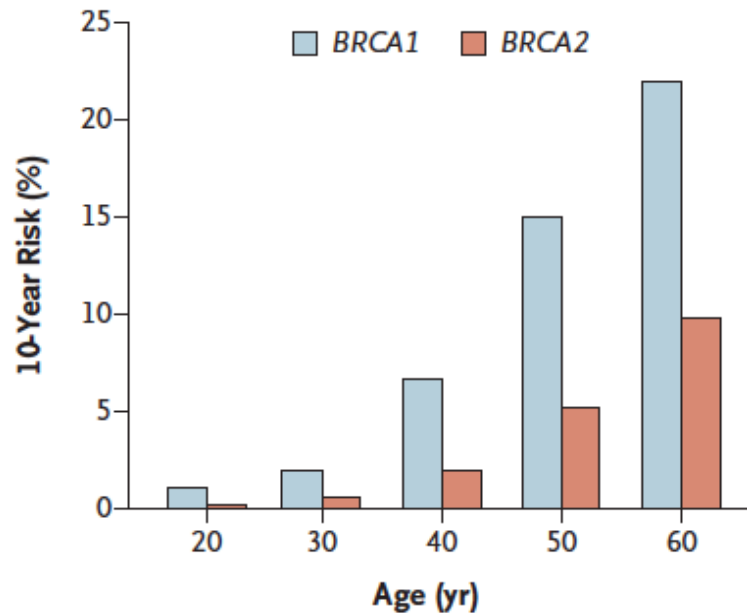
Mutation	No. of Patients	No. of Women Electing RRSO	Mean FU (months)	No. of Breast Cancers After RRSO	No. of Women Under Surveillance	Mean FU (months)	No. of Breast Cancers	Hazard Ratio	95% CI	P
<i>BRCA1</i> and <i>BRCA2</i>	597	303	36.4	19	294	36.4	19	0.57	0.29 to 0.96	.036
<i>BRCA1</i>	368	190	36.3	15	178	36.3	15	0.71	0.30 to 1.22	.16
<i>BRCA2</i>	229	113	36.6	4	116	36.6	4	0.24	0.08 to 0.92	.036

Rischio del Rischio Ca Mammario 43%

Abbreviations: RRSO, risk-reducing salpingo-oophorectomy; FU, follow-up.

A Quale Età è indicata la Chirurgia Profilattica

Ovarian Cancer



Robson and Offit., NEJM 2007

Effetti Negativi dell'Annessiectomia

Bone mineral density and fractures after risk-reducing salpingo-oophorectomy in women at increased risk for breast and ovarian cancer



Ingrid E. Fakkert^{a,1}, Elske Marije Abma^{b,1}, Iris G. Westrik^{c,1}, Joop D. Lefrandt^{c,1}, Bruce H.R. Wolffenbuttel^{d,1}, Jan C. Oosterwijk^{e,1}, Riemer H.J.A. Slart^{f,1}, Eveline van der Veer^{g,1}, Geertruida H. de Bock^{a,1}, Marian J.E. Mourits^{h,*,1}

