

# Onco-fertility in Gynecologic cancers

## Epithelial Ovarian Cancer

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# Background

- Epithelial ovarian cancer(EOC):more than 70% of patients are diagnosed at an advanced stage of disease
- Early stage Ovarian cancer: 5 year survival rate: 90 %
- < 45 y/o EOC: 12%
  
- Treatment option:
  - ✓ Radical surgery(major)
  - ✓ Fertility sparing surgery(FSS):fertility desire in early stage EOC



出生數按生母年齡、生母平均年齡及生第一胎平均年齡

按發生日期統計

單位：人；‰；歲

年 別	出 生 數 按 生 母 年 齡 (人)								育齡婦女 總生育率 (‰)	生母平均 年齡(歲)	生第一胎 平均年齡 (歲)
	總計	-20	20~24	25~29	30~34	35~39	40~44	45+			
民國70年 1981	415,808	30,653	165,892	169,108	42,187	6,284	1,490	194	2,455	25.49	23.72
民國80年 1991	320,384	14,998	84,835	143,239	62,997	12,964	1,275	76	1,720	27.16	25.47
民國90年 2001	257,866	11,801	60,019	94,117	68,883	20,353	2,530	163	1,400	28.16	26.74
民國100年 2011	198,348	2,847	17,705	60,196	82,387	30,744	4,324	145	1,065	30.88	29.92
民國101年 2012	234,599	3,115	19,882	67,712	99,237	39,095	5,399	159	1,270	31.08	30.11
民國102年 2013	194,939	2,984	16,807	50,698	81,663	37,144	5,427	216	1,065	31.36	30.35
民國103年 2014	211,399	3,045	16,833	53,139	89,693	42,446	5,999	244	1,165	31.54	30.51
民國104年 2015	213,093	3,167	17,320	51,327	88,203	46,104	6,735	237	1,175	31.67	30.58
民國105年 2016	207,600	2,972	16,866	48,817	82,738	48,276	7,587	344	1,170	31.85	30.74
民國106年 2017	194,616	2,727	16,196	45,525	73,660	47,949	8,182	377	1,125	31.97	30.83
民國107年 2018	180,656	2,422	15,565	42,280	65,983	45,420	8,557	429	1,060	32.03	30.90
民國108年 2019	175,074	2,331	15,013	40,596	62,972	44,574	9,131	457	1,050	32.12	31.01
民國109年 2020	161,288								990		



# 2018台灣卵巢癌依年齡分布

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Age	人數	%
0-4	0	0
5-9	3	0.21
10-14	7	0.48
15-19	16	1.11
20-24	20	1.38
25-29	36	2.49
30-34	66	4.56
35-39	103	7.12
40-44	109	7.54
45-49	159	11
50-54	254	17.57
55-59	201	13.9
60-64	194	13.42
65-69	115	7.95
70~	163	11.26

