TUMORE OVARICO E BRCA: CAMBIARE IL FUTURO SI PUO'

Stefano Greggi
Ginecologia Oncologica
Istituto Nazionale dei Tumori di Napoli
IRCCS Fondazione "G. Pascale"

ACTO PIEMONTE
ALLEANZA CONTRO il TUMORE OVARICO

Aula Delle Piane
P.O. Sant'Anna
AOU Città della Salute
e della Scienza

Torino
8 Maggio 2019

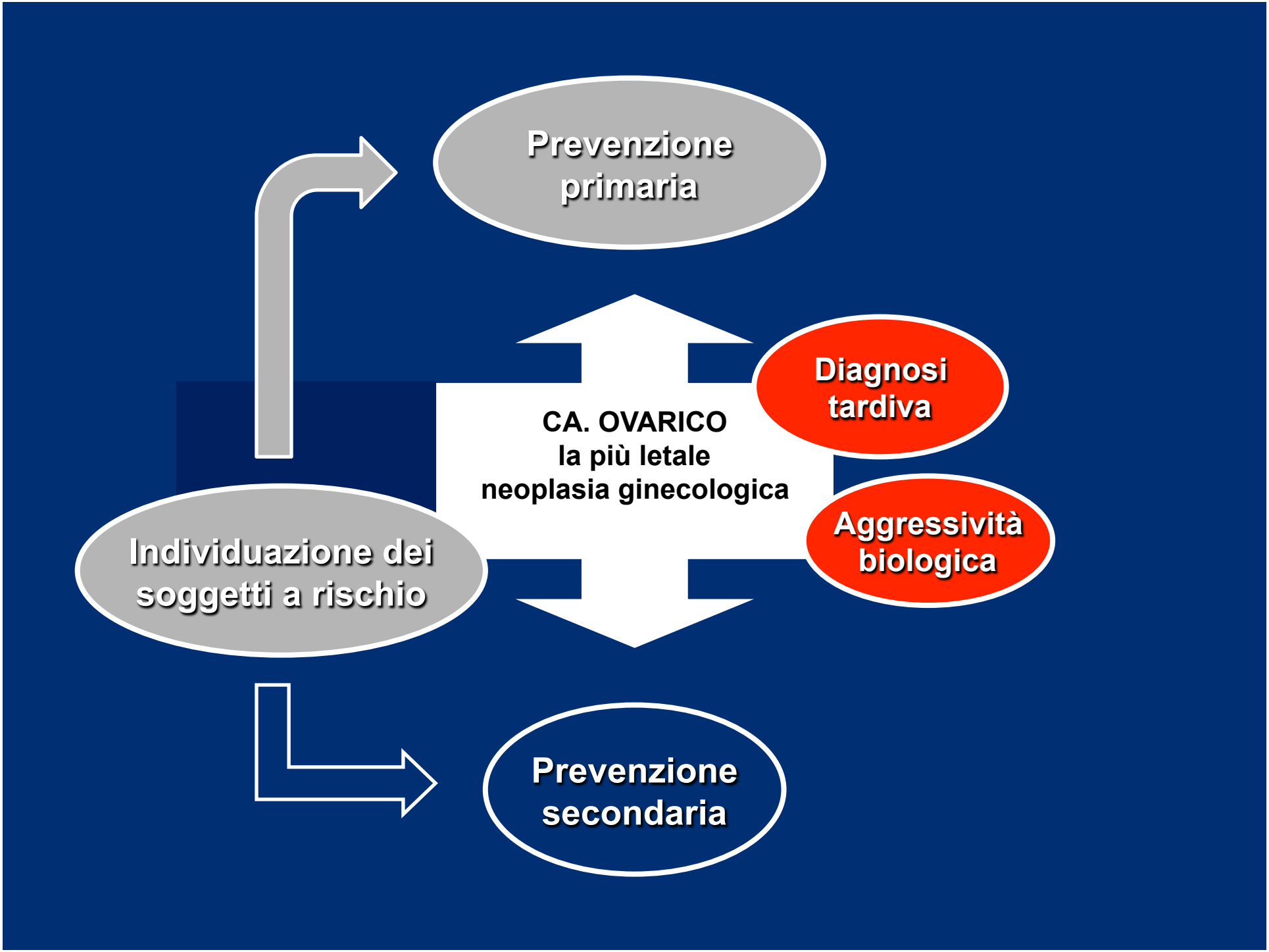
Prevenzione primaria del carcinoma ovarico

Prime 5 Cause di Morte Tumorali per sesso e fascia di età

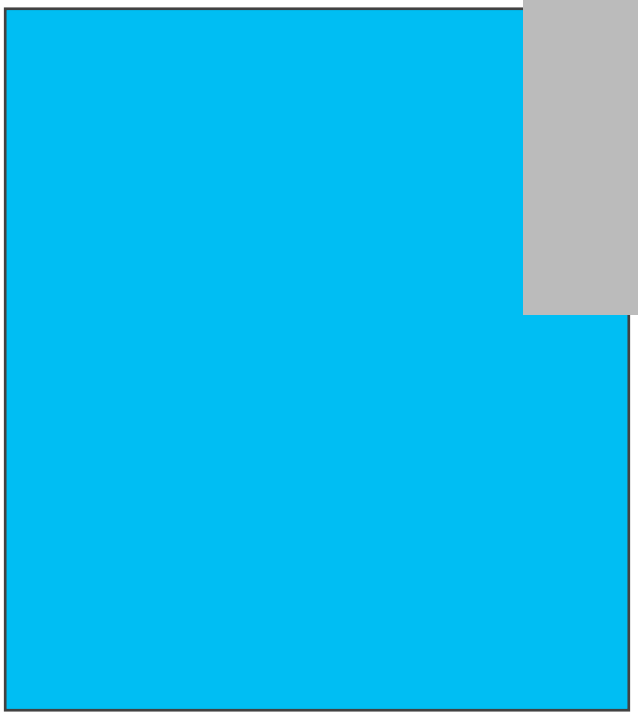
Pool AIRTUM (2007-2010)

Femmine		
anni 0-49	**anni 50-69**	**anni 70+**
Mammella (29%)	Mammella (23%)	Mammella (16%)
Polmone (10%)	Polmone (14%)	Colon-retto (12%)
Colon-retto (7%)	Colon retto (10%)	Polmone (11%)
Ovaio (6%)	Pancreas (7%)	Pancreas (8%)
Sist. nervoso centrale (6%)	Ovaio (	

CA. OVARICO
3° Causa di morte per tumore
30-50aa


Prevenzione primaria
Diagnosi tardiva
CA. OVARICO
la più letale
neoplasia ginecologica
Aggressività biologica
Individuazione dei soggetti a rischio
Prevenzione secondaria

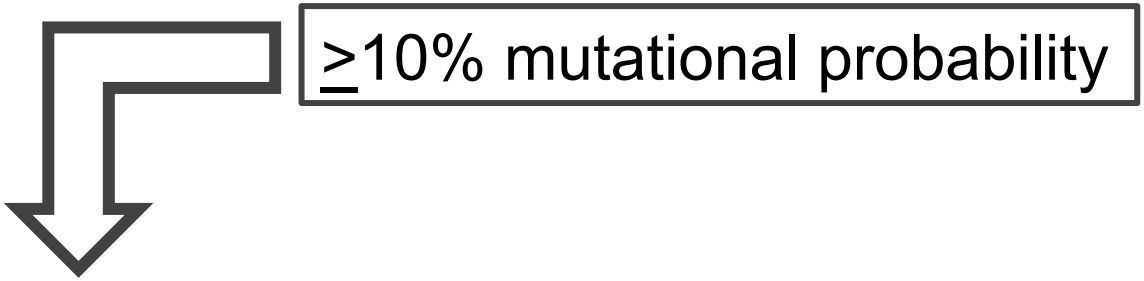
Ovarian Cancer



20% unselected OC: BRCAm
40% BRCAm: no family history
35% BRCAm: >60y
Introduction of targeted therapies

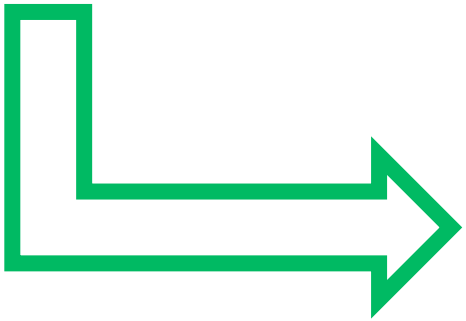
Sporadic 90%

Her./Fam. OC ≤10%



The Cancer Genetic Counseling Process

Pretest Counseling	Educational - Informative Psychological evaluation
Genetic Testing	Labs & interpretation of results