2015

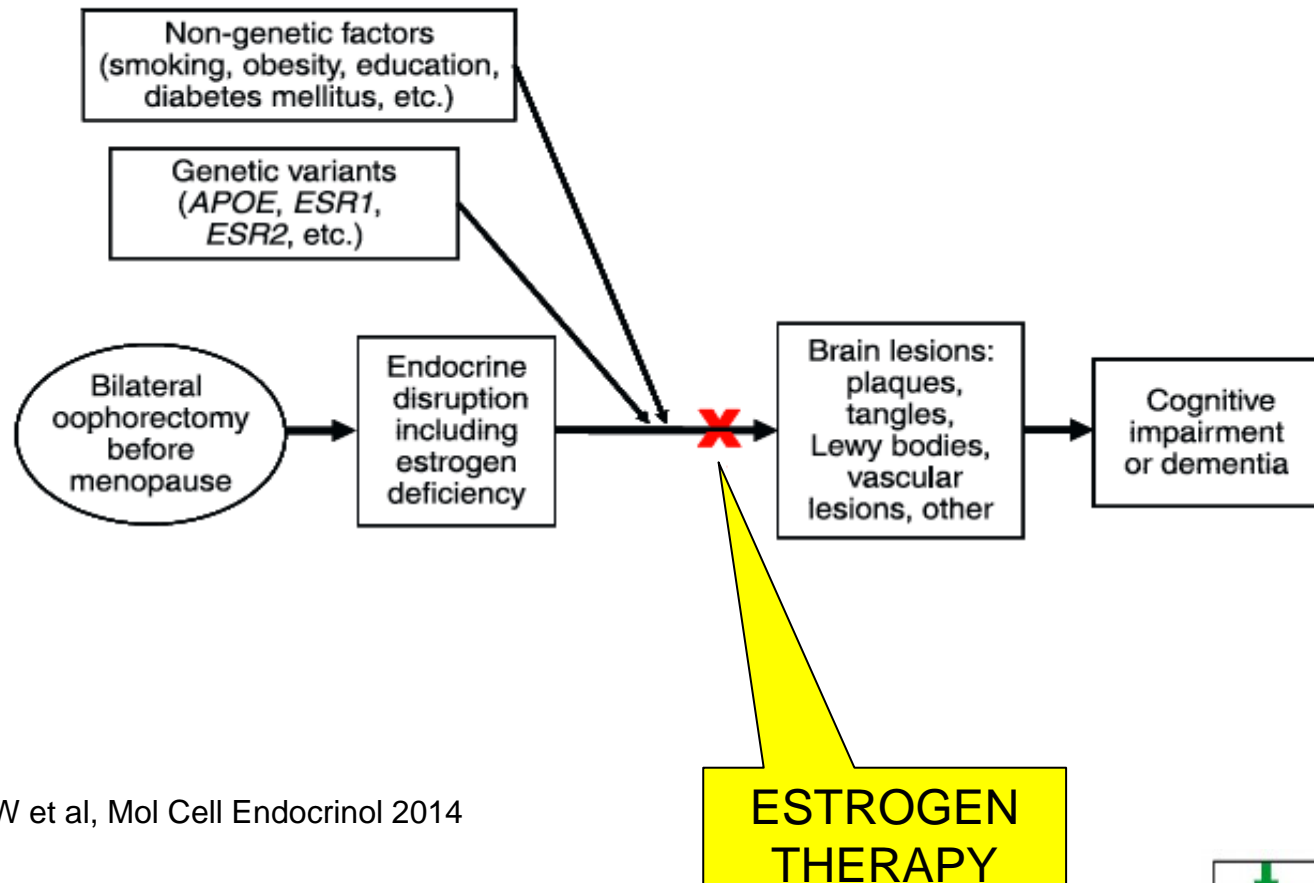
Oophorectomy, estrogen, and dementia: A 2014 update

Walter A. Rocca^{a,b,*}, Brandon R. Grossardt^c, Lynne T. Shuster^d

Oophorectomy, menopause, estrogen treatment, and cognitive aging: Clinical evidence for a window of opportunity

Walter A. Rocca^{a,b,*}, Brandon R. Grossardt^c, Lynne T. Shuster^d

Disturbi cognitivi



Rocca W et al, Mol Cell Endocrinol 2014

BRCA: CHIRURGIA PROFILATTICA ANNESSIALE

- In uno studio prospettico su oltre 1300 pazienti sani con mutazione BRCA1 e 2, la terapia ormonale sostitutiva, non è stata associata ad un aumento del rischio di tumore alla mammella