17.34%



# 2018卵巢癌發生人數及期別

## 0-39歲

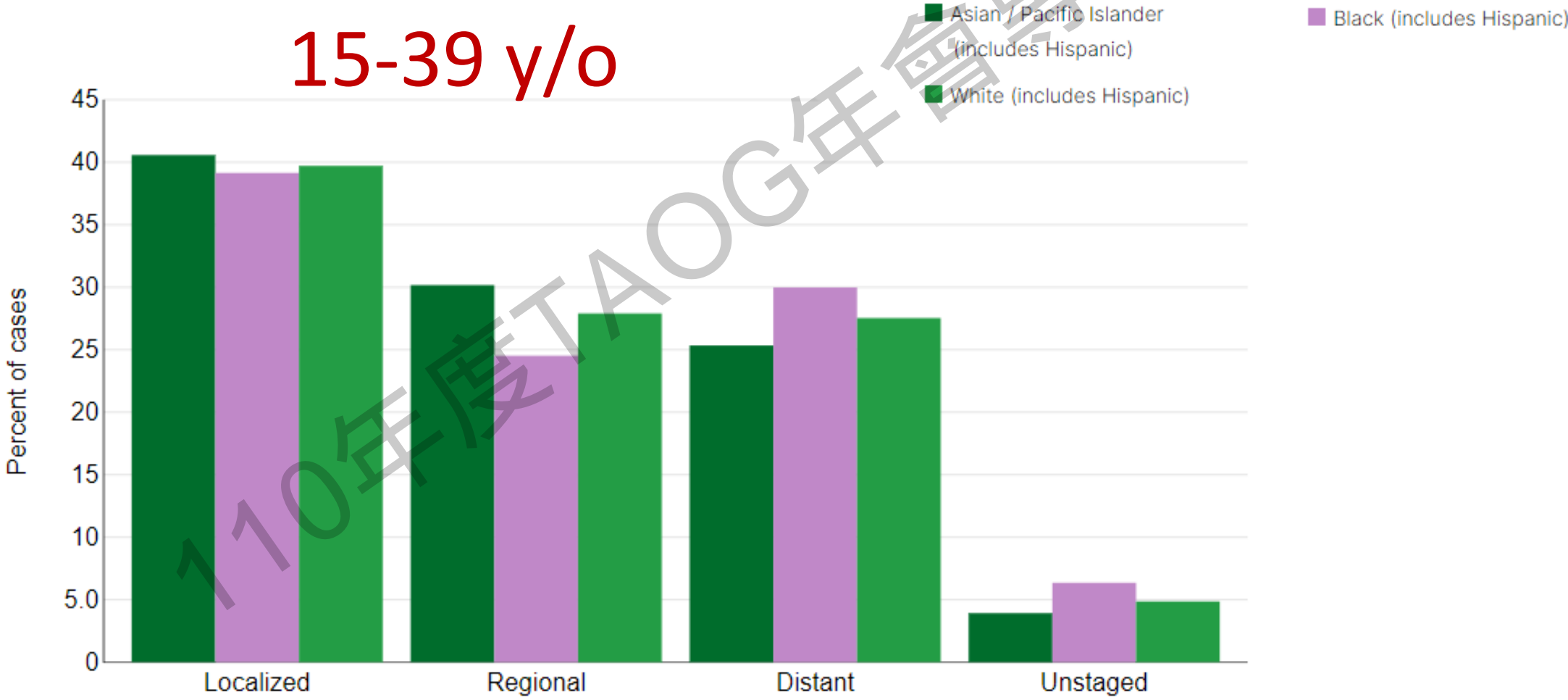
## 不限年齡

期別	人數
I	166 66%
II	17
III	39
IV	12
不詳	17
	251

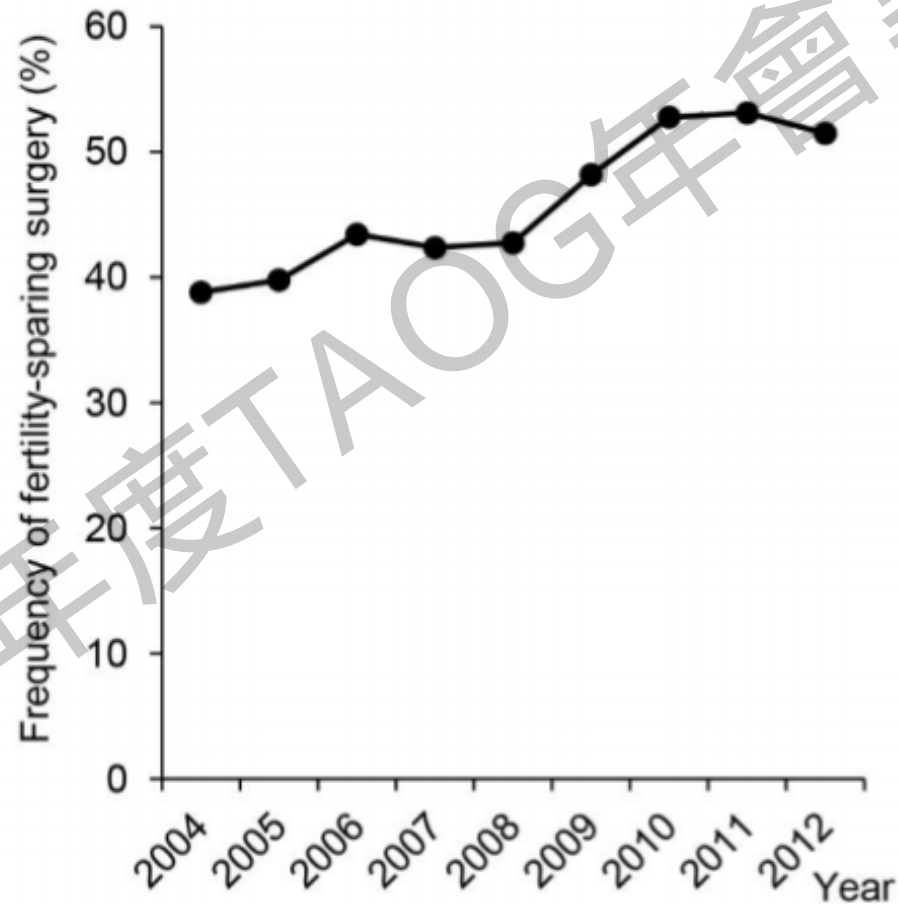
期別	人數
I	631 43%
II	118
III	429
IV	218
不詳	50
	1446