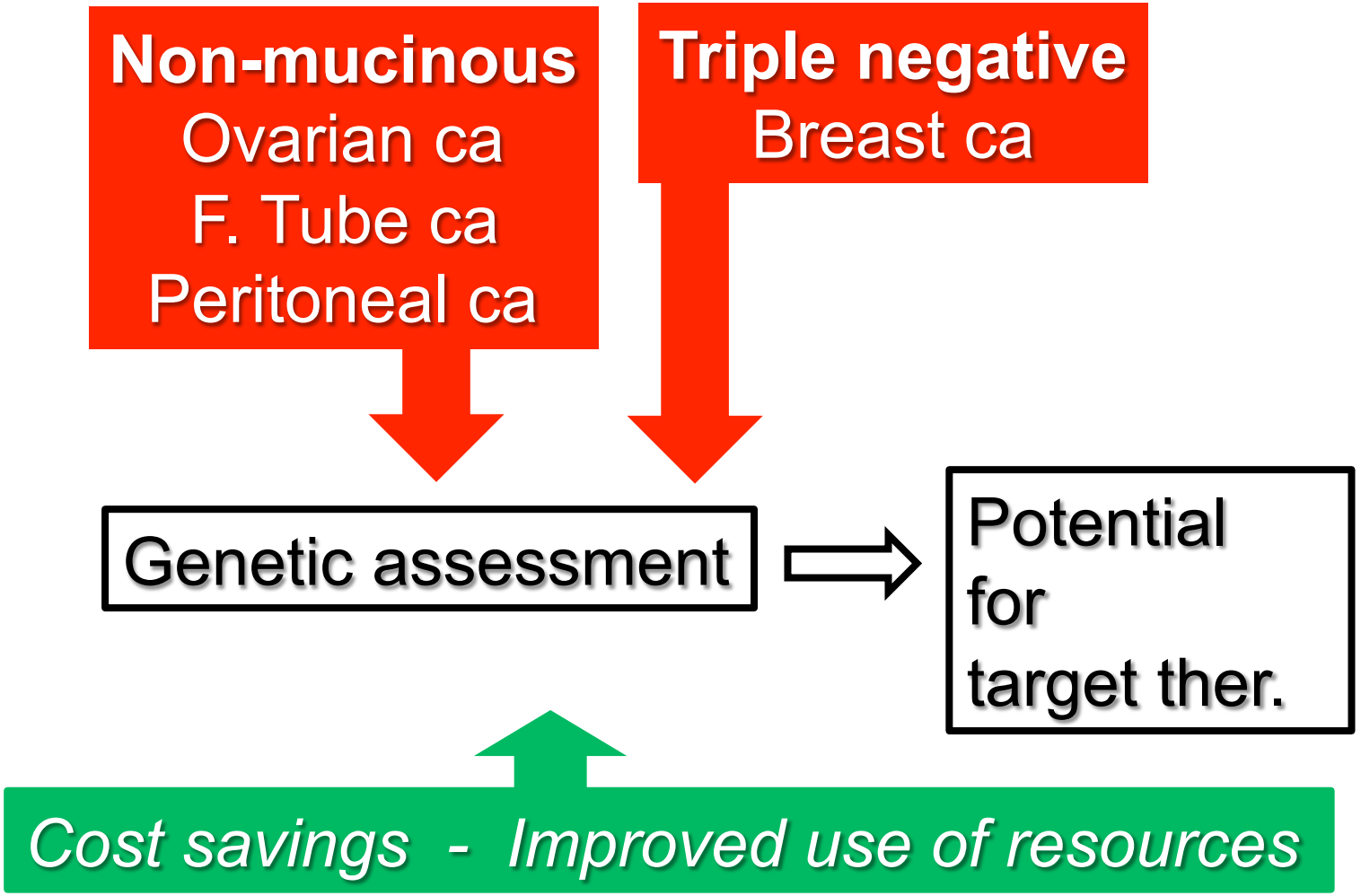


Post-test Follow-up

Preventive options & psychol. monitoring

Offit, 1987 Greggi, 2001

Utility of a Histology-based referral strategy



1980-99

Pochissimi centri
Esperienze “amatoriali”
Test gen. indisponibile

GYNECOLOGIC ONCOLOGY 39, 300–304 (1990)

Analysis of 138 Consecutive Ovarian Cancer Patients: Incidence and Characteristics of Familial Cases

STEFANO GREGGI,* MAURIZIO GENUARDI,† PIERLUIGI BENEDETTI-PANICI,* ROSA CENTO,* GIOVANNI SCAMBIA,* GIOVANNI NERI,† AND SALVATORE MANCUSO*,[1]

Istituto di Clinica Ginecologica e Ostetrica,

Eur J Cancer, Vol. 27, No. 2, pp. 113–115, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

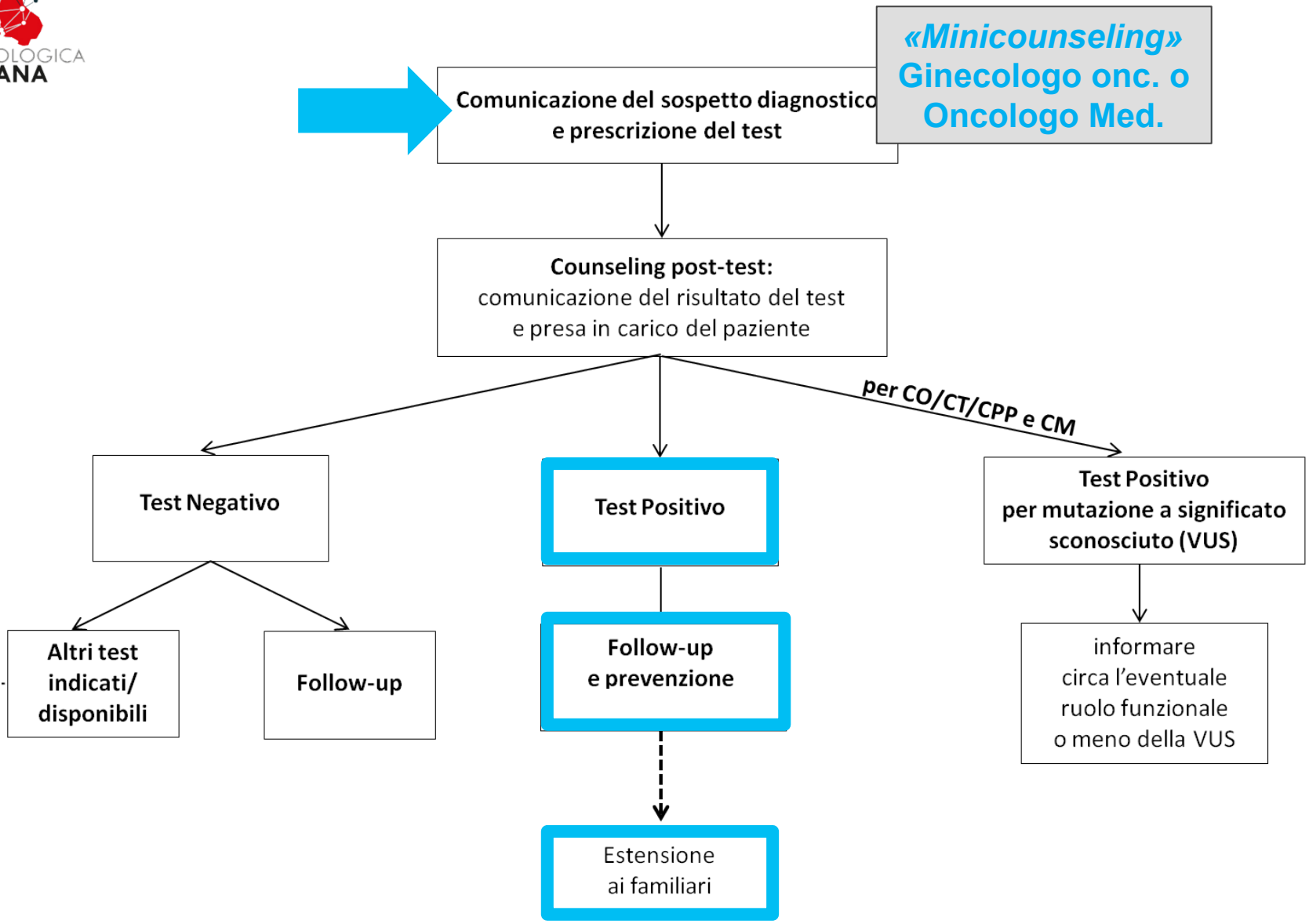
Establishment of a European Registry for Familial Ovarian Cancer

Correspondence to S. Greggi.
Received 12 Oct. 1990; accepted 23 Nov. 1990.

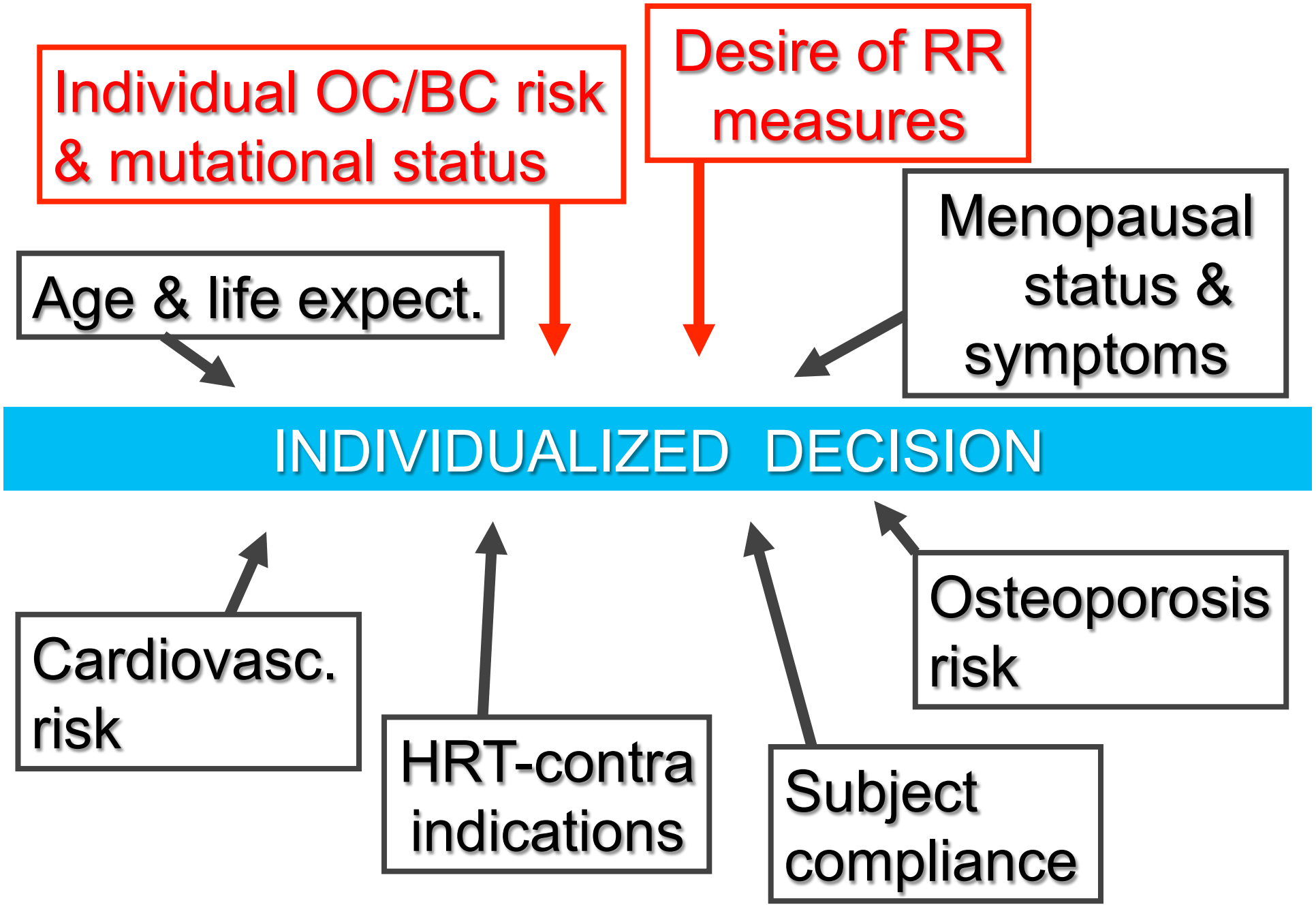
1999-00+ → Centri con adeguata esperienza di cons. oncogenetica
Test gen. disponibile

2010+ → Inizio esperienze reg. “in rete”
⬆ Problematiche SSN
⬆ Problematiche gen. mol.

