ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

Γ' ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ
ΙΑΤΡΙΚΗΣ ΣΧΟΛΗΣ ΑΘΗΝΩΝ ΕΚΠΑ
ΓΝΑ "Η ΣΩΤΗΡΙΑ"

Γυναικολογικά νεοπλάσματα

Ωραιάνθη Ε. Φιστέ
Παθολόγος – Ογκολόγος

Επιλεγόμενο μάθημα Παθολογικής Ογκολογίας 2023

Αθήνα, 23/5/2023

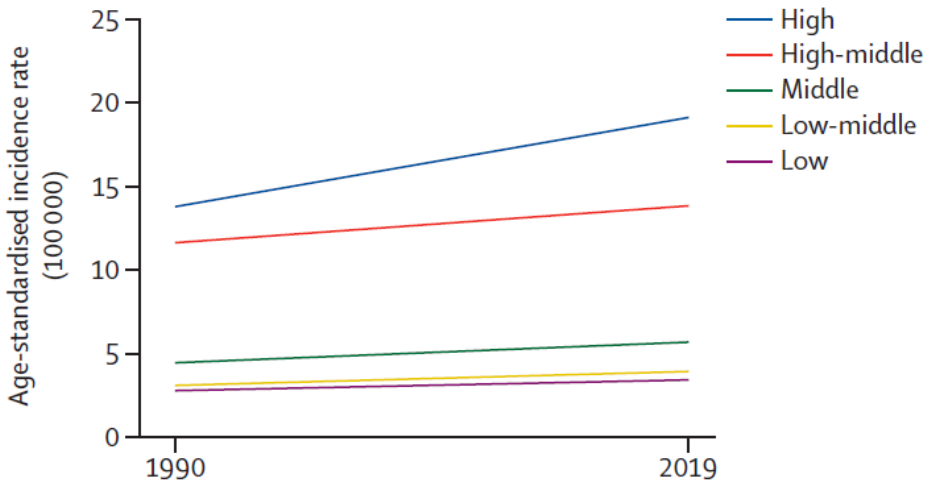
Cancer statistics, 2023

Estimated New Cases			Estimated Deaths		
Females					
Breast	297,790	31%	Lung & bronchus	59,910	21%
Lung & bronchus	120,790	13%	Breast	43,170	15%
Colon & rectum	71,160	8%	Colon & rectum	24,080	8%
Uterine corpus	66,200	7%	Pancreas	23,930	8%
Melanoma of the skin	39,490	4%	Ovary	13,270	5%
Non-Hodgkin lymphoma	35,670	4%	Uterine corpus	13,030	5%
Thyroid	31,180	3%	Liver & intrahepatic bile duct	10,380	4%
Pancreas	30,920	3%	Leukemia	9,810	3%
Kidney & renal pelvis	29,440	3%	Non-Hodgkin lymphoma	8,400	3%
Leukemia	23,940	3%	Brain & other nervous system	7,970	3%
All Sites	**948,000**	**100%**	**All Sites**	**287,740**	**100%**

Siegel et al. CA Cancer J Clin. 2023

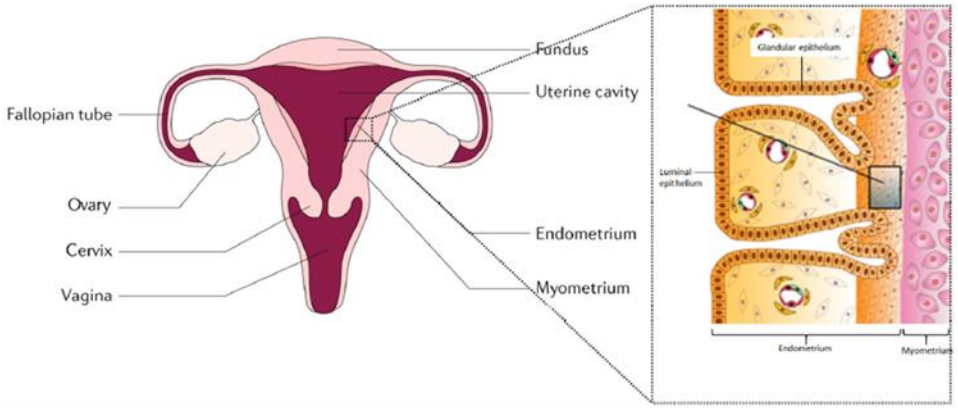
1. Endometrial cancer (EC)
Epidemiology

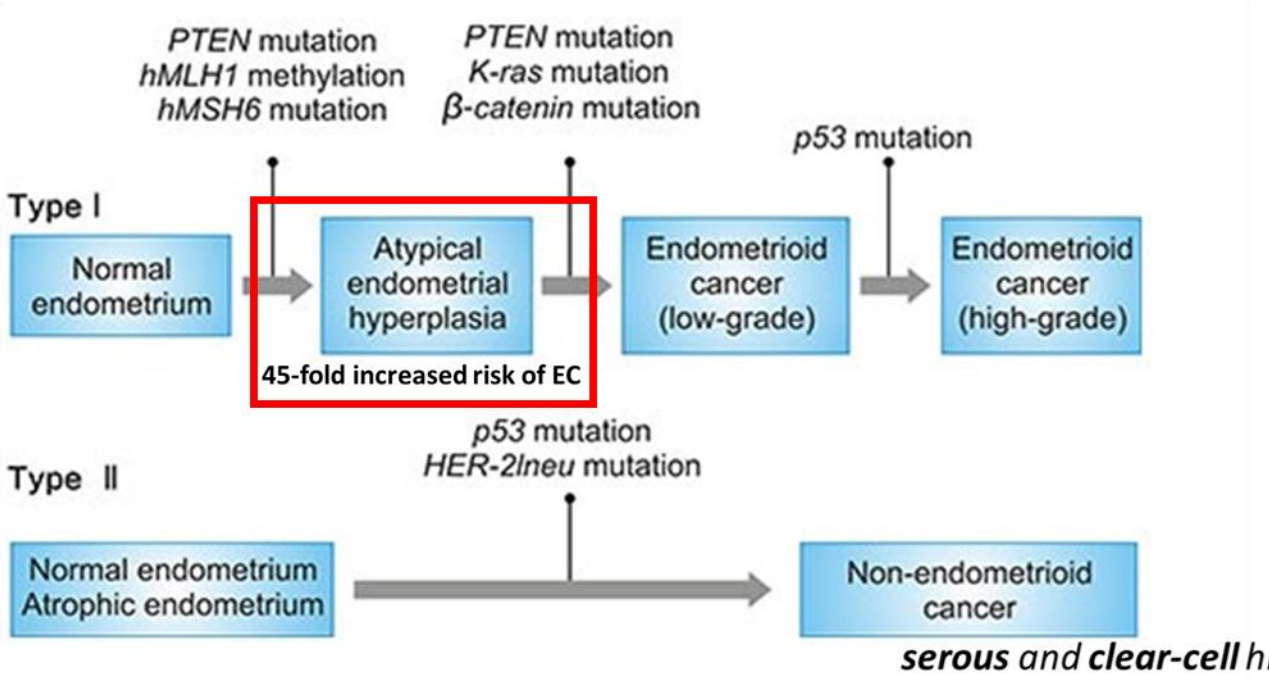
- The most common gynaecological cancer in high income countries
    - 417,000 new cases and 97,000 deaths (2020)
- Its **incidence is increasing annually**, by an estimated 1-2%



Concin N, et al. Int J Gyn Cancer. 2021
Crosbie EJ, et al. Lancet. 2022

Gene mutations in the carcinogenesis of EC





Banno K, et al. JOGR. 2014

Associated risk factors for EC

Characteristic	No. of Times Risk Increased
Obesity	
30–49 lb	3.0
>50 lb	10.0
Nulliparity	2.0
Late menopause	2.4
"Bloody" menopause	4.0
Diabetes mellitus	2.8
Hypertension	1.5
Unopposed estrogen	4–8
Complex atypical hyperplasia	29.0

*DO NOT forget older age !

Concin N, et al. Int J Gyn Cancer. 2021
Crosbie EJ, et al. Lancet. 2022

Clinical presentation of EC

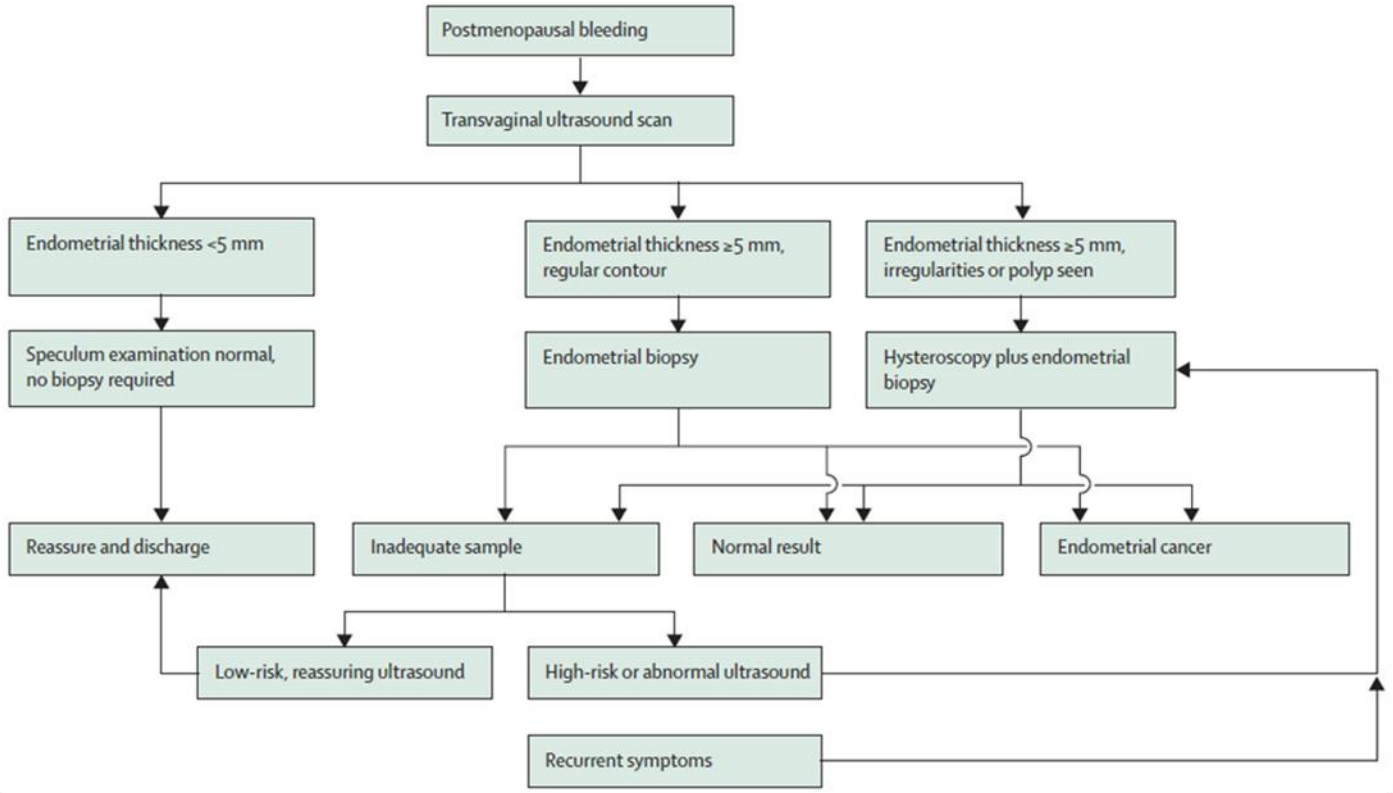
<u>The probability of EC as a cause of postmenopausal bleeding:</u>

