Asian Society of Gynecologic Oncology
1st International Workshop in Gynecologic Oncology
Seoul, August 1, 2010

Session V: Ovarian Cancer

Molecular Targeted Therapy of Ovarian Cancer: Putative Precursor Cells, Risk Factors, and Molecular Mechanisms of its Carcinogenesis

Departments of Reproductive Medicine, Surgery and Gynecology
Faculty of Life Sciences, Kumamoto University
Professor and Chairman

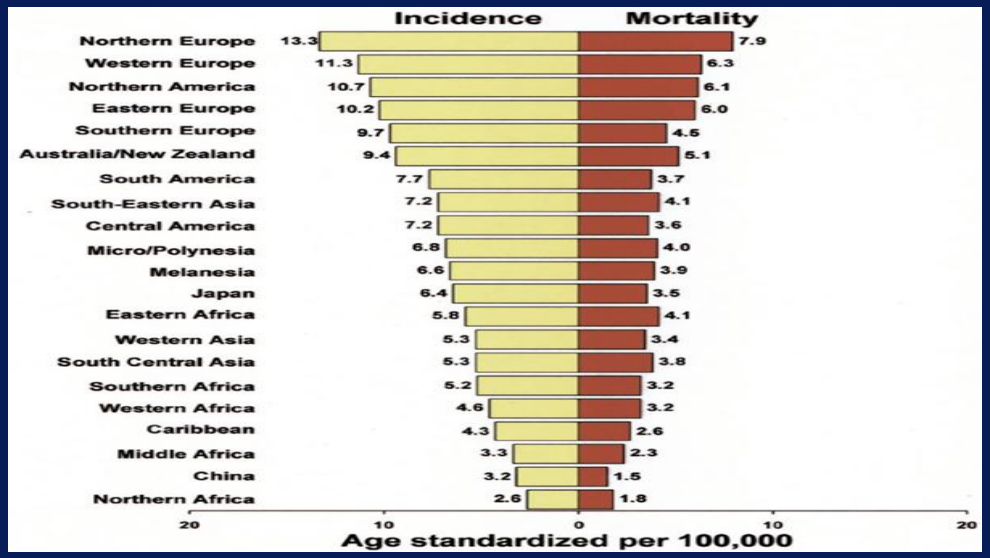
Hidetaka Katabuchi, M.D., Ph.D.

Mt. Aso and Hale-Bopp comet

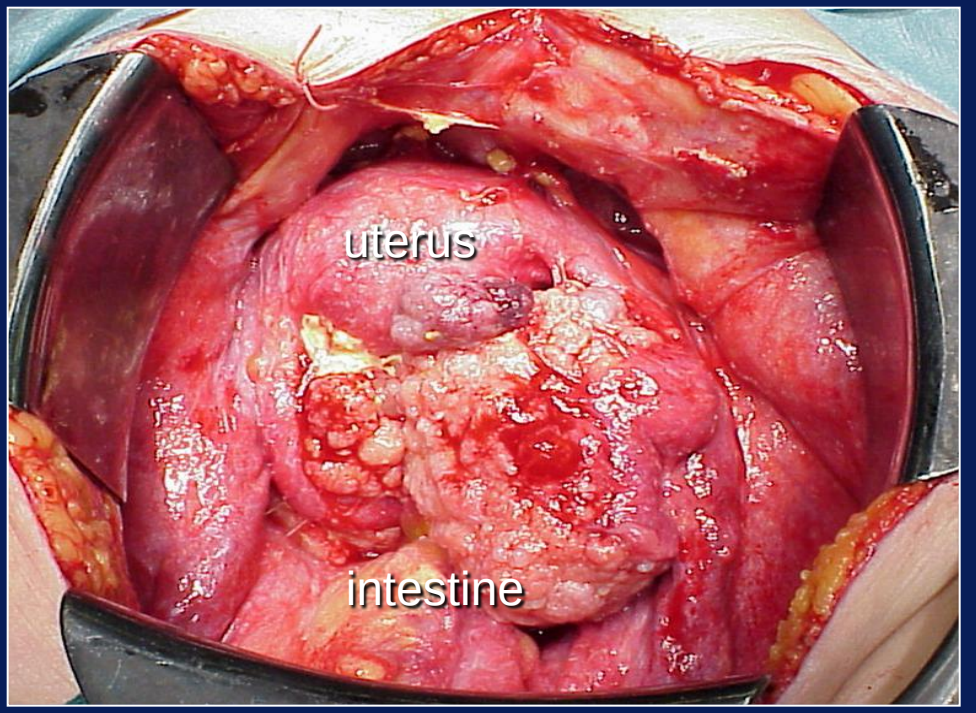
Epithelial Ovarian Cancer

Ovarian cancer (204,000 cases; 4.0%) is the sixth most common cancer and the seventh cause of death from cancer in women (125,000 deaths; 4.2%).

Global Impact 2002



Parkin A *et al*. *CA Cancer J Clin* **55**:74-108, 2005



Despite the development of combination chemotherapy, the relative 5-year overall survival rate of the epithelial ovarian cancers is still low because intraperitoneal metastases are already widespread in most patients.

Alteration and current status of chemotherapy for epithelial ovarian cancer

1980s

1990s

Introduction of CDDP	Trial of the ADM combination	Introduction of TXL	Trial of the combination platinum-drug	Evaluation of the concomitant drugs
L-PAM VS CPA+ADM	CPA+ADM VS CPA+ADM+CDDP	CPA+ADM+CDDP VS CPA+CDDP	CPA+CDDP VS TXL+CDDP	TXL+CDDP VS TXL+CBDCA	TXL+CBDCA VS TXL+CBDCA＋α

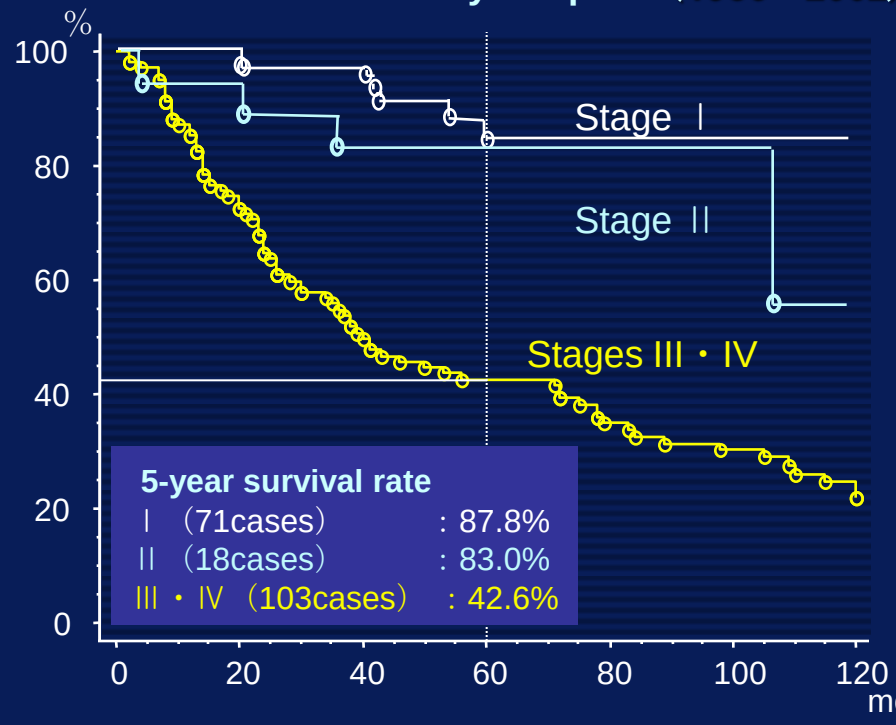
5-year survival rate according to time period and disease stage

	＊1976～1982	1983～1987	1988～1994
FIGO stage	Treatment without TXL		Treatment with TXL
Ⅰ	65.1%	89.6%	92.6%
Ⅱ	46.1%	74.3%	70.1%
Ⅲ	15.5%	29.9%	37.5%
Ⅳ	4.6%	18.0%	25.5%

＊Extracted from 26th FIGO Annual Reports(1976～1982)

Trimble EL *et al*. *Oncology* **13**: 1068, 1999

Overall survival of patients treated at the Kumamoto University Hospital（1986～2002）



Molecular target agent discovery for various malignancies

Adaptation disease	Agent（trade name ® ）	Target
Breast cancer	Trastuzumab（Herceptin ®）	HER2
Non-small cell lung cancer	Gefitinib （Iressa ®） Erlotinib （Tarceva ®）	EGFR
Colon cancer	Bevacizumab （Avastin ®） Cetuximab（Erbitux ®）	VEGF EGFR
Chronic myelocytic leukemia GIST	Imatinib （Gleevec ®）	Bcr-Abl/c-kit
Non-Hodgkin's lymphoma	Rituximab （Rituxan ®）	CD20

GIST: gastrointestinal stromal tumor, VEGF: Vascular endothelial growth factor, EGFR: Epidermal growth factor receptor

Targeting angiogenesis

Mechanism and Targets	Reagents
Hypoxia-related gene expression	Anti-HIF1α (oligonucleotide)
Sequester VEGF ligand	Bevacizumab (IgG1κ humanized) Aflibercept (VEGF binding sites)
Block ligand binding to VEGFR2	IMC 1121B (Human IgG1)
Neutralization of Angiopoietin-1/2	AMG 386 peptide-Fc fusion protein
VEGF-activated endothelium	Volociximab (anti-α5β1 integrin) Combretastatin Low-dose chemotherapy
Receptor tyrosine kinases (VEGFR, FGFR, PDGFR) Convergent intracellular pathways (PI3K, MAP, AKT)	TKI (multiple small molecules)
PKCβ and VEGF-mediated angiogenesis	Enzastaurin
mTOR	Rapamycin derivatives and others
Epithelial-Mesenchymal Transition (src)	Dasatinib (TKI)

Phase III trials evaluating addition of an Angiogenesis inhibitor in epithelial ovarian cancer

Agent	Group or Sponsor	Line of therapy	Primary Efficacy Endpoint (S)	Status
Bevacizumab	GOG0218	First	PFS	Reported at ASCO2010
	ICON7 (GCIG study)	First	PFS and OS	Closed
	Pharma/ AGO-OVAR16	*Recurrent*	PFS	Closed
BIBF	Pharma/ AGO-OVAR12	First	PFS	Active
Cediranib	ICON6 (GCIG study)	*Recurrent*	PFS and OS	Active
Pazopanib	Pharma	First (maintenance *only*)	PFS	Active

Gynecologic Oncology Group

GOG-0218

ASCO Annual '10 Meeting

Phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer: A Gynecologic Oncology Group (GOG) Study

R.A. Burger,[1] M.F. Brady,[2] M.A. Bookman,[3]
J.L. Walker,[4] H.D. Homesley,[5] J. Fowler,[6]
B.J. Monk,[7] B.E. Greer,[8] M. Boente,[9] S.X. Liang[10]

[1]Fox Chase Cancer Center, Philadelphia, PA; [2]Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY; [3]University of Arizona Cancer Center, Tucson, AZ; [4]University of Oklahoma Health Sciences Center, Oklahoma City, OK; [5]Brody School of Medicine, Greenville, NC; [6]James Cancer Hospital at the Ohio State University, Hilliard, OH; [7]University of California, Irvine Medical Center, Orange, CA; [8]Seattle Cancer Care Alliance, Seattle, WA; [9]Minnesota Oncology and Hematology, Minneapolis, MN; [10]State University of New York at Stony Brook, Stony Brook, NY, USA