RETE ONCOLOGICA CAMPANA



Surveillance
Chemoprevention
Prophylactic Surgery

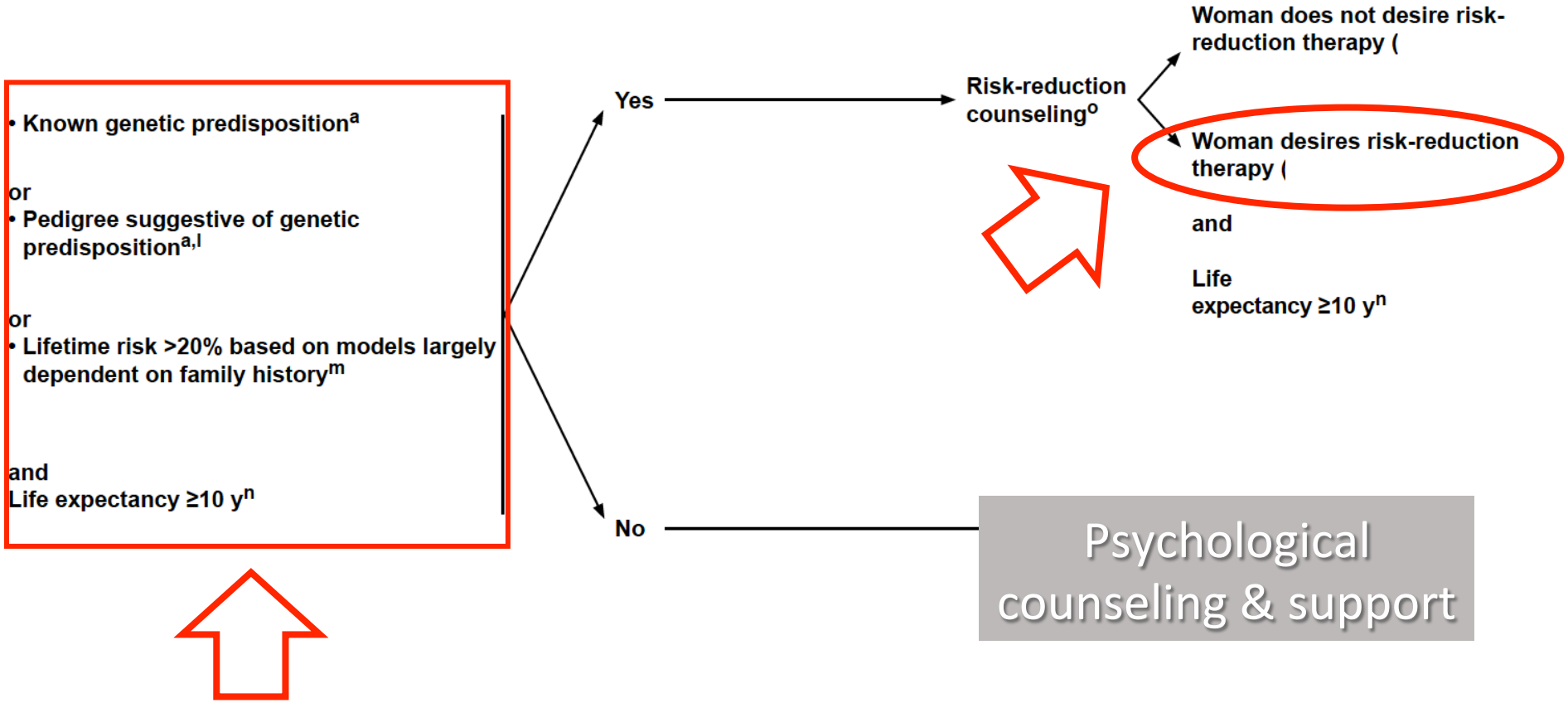

Individual OC/BC risk & mutational status
Desire of RR measures
Age & life expect.
Menopausal status & symptoms
INDIVIDUALIZED DECISION
Cardiovasc. risk
HRT-contra indications
Subject compliance
Osteoporosis risk

National Comprehensive Cancer Network®

NCCN Guidelines
Cancer Risk Reduction

NCCN Guidelines Index
Table Of Contents
Discussion

ADDITIONAL RISK ASSESSMENT



Chemioprevenzione

Contraccettivi Orali

Oral-contraceptive use	Cases (n=799)	Controls (n=2424)	Multivariable* odds ratio (95% CI)	p
Never	432 (54%)	995 (41%)	1	
Ever	367 (46%)	1429 (59%)	0·53 (0·43–0·66)	<0·0001
Duration, years				
Never	432 (54%)	995 (41%)		
0–1·0	118 (15%)	358 (15%)	0·67 (0·50–0·89)	0·006
1·1–3·0	86 (11%)	278 (11%)	0·63 (0·46–0·86)	0·004
3·1–5·0	48 (6%)	231 (10%)	0·36 (0·25–0·53)	<0·0001
>5·0	113 (14%)	541 (22%)	0·47 (0·35–0·62)	<0·0001
Missing	2 (0·3%)	21 (0·9%)		
Trend (per year)			0·95 (0·92–0·97)	<0·0001

* Variables used are parity (yes or no), breastfeeding (no, within 1 year, and more

Studio Caso-Controllo 799 *BRCA*+ cancro ovarico
2424 *BRCA*+ controlli sani

• Significativa riduzione del rischio di cancro ovarico
- *BRCA*1 44%
- *BRCA*2 61%

Hereditary Ovarian Cancer Clinical Study Group, 2007

Chemioprevenzione

Contraccettivi Orali

	Interventi	n		Cancro	OR		
		IG	CG		BRCA 1	BRCA 2	BRCA 1 o 2
Narod, 2002	Contraccettivi Orali	1344	1376	CM	1.20	0.94	-
Heimdal, 2002					2.00		
Witthemore, 2004		354	357	CO	-	-	0.4
Narod, 1998							0.85

Meta-analysis of *BRCA*1/2 mutation carriers
with (n=1503) and without (n=6315) ovarian cancer
Significant reduction of OC risk (approximately 50%)
(*BRCA*1: RR=0.51; *BRCA*2: RR=0.52)

Iodice, 2010

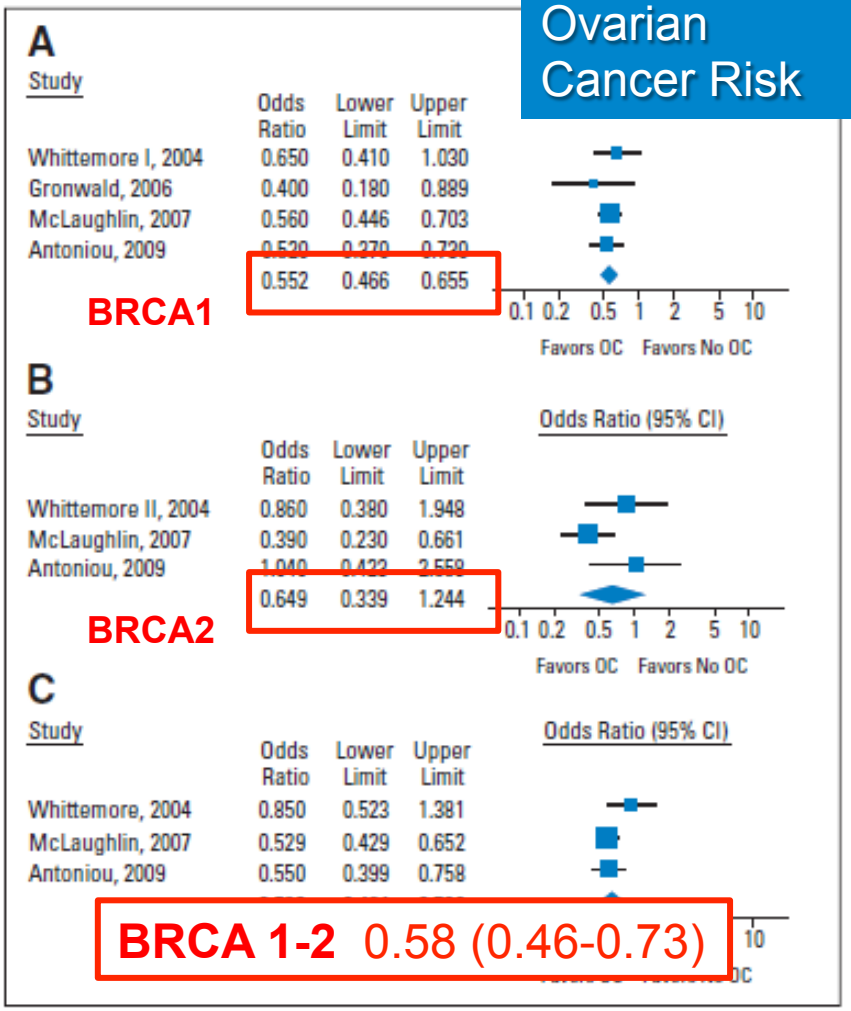
VOLUME 31 · NUMBER 33 · NOVEMBER 20 2013