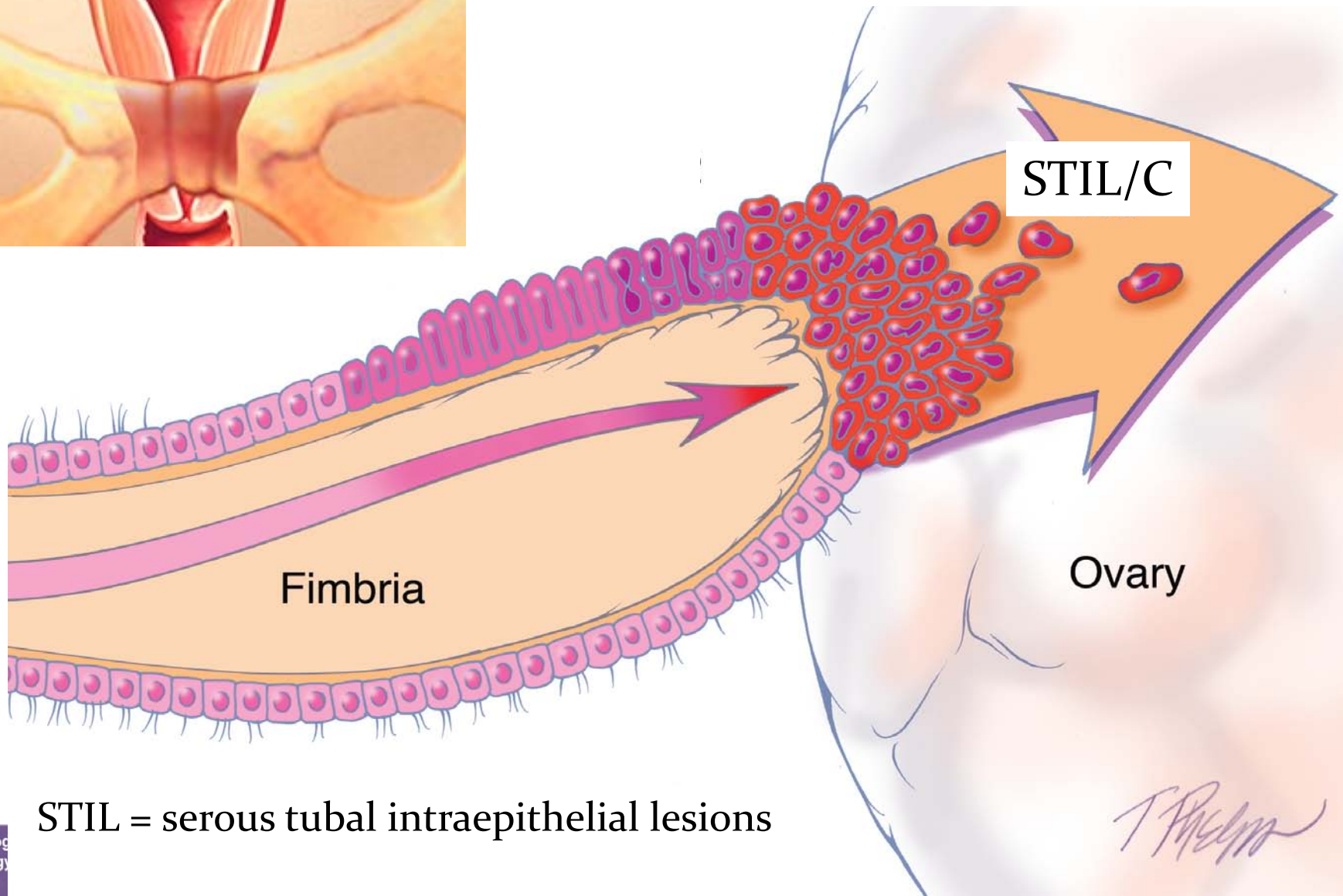
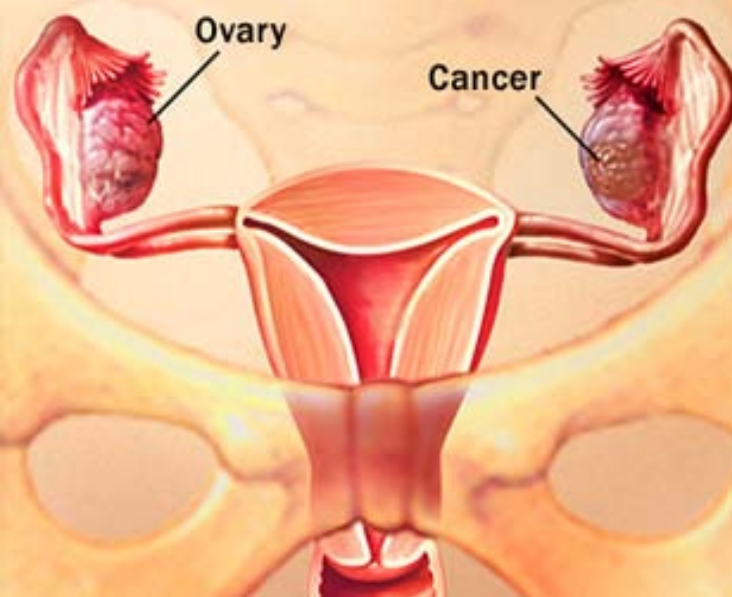
Domchek ASCO 2011

