La chirurgia ginecologica in Toscana: coniugare qualità e innovazione

L'epidemiologia dei tumori ginecologici

Angiolo Gadducci – Università degli Studi di Pisa

15 ottobre 2018 - Sede Formas, Sala delle Fanciulle

GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries

- Global Initiative for Cancer Registry Development: international partnership supporting better estimation, collection and use of local data to prioritize and evaluate national cancer control efforts
- Report on global burden of cancer worldwide using GLOBOCAN 2018 estimates of incidence and mortality produced by IARC
- 18.1 million new cancer cases (17.0 million excluding nonmelanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding nonmelanoma skin cancer) in 2018

Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries

- Incidence data: population-based cancer registries (PBCRs). Although PBCRs may cover national populations, often they cover selected urban areas in countries undergoing economic development
- ~15% of world population covered by high-quality PBCRs in 2010 (low registration in South America (7.5%),Asia (6.5%), Africa (1%)
- Such data from lower resource countries are the only relatively unbiased source of information on common cancer types in a defined population and are vital for planning local cancer prevention

Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries

- **In both sexes combined**, lung cancer is most common cancer (11.6% of cases) and the leading cause of cancer death (18.4%) followed by cancer of breast (11.6%), prostate (7.1%) and colon (6.1%) for incidence and colon (9.2%), stomach (8.2%) and liver (8.2%) for mortality
- **Among females**, breast cancer is most common and the leading cause of cancer death, followed by colon and lung cancer (for incidence), and vice versa (for mortality)
- Cervical cancer ranks fourth for both incidence and mortality

Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries

New Cases and Deaths for 36 Cancers and All Cancers Combined in 2018

CANCER SITE	NO. OF NEW CASES (% OF ALL SITES)	NO. OF DEATHS (% OF ALL SITES)
Lung	2,093,876 (11.6)	1,761,007 (18.4)
Breast	2,088,849 (11.6)	626,679 (6.6)
Prostate	1,276,106 (7.1)	358,989 (3.8)
Colon	1,096,601 (6.1)	551,269 (5.8)
Nonmelanoma of skin	1,042,056 (5.8)	65,155 (0.7)
Stomach	1,033,701 (5.7)	782,685 (8.2)
Liver	841,080 (4.7)	781,631 (8.2)
Rectum	704,376 (3.9)	310,394 (3.2)
Esophagus	572,034 (3.2)	508,585 (5.3)
Cervix uteri	569,847 (3.2)	311,365 (3.3)
Thyroid	567,233 (3.1)	41,071 (0.4)
Bladder	549,393 (3.0)	199,922 (2.1)
Non-Hodgkin lymphoma	509,590 (2.8)	248,724 (2.6)
Pancreas	458,918 (2.5)	432,242 (4.5)
Leukemia	437,033 (2.4)	309,006 (3.2)
Kidney	403,262 (2.2)	175,098 (1.8)
Corpus uteri	382,069 (2.1)	89,929 (0.9)
Lip, oral cavity	354,864 (2.0)	177,384 (1.9)
Brain, nervous system	296,851 (1.6)	241,037 (2.5)
Ovary	295,414 (1.6)	184,799 (1.9)
Melanoma of skin	287,723 (1.6)	60,712 (0.6)
Gallbladder	219,420 (1.2)	165,087 (1.7)
Larynx	177,422 (1.0)	94,771 (1.0)
Multiple myeloma	159,985 (0.9)	106,105 (1.1)
Nasopharynx	129,079 (0.7)	72,987 (0.8)
Oropharynx	92,887 (0.5)	51,005 (0.5)
Hypopharynx	80,608 (0.4)	34,984 (0.4)
Hodgkin lymphoma	79,990 (0.4)	26,167 (0.3)
Testis	71,105 (0.4)	9,507 (0.1)
Salivary glands	52,799 (0.3)	22,176 (0.2)
Anus	48,541 (0.3)	19,129 (0.2)
Vulva	44,235 (0.2)	15,222 (0.2)
Kaposi sarcoma	41,799 (0.2)	19,902 (0.2)
Penis	34,475 (0.2)	15,138 (0.2%)
Mesothelioma	30,443 (0.2)	25,576 (0.3)
Vagina	17,600 (0.1)	8,062 (0.1)
All sites excluding skin	17,036,901	9,489,872
All sites	18,078,957	9,555,027

Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

Human Development Index (HDI)

✓Summary measure of average achievement in key dimensions of human development: a long and healthy life, being knowledgeable and have a decent standard of living