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

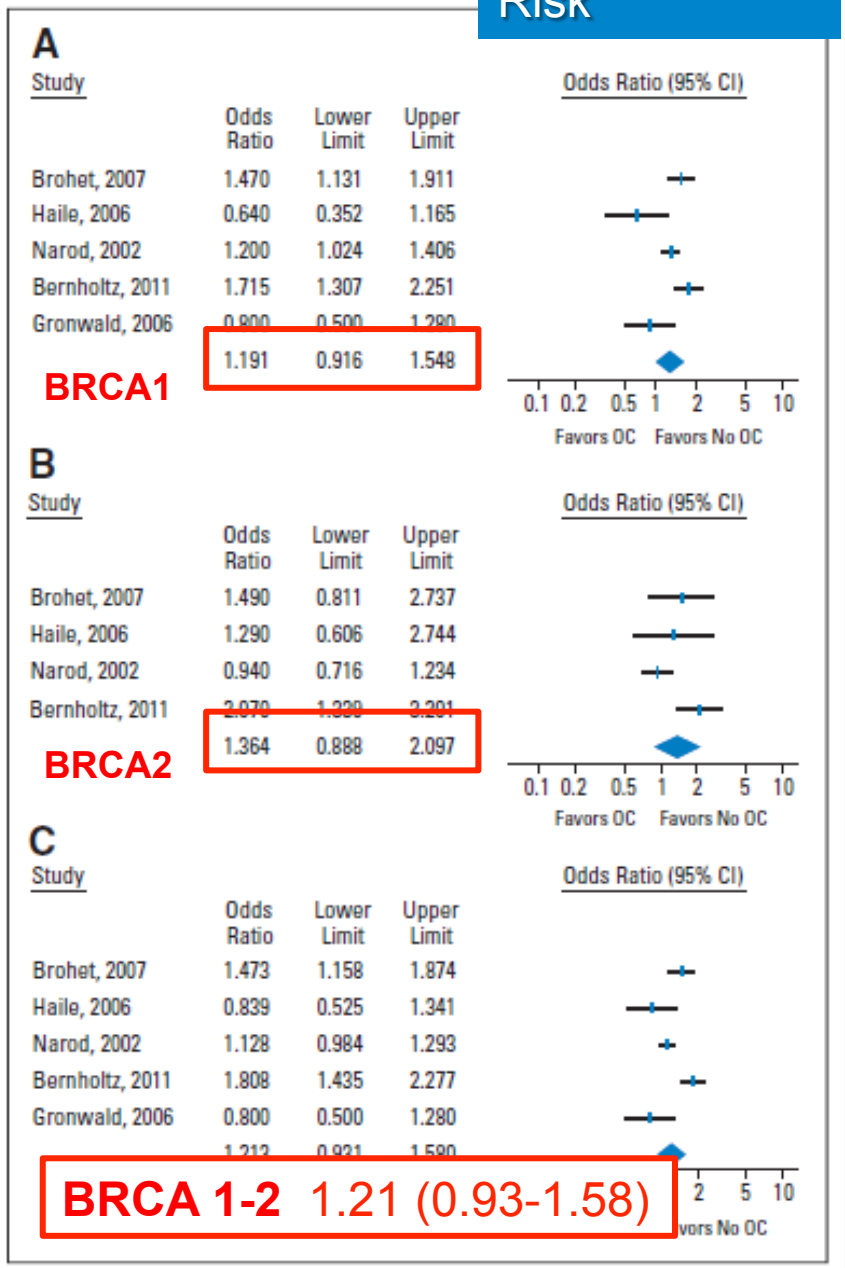
Oral Contraceptives and Risk of Ovarian Cancer and Breast Cancer Among High-Risk Women: A Systematic Review and Meta-Analysis

Patricia G. Moorman, Laura J. Havrilesky, Jennifer M. Gierisch, Remy R. Coeytaux, William J. Lowery, Rachel Peragallo Urrutia, Michaela Dinan, Amanda J. McBroom, Vic Hasselblad, Gillian D. Sanders, and Evan R. Myers

Ovarian Cancer Risk



Breast Cancer Risk



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†

Ovarian cancer risk reduction	
Lifestyle modifications/exposures	
The use of the OCP may be considered as a risk-reducing measure for ovarian cancer	II, C
Screening	
Before 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 carried out at age 35–40	II, B
Risk-reducing salpingectomy alone is not recommended, outside the setting of a clinical trial	V, C

BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

WOMEN

- Breast awareness[1] starting at age 18 y.
- Clinical breast exam, every 6–12 mo,[2] starting at age 25 y.
- Breast screening[3,4]
  - Age 25–29 y, annual breast MRI[5] screening with contrast[6] (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
  - Age 30–75 y, annual mammogram with consideration of tomosynthesis and breast MRI[5] screening with contrast.
  - Age >75 y, management should be considered on an individual basis.
  - For women with a *BRCA* pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram and breast MRI should continue as described above.
- Discuss option of risk-reducing mastectomy
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
- Recommend risk-reducing salpingo-oophorectomy (RRSO),[7] typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with *BRCA2* pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with *BRCA1* pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 y in patients with *BRCA2* pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery. See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer - Principles of Surgery.
  - Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy, and related medical issues.
  - Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be gene-specific.
- Limited data suggest that there may be a slightly increased risk of serous uterine cancer among women with a *BRCA1* pathogenic/likely pathogenic variant. The clinical significance of these findings is unclear. Further evaluation of the risk of serous uterine cancer in the *BRCA* population needs to be undertaken. The provider and patient should discuss the risks and benefits of concurrent hysterectomy at the time of RRSO for women with a *BRCA1* pathogenic/likely pathogenic variant prior to surgery.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.
- For those patients who have not elected RRSO, transvaginal ultrasound combined with serum CA-125 for ovarian cancer screening, although of uncertain benefit, may be considered at the clinician's discretion starting at age 30–35 y.
- Consider risk reduction agents as options for breast and ovarian cancer, including discussing risks and benefits (See Discussion for details). (See NCCN Guidelines for Breast Cancer Risk Reduction).
- Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.

Footnotes on next page (BRCA-A 2 of 2)

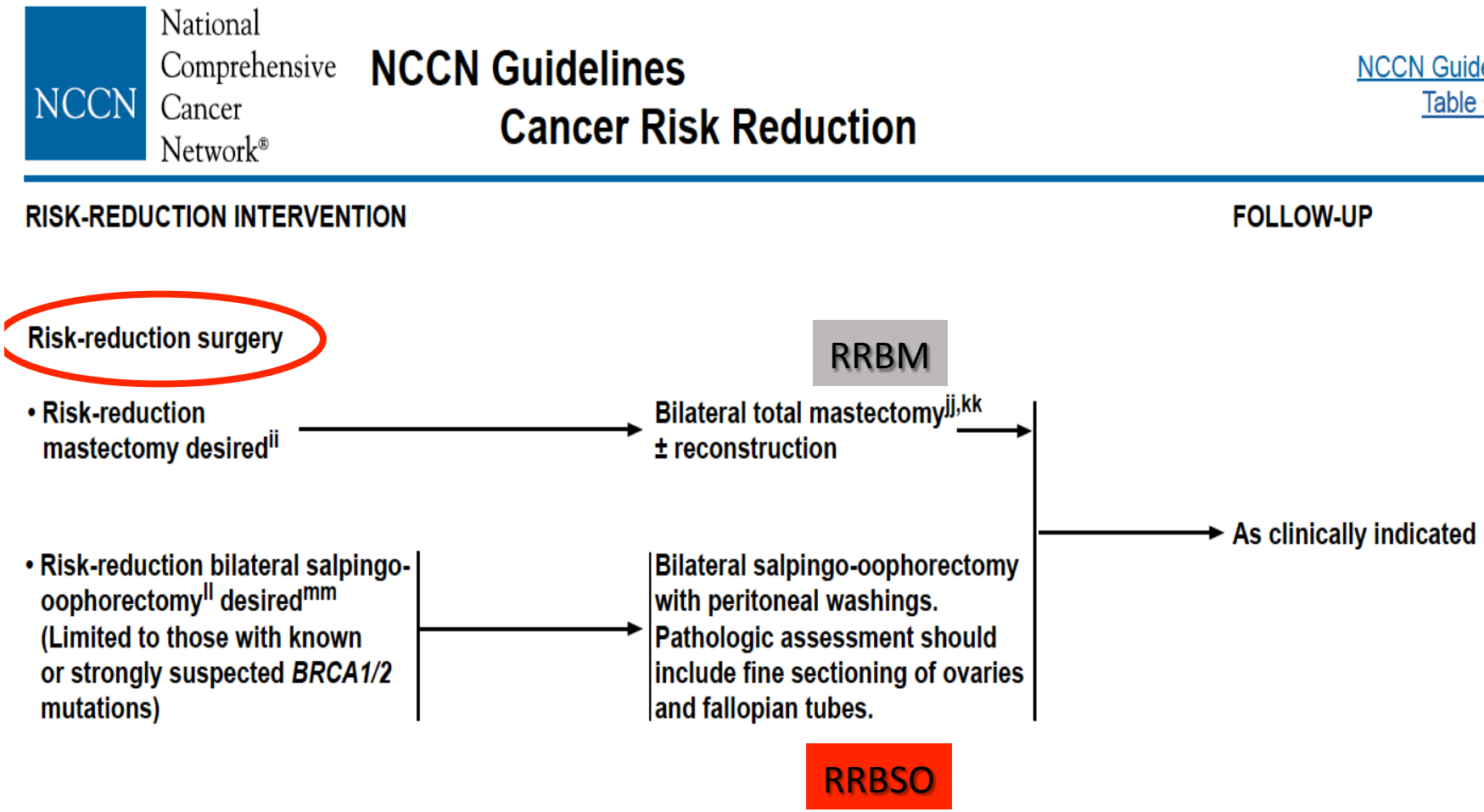
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

National Comprehensive Cancer Network®

NCCN Guidelines
Cancer Risk Reduction

NCCN Guidelines Index
Table Of Contents
Discussion



Prophylactic Salpingo ± oophorectomy

INTERVENTIONAL

in *BRCA*m women
after childbearing
Aged >30y

OPPORTUNISTIC
(*incidental*)

in the case of
pelvic surgery
for benign disease
Aged >40-45y

Annessectomia Profilattica (*RRBSO*)