- <1% in women <50 years
- 3% in women aged 55 years
- **24% in women >80 years**

Crosbie EJ, et al. Lancet. 2022

Diagnosis of EC

Routine investigation of postmenopausal bleeding*



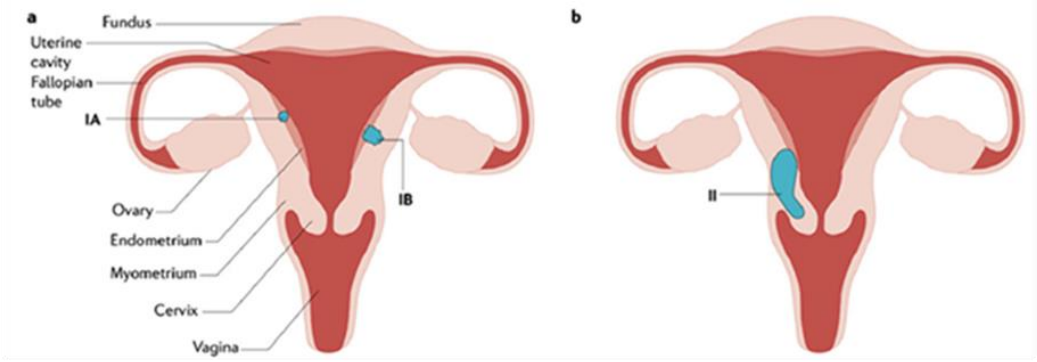
* Decision to **investigate young women** with vaginal bleeding must be guided by **risk factors**:

- family history
- obesity
- polycystic ovary syndrome (PCOS)

- Histological examination of endometrial tissue sample in those with **thickened (>5mm) endometrium**
- Preoperative assesment includes: **pelvic MRI**, **chest/abdomen CT**

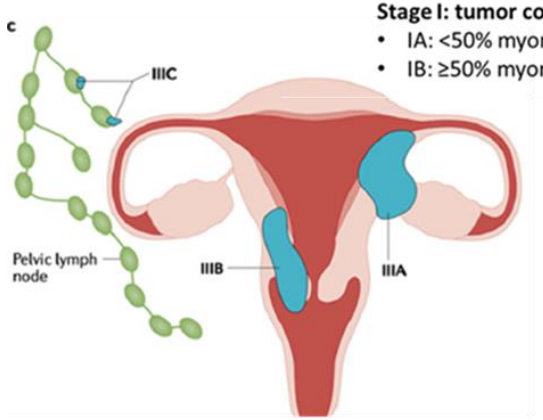
Crosbie EJ, et al. Lancet. 2022

FIGO Staging of EC

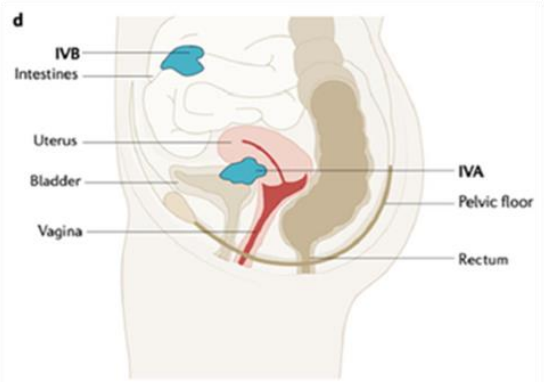


Stage I: tumor confined to the corpus uteri
- IA: <50% myometrial invasion
- IB: ≥50% myometrial invasion

Stage II: tumor invades cervical stroma, but does not extend beyond the uterus



Stage III: local and/or regional spread of the tumor
- IIIA: tumor invades the serosa of the corpus uteri *and/or* adnexae
- IIIB: vaginal *and/or* perimetrial involvement
- IIIC1: positive pelvic lymph nodes
- IIIC2: positive para-aortic lymph nodes with *or* without positive pelvic lymph nodes



Stage IV: tumor invades bladder and/or bowel mucosa, and/or distant metastases
- IVA: bladder and/or bowel mucosa invasion
- IVB: distant metastases, including inguinal lymph nodes

Makker V, et al. Nat Rev Dis Primers. 2021

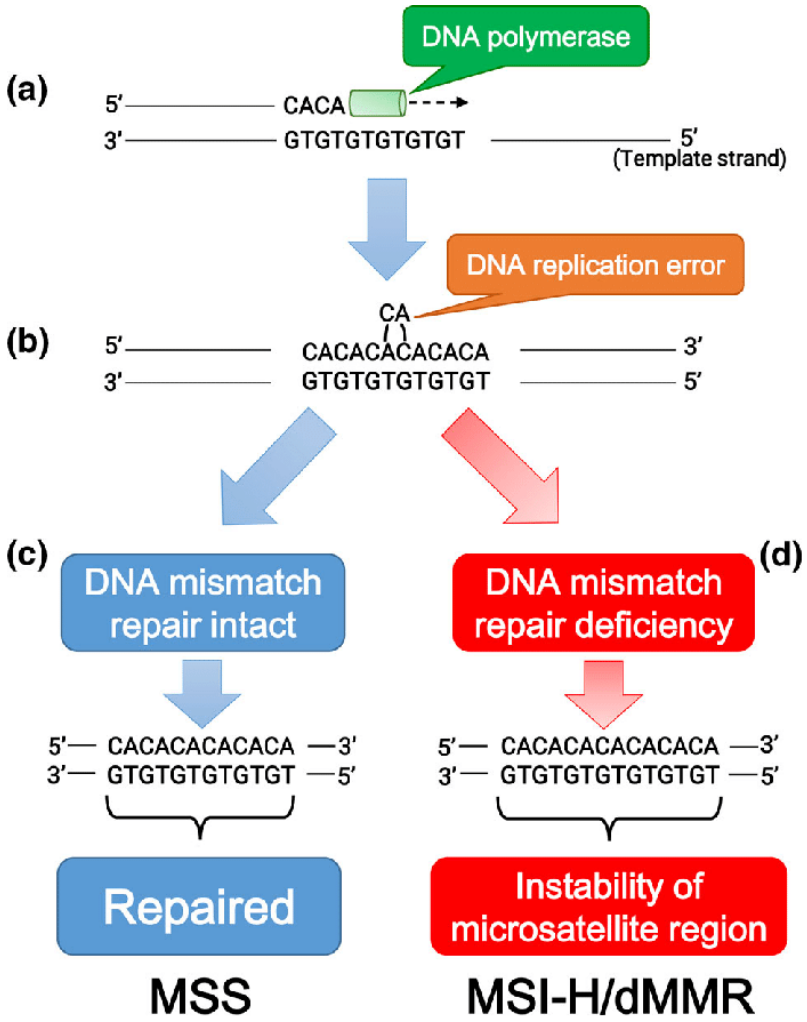
Basic principles for EC treatment

- Surgery
- Radiation therapy (External beam RT, brachytherapy)
- Systemic therapy
  - Chemotherapy
  - Immunotherapy
  - Targeted therapies (multi-targeted TKI, hormone therapy, etc.)

Crosbie EJ, et al. Lancet. 2022

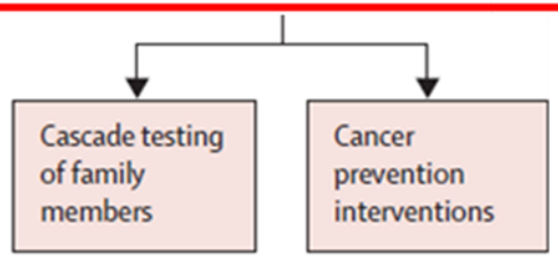
NO screening tools are available for EC

Mismatch repair (MMR)/Microsatellite instability (MSI) status



EC can be classified as:

- MMRp/MSS (70-75%)
- dMMR/MSI-H (25-30%)
- Lynch syndrome (inherited dMMR) accounts for 2-5% of all cases