✓Geometric mean of normalized indices for each of 3 dimensions

Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

Global map presenting most common type of incidence and Mortality in each country in 2018 in women

incidence

mortality

Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

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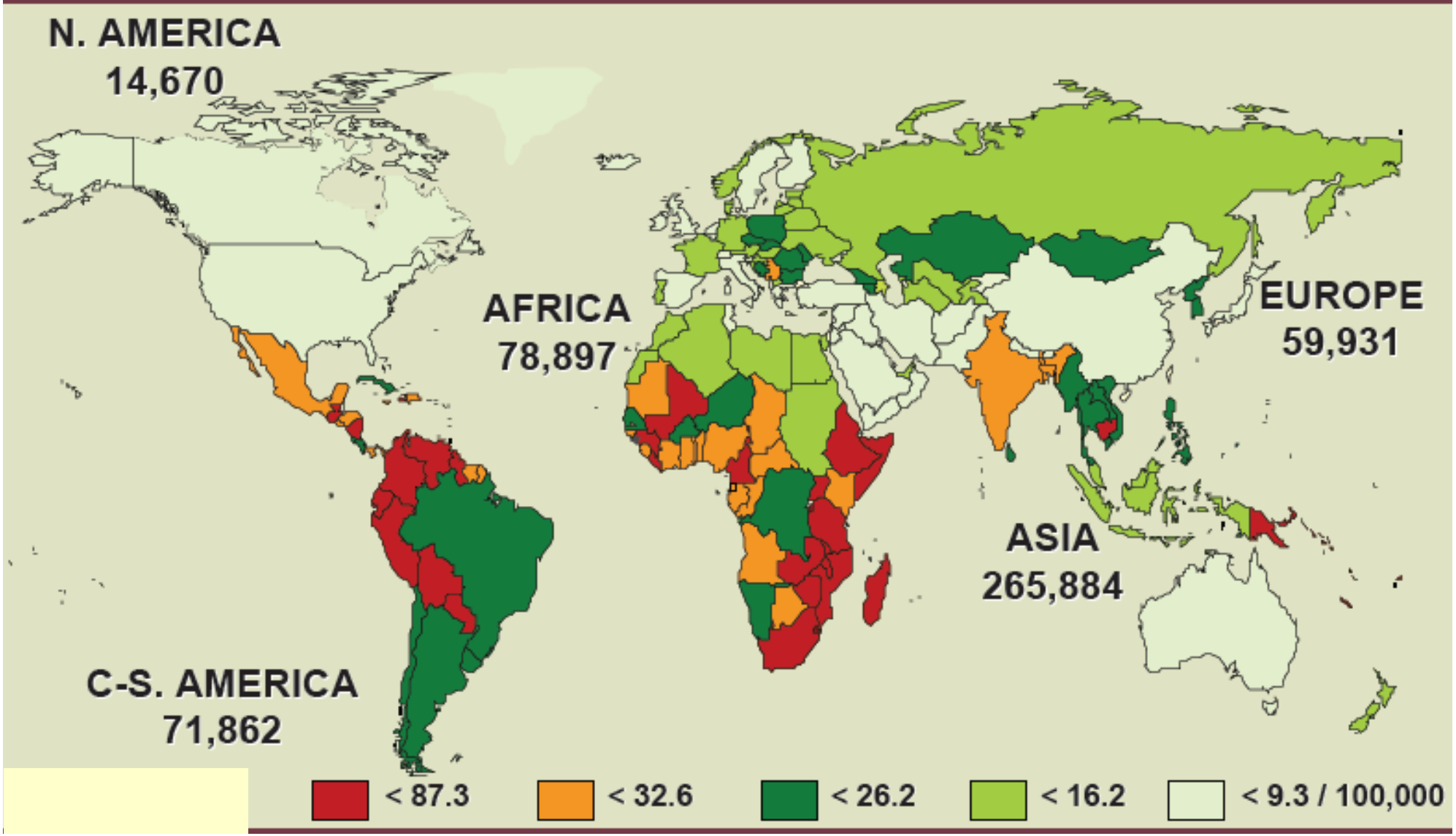
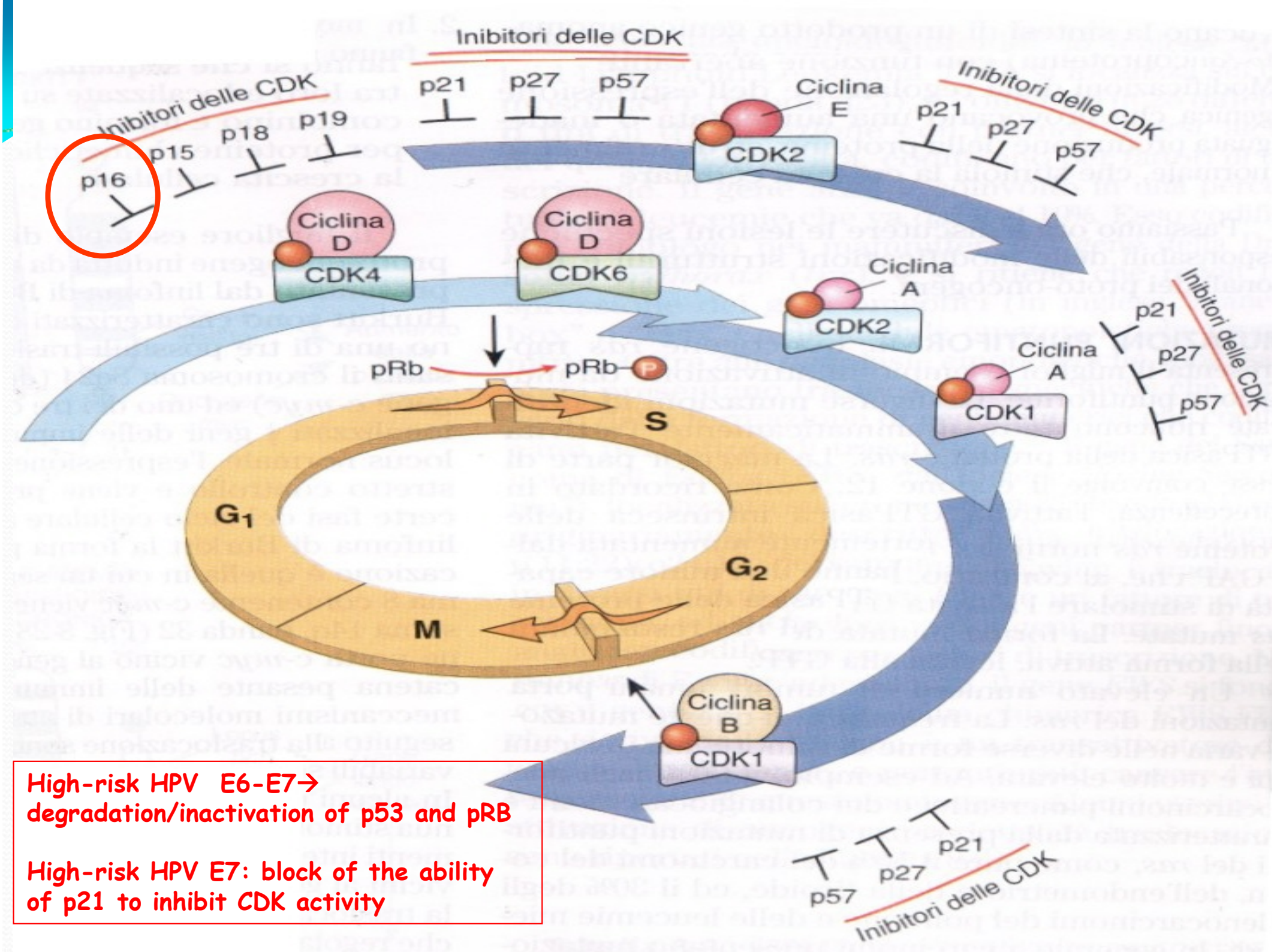
Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

Incidence and mortality Age-standardized rates for cervical cancer

Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

Estimates of the number of cases and incidence of cervical cancer

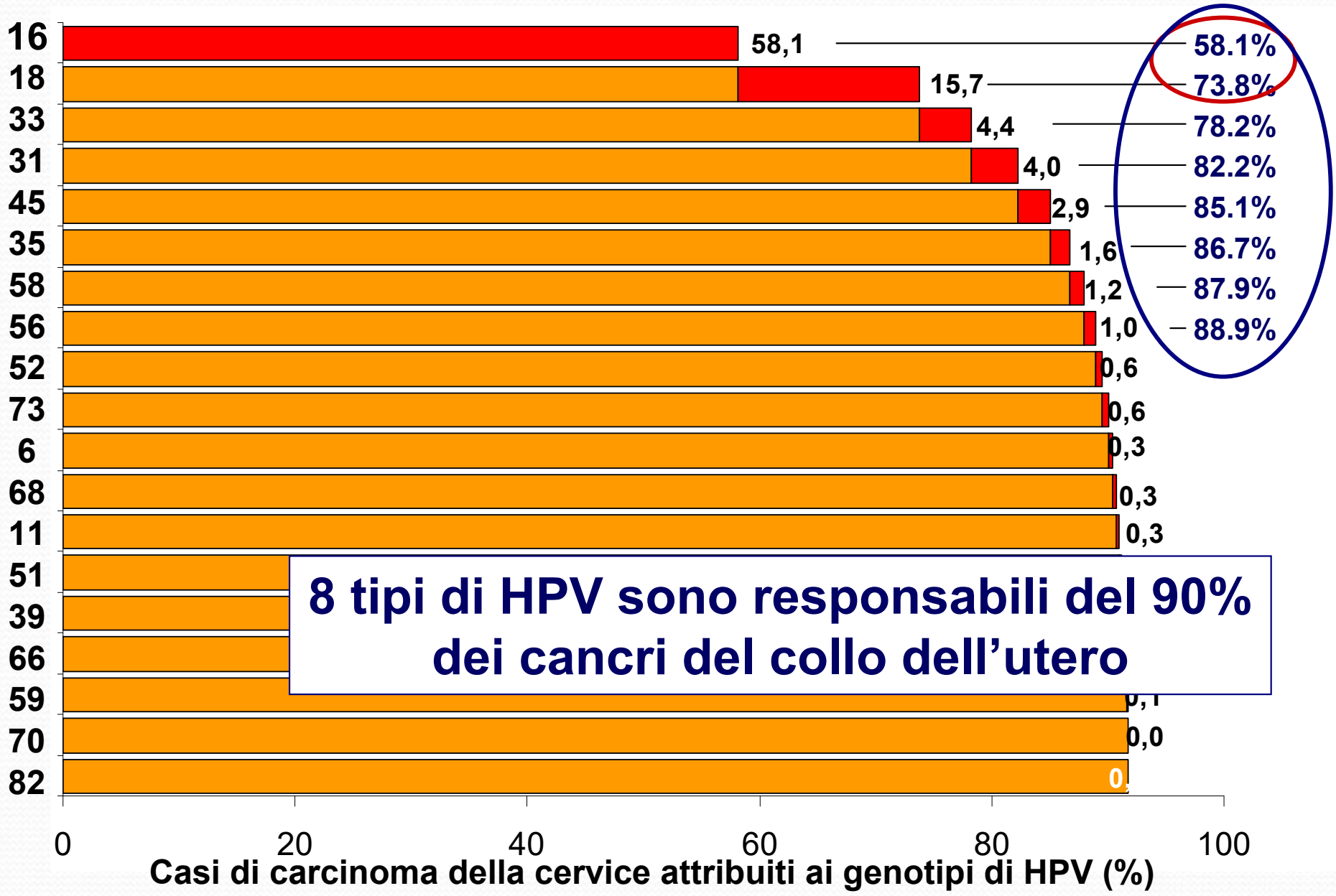




High-risk HPV E6-E7→ degradation/inactivation of p53 and pRB

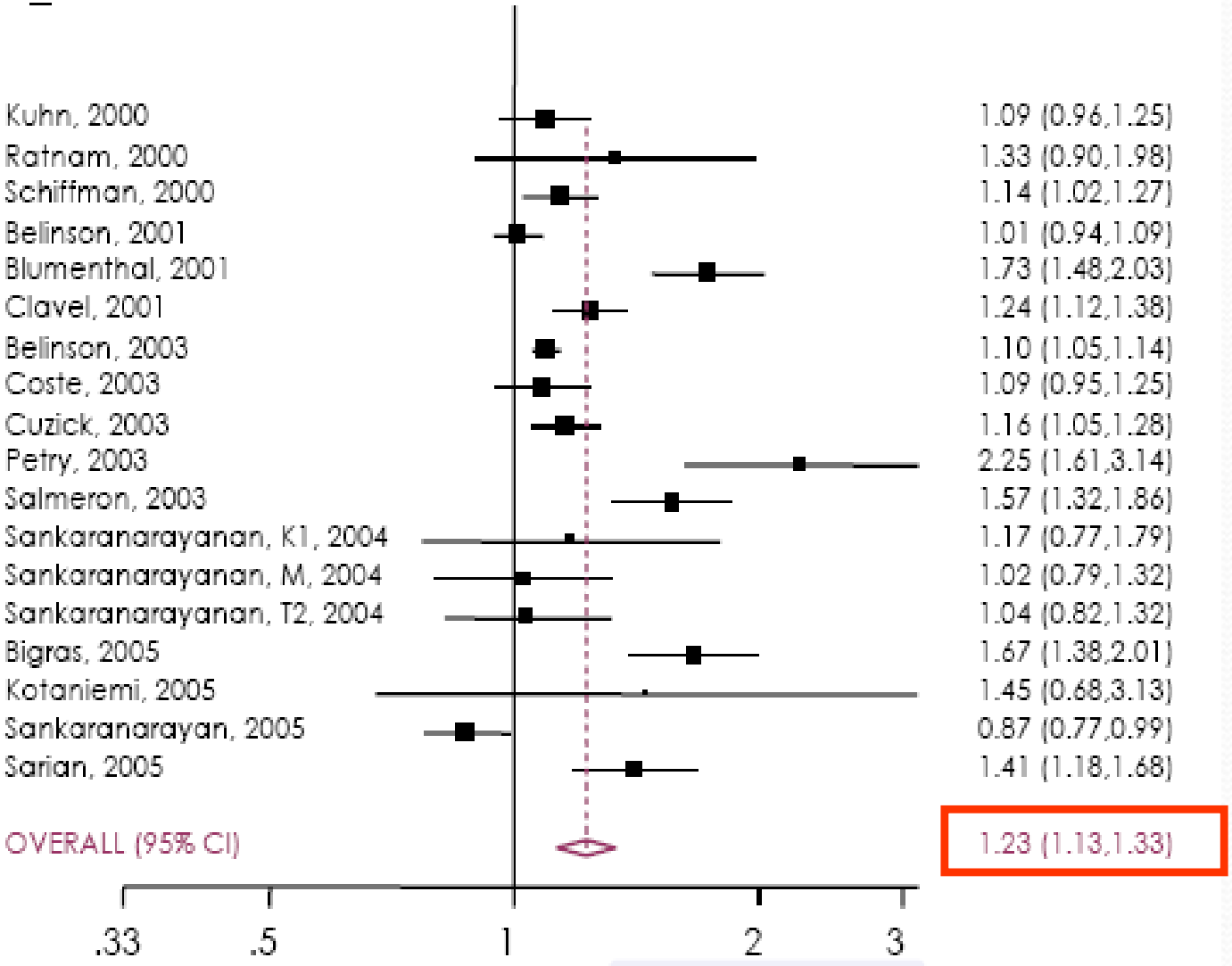
High-risk HPV E7: block of the ability of p21 to inhibit CDK activity

Distribuzione percentuale dei carcinomi del collo dell'utero, per tipo di HPV in Europa



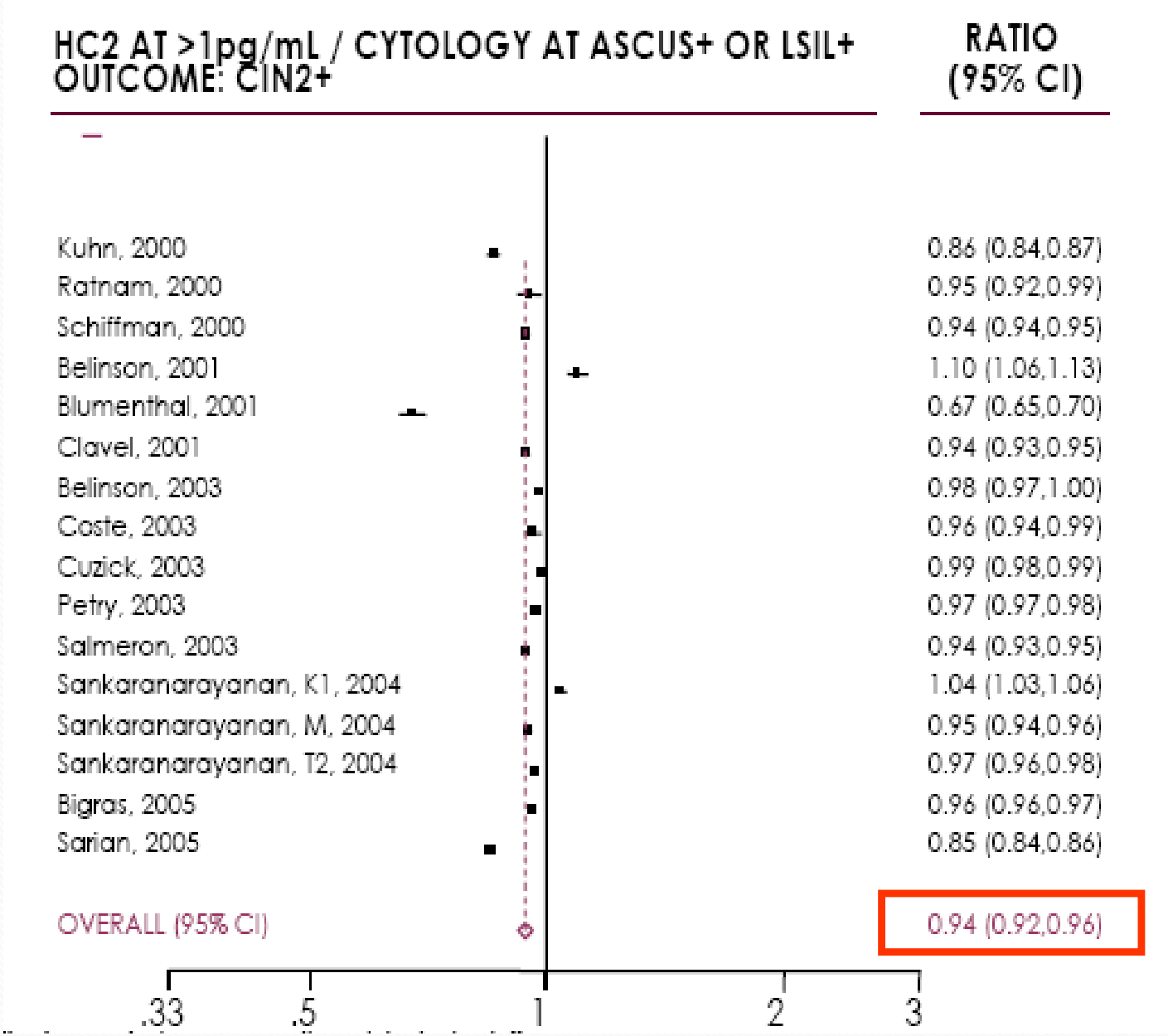
Smith JS, Lindsay L, Hoots B et al. *Int J Cancer* 2007;121:621-32