GOG-0218: Schema

Front-line: Epithelial OV, PP or FT cancer

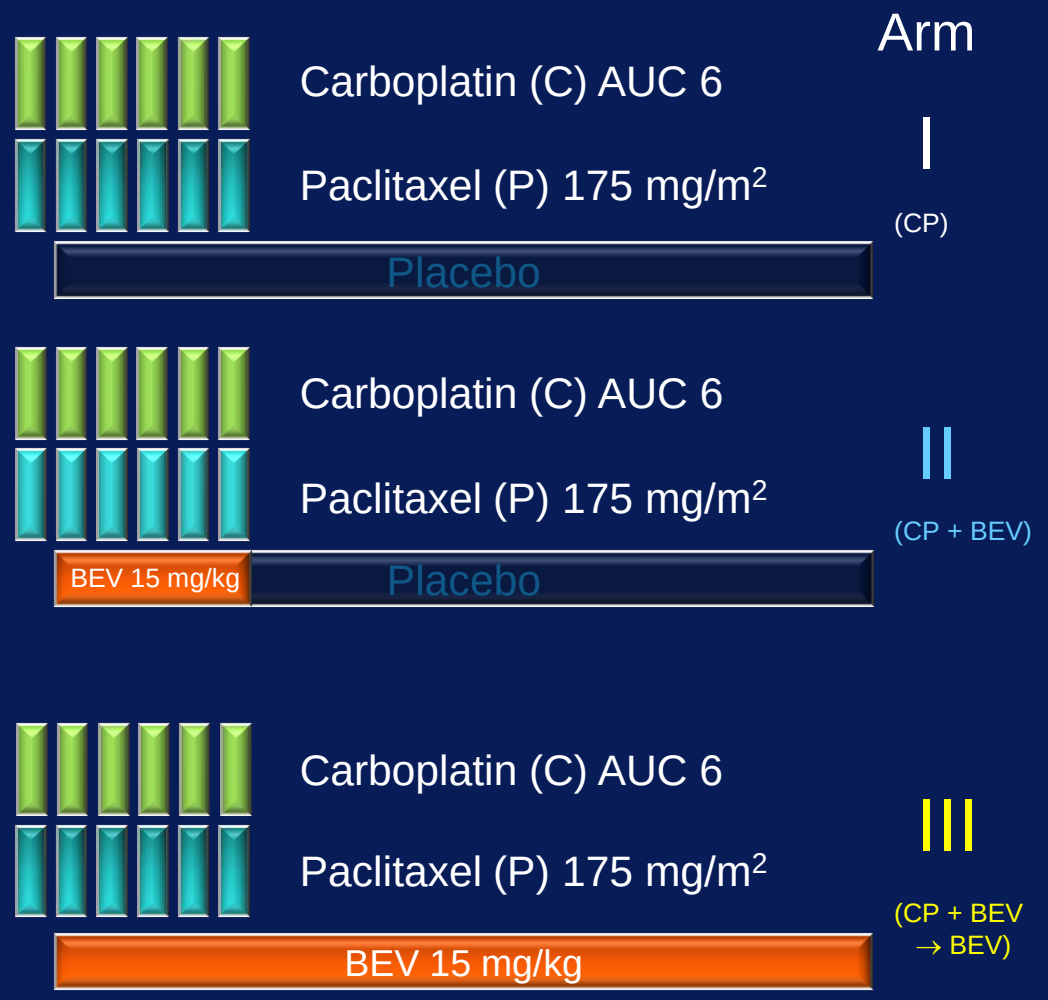
- Stage III optimal (macroscopic)
- Stage III suboptimal
- Stage IV

n=1800 (planned)

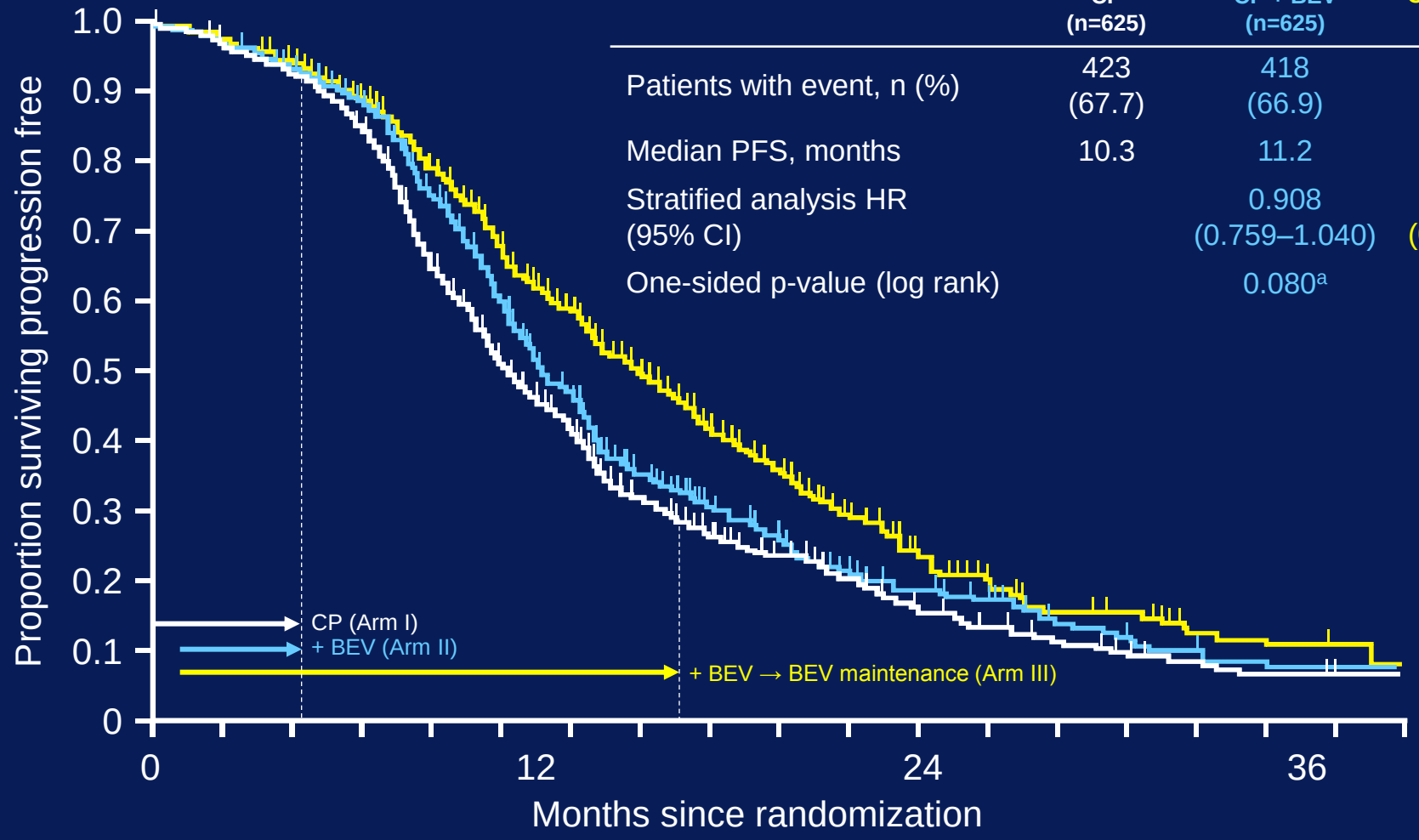
RANDOMIZE

1:1:1

Stratification variables:
- GOG performance status (PS)
- Stage/debulking status



GOG-0218: Investigator-Assessed PFS

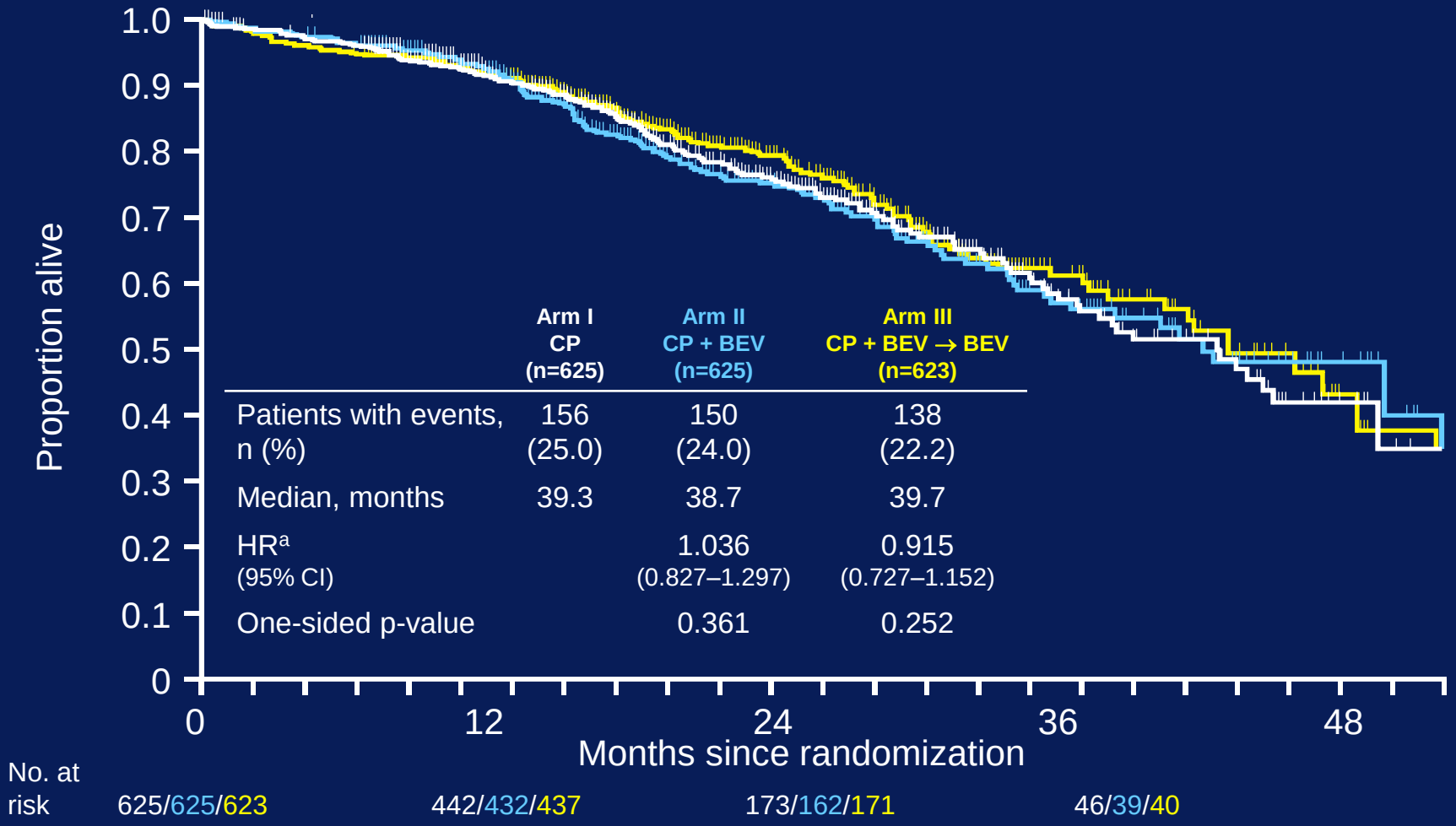


	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
Patients with event, n (%)	423 (67.7)	418 (66.9)	360 (57.8)
Median PFS, months	10.3	11.2	14.1
Stratified analysis HR (95% CI)		0.908 (0.759–1.040)	0.717 (0.625–0.824)
One-sided p-value (log rank)		0.080[a]	<0.0001[a]

[a]p-value boundary = 0.0116

GOG-0218: Overall Survival Analysis

At time of final PFS analysis



	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
Patients with events, n (%)	156 (25.0)	150 (24.0)	138 (22.2)
Median, months	39.3	38.7	39.7
HR[a] (95% CI)		1.036 (0.827–1.297)	0.915 (0.727–1.152)
One-sided p-value		0.361	0.252

No. at risk				
	625/625/623	442/432/437	173/162/171	46/39/40

[a]Stratified analysis

Reflections on GOG-0218 results
VEGF inhibition and ovarian cancer

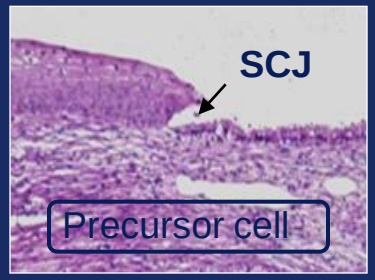
- Why was there no meaningful effect of bevacizumab in concurrent only arm?
  - High response rate in ovarian cancer with standard chemotherapy (70-80%), so no gain from bevacizumab?
  - Would concurrent treatment be more effective in recurrent disease where chemotherapy is less effective?
- Can gain in PFS in concurrent maintenance arm be explained by the *maintenance portion only ?*
  - Consider exploratory analysis of GOG-0218 patients non-progressive at end of chemotherapy.
  - RCT of pazopanib maintenance in ovarian cancer.
- Biomarkers…. more on that later

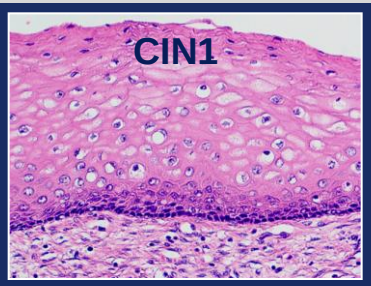
What are implications for practice or ongoing trials ?