Tumori ovarici, tubarici e peritoneali

Author	Interventions	Population n		Follow-up y		Cancers		HR range
		IG	CG	IG	CG	IG	CG	
Laframboise, 2002 Rebbeck, 2002	PBO vs Surveillance	274	308	5 8.2	7 8.8	2 PC	58 OC	0.04
Kauff, 2002 Meeuwissen, 2005	PBSO vs Surveillance	184	138	1.95 2.4	2.1 2.6	2 PC	4 OC 1 PC	0.15
Olivier, 2004	PBO vs PBSO	65	65	3.4	1	3 PC	-	-

➡ **Riduzione del Rischio 85-96%**

Greggi, 2009

Annessiectomia Profilattica (*RRBSO*)

Meta-analisi di 346 studi (1999-2007)

	Ovarian and/or fallopian tube cancer by mutation status			Breast cancer by mutation status		
Summary characteristic	***BRCA1/2***	***BRCA1***	***BRCA2***	***BRCA1/2***	***BRCA1***	***BRCA2***
HR (95% CI)	0.21 (0.12 to 0.39)	NA	NA	0.49 (0.37 to 0.65)	0.47 (0.35 to 0.64)	0.47 (0.26 to 0.84)
P value for heterogeneity among studies†	.999	NA	NA	.998	1.000	.604
P value for publication bias‡	.999	NA	NA	.602	.176	.602

79% riduzione del rischio di ca. ovarico/tubarico
51% riduzione del rischio di cancro mammario

Rebbeck TR, 2009

Annessiectomia Profilattica (*RRBSO*)

Studio Prospettico Multicentrico (1,079 donne, 1994-2004)

BRCA1* & *BRCA2

87% riduzione del rischio di cancro ginecologico
47% riduzione del rischio di cancro mammario

	Cancro Ginecologico		*Cancro Mammario*	
Mutation	Hazard Ratio	*P*	Hazard Ratio	*P*
BRCA1 and *BRCA2*	0.12	.001	0.53	.036
BRCA1	0.15	.005	0.61	.16
BRCA2	0.00		0.28	.036

Kauff ND, 2008

Annessiectomia Profilattica (*RRBSO*)

Studio Prospettico di Coorte (n=188 vs. 478)

	Number of deaths	Number alive, with or without cancer	Mean follow-up, years (SD)	Hazard ratio (95% CI)*	Hazard ratio (95% CI)†
Overall mortality					
BPSO	5	183	5·7 (3·2)	0·28 (0·10–0·74)	0·47 (0·15–1·46)
No BPSO	18	460	4·4 (3·1)		
Breast-cancer-specific mortality					
BPSO	1	183	5·7 (3·2)	0·15 (0·02–1·18)	0·23 (0·03–2·07)
No BPSO	8	460	4·4 (3·2)		
Ovarian and peritoneal-cancer-specific mortality					
BPSO	2	183	5·7 (3·2)	0·23 (0·02–1·87)	0·33 (0·03–3·35)
No BPSO	7	460	4·4 (3·2)		

*Adjusted for birth year and gene (*BRCA1* vs *BRCA2*), and stratified by centre. †Adjusted for birth year and gene (*BRCA1* vs *BRCA2*), and stratified by centre using BPSO as a time-dependent covariate.

- 95% riduzione della mortalità per ca. ginecologico
- 90% riduzione della mortalità per ca. mammario
- 76% riduzione globale della mortalità

Domchek SM, 2006

ELSEVIER
JMIG The Journal of Minimally Invasive Gynecology
Journal of Minimally Invasive Gynecology, Vol 25, No 7, November/December 2018

Review Article

Cancer Risk-Reducing Opportunities in Gynecologic Surgery

Carolyn Piszczek, MD, Jun Ma, AOCNP, PhD, Claire H. Gould, MD, and Paul Tseng, MD

From the Division of Women's Services, Legacy Health System, Portland, Oregon (Dr. Piszczek), Divisions of Gynecologic Oncology (Drs. Ma and Tseng), and Advanced Gynecology, Legacy Medical Group, Portland, Oregon (Dr. Gould).

Table 2

Ovarian and Breast Cancer Characteristics by *BRCA* Gene Mutation

	BRCA1 (95% CI)	*BRCA2* (95% CI)
Ovarian cancer		
Cumulative risk by age 70 [27]	39% (18–54)	11% (2–19)
Cumulative risk by age 80 [28]	44% (36–53)	17% (11–25)
Median age at diagnosis [29]	51 years	56 years
Youngest age at diagnosis [28]	31–40 years	31–40 years
	(1.8 per 1000 person years)	(0.3 per 1000 person years)
Tumor characteristics [30]*	HGSC 66%	HGSC 70%
Breast cancer		
Cumulative risk by age 70 [27]	65% (44–78)	45% (31–56)
Cumulative risk by age 80 [28]	72% (65–79)	69% (61–77)
Median age at diagnosis [29]	40 years	43 years
Youngest age at diagnosis [28]	21–30 years	21–30 years
	(5.9 per 1000 person years)	(4.8 per 1000 person years)
Tumor characteristics [30]*	ER negative 78%	ER negative 23%
	Triple negative 69%	Triple negative 16%
Mortality reduction to age 70 after RRSO	HR = 0.21 (0.12–0.37) [31]	HR = 0.67 (0.08–5.35) [31]
	HR = 0.38 (0.24–0.62) [32]	HR = 0.52 (0.22–1.23) [32]

CI = confidence interval; ER = estrogen receptor; HGSC = high-grade serous carcinoma; HR = adjusted hazard ratio; Triple negative = ER negative, progesterone receptor negative, and human epidermal growth factor receptor 2 negative.

* Consortium of Investigators of Modifiers of *BRCA1/2* only included women who self-reported as white of European ancestry; therefore, morphology and grade distributions in *BRCA1/2* mutation carriers might differ for other races and ancestral groups.

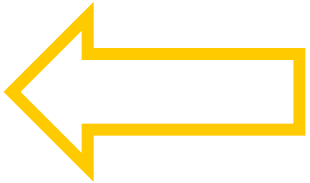
RRBSO

NCCN recommends RRBSO between ages 35-40y and upon completion of childbearing, regardless of the type of BRCA mutation

- *Risk of OC at an earlier age for BRCA1 compared to BRCA2 mutation carriers*

RRBSO appears appropriate

- **35-40y for *BRCA*1**
- **40-45y for *BRCA*2**



These reccomendations may be modified based on the age of the youngest affected relative with OC

Programma preventivo per pazienti o portatori di mutazione BRCA1/2

SORVEGLIANZA CLINICO-STRUMENTALE INTENSIVA				
	STATO MUTAZIONALE	**SEDE**	**ESAME**	**FREQUENZA**
Donne	**Carrier BRCA1/2** **Test non informativo (con alta familiarità)**	**Mammella**	Esame clinico senologico Ecografia mammaria Mammografia (dai 35 anni) RMN mammelle + mdc	Semestrale Semestrale Annuale Annuale
	Carrier BRCA1/2 **Test non informativo (con alta familiarità)**	**Tube/ovaie**	Eco pelvica transvaginale Ca125	Semestrale Semestrale
	Carrier BRCA1	**Colon-retto**	Sangue occulto nelle feci Colonscopia	Annuale Individualizzata sulla base del pedigree
	Carrier BRCA2	**Cute**	Visita dermatologica (prevenzione melanoma)	Annuale
	Carrier BRCA2	**Occhio**	Visita oculistica con valutazione del fondo oculare (prevenzione melanoma della coroide)	Annuale

Uomini (dai 40 anni)	**Carrier BRCA1/2**	**Mammella**	Esame clinico senologico Ecografia mammaria Mammografia (se ginecomastia)	Annuali
	Carrier BRCA1/2	**Prostata**	PSA sierico e visita urologica	Annuale
	Carrier BRCA2	**Cute**	Visita dermatologica (prevenzione melanoma)	Annuale
	Carrier BRCA2	**Occhio**	Visita dermatologica (prevenzione melanoma)	Annuale

Chirurgia profilattica (solo per le donne)	
Carrier BRCA1/2	Mastectomia profilattica bilaterale con ricostruzione contestuale (offerta in casi selezionati nell'ambito del SSN e/o SSR
Carrier BRCA1/2	Salpingo-ooforectomia profilattica (offerta a partire dai 35-40 anni nell'ambito del SSN e/o SSR, raccomandata entro i 40 anni per le carrier BRCA1 ed entro i 45-50 anni per le carrier BRCA2)

RRBSO

- ***Peritoneal cytology*** may be helpful:

  +ve cytology may increase the index of suspicion for occult lesions and upstage a possible early invasive ca.

- No case reported of +ve ***random omental or peritoneal biopsies***

- ***Additional hysterectomy*** (*BRCA1mut.*-induced small increase of HG serous EC) may be a possible option:

  to eliminate the small risk of HGSEC (and tamoxifen-induced EC)

  to avoid the need for a progestin if HRT is planned

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
BRCA-Related Breast and/or Ovarian Cancer Syndrome

- Recommend risk-reducing salpingo-oophorectomy (RRSO),[f] typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with *BRCA2* pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with *BRCA1* pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 y in patients with *BRCA2* pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery.
  - Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy, and related medical issues.
  - Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be gene-specific.
- Limited data suggest that there may be a slightly increased risk of serous uterine cancer among women with a *BRCA1* pathogenic/likely pathogenic variant. The clinical significance of these findings is unclear. Further evaluation of the risk of serous uterine cancer in the *BRCA* population needs to be undertaken. The provider and patient should discuss the risks and benefits of concurrent hysterectomy at the time of RRSO for women with a *BRCA1* pathogenic/likely pathogenic variant prior to surgery.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mast[illegible]and/or salpingo-oophorectomy.

RRBSO AND MORTALITY

RRBSO on all-cause mortality is equally strong for BRCA1 and BRCA2 mutation carriers

BUT….