Hause RJ, et al. Nat Med. 2016
Crosbie EJ, et al. Lancet. 2022

2. Ovarian cancer (OC)

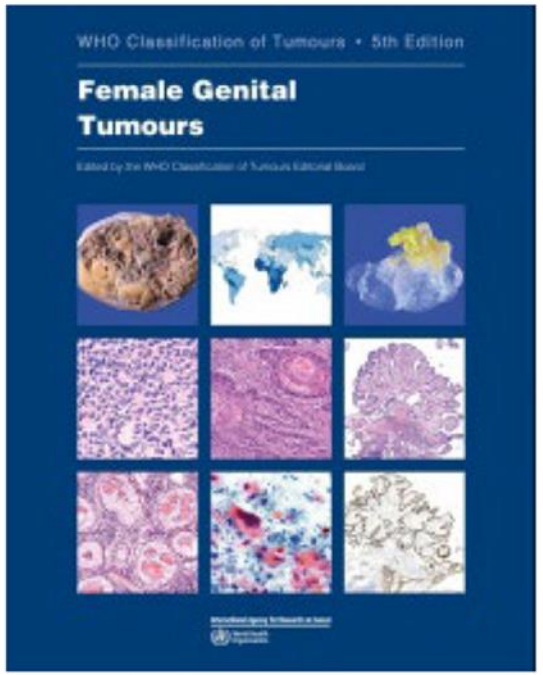
Epidemiology

- The most lethal gynecological cancer in high income countries
  - 313,000 new cases and 208,000 deaths (2020)
- Its **incidence is slowly decreasing** (since 2000s)
- >70% of patients present with late-stage (III-IV) OC
- 5-year survival rates
  - Stage I: 93% → Stage IV: **30%**

Jiang G, et al. Front Oncol. 2022

Pathological classification of ovarian tumors

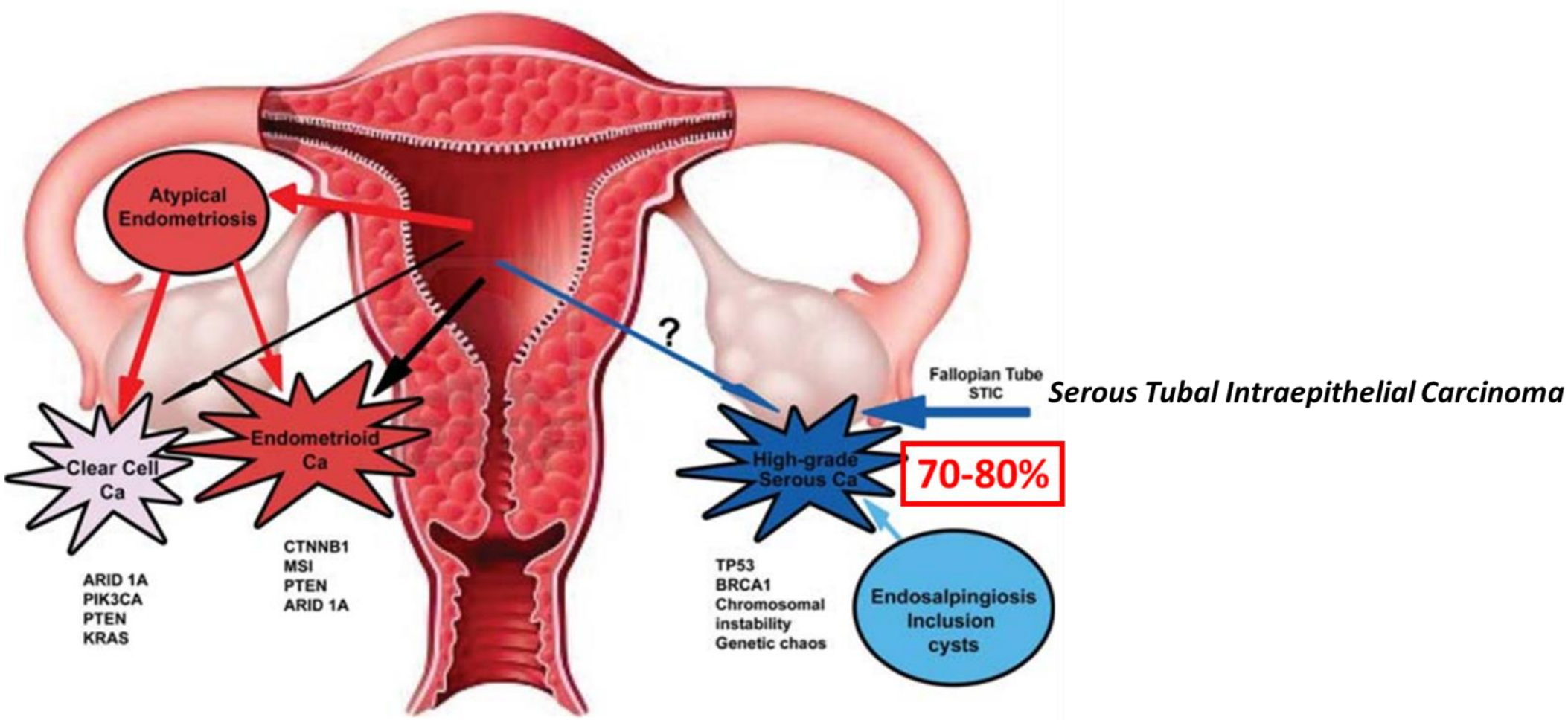
		All tumors	Malignant tumors
1.	Epithelial	55%	80%
2.	Sex-cord stromal	8%	
3.	Germ cell	30%	2%
4.	Mesenchymal (leiomyoma, hemangioma)		
5.	Mixed epithelial/mesenchymal (adenosarcoma)		very uncommon
6.	Miscellaneous (FATWO, small cell carcinoma hypercalcemic type)		
7.	Metastases	6-10%	



WHO classification, 2020

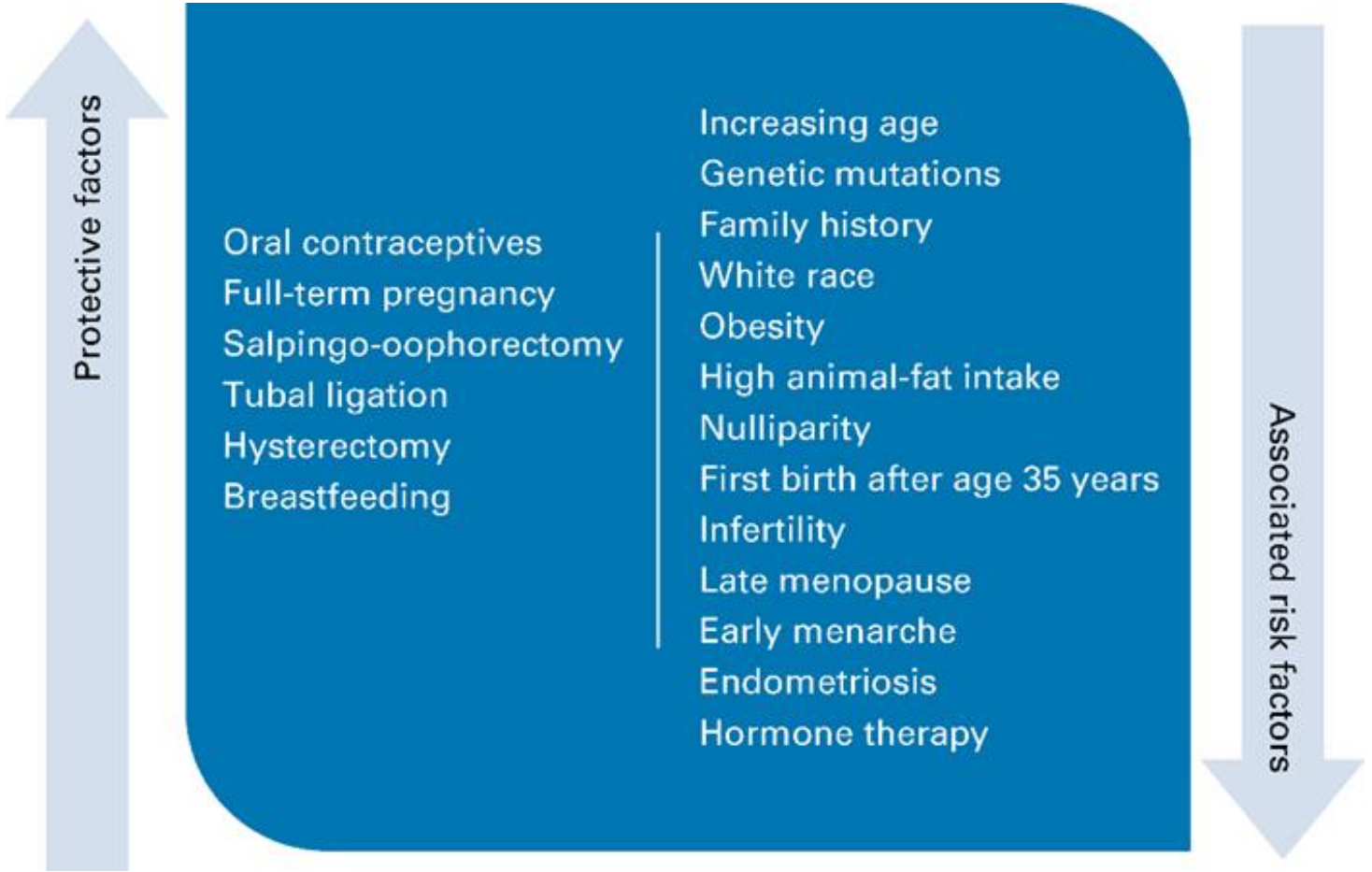
Epithelial OC is **not** a single disease