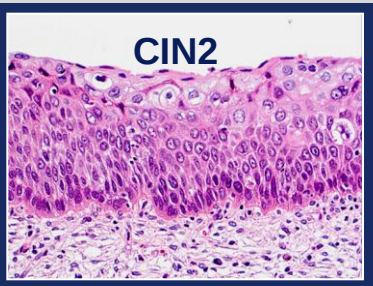
Chaotic state in epithelial ovarian cancer study: Compared to uterine cervical and endometrial cancers

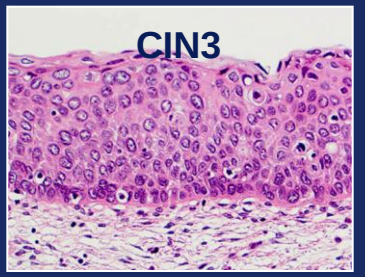
Cervical cancer

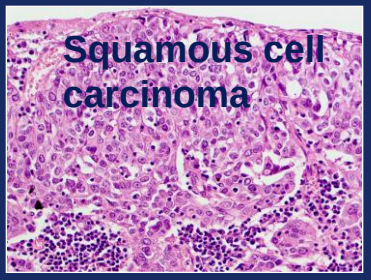
HPV infection → Precancerous lesion → Cancer





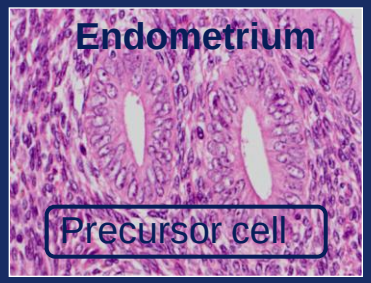


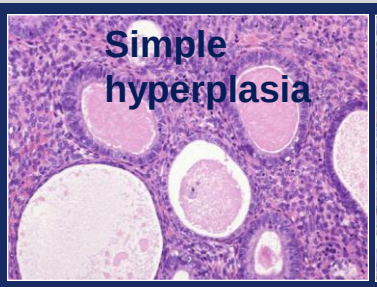


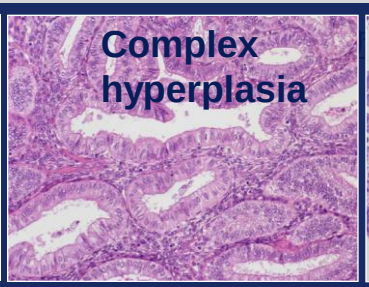


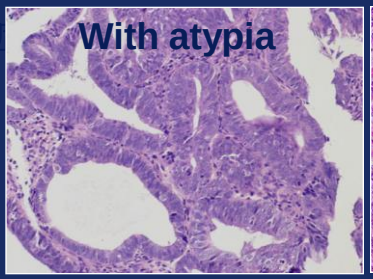
Endometrial cancer

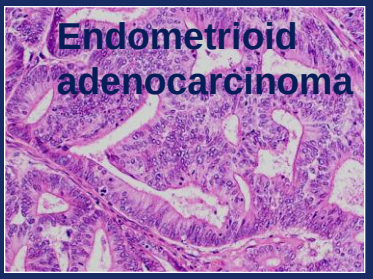
High levels of estrogen → Precancerous lesion → Cancer









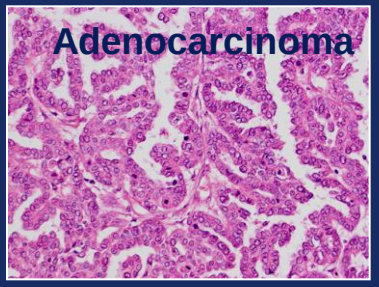


Ovarian cancer

Ovulation ? Hormone ? Chemical ? → Precancerous lesion → Cancer

Precursor cell
OSE ?
Endometriosis ?
Tubal epithelium ?
? ?

arise *de novo* from the OSE ?
coelomic metaplasia ?
atypicalendometriosis ?
? ?
? ?
adenoma-cancer sequence ?



Okamura H and Katabuchi H. *Int Rev Cytol* **242**: 1-54, 2005

- Putative precursor cells of epithelial ovarian cancer
- Risk factors of epithelial ovarian cancer
- Molecular mechanisms of ovarian carcinogenesis
- Conclusions and Perspectives

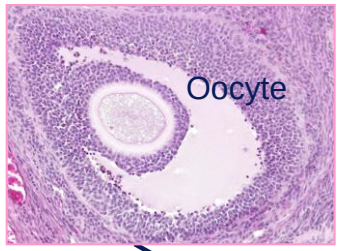
Putative precursor cells of epithelial ovarian cancer

Histological classification of ovarian tumors (WHO)

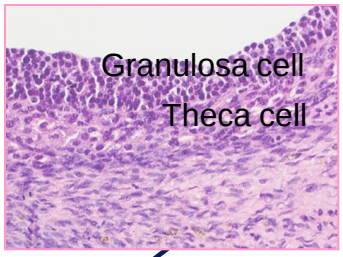
Germ cell tumors

30%

1. Dysgerminoma
2. Yolk sac tumor
   (Endodermal sinus tumor)
3. Embryonal carcinoma
4. Polyembryoma
5. Choriocarcinoma
6. Teratoma
7. Mixed germ cell tumors

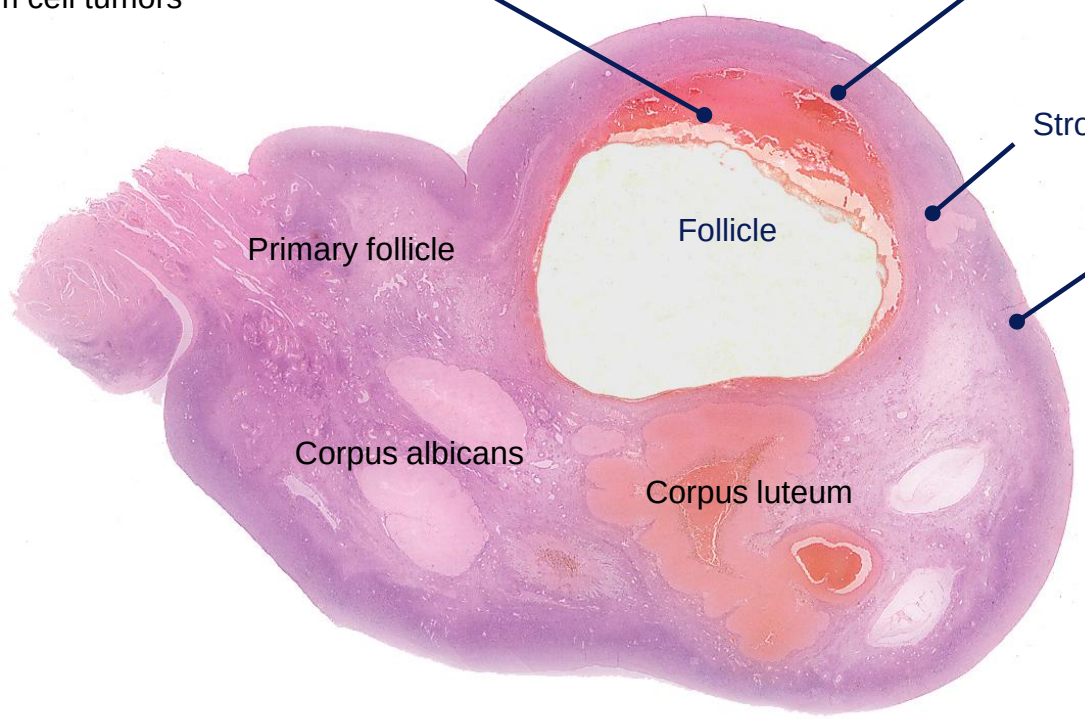


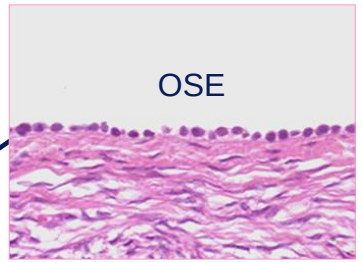
8%



Sex cord-stomal tumors

1. Granulosa-stromal cell tumors
2. Sertoli-stromal cell tumors
   (Androblastoma)
3. Sex cord tumor with annular tubules
4. Gynandroblastoma
5. Unclassified



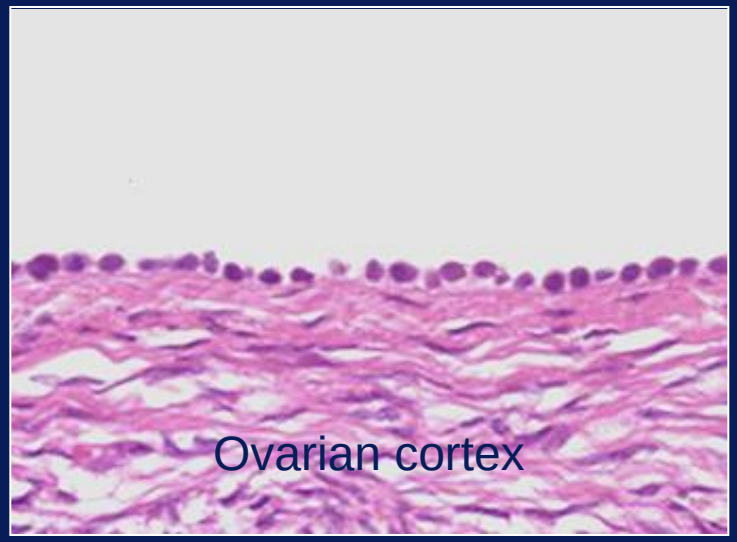


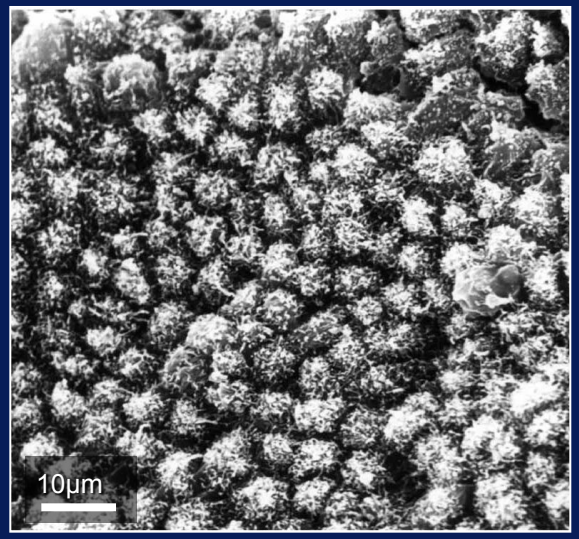
62%

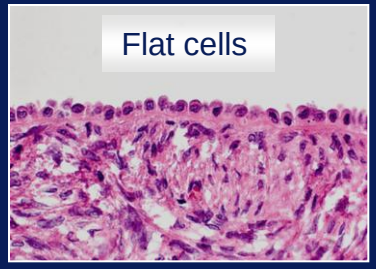
Surface epithelial-stromal tumors

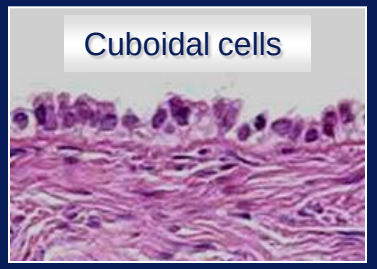
1. Serous tumors
2. Mucinous tumors
3. Endometrioid tumors
4. Clear cell tumors
5. Transitional cell tumors
6. Squamous cell tumors
7. Mixed epithelial tumors
8. Undifferentiated carcinoma