After early RRBSO: increase in vasomotor symptoms, loss of libido, and a modest diminution of overall QoL

It is difficult to compare the decline in QoL with an increase in life expectancy

Finch APM et al. JCO 2014

HRT AFTER RRBSO

Prospective cohort of 462 BRCA1/2 mutation carriers, 115 undergoing RRBSO

- *Women with RRBSO were more likely to use HRT (60% vs 7%)*

- ***After RRBSO + HRT, BC risk was 60% lower compared to women without RRBSO***

The use of HRT of any type did not alter the BC risk reduction derived from RRBSO (HR 0.37)

Rebbeck, 2010

BC WITH AND WITHOUT RRSO (+/-HRT)

HRTUse:	Never	Never	Post-RRSO
RRSO:	No	Yes	Yes
Mean age at RRSO	--	45.0 (20.5-79.0)	40.8 (29.4-63.4)
Mean age at start of follow up	34.4 (18.1-90.4)	--	--
Mean follow-up to BC	4.8 (0.5-17.6)	2.7 (0.5-6.0)	4.9 (0.8-20.2)
Mean age at BC	40.9 (22.2-71.9)	46.3 (33.3-63.3)	46.5 (36.1-63.1)
Mean follow-up to censoring (Yrs)	5.1 (0.5-27.8)	3.6 (0.5-18.8)	5.4 (0.6-27.4)
Total Sample (N)	867	177	144
BC Diagnosed During Follow-up	194 (22%)	22 (12%)	20 (14%)
HR (95% CI)	**[1]**	**0.56 (0.34-0.93)**	**0.43 (0.26-0.72)**
***BRCA1* (N)**	520	115	105
BC Diagnosed During Follow-up	118 (23%)	16 (14%)	17 (16%)
HR (95% CI)	**[1]**	**0.58 (0.32-1.05)**	**0.49 (0.28-0.86)**
***BRCA2* (N)**	347	62	39
BC Diagnosed During Follow-up	76 (22%)	6 (10%)	3 (8%)
HR (95% CI)	**[1]**	**0.46 (0.18-1.13)**	**0.22 (0.05-1.00)**

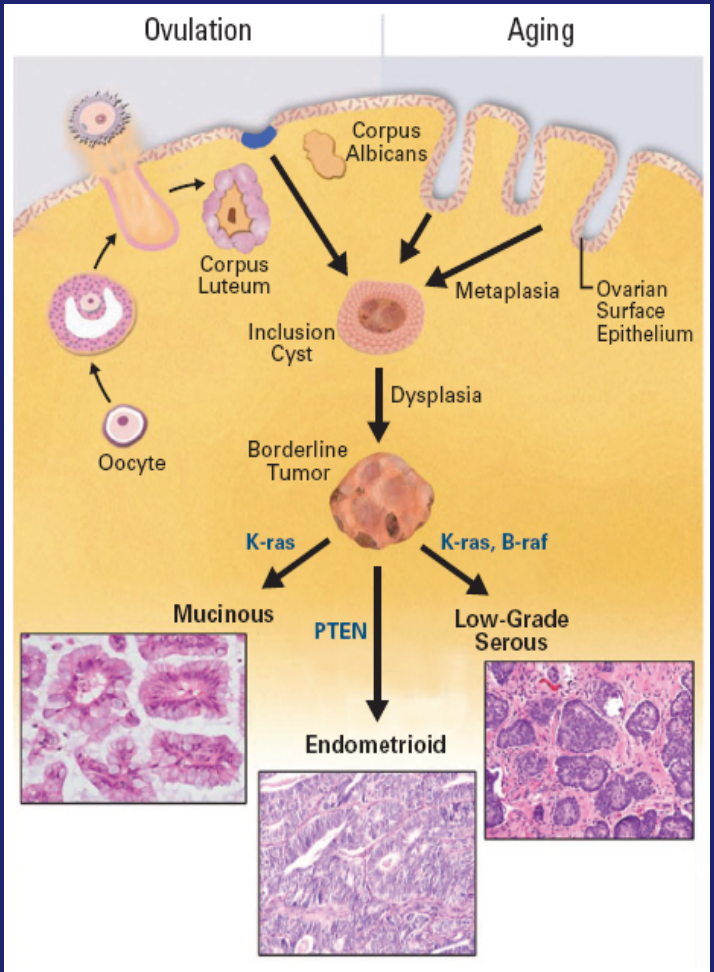
Domchek , 2011

HRT in *BRCA* mutations carriers

- In BRCA mutation carriers who have undergone RRSO ± hysterectomy *without* a personal history of breast cancer or other absolute contraindications to HRT use, and who experience significant menopausal symptoms, it is reasonable to offer a short course of HRT treatment (Level II evidence).
- In BRCA mutation carriers *with* a personal history of hormone-dependent breast cancer, HRT should be avoided and non-hormonal alternatives should be first-line in the treatment of menopausal symptoms (Level II evidence).

HOCCSG, 2015

Pathway



Ovulation scarring process

↓

Deep epithelial invaginations

↓

Inclusion cysts

↓

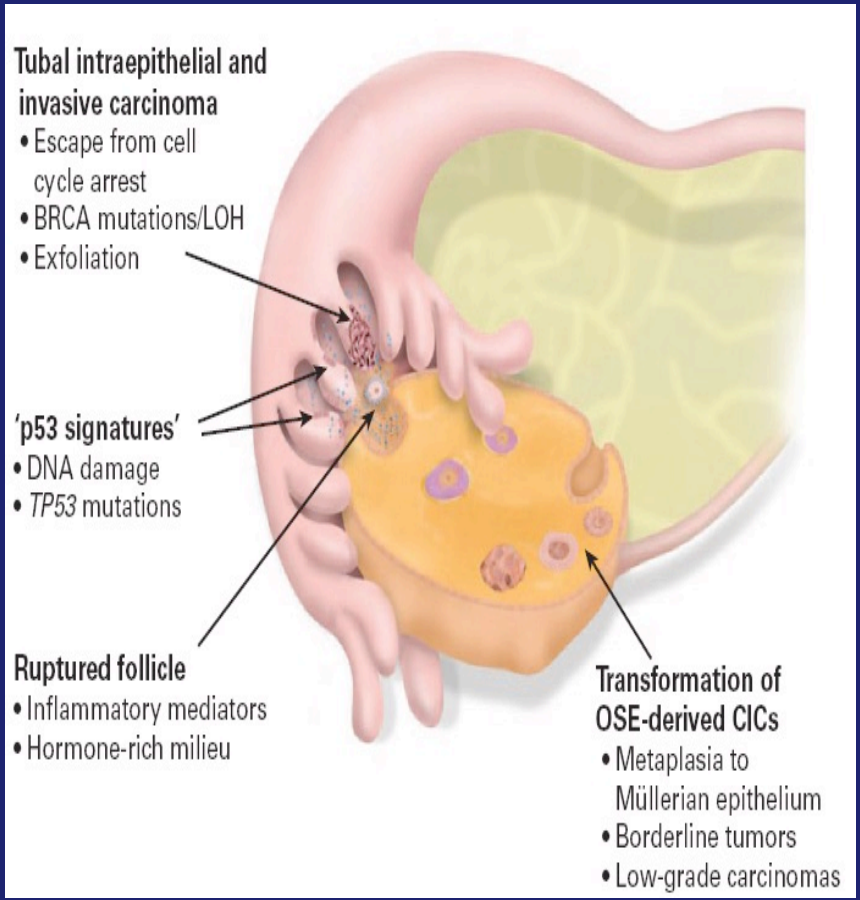
Ep. cells covering the cysts: mullerian metaplasia

Stromal hormones
Pro-inflammatory cells

Malignant transformation

Fathalla 1971, Cusberg, Deligdisch, 1984, Tressera, Plaxe, Resta, Stratton,1990-2000