RELATIVE SENSITIVITY OF HPV DNA PRIMARY SCREENING USING THE HIGH-RISK PROBE OF HC2 ASSAY TO DETECT HIGH-GRADE CERVICAL NEOPLASIA COMPARED TO CYTOLOGICAL SCREENING USING ASCUS OR WORSE AS POSITIVITY CRITERION*



pnk

RELATIVE SPECIFICITY OF HPV DNA PRIMARY SCREENING USING THE HIGH-RISK PROBE OF THE HC2 ASSAY TO EXCLUDE PRESENCE OF HIGH-GRADE CERVICAL NEOPLASIA COMPARED TO CYTOLOGICAL SCREENING USING ASCUS OR WORSE AS POSITIVITY CRITERION*



pnk

Raccomandazioni ESIDOG [1]

Nelle donne dai 30 anni in poi come screening primario del cervicocarcinoma in aggiunta all'esame citologico

Raccomandazioni ACOG [2]

L'impiego combinato di un esame citologico della cervice uterina e dello screening del DNA dell'HPV è adatto per le donne dai 30 anni in poi

Raccomandazioni FDA [3]

The new indication allows the test to be used for screening, in conjunction with the Pap test, of women over age 30 for HPV infection

Raccomandazioni American Cancer Society [4]

Another reasonable option for women over 30 is to get screened every 3 years (but not more frequently) with pap test plus the HPV DNA test

1. European Journal for Infectious and Immunological Diseases in Obstetrics and Gynaecology, February 2001
2. ACOG Practice Bulletin, Number 45, August 2003.
3. FDA news. March 31, 2003
4. www.cancer.org

Cervical cancer

✓HPV vaccination programs could reduce the long-term future burden of cervical cancer, and WHO recommends vaccinations against HPV (2 doses) of girls aged 9 to 13 years.

✓WHO recommends screening of women aged 30 to 49 years (PAP every 3-5 years, or HPV testing every 5 years) coupled with timely treatment of precancerous lesions.

✓Integration of HPV vaccine programs with HPV-based testing via screening programs has the potential to virtually eliminate the burden of cervical cancer in every country of the world in this century.

Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

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Ovary	295,414 (1.6)	184,799 (1.9)
Vulva	44,235 (0.2)	15,222 (0.2)
Vagina	17,600 (0.1)	8,062 (0.1)