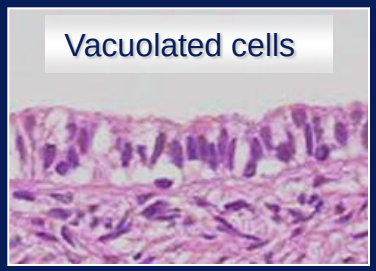
Ovarian surface epithelium (OSE)

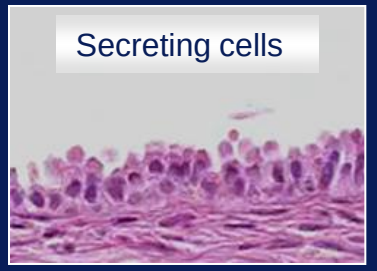












Katabuchi H and Okamura H. *Med Electron Microsc* **36**: 74-86, 2003

Immunohistochemical findings of human OSE

EMA: epithelial membrane antigen

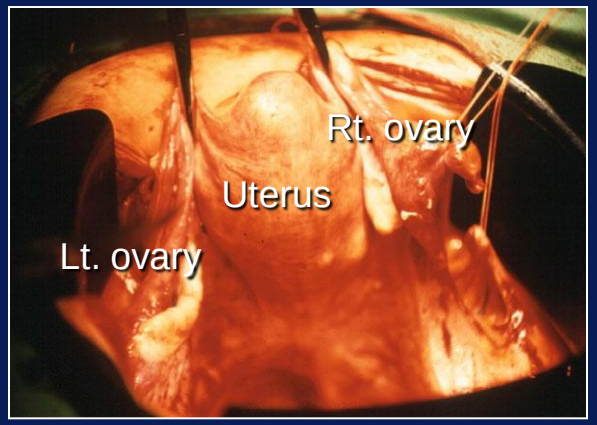
Nakamura M *et al*. *Hum Reprod* **8**: 2218-2226, 1993

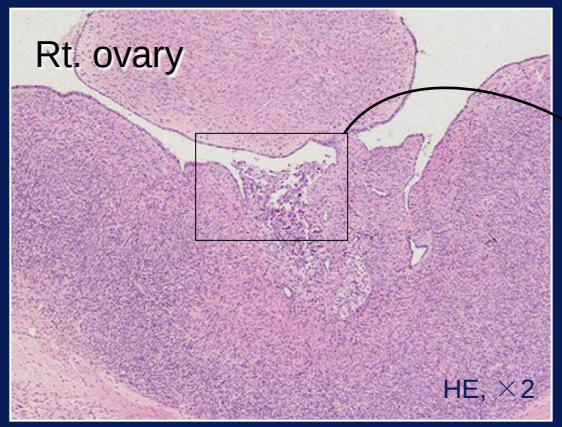
Cytological properties of human OSE

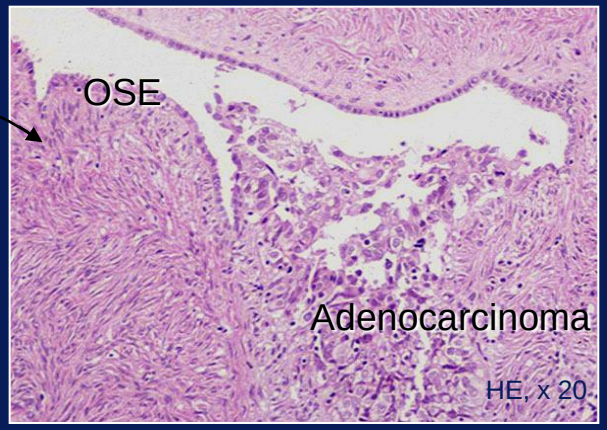
Expression products	Hormones	GnRH-I, -II, activin, inhibin
	Sex steroids	Estrogen , progesterone
	Growth factors	TGF α, TGFβ, HGF, KGF
	Cytokines	IL-1, IL-6, M-CSF, G-CSF, GM-CSF
	Extracellular matrices	Cytokeratin, vimentin, laminin Collagen types I, II, IV
Receptors	Hormones	GnRH, FSH, LH/hCG, activin
	Cell adhesion molecules	N-cadherin, catenin, vitronectin
	Sex steroids	Estrogen, progesterone, androgen
	Growth factors	EGF,TNF α, TGFβ, HGF, PDGF α, β

Histopathological findings: Transition from OSE/inclusion cyst to ovarian cancer

Early *de novo* ovarian cancer (Bell DA and Scully RE ; 1994)

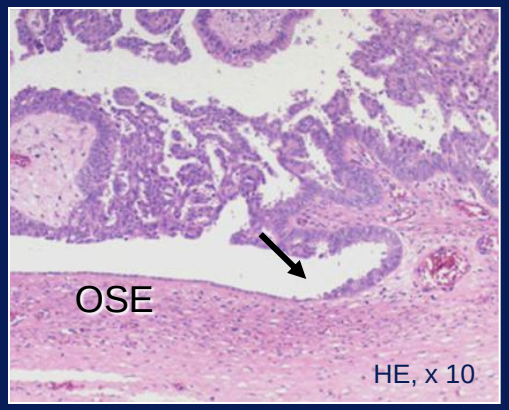




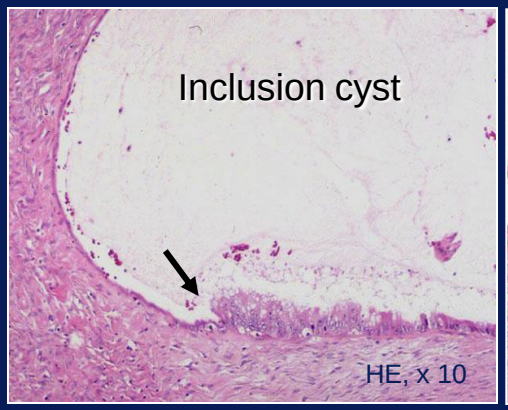


Katabuchi H *et al. J Jpn Soc Gynecol Pathol Colposc* **13**: 162-166, 1995

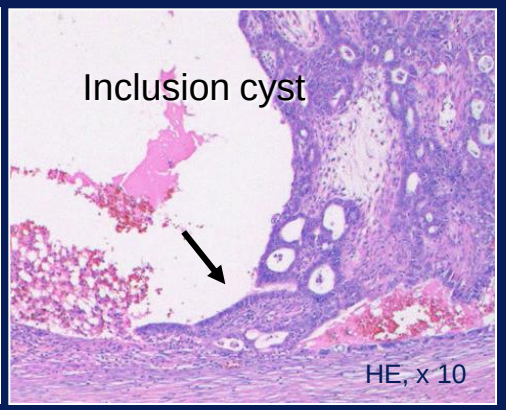
Serous



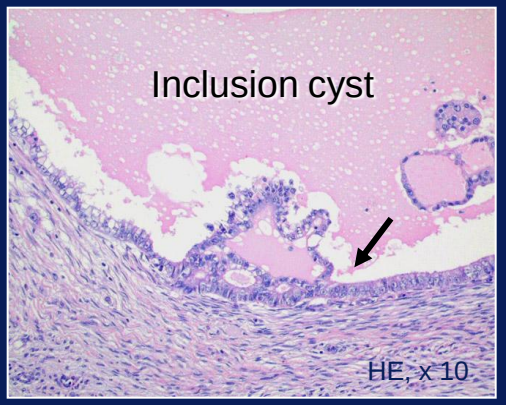
Mucinous



Endometrioid

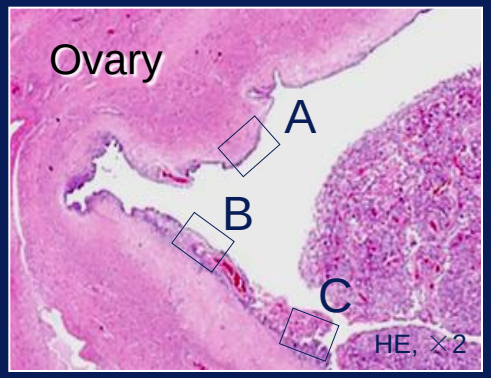


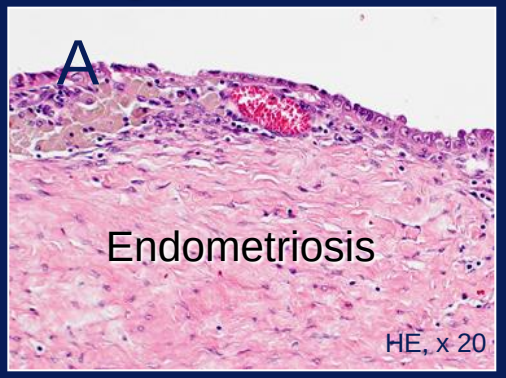
Clear cell

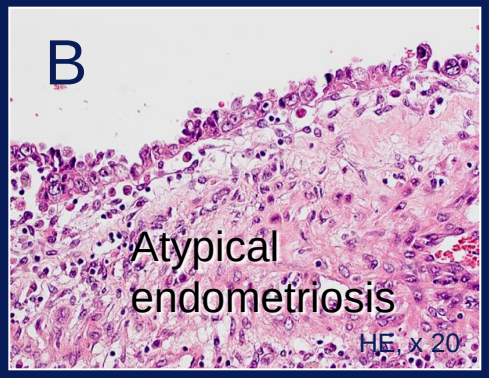


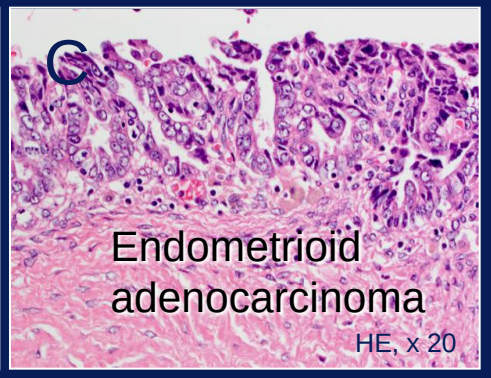
Okamura H and Katabuchi H. *Ital J Anat Embryol* **106**: 163-176, 2001

Histopathological findings: Transition from atypical endometriosis to ovarian cancer









Okamura H and Katabuchi H. *Ital J Anat Embryol* **106**: 263-276, 2001

Incidence of endometriosis synchronous with gynecological malignancies
（1991～2000: Kumamoto university）

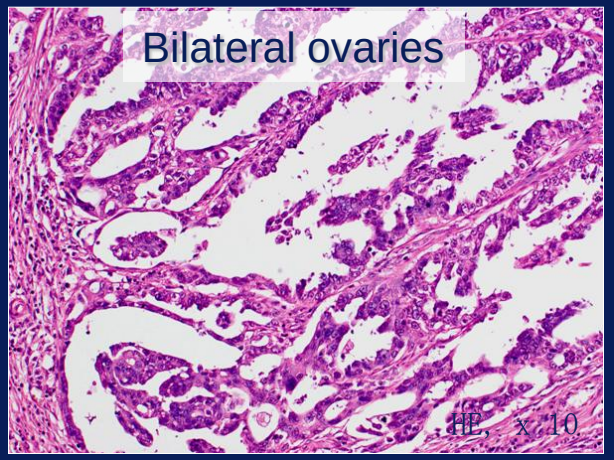
	Cervical cancer	Endometrial cancer	Ovarian cancer
Cases	320	166	146
Age	49.6	57.2	53.3
Endometriosis	11.9%	8.2%	21.1%
Adenomyosis	11.3%	17.0%	10.0%
Myoma uteri	21.3%	28.7%	23.3%

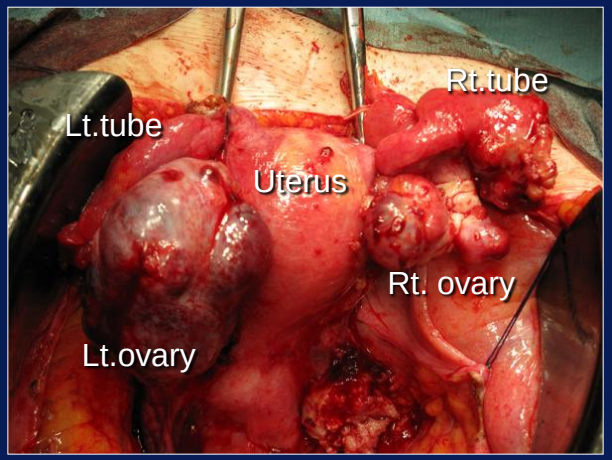
Incidence of ovarian cancer synchronous with ovarian endometrioma

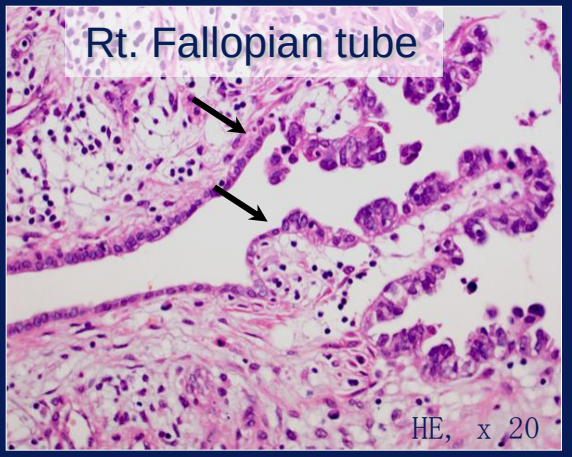
	Ovarian endometrioma	Ovarian cancer	
	n	n	%
Corner *et al.* (1950)	889	3	0.3
Scully *et al.* (1966)	950	4	0.4
Fathalla *et al.* (1967)	592	4	0.7
Nishida *et al.* (2000)	147	1	0.7
Stern *et al.* (2001)	484	4	0.8
Prefumo *et al.* (2002)	339	14	4.1
Kobayashi *et al.* (2007)	6,398	46	0.7

Histopathological findings: Transition from tubal epithelium to ovarian cancer

Ovarian serous adenocarcinoma harbor concurrent tubal carcinoma







Evidence supporting the Fallopian tube as a source of ovarian/peritoneal serous carcinoma

- ☐ Proximity of the fimbriae to the ovarian and peritoneal surfaces.
- ☐ High relative frequency of fallopian tube carcinoma, including the fimbrial end, in prophylactic salpingo-oophorectomies from BRCA+ Women.
- ☐ Tubal intraepithelial carcinoma(TIC) is a recognized entity in presumed primary tubal carcinomas and prophylactic salpingectomies from BRCA+ women.
- ☐ TIC is identified in 5 of 8 (63%) and 19 of 39 (49%) consecutive pelvic serous carcinomas classified as primary peritoneal and ovarian.
- ☐ A genetic link (p53 mutation status) between TIC and ovarian serous carcinoma.

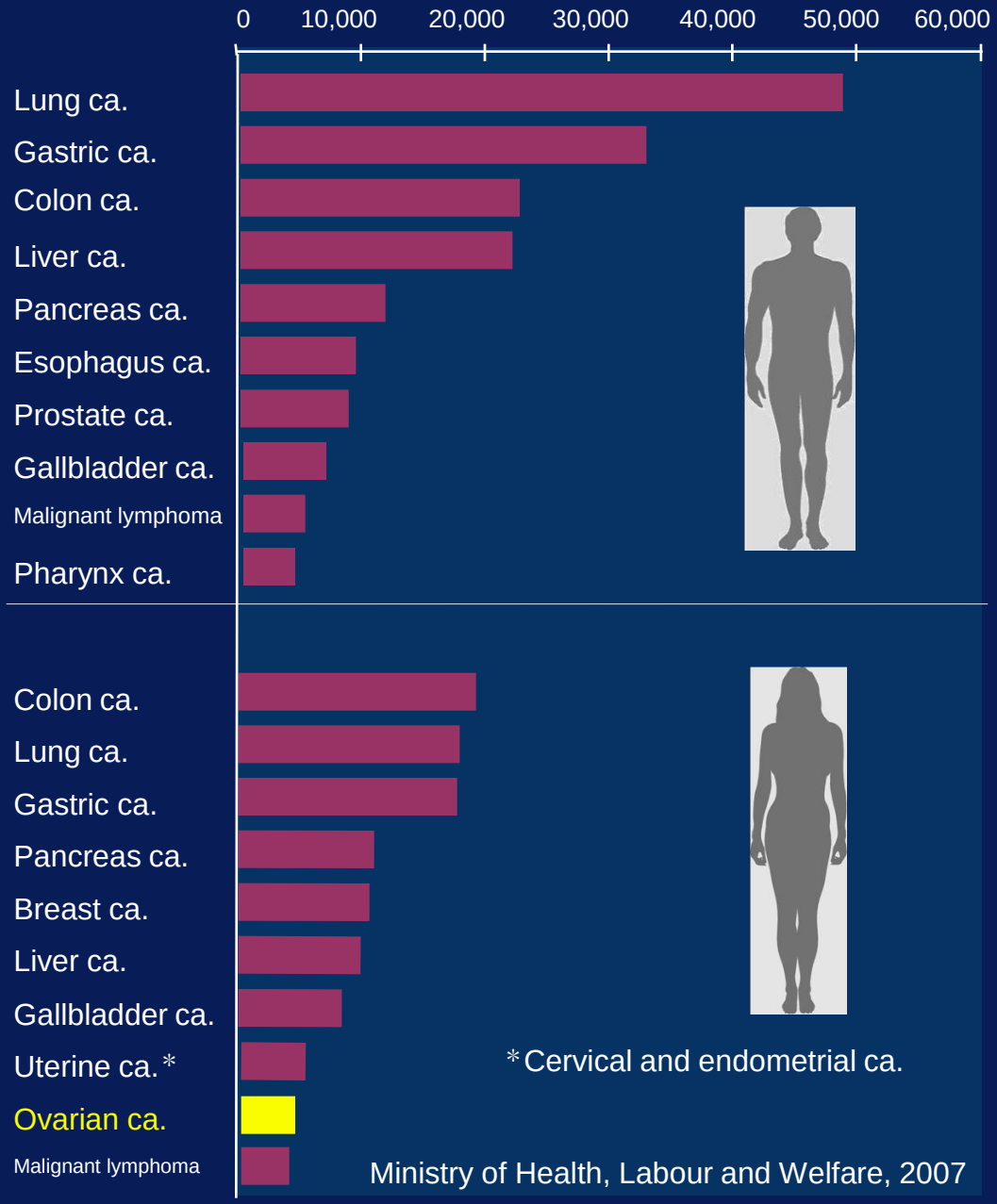
Kindelberger DW *et al. Am J Surg Pathol* 31: 161-169, 2007

The leading role of the precursor cell to play in epithelial ovarian cancer is・・・

Ovarian Surface Epithelium
（OSE）

Risk factors of epithelial ovarian cancer

Number of deaths, by cancer site (Japan, 2007) and its risk factor



Risk factors

Smoking

Lung ca., Pharynx ca., Esophagus ca., Gastric ca., Cervical ca., Pancreas ca.

Alcohol

Pharynx ca., Esophagus ca., Liver ca., Breast ca.

Ionizing radiation

Leukemia, thyroid cancer, Breast ca., Lung ca., Gastric ca.

Chemicals （asbestos, vinyl chloride, etc.）

Lung ca., pleural mesothelioma, Bladder ca., Skin cancer

Virus, Microorganism

Liver ca., Cervical ca., Gastric ca., Malignant lymphoma, Bladder ca.

Reproductive factors, Hormone

Breast ca., Endometrial ca.

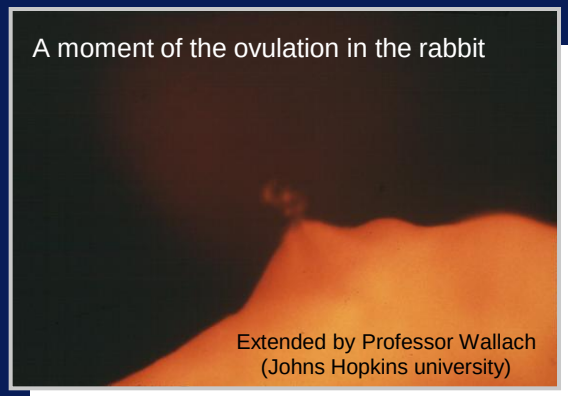
NCI（National Cancer Institute) home page
Cancer causes and risk factors（http://www.cancer.gov/)

Risk factors for epithelial ovarian cancer

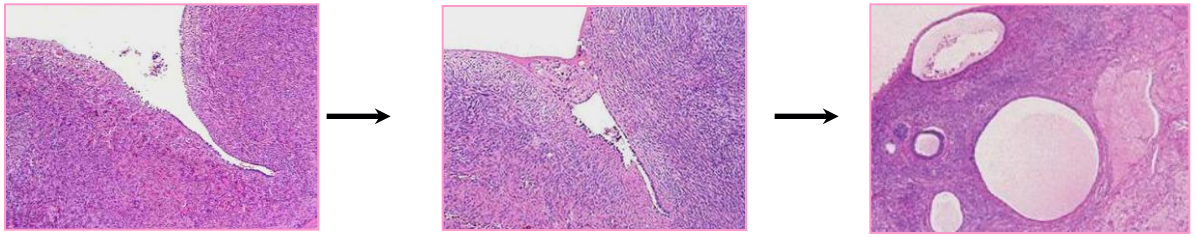
	Factors influencing risk	Estimated relative risk
☐	Older ages: Forties ~ Seventies	3
☐	Residence in North America, Northern Europe	2-5
☐	Higher levels of education or income	1.5-2
☐	White race	1.5
☑	Nulligravidity	2-3
☑	History of infertility or use of infertility drugs	2-5
☑	Early ages at menarche	1.5
☑	Late ages at natural menopause	1.5-2
☐	History of a hysterectomy	0.5-0.7
☑	Use of oral contraceptives	0.3-0.5
☐	Peritoneal talc exposure	1.5-2
☐	Female relative with epithelial ovarian cancer	3-4

Schiffman MH and Brinton LA: Blaustein's Pathology of the Female Genital Tract. 4th *ed. pp*1199-1223, 1994

Hypothesis of epithelial ovarian carcinogenesis



Periodical and incessant ovulation



Invagination of ovarian surface epithelium

Ovulation

Formation of inclusion cyst

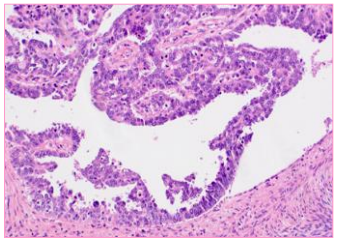
Accumulation of genetic changes

Carcinogens

Tumorigenesis

Follicle

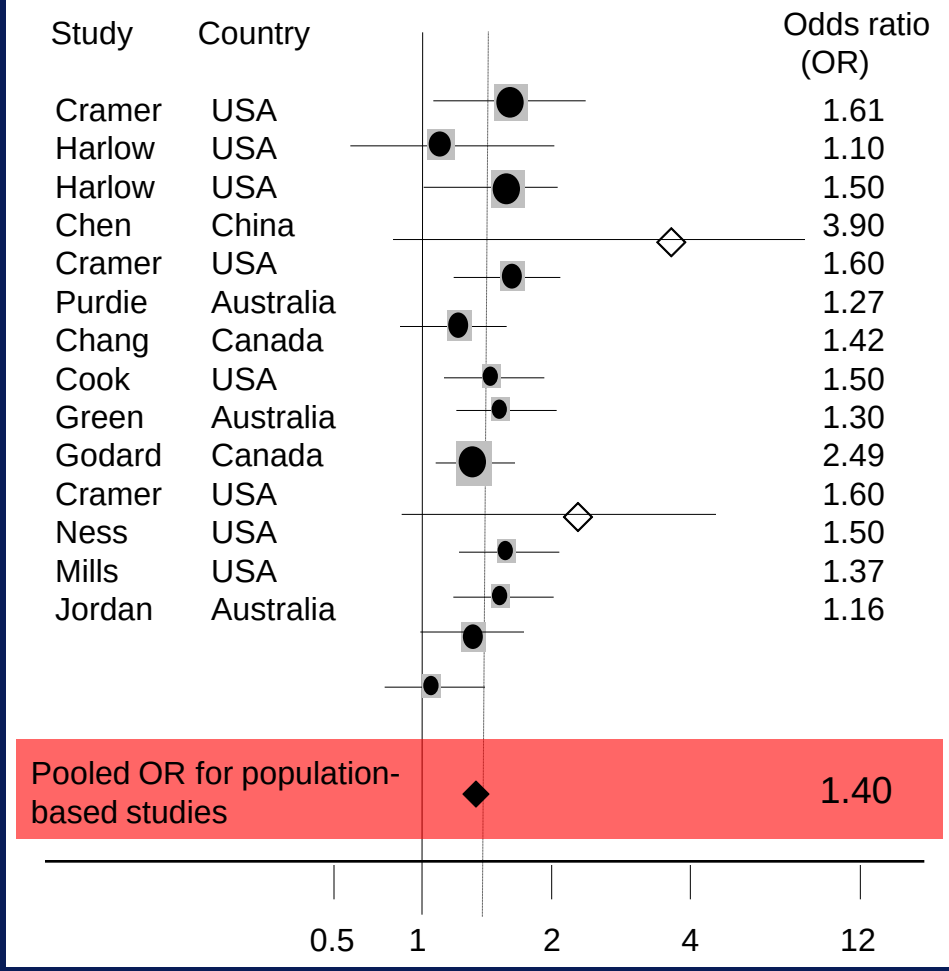
Ovary



Okamura H and Katabuchi H. *Int Rev Cytol* 242: 1-54, 2005

Perineal use of talc and risk of ovarian cancer

Case-control studies contributing data on perineal talc use and ovarian cancer



Langseth H *et al. J Epidemiol Com Health* 62: 358-360, 2008

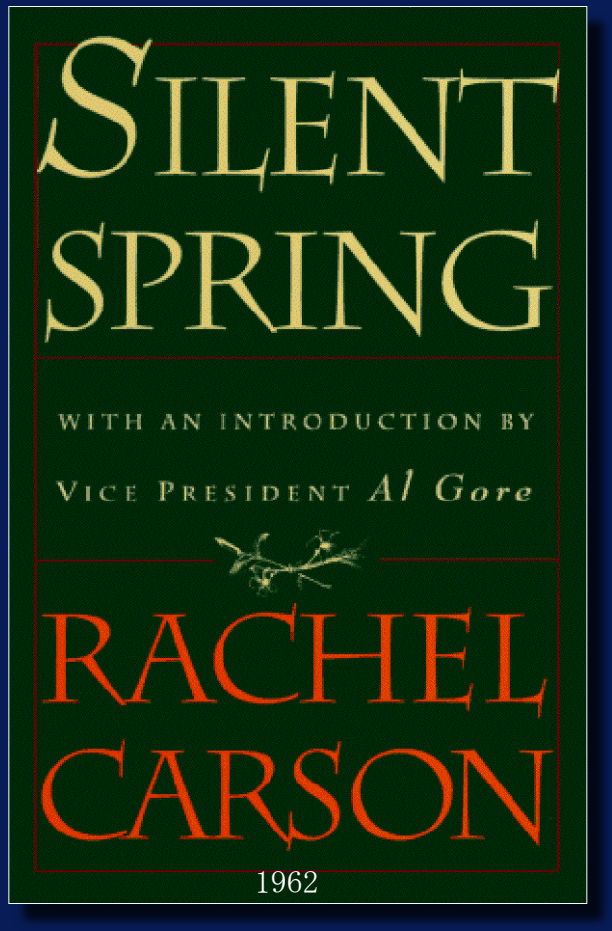
Anatomic characteristics in woman and risk factor of ovarian cancer

Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer

		Ovarian cancer	Controls	Relative risk
Tubal sterilisation	without	720 (87%)	661 (77%)	1.0
	with	104 (13%)	194 (23%)	0.61
Hysterectomy	without	708 (86%)	684 (80%)	1.0
	with	114 (14%)	171 (20%)	0.64

Green A *et al*. *Int J Cancer* **71**: 948 – 951, 1997

The possibility that ovarian cancer may be caused by exposure of chemical substances…



Rachel Carson has already pointed out an environmental problem by the chemical substance half a century ago.

Endocrine disruptor linked to ovarian cancer

- ☐ Dioxine
- ☐ DDT
- ☐ Polychlorobiphenyl (PCB)
- ☐ Diethylstilbestrol (DES)
- ☐ Bis Phenol A (BPA)
- ☐ Tributyltine (TBT) …etc.

Environmental survey of chemicals in Japan

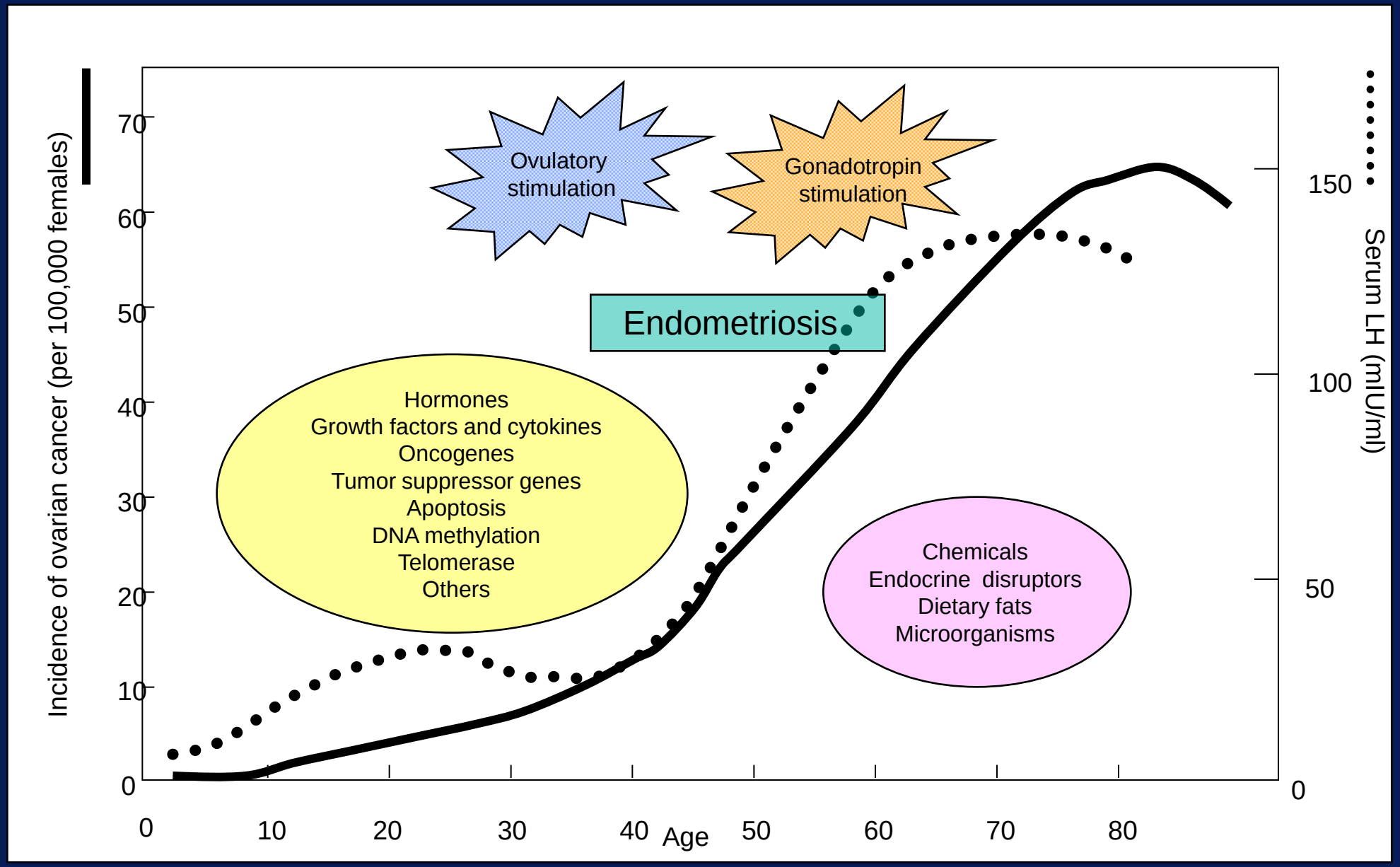
	Surface water	Bottom sediment	Aquatic wildlife	Air
4-Aminophenol	1/2*			
cis-1,3-Dichloropropene			8/20	
Dicohol		2/5		
Diphenylmethane		2/6		
Formaldehyde			2/2	
Pentachloronitrobenzene				1/15
⋮	⋮	⋮	⋮	⋮
Total	162/788	243/748	107/259	184/275

* Number of detected substances/Number of surveyed substances

Source: Report on Environmental Survey and Monitoring of Chemicals in FY2005, Ministry of the Environment

A total of 837 substances were surveyed in the past (from FY1974 to FY2004), of which 381 substances were detected in the general environment.

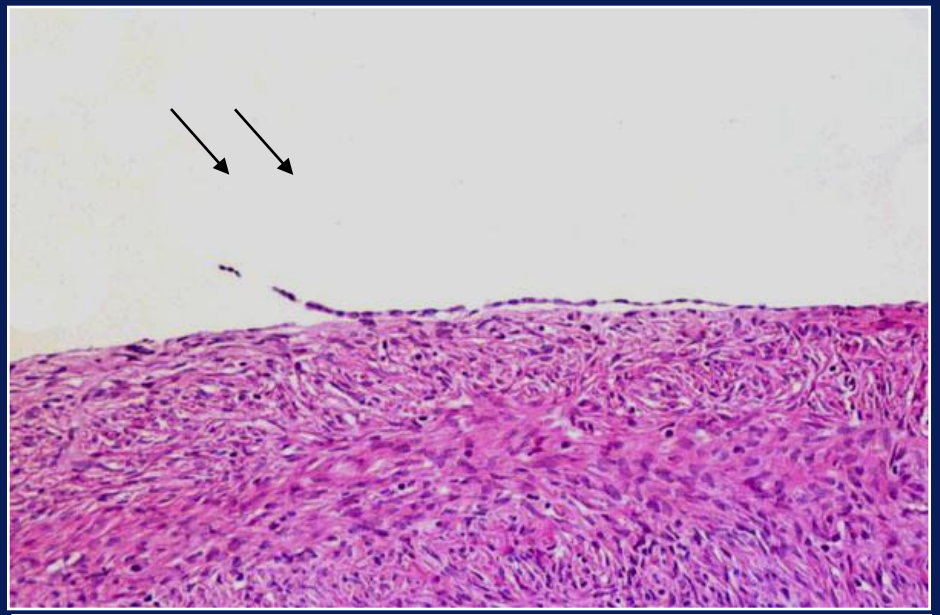
Factors influencing human epithelial ovarian carcinogenesis

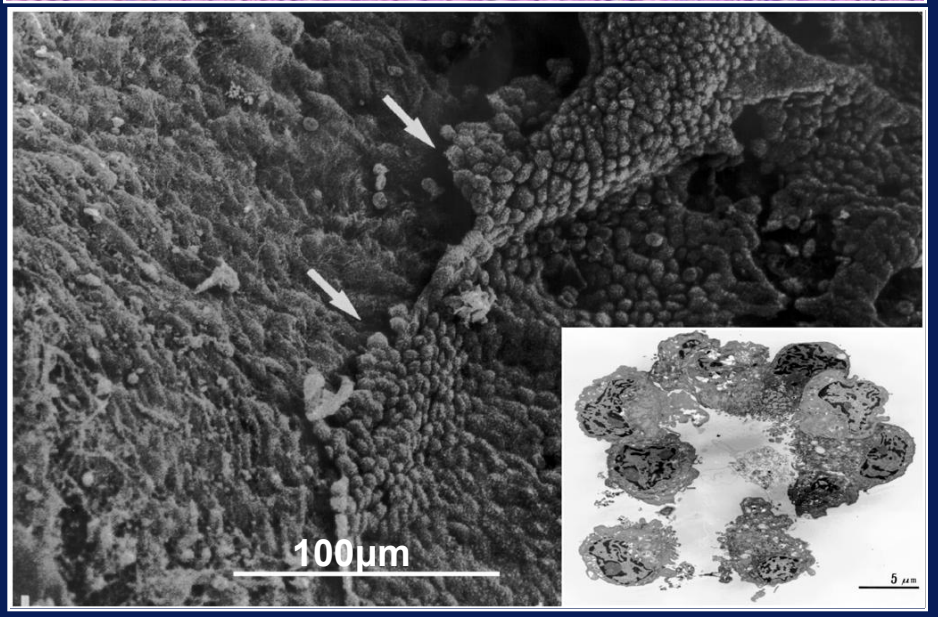


Okamura H and Katabuchi H. *Int Rev Cytol* **24**2: 1-54, 2005

Molecular mechanisms of ovarian carcinogenesis

Isolation of human ovarian surface epithelium

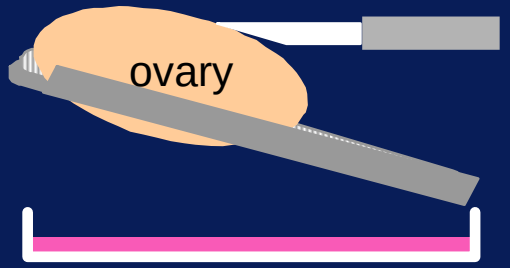




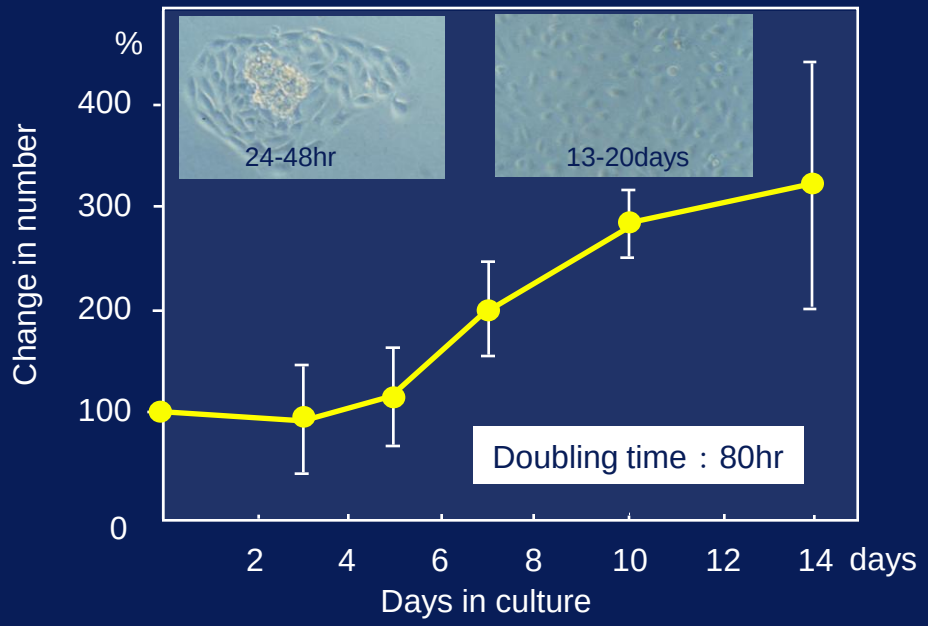
Nakamura M *et al. Virchow Arch* **424**: 59-67, 1994

Scraping Method

Ovarian surface is scraped with a surgical blade



Growth of human ovarian surface epithelium in primary culture



Precursors and molecular genetic alterations of ovarian cancer

	Histological type	Precursors	Known molecular genetic alterations
Type 1	Low-grade serous carcinoma (invasive MPSC)	Serous cystadenoma/adenofibroma Atypical proliferative serous tumor Noninvasive MPSC	*BRAF* and *KRAS* mutations (～67%)
	Mucinous carcinoma	Mucinous cystadenoma Atyical proliferative mucinous tumor	*KRAS* mutations (＞60%)
	Endometrioid carcinoma	Endometriosis Endometrioid adenofibroma Atypical proliferative endometrioid tumor	LOH or mutations in *PTEN* (20%) β-catenin gene mutations (16-54%) *KRAS* mutations (4-5%) Microsatellite instability (13-50%)
	Clear cell carcinoma	Endometriosis Clear cell adenofibroma Atypical proliferative clear cell tumor	*KRAS* mutations (5-16%) Microsatellite instability (～13%) TGF- RII mutation (66%)
Type 2	High-grade serous carcinoma Undifferentiated carcinoma	Not yet identified	*p53* mutations (50-80%) Amplification and overepxression of *HER2/neu* gene(10%-20%) and *AKT2* gene (12%-18%) Inactivation of *p16* gene (10%-17%)
	Malignant mixed mesodermal tumor (carcinosarcomas)	Not yet identified	*p53* mutations (～90%)

LOH: loss of heterozygosity

Shih IM and Kurman RJ. *Am J Pathol* **164**: 1511-1518, 2004

An *in vitro* multistep model of epithelial ovarian cancer

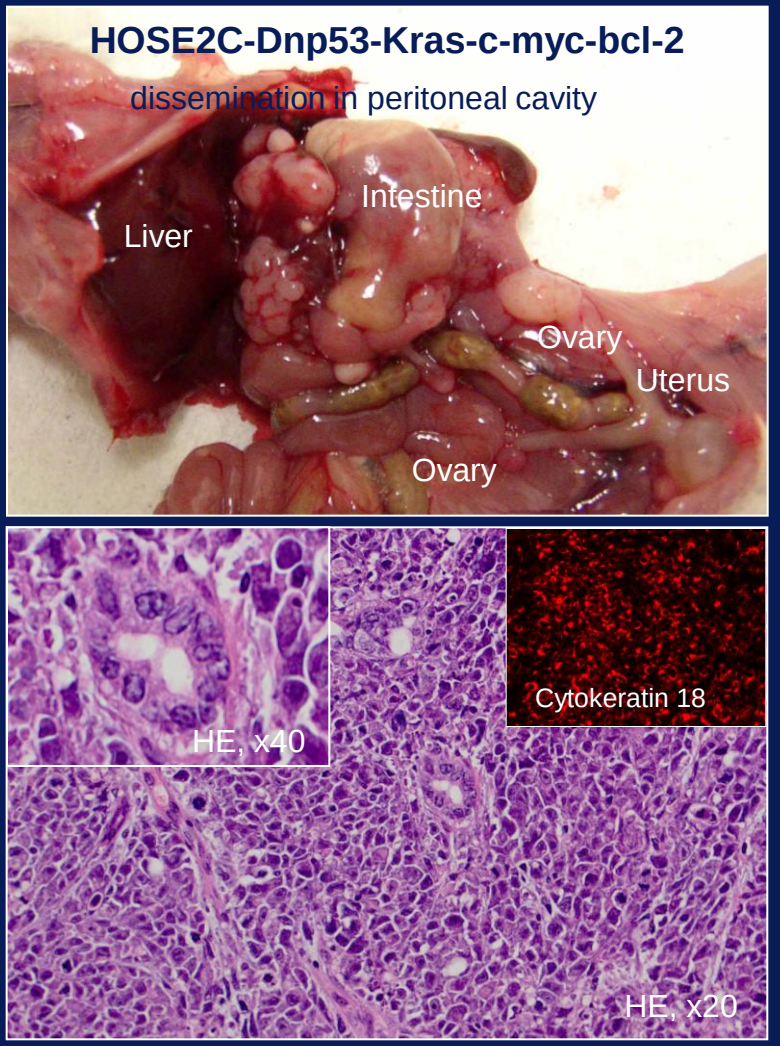
Molecular genetic alterations in serous carcinoma

p53, K-RAS , c-myc, bcl-2, HER2/neu
AKT2, BRAF, BRCA1, BRCA2

Introduction of transgenes into HOSE2C cells

Mutant p53 dominat negative form of p53 (Dnp53)	Transformation (-)
Oncogeneic Kras	Anchorage independent growth (+)
c-myc	Anchorage independent growth (+++) Tumor-forming ability (-)
Bcl-2	Resistance to apoptosis (+) Tumor-forming ability (+)

Tumor formation assay in SCID mice

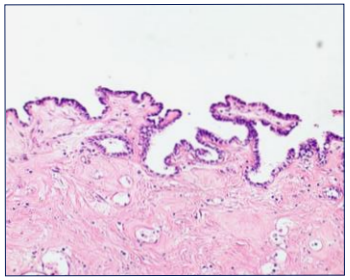


Using immortalized OSE cells, we succeeded in establishment of an *in vitro* carcinogenesis model of epithelial ovarian cancers with defined genetic elements.

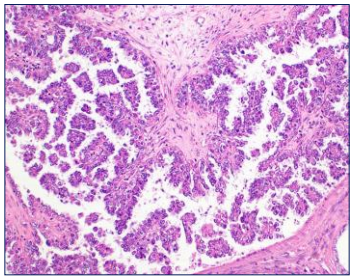
HOSE2C-derived carcinoma and Type 2 carcinogenesis

APST: atypical proliferative serous tumor
MPSC: micropapillary serous carcinoma

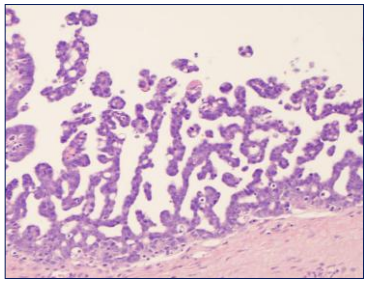
Type 1



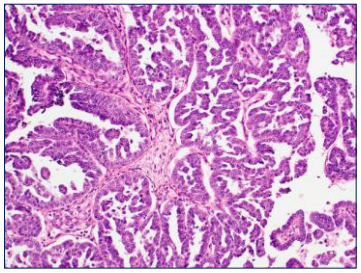
APST



MPSC



Invasive MPSC



- Frequent BRAF/KRAS mutations
- Low cellular proliferation
- Gradual increase in CIN
- 5-year survival - 55%

serous borderline tumor

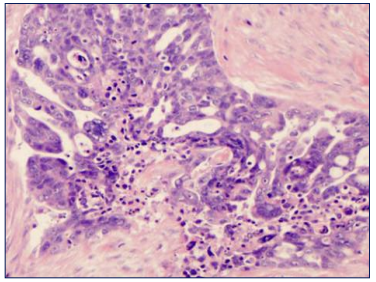
OSE inclusion cyst

Serous cystadenoma

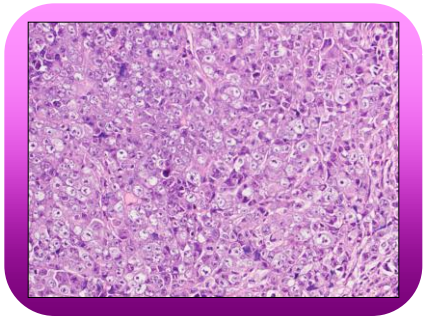
?

low grade serous carcinoma

Type 2



high-grade serous carcinoma



undifferentiated carcinoma

- Frequent p53 mutations
- High cellular proliferation
- High CIN
- Frequent HLA-G expression
- 5-year survival ～30%

Sehdev AES, Sehdev PS, Kurman RJ. *Am J Surg Pathol* **27**: 725-736, 2003

Conclusions and perspectives

Keywords in epithelial ovarian cancer research

Precursor cells

- OSE
- Inclusion cyst
- Endometriosis
- Tubal epithelium/peritoneum
- etc.

Risk factors

- Ovulation
- Gonadotropin
- Sex steroid
- Environment factor/Chemicals
- etc.

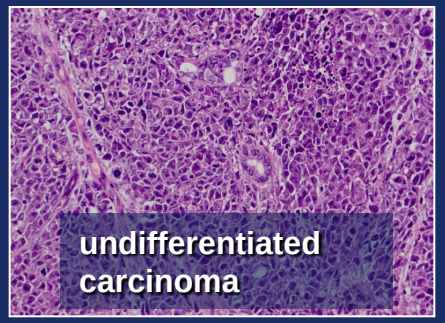
Molecular mechanisms of carcinogenesis

- Genetic mutation depend on the histological type
- *de novo*
- Multistep carcinogenesis
- Familial cancer
- etc.