Alternative Pathway



Secretory cell outgrowths SCOUTs

↓

Benign prolif. lesions (p53 sign.) STILs

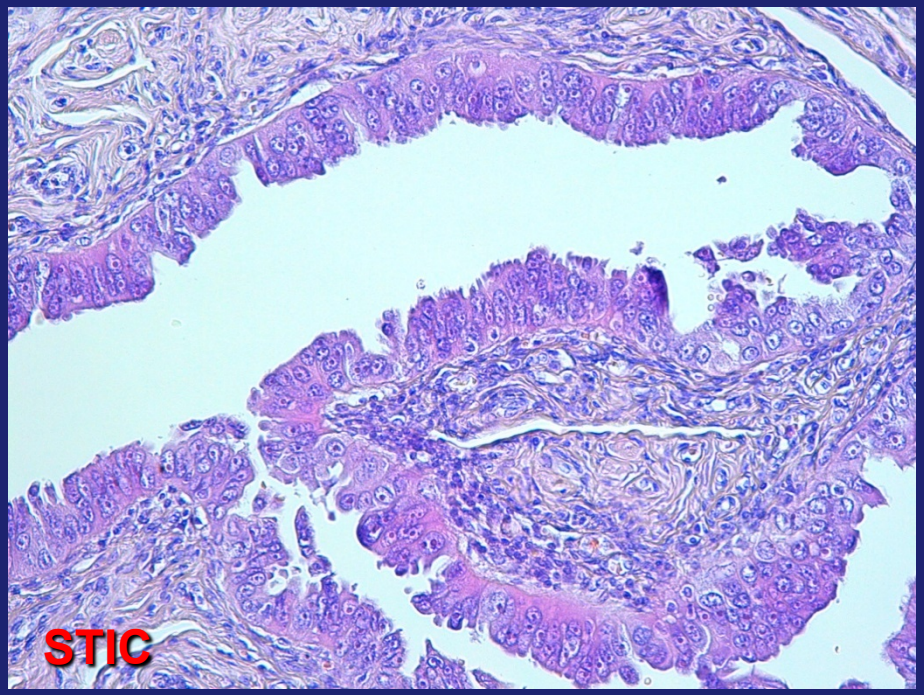
↓

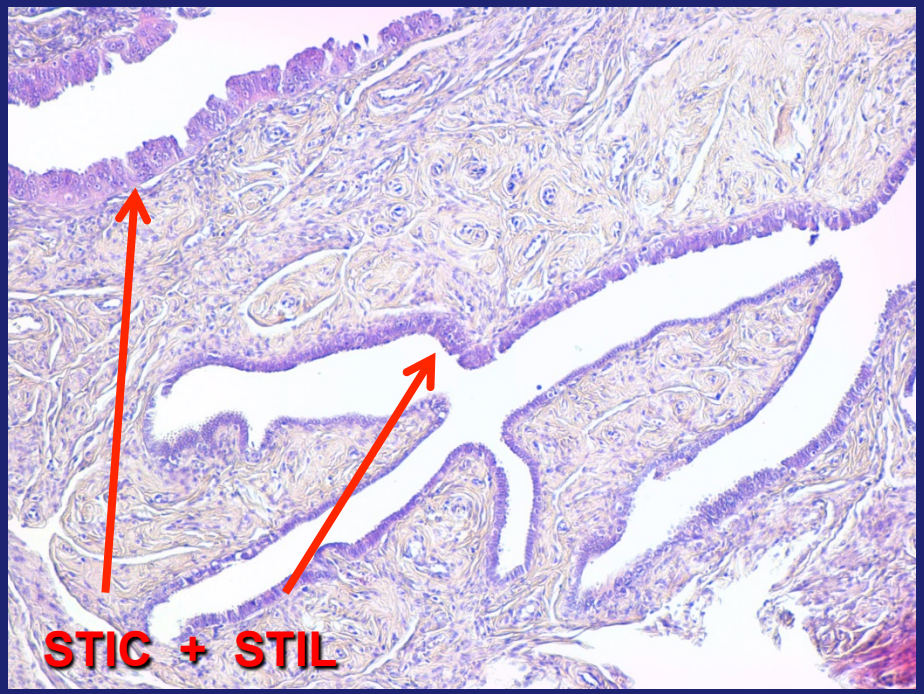
Serous tubal intraepithelial ca. STICs

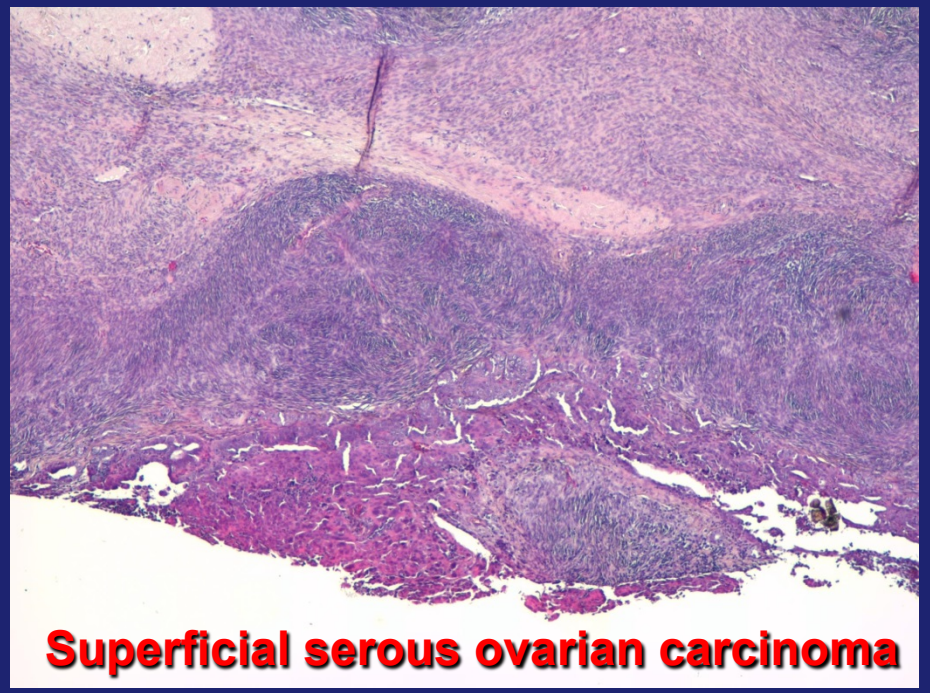
↓

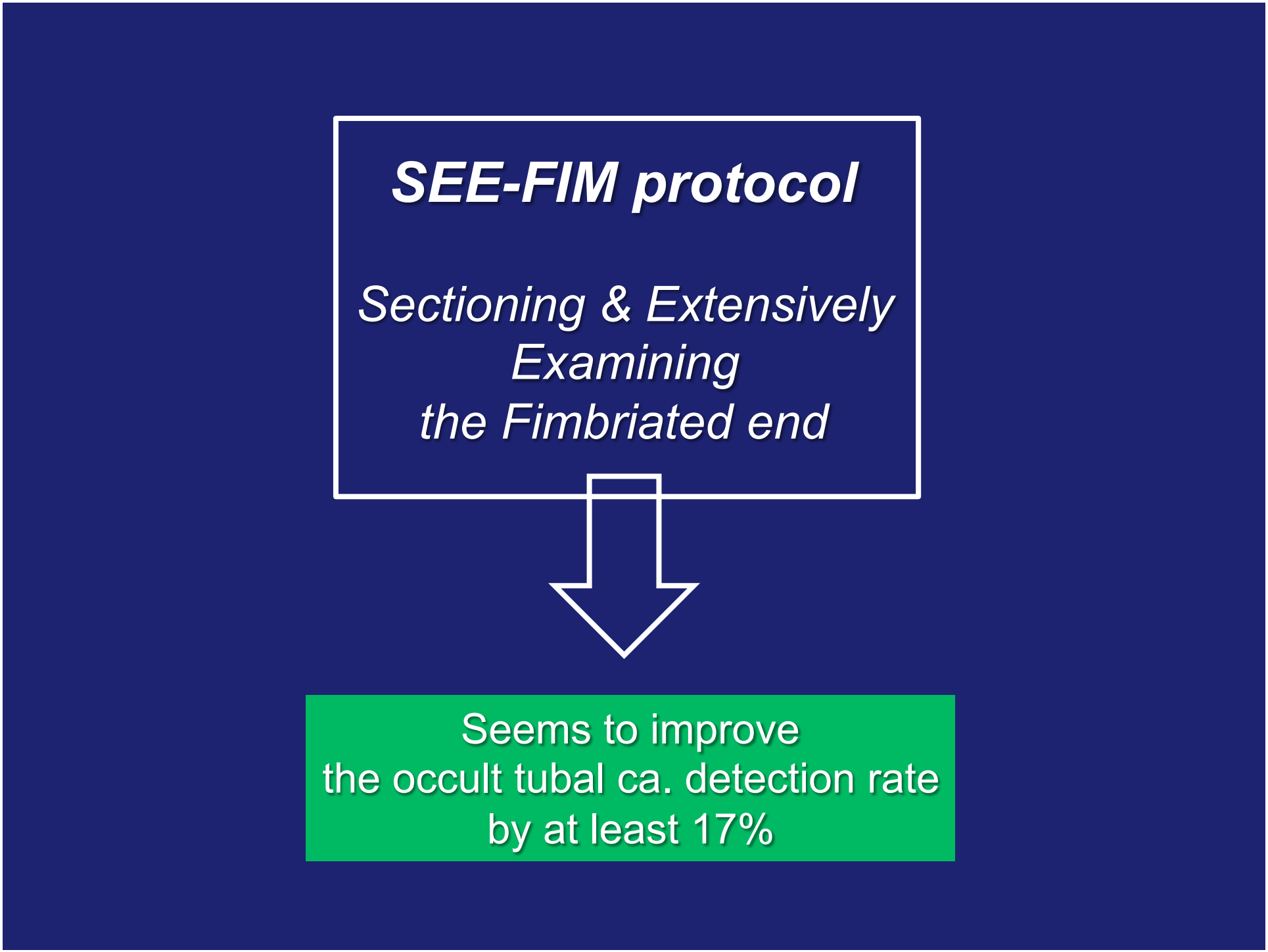
Invasive carcinoma

Pick 2001, Crum, Kurman, Jarboe, Rabban, … 2005-2012

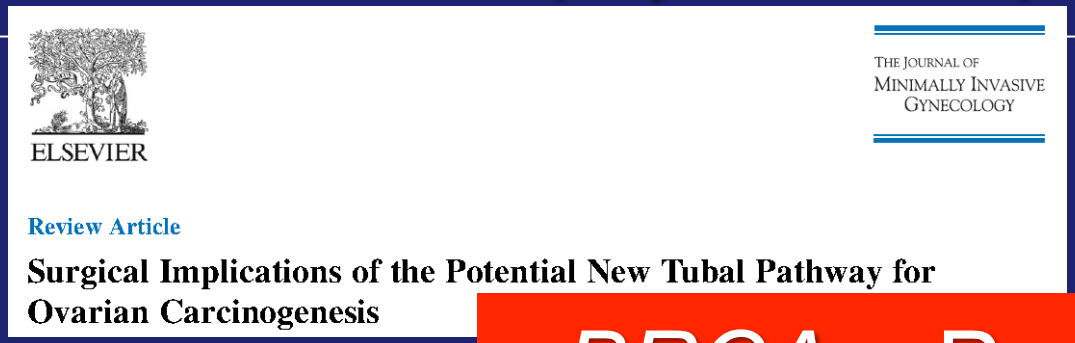

STIC


STIC + STIL


Superficial serous ovarian carcinoma


SEE-FIM protocol
Sectioning & Extensively Examining
the Fimbriated end
Seems to improve
the occult tubal ca. detection rate
by at least 17%

OC Prophylaxis – *Open Questions*


ELSEVIER

THE JOURNAL OF MINIMALLY INVASIVE GYNECOLOGY

Review Article

Surgical Implications of the Potential New Tubal Pathway for Ovarian Carcinogenesis

*BRCA*m Population

Is an interventional RRBS after childbearing followed by (menopause) RRBO better than RRBSO at the same time

?

- While arguments in favor of the ***"tubal hypothesis"*** are convincing, they in no way rule out the likelihood that ***pure ovarian surface epithelium is an additional, and likely significant, source of these neoplasms***

- This problem should be kept in mind when clinical decisions are made concerning:

✓ interventional prophylactic surgery for women at genetic risk

✓ opportunistic salpingo±oophorectomy in general population

Probable tubal origin

Occult cancers from RRBSOs in BRCAm populations

Author, year	No.	Occult cancers	*STIC*	*SOC*
Leeper, 2002	30	5	3	2
Finch, 2006	159	7	3	4
Hirst, 2009	45	5	4	(1 BCm)
Rabban, 2009	108	8	5	2 (+ 1 BCm)
Powell, 2011	111	10	7	3
INT-Na (unpubl.)	21	2	1	1
Total	**474**	**37 (7.8%)**	**23 (68%)**	**12 (32%)**

BCm: breast ca. met;
SOC: superficial serous ovarian ca.