- In uno studio retrospettivo su oltre 400 pazienti BRCA, ha dimostrato che la terapia estrogenica dopo chirurgia profilattica non aumenta il rischio di tumore mammario

Rebbeck et al., JCO 2005

- Maggiore evidenza è necessaria

IPOTESI PATOGENETICA

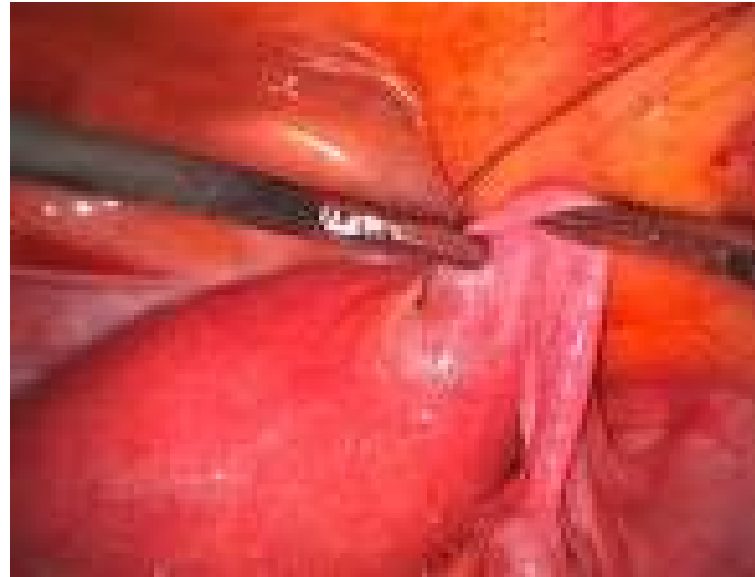


STIL = serous tubal intraepithelial lesions

Salpingectomy



TAKE A STEP
FORWARD



La salpingectomy dovrebbe garantire gli stessi risultati della annessiectomia, con minor incidenza di effetti collaterali legati alla deprivazione estrogenica

Salpingectomy/Fimbriectomy



Prophylactic Salpingectomy With Delayed Oophorectomy

Estimated Completion Date: 2018



Early Salpingectomy (Tubectomy) With Delayed Oophorectomy in BRCA1/2 Gene Mutation Carriers (TUBA)

Estimated Completion Date: 2025



ClinicalTrials.gov



Take Home Messages

Mastectomia Profilattica:

- ❖ Importanza della comunicazione e della corretta informazione
- ❖ Ponderare costi e benefici



Take Home Messages

Annessectomia Profilattica:

- ❖ Riduce il rischio di ca Ovarico/tubarico
- ❖ Riduce il rischio di ca mammario
- ❖ Importanza della Informazione

Grazie



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