High-grade serous ovarian cancer (HGSOC) is the most common



Prat J. Ann Oncol. 2012

Protective and associated risk factor for OC



ASCO SEP

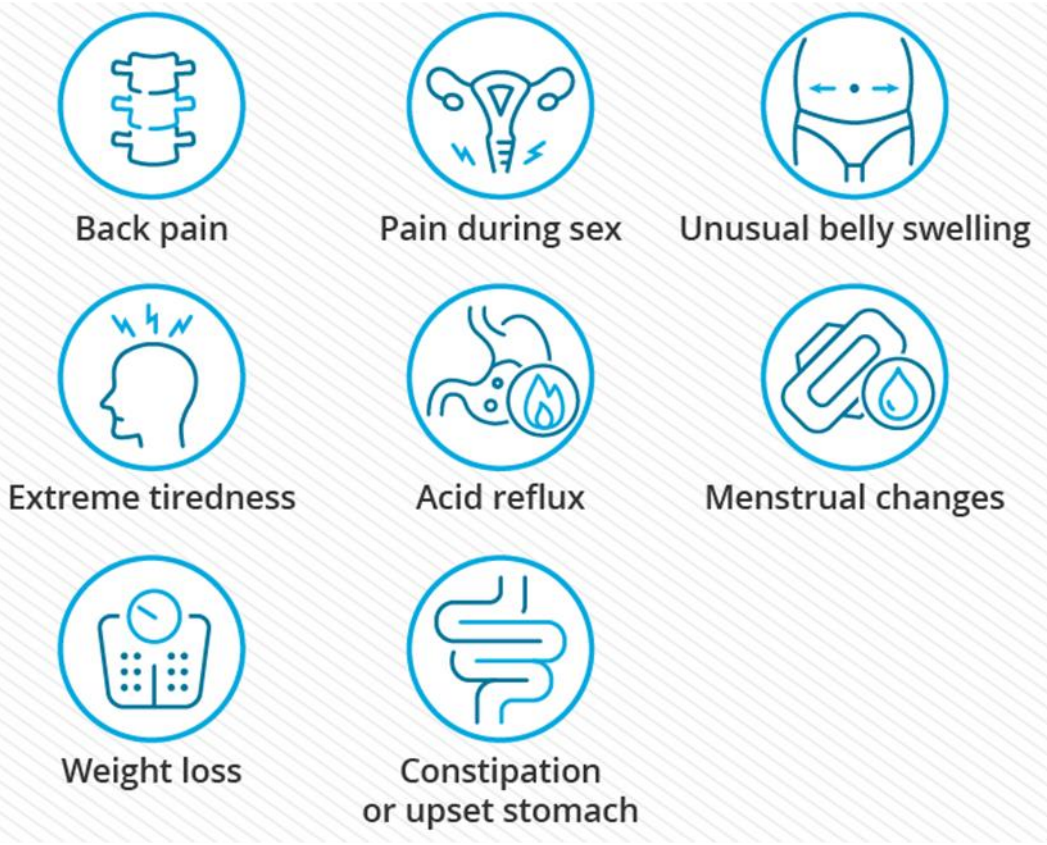
- Carriers of a g*BRCA1/2* pathogenic variant have a high lifetime risk of HGSOC
  - *BRCA1* PV: **44%**
  - *BRCA2* PV: **17%**

  } Vs general population: 1.3% (80 years of age)

- Risk does not start to increase above that of the general population until:
  - *BRCA1* PV: **mid-30s** — between age 35-40 years
  - *BRCA2* PV: **50 years of age** — between age 40-45 years

Risk-Reducing Bilateral Salpingo-Oophorectomy (rrBSO)

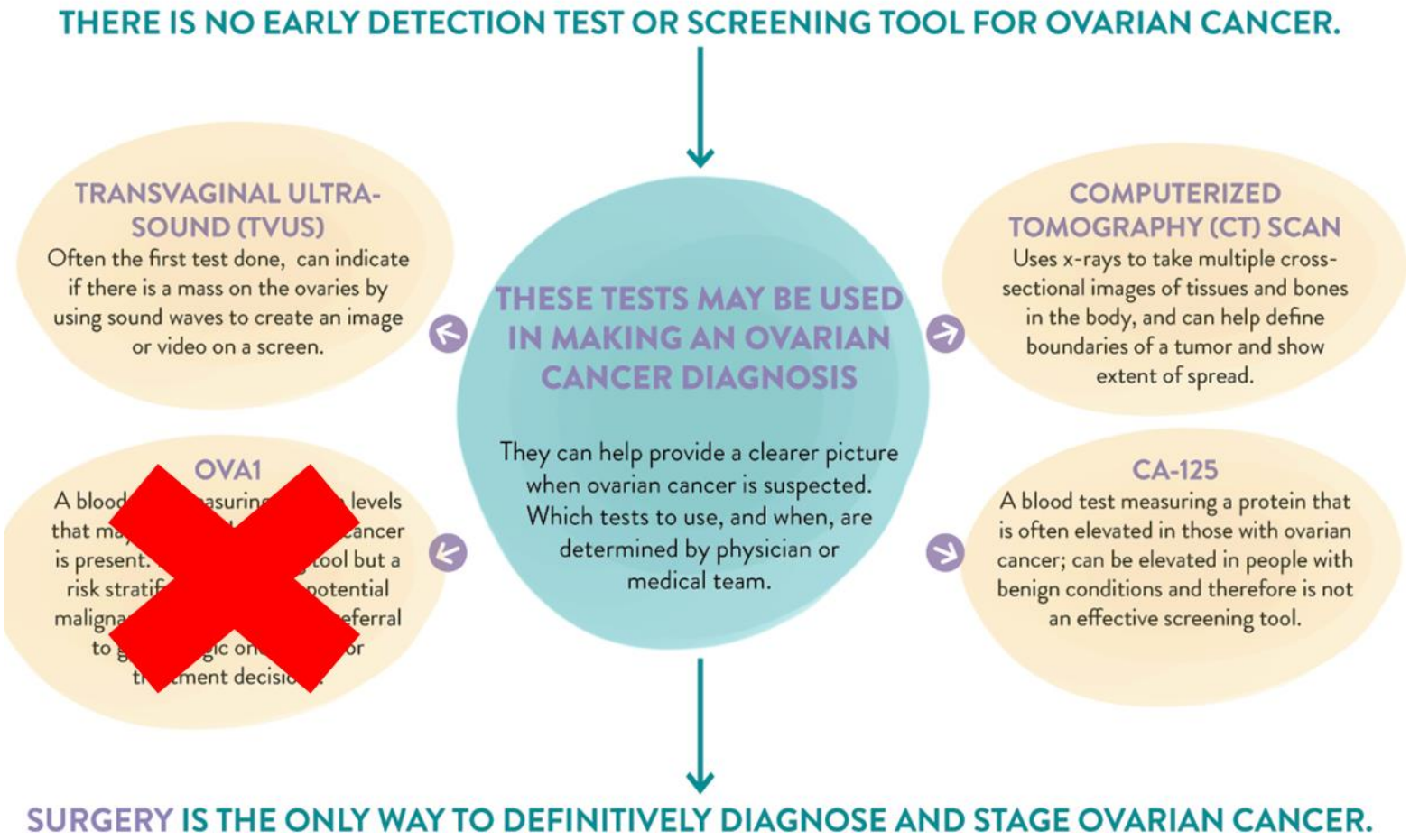
Clinical presentation of OC



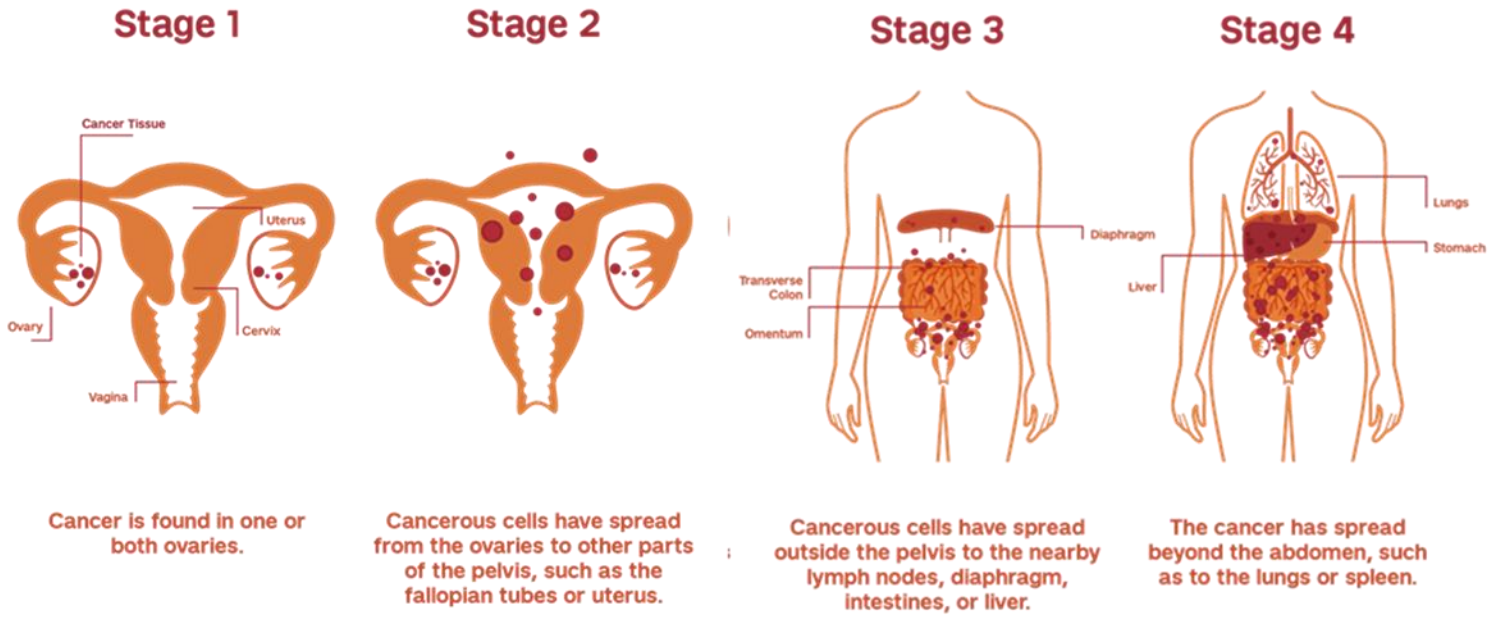
NO screening tools are available!

Lheureux S, et al. Lancet. 2019

Diagnosis of OC



AJCC/FIGO Staging of OC



AJCC stages	Number of cases annually	Proportion of all cases diagnosed	Vital status at 10 years		10-year survival
			Alive (proportion of all survivors)	Dead (proportion of all deaths)	
I and II	1,716	13%	944 (35.4%)	772 (7.3%)	55%
III and IV	11,484	87%	1,723 (64.6%)	9,761 (92.7%)	15%

Narod S. Nat Rev Clin Oncol. 2016

Basic principles for OC treatment

Early stage (IA-IC) OC

Summary of recommendations	LoE	Go R	Consensus
Laparotomy is the standard surgical approach to treat and stage patients with apparent early stage ovarian carcinoma	V	A	Yes: 100% *(40 voters)*
Whatever the approach used, rupture of an intact tumour with spillage of cancer cells at the time of surgery must be avoided	IV	A	Yes: 100% *(40 voters)*
For patients with early stage disease requiring adjuvant chemotherapy, acceptable treatment regimens are: • carboplatin alone or • carboplatin /paclitaxel	 I II	 A A	 Yes: 100% *(40 voters)* Yes: 100% *(40 voters)*

ESMO/ESGO consensus statement 2018

Can advanced-stage OC be cured?