Greggi, 2015

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Radical fimbriectomy: A reasonable temporary risk-reducing surgery for selected women with a germ line mutation of BRCA 1 or 2 genes? Rationale and preliminary development

Eric Leblanc [a,*], Fabrice Narducci [a], Isabelle Farre [b], Jean-Philippe Peyrat [c], Sophie Taieb [d], Claude Adenis [e], Philippe Vennin [e]

Characteristics of 14 patients

	Scissors	Stapler	Bipolar scalpel	Harmonic scalpel	Total
N	4	3	4	3	14
BMI	22.1 (SD 2.5)				
History of breast cancer	4	2	3	2	11
BRCA1	1	1	2	2	6
BRCA2	3	2	2	1	8
Associated total hysterectomy	3	0	1	0	4

Pathological Results

	BRCA1	BRCA2	Total
Carcinoma*	0	0	0
STIC *,**	1	0	1
p53 signature/ Ki 67 on fimbria**	2/0	0/1	2/1
p53 signature/ Ki 67 on the attached part of ovary**	1/0	0/0	1/0
p53 signature/Ki 67 on rest of ovary**	0/0	0/0	0/0

* Standard examination using Hematoxylin Eosin Safran (HES) staining.
** Immunohistochemistry using antibodies p53 and Ki 67.

not designed to replace RRBSO but could be a temporary solution for *BRCA* mutation carriers who decline BSO, those with a history of BC or contraindication for HRT

Leblanc et al. Gynecol Oncol 121(2011) 472-476

STIC - *ADJUVANT TREATMENT ?*

- 100% overall survival supports not adding adjuvant CT
  (Connor, 2013; Powell, 2014)

- Adjuvant CT if STIC associated with +ve cytology ?

  Data extremely limited with about half receiving CT:

  No recurrences have been reported when +ve cytology is associated with only STIC

OC Prophylaxis – *Open Questions*

*BRCA*m Population

RRBS

CONTRA

- not yet clinical data
- two-step intervention (although minimally invasive)
- no decreased BC risk as following RRBSO in premenopausal *BRCA*m carriers

The Oncologist
Gynecologic Oncolgy

Risk-Reducing Strategies for Ovarian Cancer in *BRCA* Mutation Carriers: A Balancing Act

Ilot Tschernichovsky[a] Annekathryn Goodman[b,c]
Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [b]Division of Gynecologic Oncology, [c]Department of Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

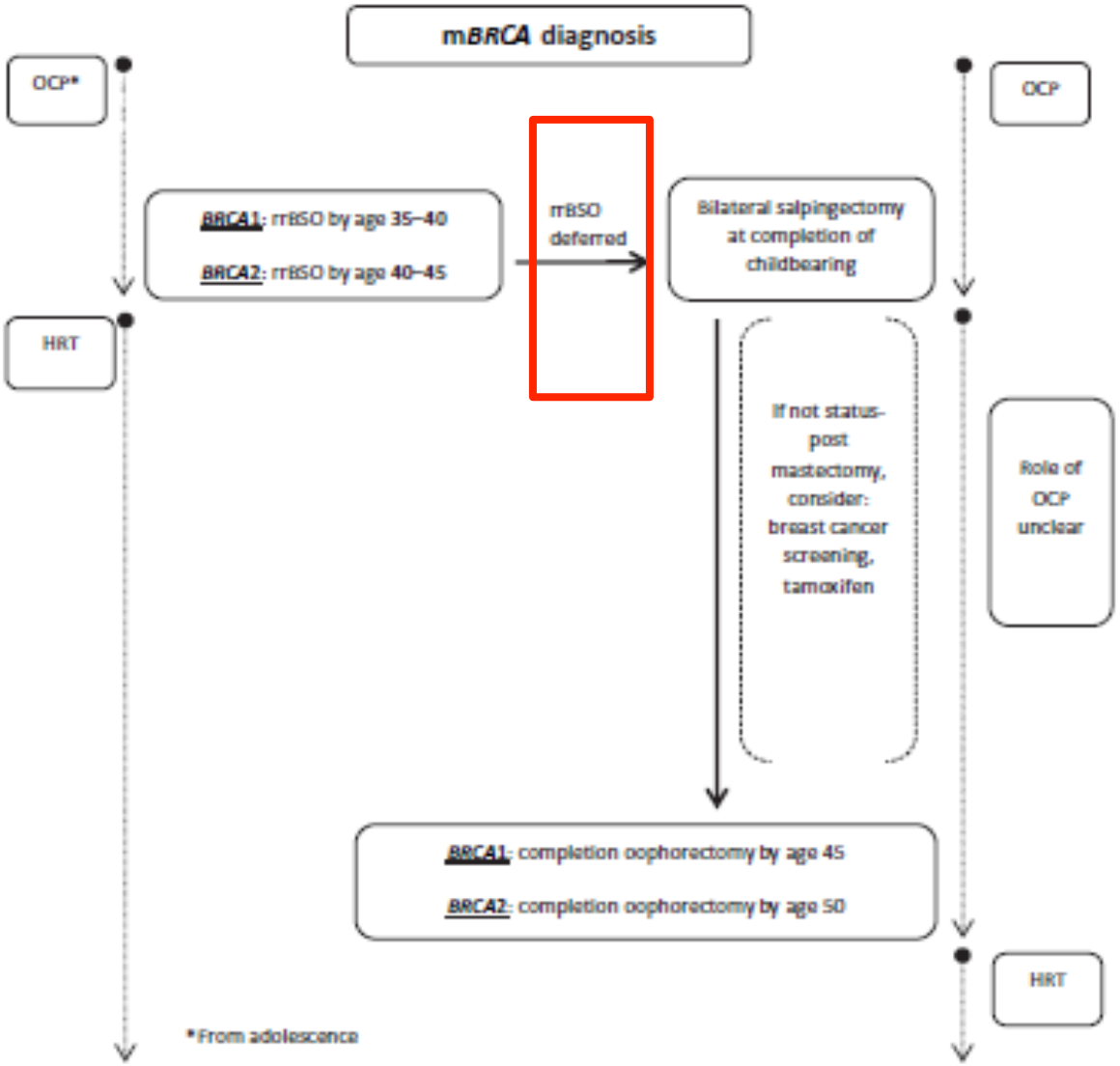


Figure 1. Decision flowchart for rrBSO versus PSDO.
Abbreviations: HRT, hormonal replacement therapy; m*BRCA*, BRCA mutation; OCP, oral contraceptive pills; PSDO, prophylactic salpingectomy with delayed oophorectomy; rrBSO, risk-reducing bilateral salpingo-oophorectomy.

RRBS - Ongoing (*under development) trials

- ***Netherlands (TUBA)***

multicenter nonrandomized study: RRBS after completion of childbearing with BilOoph. at age 40–50 vs with upfront RRBSO
(QoL, OC incidence)

- **MDACC**

nonrandomized trial: 3 patient-selected interventions: (a) multimodal screening; (b) RRSDO with ooph. 3ys after salpingect.; (c) RRBSO
(RRSDO compliance, QoL, OC incidence)

- **MDACC, Mayo, MSLCC, Uni-Chicago, DF-Cancer Inst, Royal Melbourne H*. (WISDOM *)***

multicenter nonrandomized two-arm trial: RRSDO vs RRBSO
(QoL, OC incidence)

Ovarian Ca. Prophylaxis

4 -14% OC Patients

Antecedent hysterectomy with retained ovaries

Ovarian Ca. Prophylaxis

1/3 gynecologists

BSO

in the case of hysterectomy for benign dis., age >50y

HCUP, Health Care & Utilization Project, US 1988-2000
Progetto Menopausa Italia, 2000
AOGOI survey, 2012

ELSEVIER

JMIG The Journal of Minimally Invasive Gynecology

Review Article

Cancer Risk-Reducing Opportunities in Gynecologic Surgery

Carolyn Piszczek, MD, Jun Ma, AOCNP, PhD, Claire H. Gould, MD, and Paul Tseng, MD

From the Division of Women's Services, Le... and Advanced Gynecology, Legacy Medical...

Society reccomandations for RRBS

	***BRCA*m carriers**	**Pop. Risk – «Opportunistic»**
SGO	Women with *BRCA* mutations who decline RRSO "should be counseled regarding risk-reducing salpingectomy when childbearing is complete followed by oophorectomy in the future, although the safety of this approach has not been studied."	In women at population risk of ovarian cancer, "risk-reducing salpingectomy should also be discussed and considered with patients at the time of abdominal or pelvic surgery, hysterectomy, or in lieu of tubal ligation." • BS at the time of hysterectomy appears safe. • Surgeon should discuss potential benefits of concomitant bilateral salpingectomy with patients before hysterectomy for benign disease. • Surgeons can communicate with patients that BS is an effective means of contraception. • Complete salpingectomy up to the uterotubal junction is preferable to fimbriectomy. • The approach to hysterectomy or sterilization "should not be influenced by the theoretical benefit of salpingectomy."
ACOG	Not recommended	
NCCN	"Salpingectomy alone is not the standard of care for risk reduction although clinical trials are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be gene-specific."	"Despite some evidence regarding the safety and feasibility of this procedure, more data are needed regarding its efficacy in reducing the risk for ovarian cancer."
SOGC		• When considering permanent contraception, physicians should discuss with patients the possible additional protective benefit of BS • BS should be performed at the time of hysterectomy for benign disease

ACOG = The American College of Obstetricians and Gynecologists; BS = bilateral salpingectomy; NCCN = National Comprehensive Cancer Network; PSDO = prophylactic salpingectomy with delayed oophorectomy; RRSO = risk-reducing salpingo-oophorectomy; SGO = Society of Gynecologic Oncologists; SOGC = Society of Gynecologic Oncology of Canada; US = unilateral salpingectomy.

Prophyl. Salpingo-Oophorect. RRBSO SGO-ACOG Recommendations

- *Individualized decision*
- OC High-risk subjects: YES
- OC Average-risk subjects (incidental): <40y NO
- OC Average-risk subjects (incidental): >55y YES
- OC Average-risk subjects (incidental): 40-55y

to be discussed

La Buona Eredità

"Every breast or ovarian cancer patient with a *BRCA1* or *BRCA2* mutation detected after diagnosis is a missed opportunity to prevent a cancer.

No woman with a mutation in *BRCA1* or *BRCA2* should die of breast or ovarian cancer."

ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale