

Risk Reducing Salpingectomy Prior to Oophorectomy in patients with BRCA mutations

ESGO 2015

Inherited Epithelial Ovarian Cancer (EOC)

- 10 % (30-40% in Israel) of EOC are caused by BRCA mutations
- Risk of developing ovarian cancer at age 70 is:
 - 30-40% for BRCA1 carriers, average age 51y
 - 6-18% for BRCA2 carriers, average age 57y
- Risk reducing salpingo-oophorectomy (RRSO):
 - Decreases EOC risk by 80-90% and mortality by 69%
 - Decreases breast cancer risk by 50%

Finch & Narod, JCO 2014
Rebbeck, JNCI 2009

Concerns with RRSO

- 34% of BRCA carriers are reluctant to undergo premenopausal RRSO
 - Effects of early menopause - quality of life, osteoporosis, cardiovascular effect
- Carriers previously diagnosed with breast cancer - not allowed to take HRT
- Safety of long term HRT use in BRCA carriers – not determined
 - Increased risk of breast (HR 1.2) and ovarian (HR 1.4) cancer in general population

Greene, CEBP 2008

WHI, JAMA 2002
Collaborative Group on Epidemiological
Studies of Ovarian Cancer. Lancet 2015

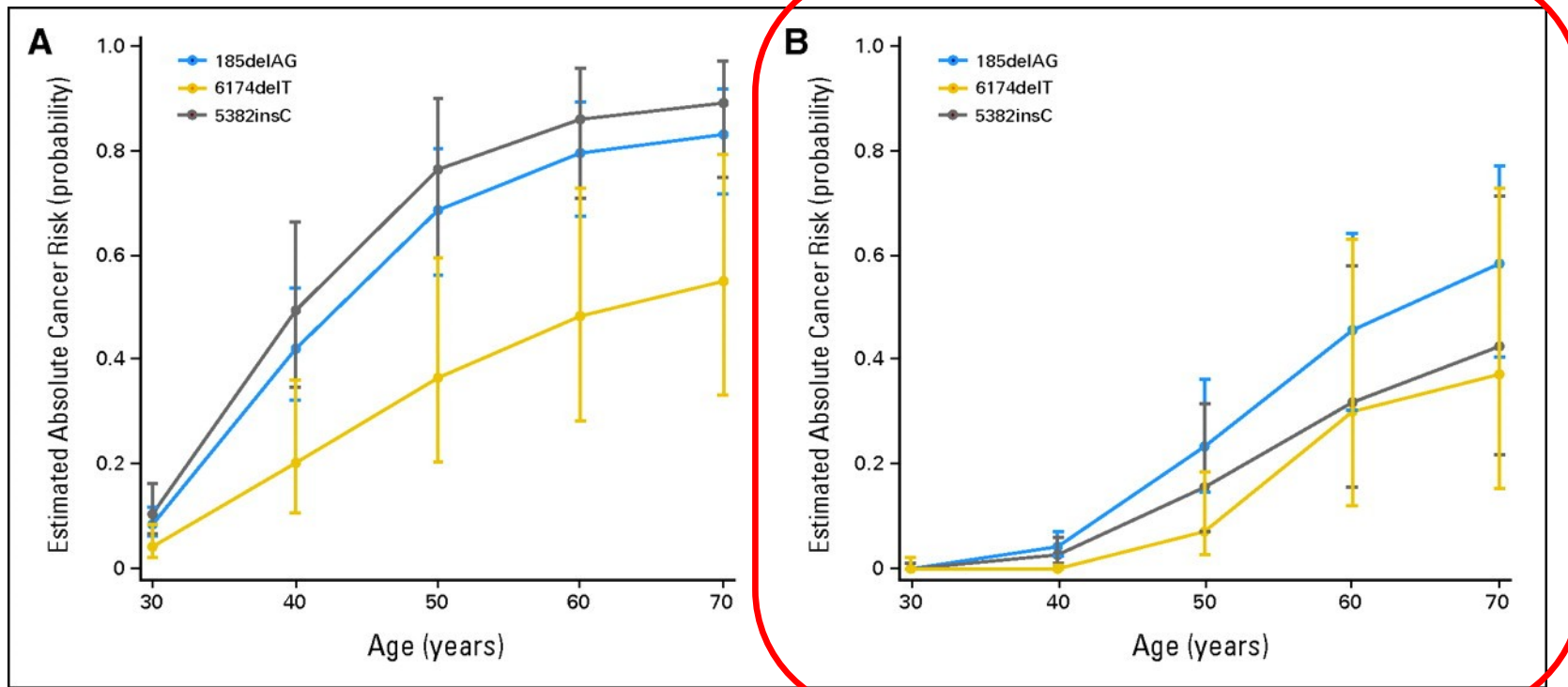
Concerns with RRSO: *What is the best timing?*