The three phases of OC treatment

- **Resectability**
  - Aim to achieve a status of no (visible) residual disease
- **Eradication**
  - Aim to eliminate all cancer cells present after debulking surgery with (neo)adjuvant chemotherapy
- **Prevention of recurrence**
  - Aim to prevent or delay recurrence after surgery and chemotherapy with maintenance therapy

Narod S. Nat Rev Clin Oncol. 2016

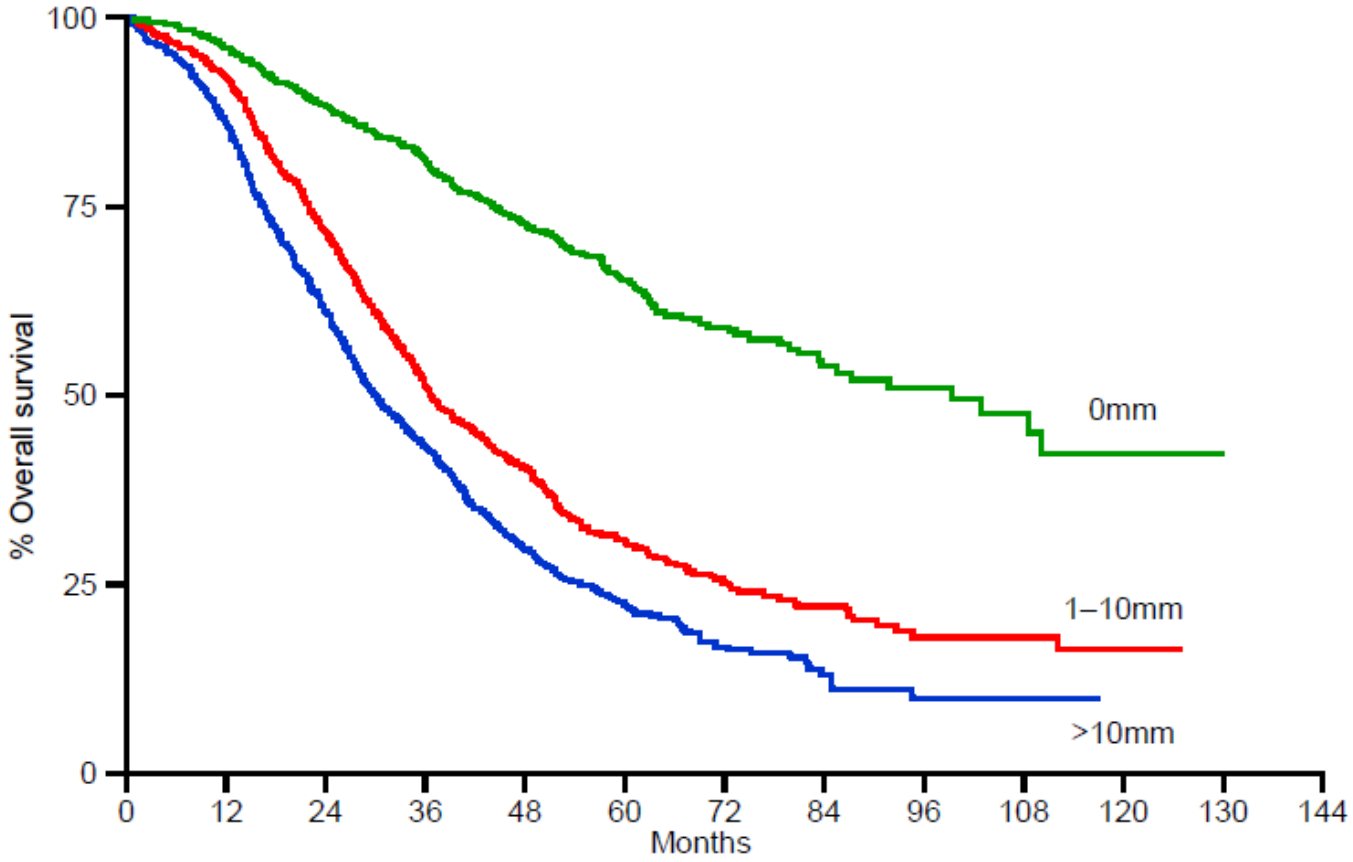
R0 cytoreduction

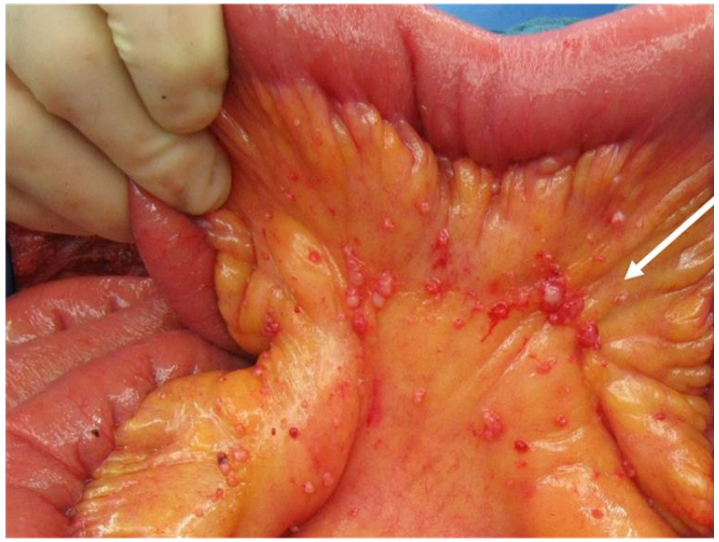
The most significant prognostic factor in advanced EOC

70%
no
gross
resid.
disease

20%
1–10mm
res.-disease

10%
>10mm





Du Bois, et al. Cancer. 2009

Basic principles for OC treatment
Advanced stage (II-IV) OC

Gynaecological Cancers 1

Clinical research in ovarian cancer: consensus recommendations from the Gynecologic Cancer InterGroup

Ignace Vergote, Antonio Gonzalez-Martin, Domenica Lorusso, Charlie Gourley, Mansoor Raza Mirza, Jean-Emmanuel Kurtz, Aikou Okamoto, Kathleen Moore, Frédéric Kridelka, Iain McNeish, Alexander Reuss, Bénédicte Votan, Andreas du Bois, Sven Mahner, Isabelle Ray-Coquard, Elise C Kohn, Jonathan S Berek, David S P Tan, Nicoletta Colombo, Rongyu Zang, Nicole Concin, Dearbhaile O'Donnell, Alejandro Rauh-Hain, C Simon Herrington, Christian Marth, Andres Poveda, Keiichi Fujiwara, Gavin C E Stuart, Amit M Oza, Michael A Bookman, on behalf of the participants of the 6th Gynecologic Cancer InterGroup (GCIG) Ovarian Cancer Consensus Conference on Clinical Research*

Statement 3

Acceptable reference groups for systemic treatment (33 of 33 groups approved)

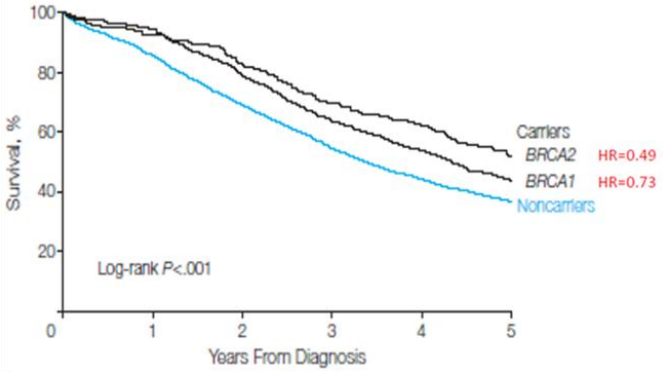
1 Backbone systemic therapy is based on the carboplatin–paclitaxel combination

- Six cycles of intravenous carboplatin (target AUC 5–6 mg/mL per min) every 3 weeks and paclitaxel 175 mg/m² remains the reference group for first-line chemotherapy in advanced ovarian cancer; the addition of bevacizumab is acceptable

ESMO/ESGO consensus statement 2018

Basic principles for OC treatment
Maintenance therapy in advanced stage (II-IV) OC

- **All HGSOC patients**, regardless of stage and/or age, should be referred for **genetic counseling**
  - ***BRCA1/2mut*** in **~25%** of cases
  - ***BRCA1/2mut*** OC is associated with **better prognosis**
  - ***BRCAmut*** OC patients derive unprecedented **benefit from PARP inhibitors**



Meta-analysis of 26 studies BRCA1 (n=909), BRCA2(n=304) et 2666 non-carriers

Bolton, *JAMA* 2012

Konstantinopoulos PA, et al. Cancer Discov. 2015

DiSilvestro P. ESMO 2022

González-Martín A. ESMO 2019

Ray-Coquard I.L. ESMO 2022

Basic principles for OC treatment

Recurrent disease

Platinum resistant disease

Platinum-free interval <6 months

(mOS <9-12 months)