Germ cell tumor : 59  
Sex cord tumor: 74

# Ovary Stage Distribution of SEER Incidence Cases 2009-2018



# fertility-sparing surgery for young women with stage I epithelial ovarian cancer 2004–2012







# Fertility sparing surgery

- Preservation at least one adnexa and uterus
- Delay initiation of childbearing
- Large retrospective study revealed no difference in OS and disease free survival between FSS and RS in stage I EOC

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# FSS choice in EOC

- Age and reproductive desire
- Stage
- Tumor histology
- Grade
- Genetic counseling

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# Age

- Young age :have higher rates of *localized disease*

- ✓ < 50 y/o: 42 %

- ✓ >50 y/o: 17%

- Grade:

- ✓ G1: 40.4 years

- ✓ G2: 48.6 years

- ✓ G3: 52.3 years

- Decrease 5 year-survival with increasing age

- ✓ <30: 78.7%

- ✓ 30-60:58.8%

- ✓ >60:35.3 %

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# Ovarian cancer stage

Stage I :Tumor confined to ovaries		Stage II	
IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings.	IIA	Extension and/or implant on uterus and/or Fallopian tubes
IB	Tumor involves both ovaries otherwise like IA.	IIB	Extension to other pelvic intraperitoneal tissues
IC			
IC1	Surgical spill		
IC2	Capsule rupture before surgery or tumor on ovarian surface		
IC3	Malignant cells in the ascites or peritoneal washings.		



# Stage

- **Stage** is the most important prognostic factor
- Stage I: 5-year-survival : 89%
- RS 5 years recurrence rate:15-25%
- FSS 5 years recurrence rate:
  - IA : 10%
  - IC: 16% IC1: 12%, IC2/IC3: 23%
  - II~III: near 40 %



# Stage Upgrade

- 18.7% of the clinically early-stage EOC patients get upstaged based on surgical staging.

Site	Upgrade rate
Contralateral ovary	0.8~2.5%
omentum	3.9%
peritoneal	3.5%
Para-aortic LN	6.8%
Pelvic LN	4.2%
Appendix	1.6%
cytology	8.5%

The attributive value of comprehensive surgical staging in clinically early-stage epithelial ovarian carcinoma: A systematic review and meta-analysis, *Gynecologic Oncology*, Available online 10 April 2021



- Synchronous endometrial cancer: 3-11%
- Endometrioid and clear cell type

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# Operation method Suggest

- Full surgical staging, including washings, omentectomy, pelvic and paraaortic lymphadenectomy, and peritoneal biopsies.
- Biopsy of any abnormal areas
- Endometrial biopsy to exclude synchronous endometrial cancer
- Caution: Stage III can be missed if unadequate staging operation