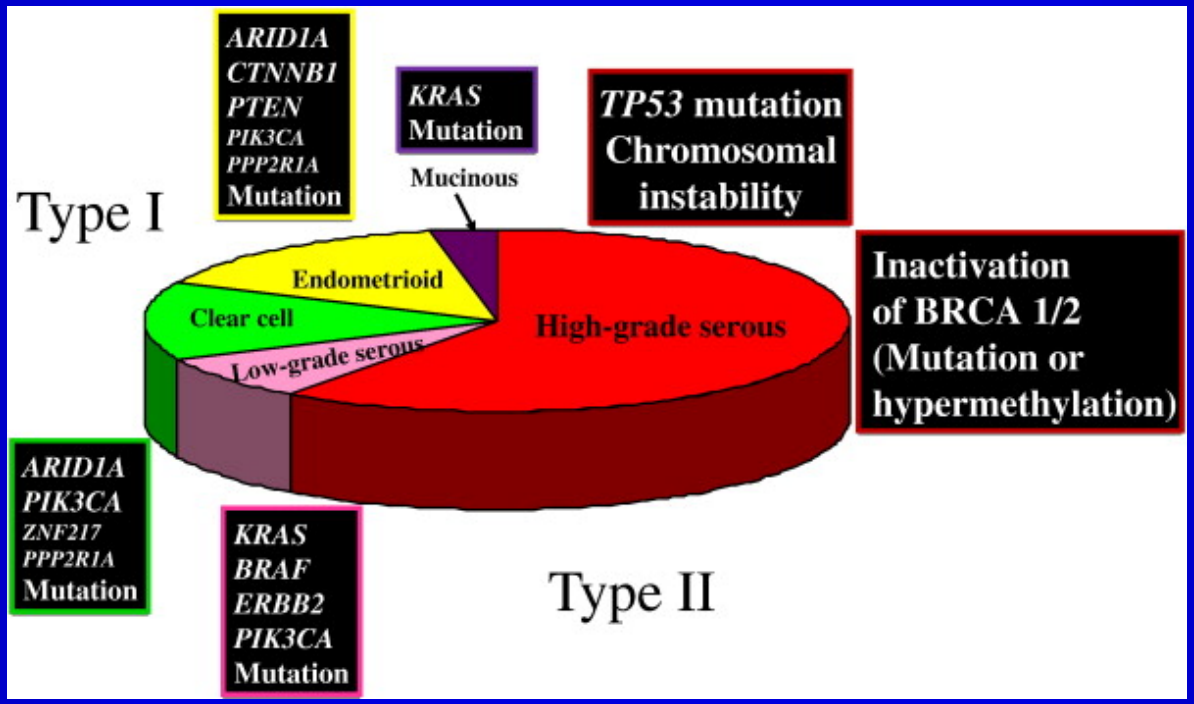
Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

Ovarian cancer pathology

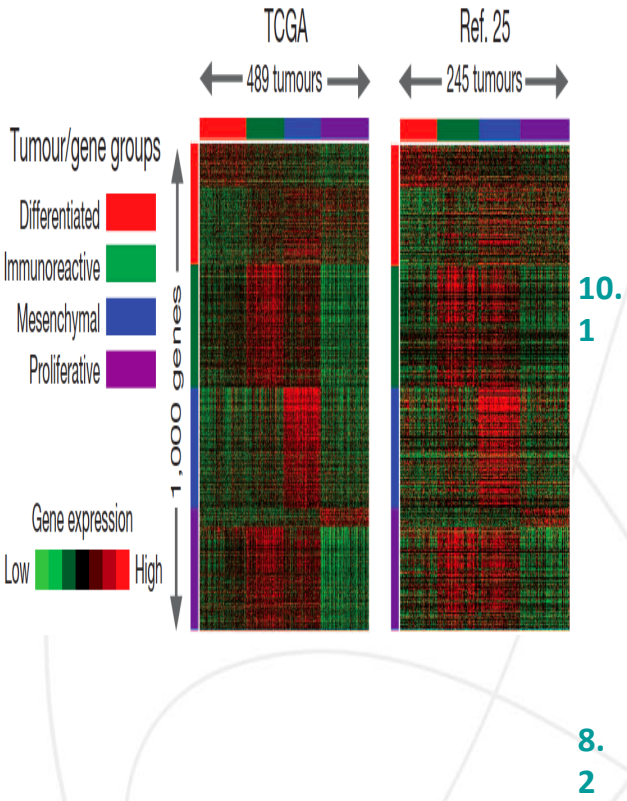
Two groups:

- Type I:
  - Slow growing, generally confined to the ovary
  - Develop from borderline tumors
  - Mutations of different genes (KRAS,B-RAF, PTEN, PI3KASE, ARID1A, B-catenin)
- Type II:
  - Rapidly growing ,highly aggressive
  - Precursor lesion not well described
  - P53 mutations