	ORR	mPFS	Ref.
Paclitaxel weekly	4-35%	3.7 - 7 m	Markman et al. JCO 2002;20:2365 Ghamande et al. Int J Gynecol Cancer 2003;13:142 Kita et al. Gynecol Oncol 2004;92:813 ten Bokkel Huinink et al. Ann Oncol 2004;15:100 Dunder et al. Eur J Gynaecol Oncol 2005;26:79 Le et al. 2006;102:49 Markman et al. 2006;101:436 Lortholary et al. Ann Oncol 2012;23:346 Poveda et. JCO 2015;33:3836
Paclitaxel 3-weekly	16-33 %	3.5 - 4 m	Thigpen et al. 1994;12:1748 Bolis et al. Gynecol Oncol 1999;72:60 Piccart et al. JCO 2000;18:1193
PLD	8-26%	4 - 7 m	Muggia et al. JCO;1997;15:987 Gordon et al. JCO 2001;19:3312 Ferrandina et al. JCO 2008;26:890 Poveda et. JCO 2015;33:3836
Topotecan	3-20%	2.1 - 5.7 m	Creemers et al. 1996;14:3056 Gordon et al. JCO 2001;19:3312 Abushahin 2008 ten Bokkel Huinink et al. Ann Oncol 2004;15:100 Poveda et. JCO 2015;33:3836
Gemcitabine	25-29%	5 - 7.2 m	Ferrandina et al. JCO 2008;26:890
	3-35%	2.1 – 7.2 m	

Platinum sensitive disease

Platinum-free interval >6 months

(mOS: 24-36 months)

	ORR (%)	PFS (months)
Carboplatin mono	30 – 54 %	7.3 – 10.0
Carboplatin-paclitaxel	66 %	9.4 – 13.0
Carboplatin-gemcitabine	47 – 63 %	8.4 – 10.0
Carboplatin-PLD	63 %	11.3
ORR: overall response rate PFS: progression free survival PLD: pegylated liposomal doxorubicin	30 – 66 %	7.3 - 13

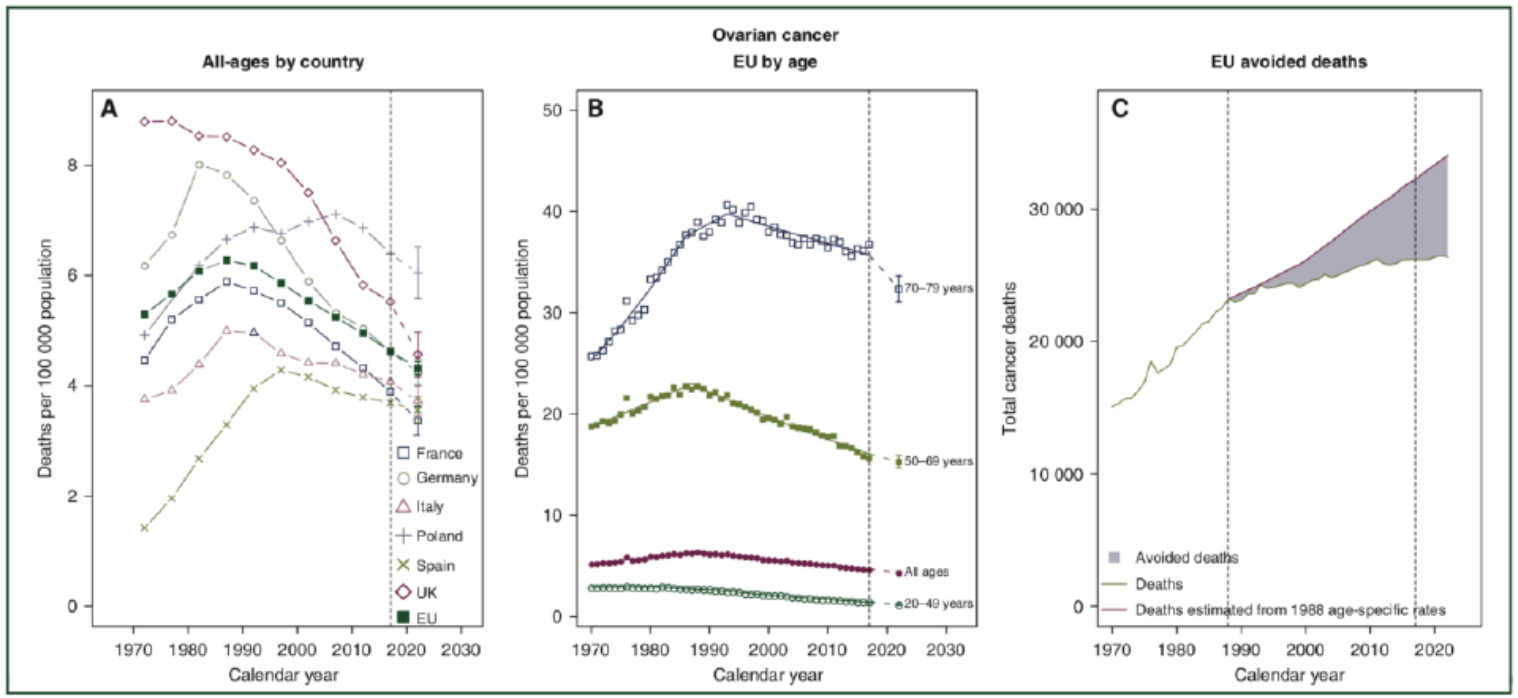
Do NOT forget the feasibility of Secondary Cytoreductive Surgery (CRS)

ESMO/ESGO consensus statement 2018

European cancer mortality predictions for the year 2022 with focus on ovarian cancer

M. Dalmartello[1], C. La Vecchia[1*], P. Bertuccio[1], P. Boffetta[2,3], F. Levi[4], E. Negri[1,3,5] & M. Malvezzi[1]

111 000 cancer deaths have been avoided (during a period of 34 years).
In 2022 alone, 8000 are predicted to be avoided



Annals of Oncology Volume 33 - Issue 3 - 2022

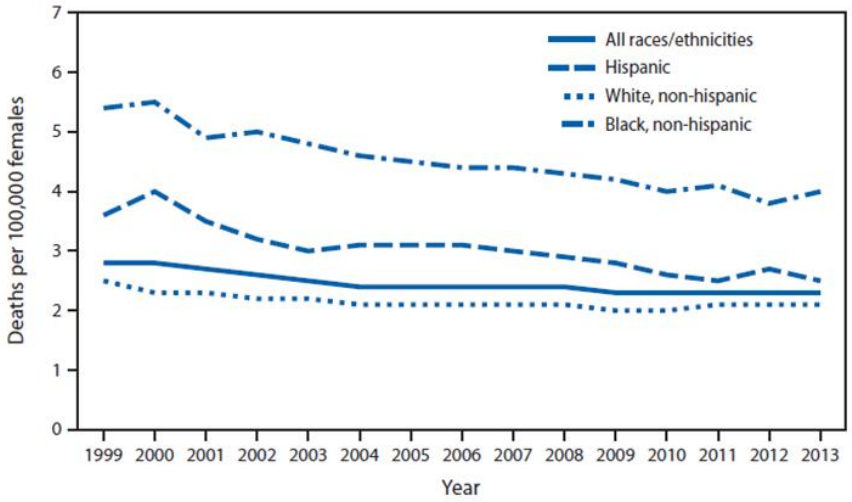
Main driving factors (by Dalmartello et al)

- Use of oral contraceptives
- Early diagnosis ?
- Improved surgery
- Platinum in the 80s
- Taxanes in the 90s
- ~~Gemcitabine~~
- ~~Intraperitoneal CT~~
- Possibly bevacizumab ?
- Prophylactic BSO in BRCAmut carriers
- PARPi

3. Cervical cancer (CC)

Epidemiology

- The 4th most common malignancy in female, worldwide
  - 604,000 new cases and 342,000 deaths (2020)
- Its **incidence is decreasing** (>**25%** since the early 1990s)
  - Global HPV vaccine uptake
- 5-year survival rates
  - Stage I: 92% → Stage IV: **18%**