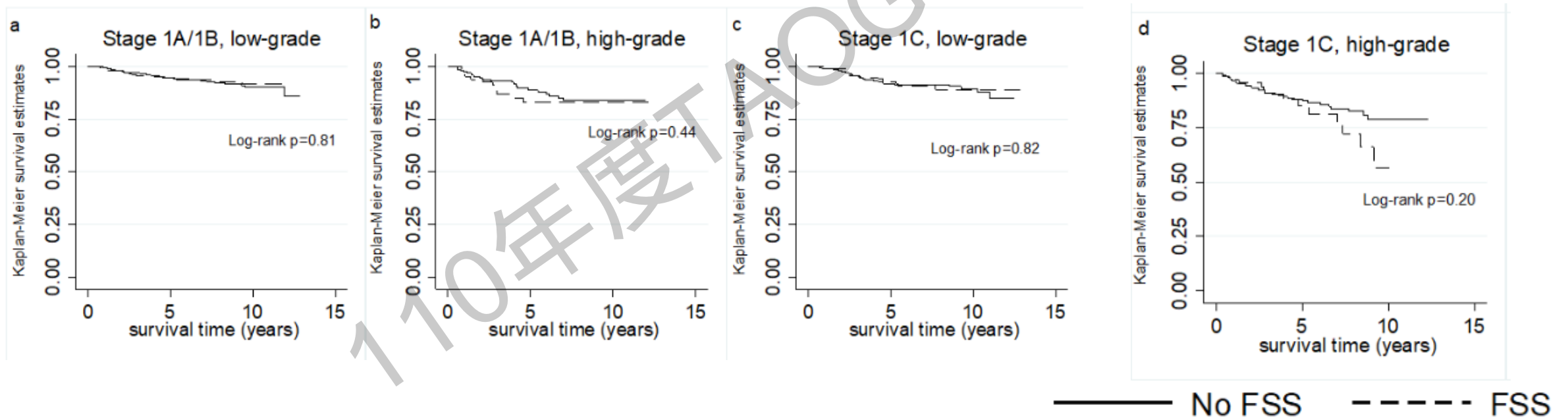




# Tumor Differentiation

- FSS: acceptable in Grade 1 to 2 EOC
- Recurrence Rate: Gr1~2: 9.1%  
Gr3: 25%
- increasing grade : associated with increased risk of recurrence and decreasing survival following FSS
- Mortality rate: Gr1~2: 5.8%  
Gr3(including clear cell carcinoma):14.1%
- prognosis is determined by grade

# Association between FSS and overall survival according to stage and grade subgroups NCDB (2004-2015)





# Histology

- Histological subtype: serous, mucinous, endometrioid, clear cell
- Clear cell: poor outcomes compared to other histological types

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# Controversial

- Grade 3
- Stage IC
- Clear cell carcinoma

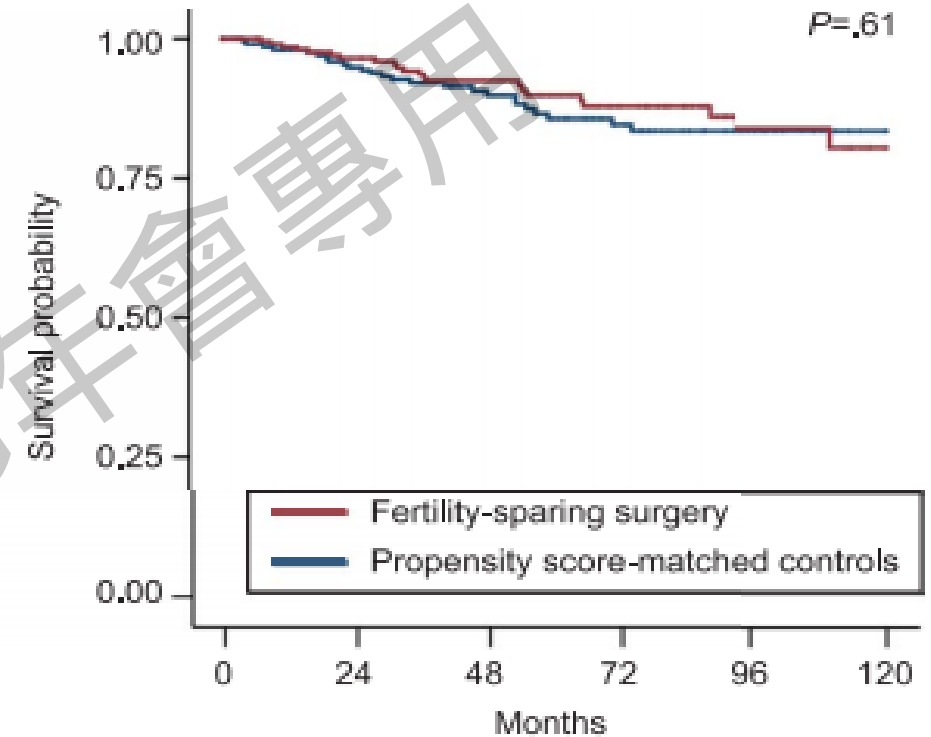
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- Between stage IC1 and stage IA: no significant survival differences
- Recurrence rate in the IC3 and G3/CCC :high
- OS: no significant difference
- G3/CCC: extraovarian recurrence rate :higher than G1/G2