Human OSE → **Immortalized cell** → ***in vitro*** **carcinogenesis model**

Tumor suppressor genes
p53

Oncogene
Kras
c-myc
bcl-2



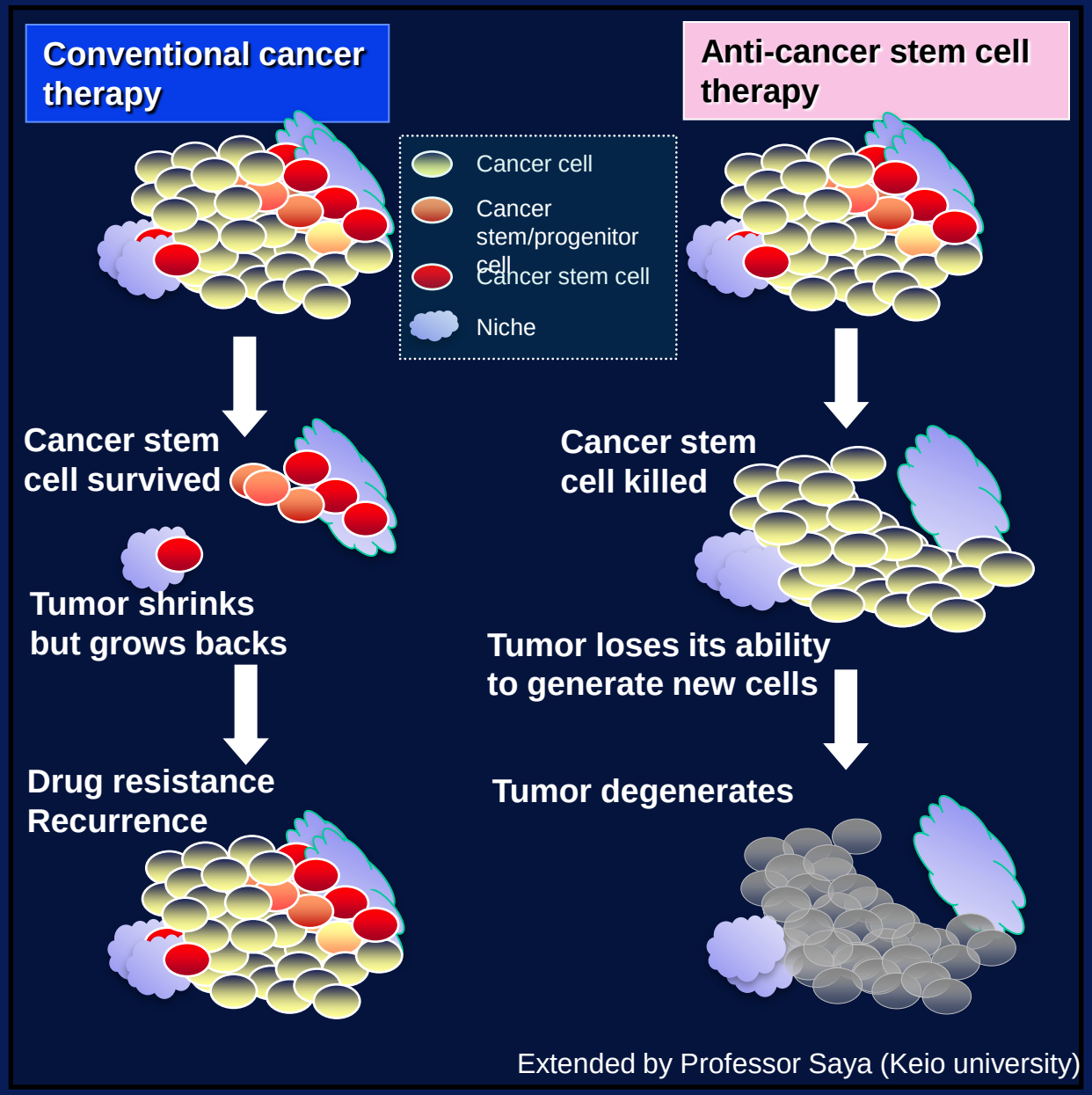
Inactivation of Rb pathway

Activation of telomerase

Inactivation of p53 and multistep carcinogenesis

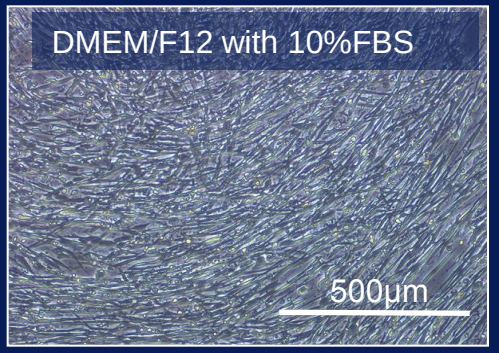
In recent studies involving the transfer of abnormal candidate genes using immortalized ovarian surface epithelium, the tumor formation stage has been reached, but differentiation to ovarian cancer-specific tissue types has not been achieved. Further elucidation of ovarian cancer-specific precursor cells, risk factors, and the mechanisms of carcinogenesis is needed. Based on such findings, a change in our current perspective can pave the way for the development of novel molecular target therapy for epithelial ovarian cancer.

A new frontier in ovarian cancer research : Therapeutic predictions of cancer stem cell model

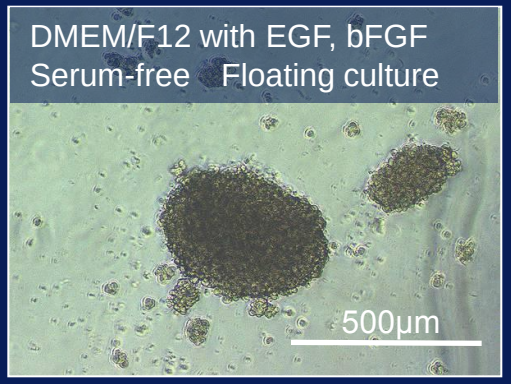


◆ **Identification of a Cancer Stem Cell in HOSE2C**

Differentiation condition



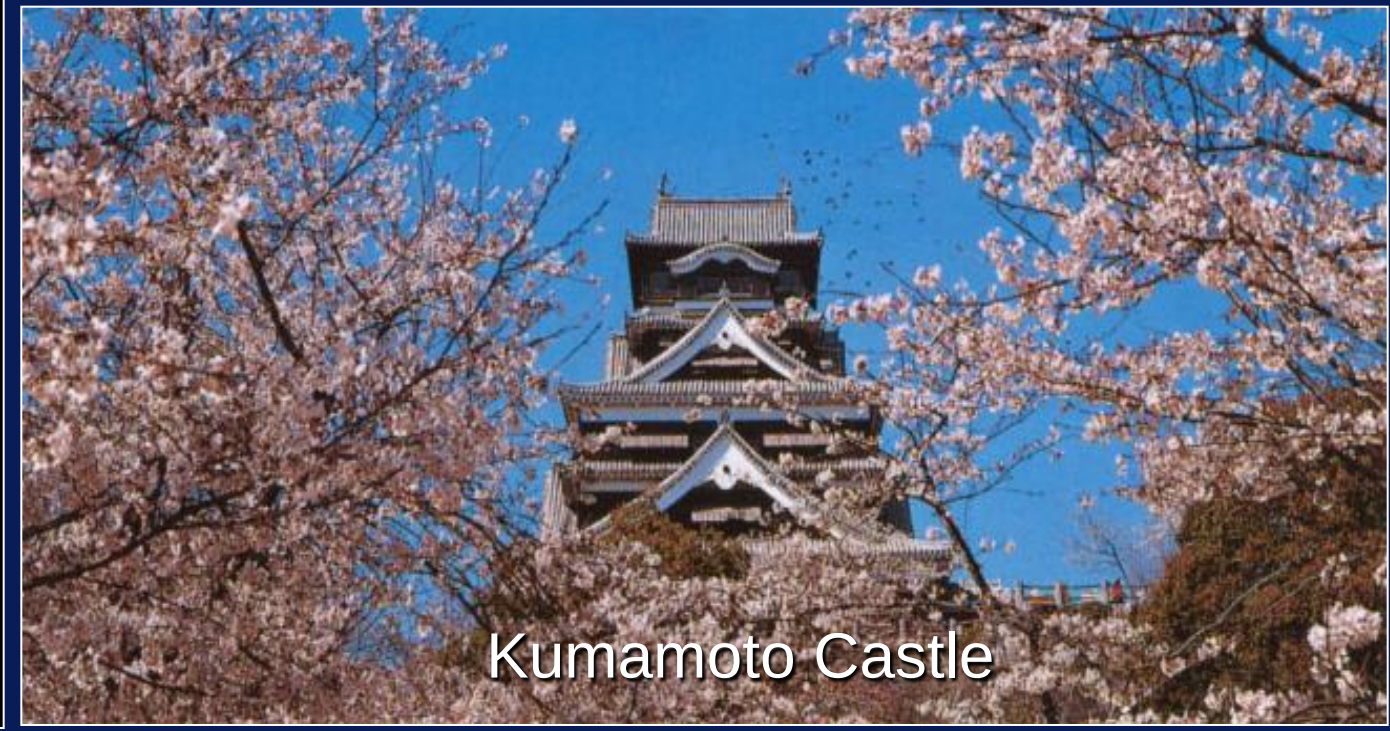
Stem cell condition



- Sphere formation
- Overexpression of stem cell-associated genes OCT4 and NANOG

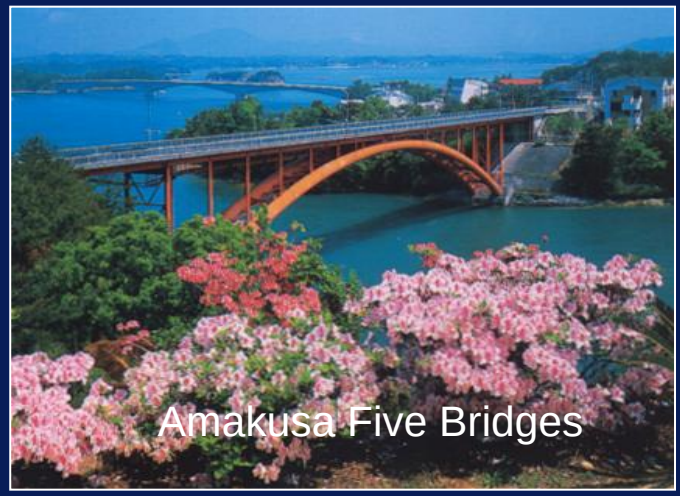

Korea
Japan
Seoul
Kumamoto
Hokkaido
Honshu
Shikoku
Kyusyu
CHINA
NORTH KOREA
SOUTH KOREA
RUSSIA
JAPAN
Sea of Okhotsk
Sea of Japan (East Sea)
Yellow Sea
East China Sea
PACIFIC OCEAN
ARCTIC OCEAN
GREENLAND (DEN.)
FEDERATED STATES OF MICRONESIA
Pyongyang
Seoul
Incheon
Busan
Daegu
Gwangju
Ulsan
Changchun
Harbin
Shenyang
Dalian
Shanghai
Tokyo
Nagoya
Osaka
Hiroshima
Fukuoka
Sapporo
Vladivostok
Khabarovsk
Yuzhno-Sakhalinsk

You are welcome to Kumamoto !!


Kumamoto Castle


Mt Aso


Suizenji Park


Amakusa Five Bridges

H. Katabuchi, M.D., Ph.D., e-mail address: buchi@kumamoto-u.ac.jp

Co-workers

Departments of Reproductive Medicine and Surgery, and Gynecology, Faculty of Life Sciences, Kumamoto University, Japan

Masaya Nakamura, M.D., Ph.D.
Hideyuki Ohtake, M.D., Ph.D.
Makoto Nitta, M.D., Ph.D.
Tomoko Maeda, M.D., Ph.D.
Rumi Sasaki, M.D., Ph.D.
Kiyomi Takaishi, M.D.
Takeshi Motohara, M.D.
Ken-ichi Motohara, M.D., Ph.D.
Hironori Tashiro, M.D., Ph.D., Assocoaite Professor

Institute of Molecular Embryology and Genetics, Kumamoto University, Japan

Masaru Yamaizumi, M.D., Ph.D.

Virology Division, National Cancer Center Research Institute, Japan

Toru Kiyono, M.D., Ph.D.

Division of Gene Regulation, Institute for Advanced Medical Research, School of Medicine, Keio University, Japan

Hideyuki Saya, M.D., Ph.D

Department of Pathology, University of Michigan, U.S.A.

Kathy R. Cho, M.D., Ph.D.

An evening scene of Kumamoto Castle