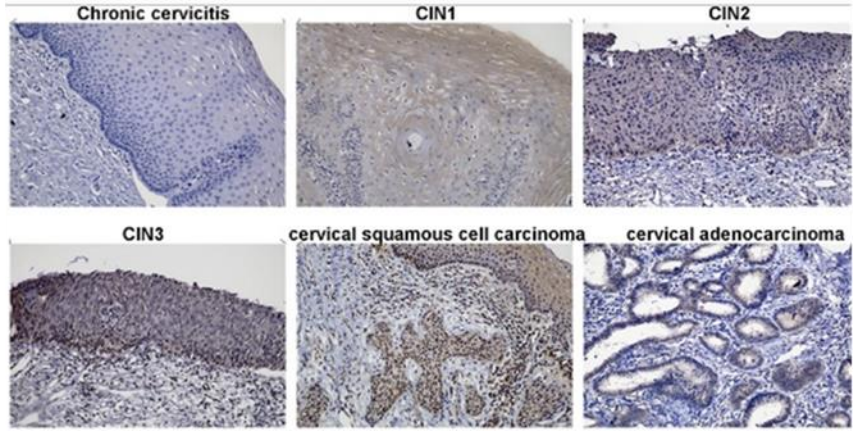
Duranti S, et al. Cancers (Basel). 2021

Pathogenesis of CC

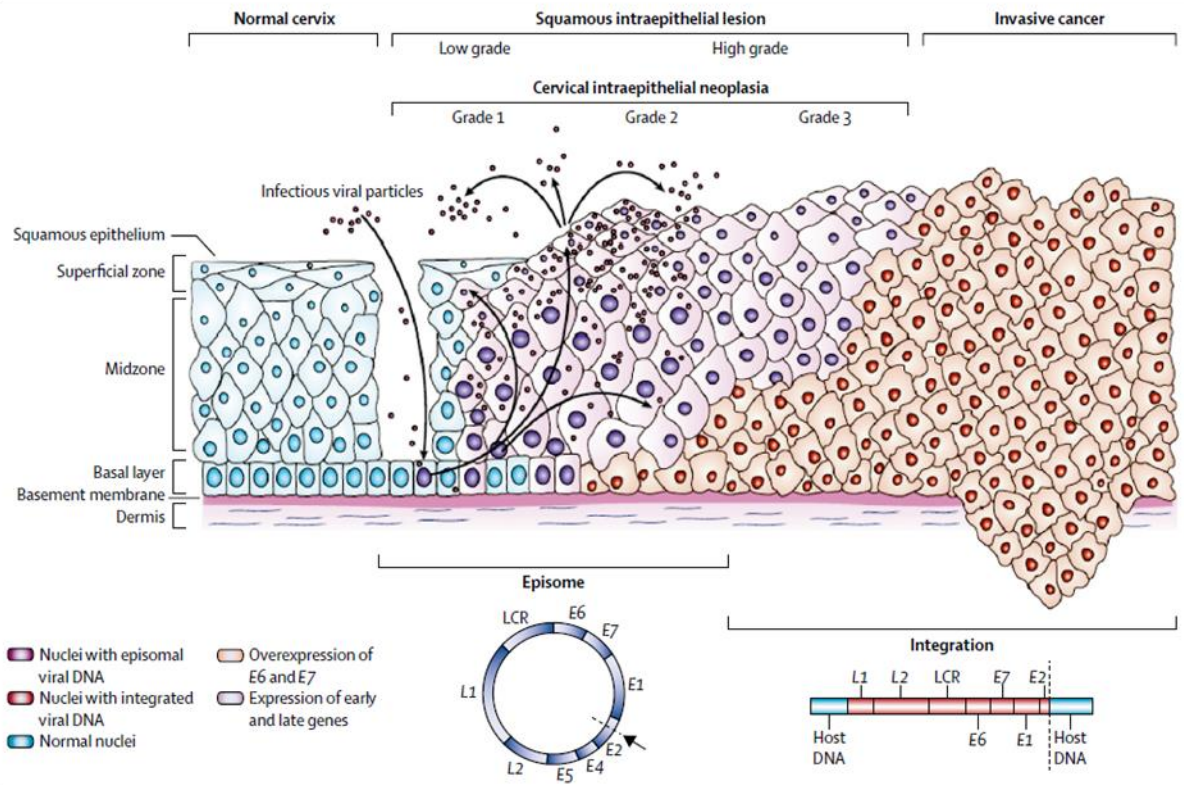
Chronic HPV infection causes almost all cases

- Risk factors include:
  - early age of sexual debut
  - multiple sexual partners
  - history of sexually-transmitted infection
  - tobacco smoke

p16-immunostaining pattern

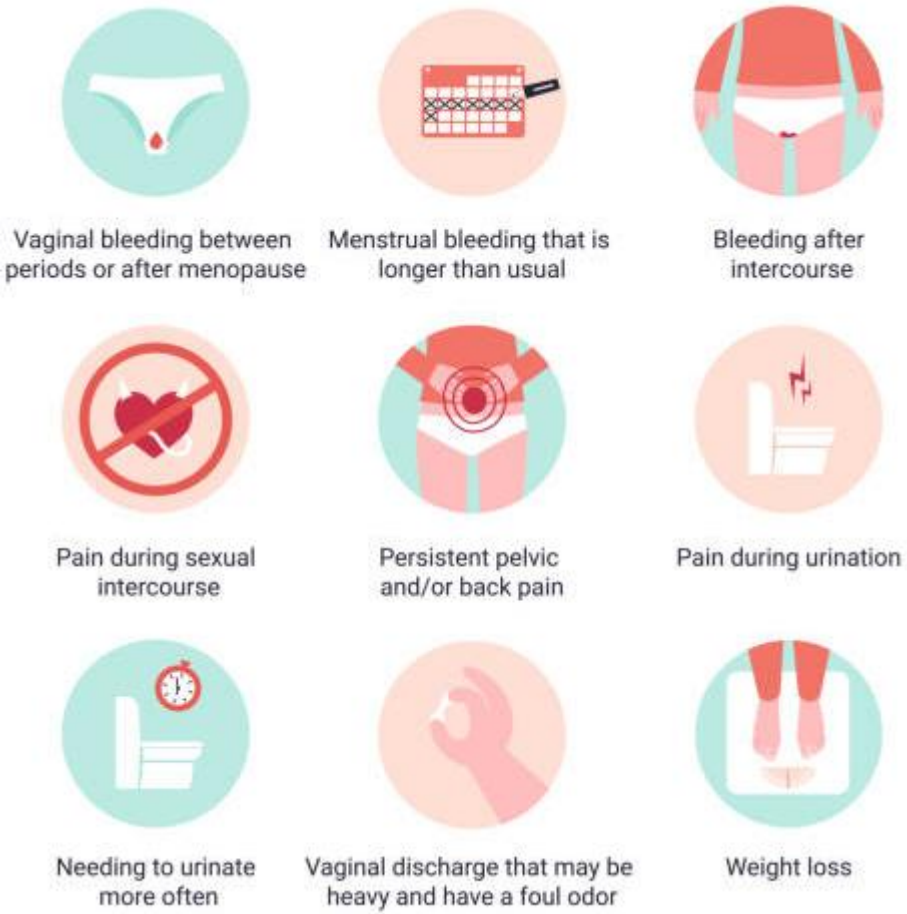


IHC stains of the HPV16 E7 protein in cervical lesions



Cohen PA, et al. Lancet. 2019
Voidăzan ST, et al. Biology (Basel). 2022

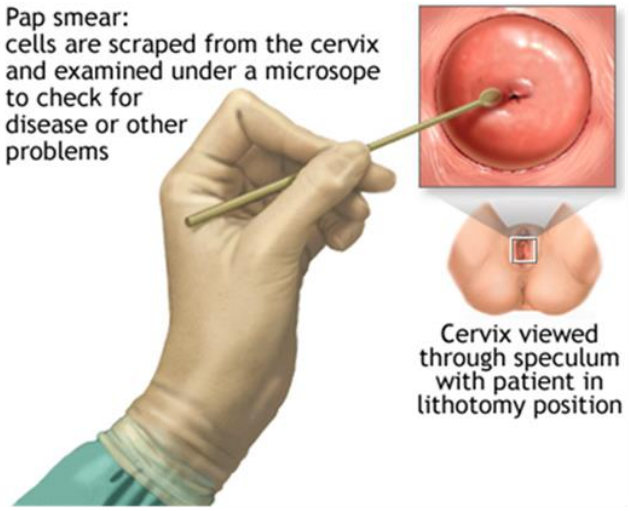
Clinical presentation of CC

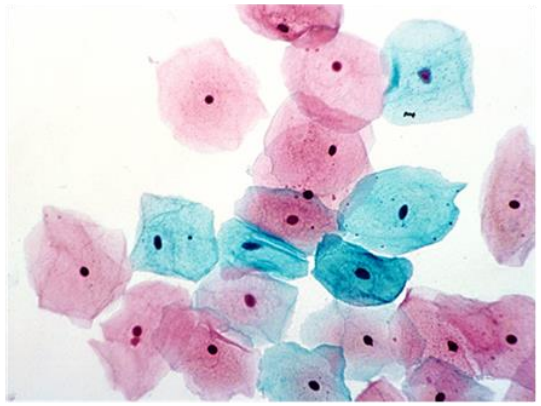


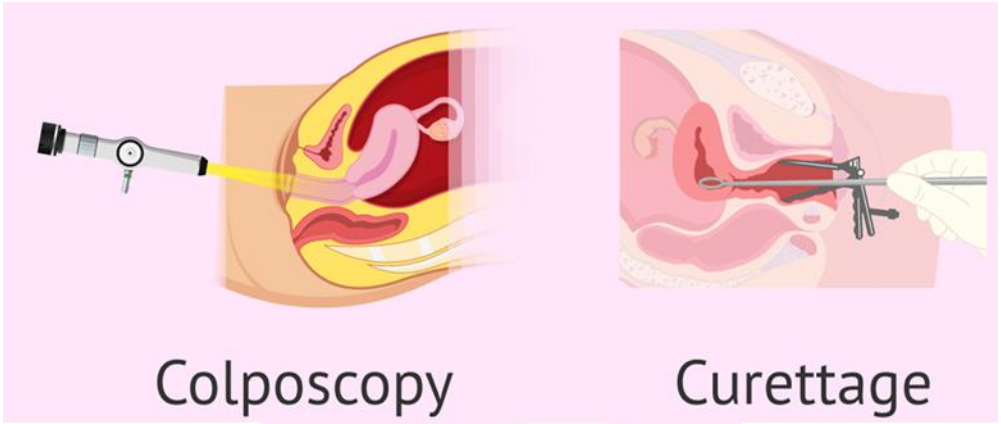
- In its early stages, CC is often **asymptomatic**
- The trial of lower limb oedema, flank pain, and sciatica suggest pelvic sidewall invasion

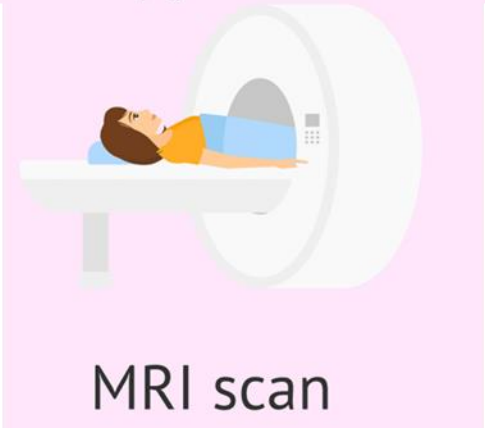
Cohen PA, et al. Lancet. 2019

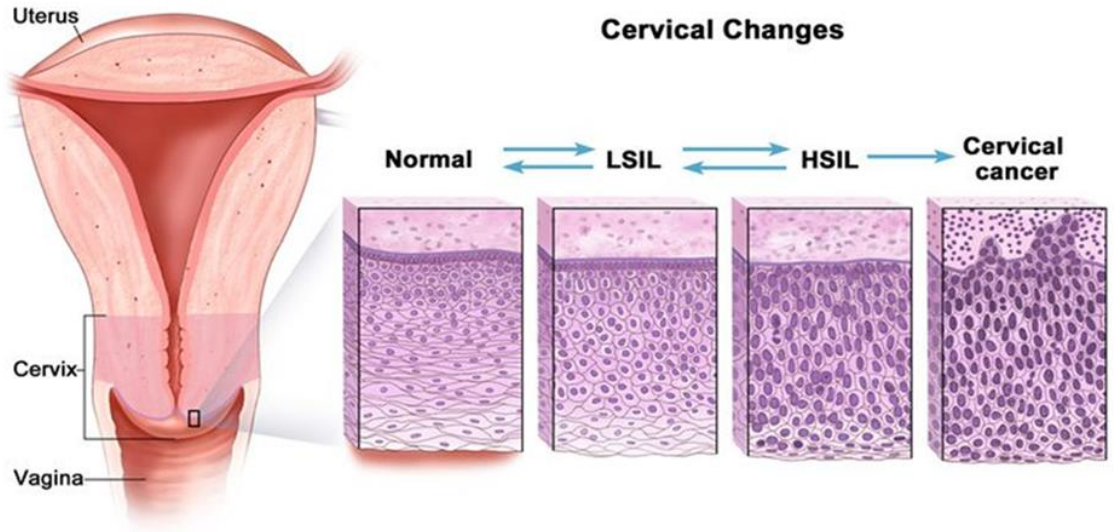
Diagnosis of CC











Cohen PA, et al. Lancet. 2019

Who should be screened?!