# Stage IC, Gr3, or CCC

- high-risk: no significant association between fertility sparing status among patients (OR 0.86, 95% CI 0.49–1.53).
- FSS and RS
- 5-year survival was 89.9% (95% CI 84.7–90.3)
- 10-year survival was 80.5% (95% CI 76.0–88.7)



	Number at risk					
	0	24	48	72	96	120
Fertility-sparing	211	182	125	73	39	14
Conventional	201	180	117	78	38	16



# Clear cell carcinoma

- American College of Obstetricians and Gynecologists (ACOG) and ESMO: CCC is classified as an unfavorable histological type for FSS
- great risk of recurrence and poor prognosis
- Recurrence time in FSS: most in first two years
- Adjuvant chemotherapy: stage IC with or without C/T , recurrence rate: 18% : 75 %
- Pregnancy rate: 32 %
- Fertility-sparing treatment for stage IA/IC clear cell histology seems to be an acceptable treatment option for selected women



# Stage IB

- safety of FSS for Stage IB disease has not been confirmed
- Need further study

Series of stage I EOC patients treated conservatively in the literature.

Report	Zanetta (1997)		Schilder (2002)		Morice (2005)		Park (2008)		Kajiyama (2010)		Satoh (2010)		Total	
	N	Rec	N	Rec	N	Rec	N	Rec	N	Rec	N	Rec	N	Rec (%)
Total/Age <sup>a</sup>	56	5	52	5	33	11	62	11	60	8	211	18	474	58 (12.2%)
	29		26		34		26		30		29			
Stage														
IA	32	4	42	4	30	7	36	5	30	2	126	7	296	29 (9.8%)
IB	2	0	0	0	0	0	2	0	1	1	ND	ND	5	1 (20.0%)
IC	22	1	10	1	3	3	21	4	29	5	85	11	170	25 (14.7%)
IC1 <sup>b</sup>	ND	ND	ND	ND	ND	ZND	ND	ND	17	0	55	7	72	7 (9.7%)
IC2/3 <sup>c</sup>	ND	ND	ND	ND	ND	ND	ND	ND	12	5	30	4	42	9 (21.4%)
Others <sup>d</sup>	0	0	0	0	1	1	3	2	0	0	ND			

Recurrence-predicting prognostic factors for patients with early-stage epithelial ovarian cancer undergoing fertility-sparing surgery: a multi-institutional study, *European Journal of Obstetrics & Gynecology and Reproductive Biology* 175 (2014) 97–102





# Genetic Factor

- BRCA1
- BRCA2
- HNPCC
- BRCA mutation:risk of ovarian cancer about 15-60 %

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# Risk of Recurrence with FSS

- Recurrence rates in stage I: 10-15 %
- Most study revealed :no difference in survival (FSS and Radical surgery)
- FSS recurrent site: remaining or contralateral site: 82 %
- Mortality : not at increased risk of death



# Chemotherapy effect

- Chemotherapy: recommended in high risk stage I EOC
- Chemotherapy: induce massive recruitment and growth of dormant follicles, which then undergo apoptosis
- Premature ovarian insufficiency

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# GnRH agonist

- Reduced risk of chemotherapy induced ovarian insufficiency : 60%
- Cochrane review:GnRH agonist:
  - ✓ decreased 50% risk of premature ovarian failure
  - ✓ Increased 60% of recovery of menses
  - ✓ Increased 60% odds of pregnancy



# Timing for pregnancy

- conceived less than 1 year after starting chemotherapy: twice the risk of having a preterm birth and delivering a low birth weight infant
- Suggest pregnancy after chemotherapy complete 12 months later

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# Fertility Outcome

- successful pregnancy rates average 60%
- miscarriage rates average 15%
- congenital anomalies: not increased following FSS
- risk of recurrence during pregnancy: clear cell carcinoma most recurrence in the first 2 years
- Artificial reproduction technology



# Take Home Message –FSS Candidate

- Desire fertility sparing treatment for pregnancy (well selection: age <40 y/o, no major comorbidities)
- Stage IA and grade 1-2 with non-clear cell histology
- Examination abdominal cavity during operation
- Fully informed and accept oncological and obstetrical risks
- Genetic issues with high risk to second de novo ovarian cancer (ex: BRCA1, BRCA2, HNPCC)
- Still Controversial: stage IC, Gr3, clear cell carcinoma