Risks of Ovarian cancer in BRCA Mutation Carriers

Age Group (years)	BRCA1				BRCA2			
	No. of Patients	No. of Cancers	Person-Years	Annual Risk (per 100,000 per year)	No. of Patients	No. of Cancers	Person-Years	Annual Risk (per 100,000 per year)
30-34	413	2	865.6	231.1	47	0	90.4	0
35-39	566	6	2,223.1	269.9	92	0	388.7	0
40-49	1,009	43	3,958.6	1,086.2	276	1	1,174.3	85.2
50-59	549	34	2,029.9	1,675.0	207	5	853.2	586.1
60-69	216	9	975.3	922.8	98	3	475.2	631.3
70-74	128	4	659.1	606.9	59	1	363.2	275.3
Total	2,881	98	10,711.6	914.9	779	10	3,344.9	299.0

Concerns with RRSO: *What is the best timing?*

Estimated risk of (A) breast and (B) ovarian cancers by mutation



Finkelman, JCO 2012

Pathogenesis of Ovarian Cancer

	Type 1	Type 2
Histology	Low-grade serous/endometrioid Clear cell Mucinous	High-grade serous/endometrioid Undifferentiated tumors Carcinosarcoma
Molecular findings	LG serous – KRAS, BRAF, ERBB2, PIK3CA LG endometrioid – MLH1, MSH2, PTEN, ARID1A Clear cell – ARID1A, PIK3CA, PTEN	P53 (95% of cases) BRCA mutations
Pathogenesis	Associated with endometriosis	From tubal precursor

Evidence for tubal origin of high-grade pelvic serous carcinoma

- 68% of occult carcinomas are found in the tubes

Walker, Cancer 2015

- Serous Tubal Intraepithelial Carcinoma (STIC) is found in:

- 2-7% of RRSO's

Callahan, JCO 2007

- 80% of pelvic cancers in BRCA carriers

Carlson JCO, 2008

- 36-60% of sporadic pelvic cancers

Roh, Am J Sur Pathol 2009,
Przybycin, Am J Surg Pathol 2010

Evidence for tubal origin of high-grade pelvic serous carcinoma..

- Identical TP53 mutation - in STIC and pelvic carcinoma cells

Kuhn, J Pathol 2012

- Pelvic serous carcinomas resemble tubal epithelium
 - Express Müllerian (ie tubal) markers as PAX8
 - Lack mesenchymal (ovarian) markers such as Calretinin.

Tone, Clin Cancer Res 2008

- Tubal ligation is protective against ovarian cancer:
 - 34% risk reduction in general population
 - 48-61% risk reduction in BRCA1 mutation carriers

Cibula, Human Reprod Update 2011

Narod, Lancet 2001

Antoniou, CEBP 2009

The Rationale for Early Salpingectomy

- Disadvantages of RRSO
- Role of the Fallopian Tube in “ovarian” carcinogenesis

Advantages of delayed oophorectomy

- Premature menopause will be delayed
- Early opportunity for abdominal cavity inspection and peritoneal cytology collection
- Early detection of occult tubal lesions
- Preserve the option of pregnancy
- An alternate options for patients declining to undergo RRSO (~30%)

Problems with delayed oophorectomy

- No data to estimate the magnitude of pelvic cancer reduction
- Decrease / eliminate the risk reduction in breast cancer
- Some women may delay oophorectomy
- Two surgeries instead of one

Cost-Benefit Model

- Compared 3 strategies
 - RR Salpingectomy at 40y
 - RR Salpingectomy at 40y + RR Oophorectomy at 50y
 - RRSO at 40y
- RRSO at 40y is the superior strategy – lowest cost and highest life expectancy
- RR salpingectomy with delayed oophorectomy – highest life expectancy when QOL measures were taken into account
- Ovarian cancer risk reduction
 - 80% with RRSO
 - 60% with salpingectomy

Ongoing Trials

- Radical Fimbriectomy - France
- Prophylactic Salpingectomy with Delayed Oophorectomy (PSDO) study - MD Anderson, USA
 - Salpingectomy after childbearing and delayed oophorectomy
- TUBA study – The Netherlands
 1. RRSO: BRCA1 age 35-40, BRCA2 age 40-45
 2. Salpingectomy after childbearing + oophorectomy postponed by 5y