- Women **aged 21-29** should receive **PAP smear screening** **every 3 years**, with the choice to continue until 65

OR

- Women **aged 30-65** should receive combination **high-risk HPV testing plus PAP smear** **every 5 years**

U.S. Preventive Services TASK FORCE

Who should NOT be screened?!

- Women **under 21 years**
- Women **older than 65** who have had **three consecutive negative cytology results** *or* **two consecutive negative HPV tests**

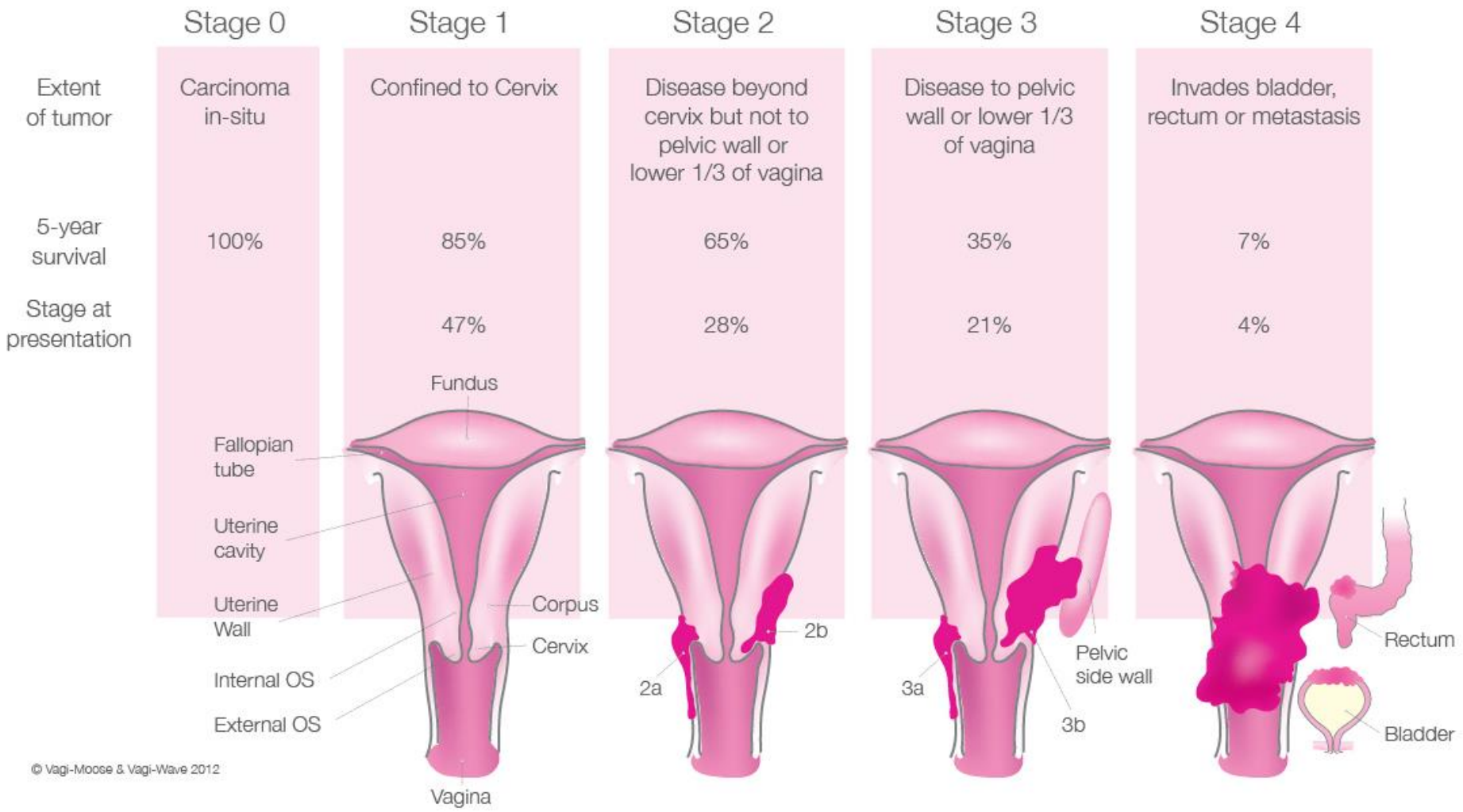
U.S. Preventive Services
TASK FORCE

Has your teen had both doses of the HPV vaccine?

Δ. Η γνωμοδότηση της Εθνικής Επιτροπής Εμβολιασμών

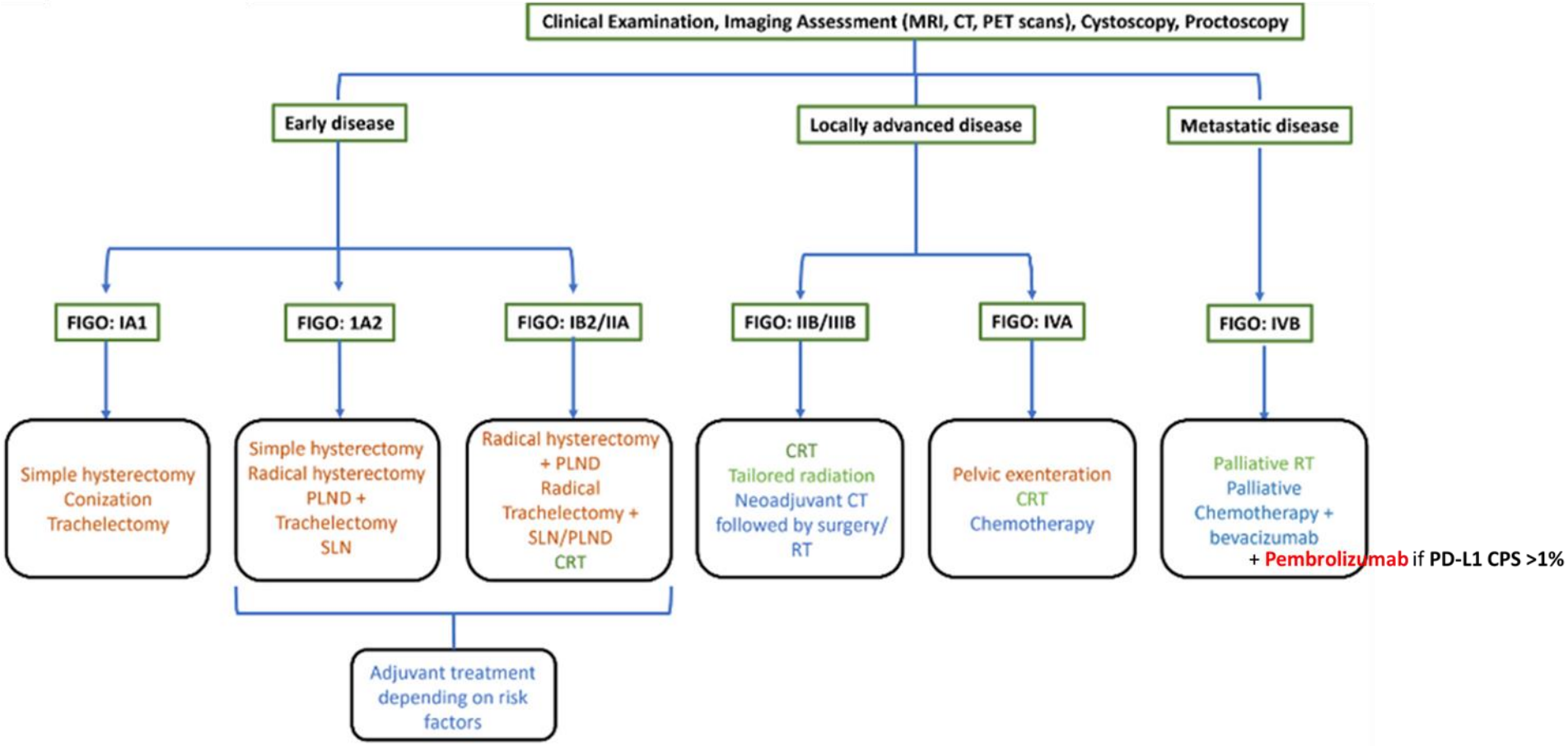
Με βάση τη διεθνή βιβλιογραφία και συνεκτιμώντας τα παραπάνω δεδομένα, η γνωμοδότηση της Εθνικής Επιτροπής Εμβολιασμών περιλαμβάνει τις ακόλουθες αλλαγές στο εμβολιαστικό σχήμα έναντι του HPV: (α) σύσταση για γενικό εμβολιασμό αγοριών και κοριτσιών, (β) το ενδεικνυόμενο διάστημα εμβολιασμού και για τα δύο φύλα είναι η ηλικία 9 έως 11 ετών, (γ) σε περίπτωση που ο εμβολιασμός και για τα δύο φύλα δεν πραγματοποιηθεί στη συνιστώμενη ηλικία, μπορεί να γίνει αναπλήρωση (catch-up) του εμβολιασμού, (δ) επισημαίνεται ότι το εμβόλιο HPV θα αποζημιώνεται πλήρως σε αγόρια και κορίτσια ηλικίας 15-18 ετών μέχρι 31.12.2023, και (ε) ο περιορισμός στην αποζημίωση μετά τις 31.12.2023 δεν αφορά τις ομάδες αυξημένου κινδύνου.

FIGO Staging of CC



Cohen PA, et al. Lancet. 2019

Basic principles for CC treatment



Burmeister CA, et al. Tumour Virus Res. 2022