Ovarian cancer pathology

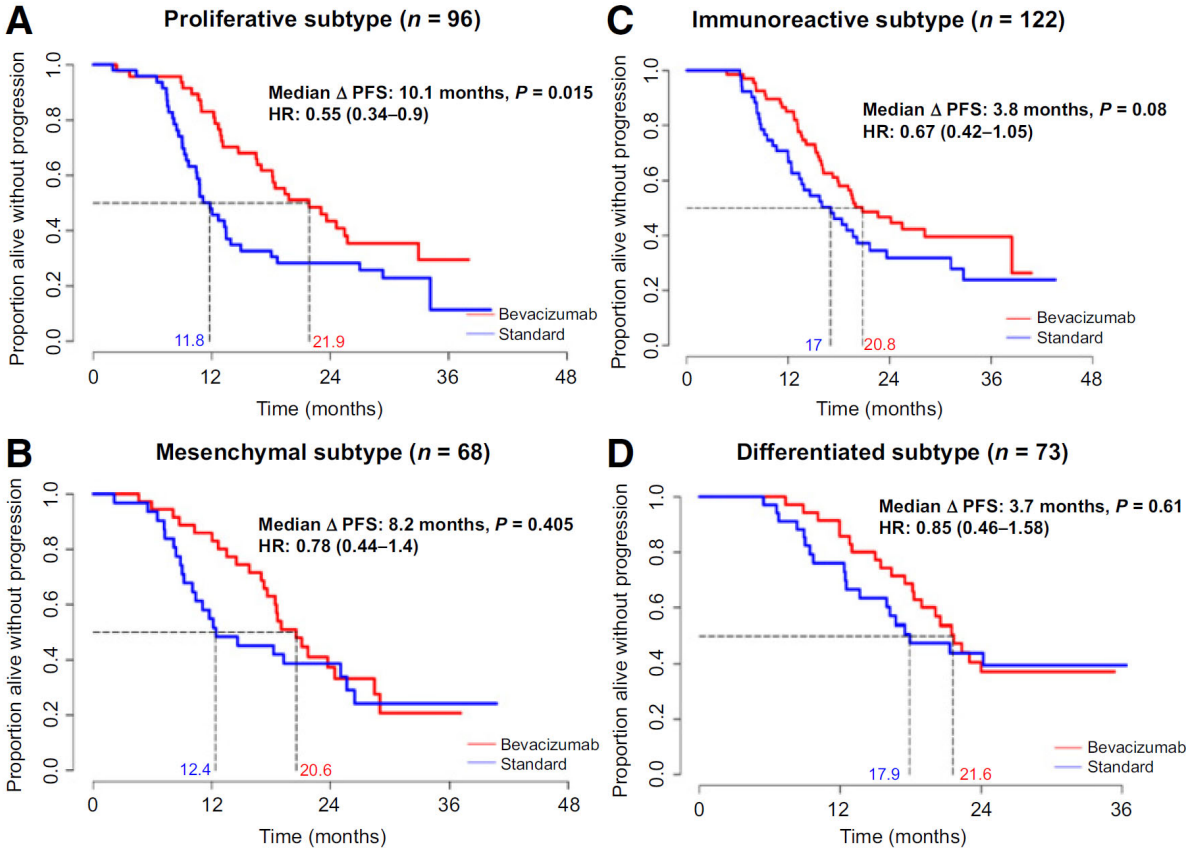


AGO-ICON7 PFS by molecular subtypes (TGCA)

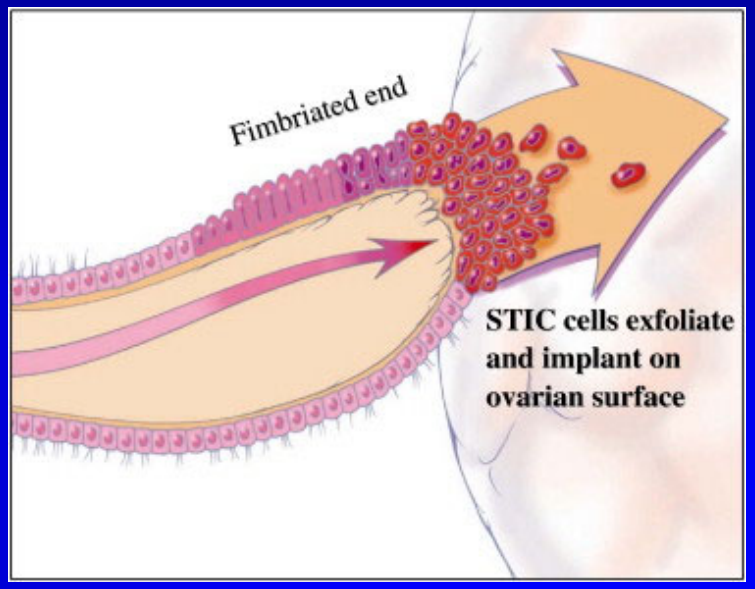


10.1

8.2



Kommos et al, Cancer Clinical Research, 2017


Fimbriated end
STIC cells exfoliate
and implant on
ovarian surface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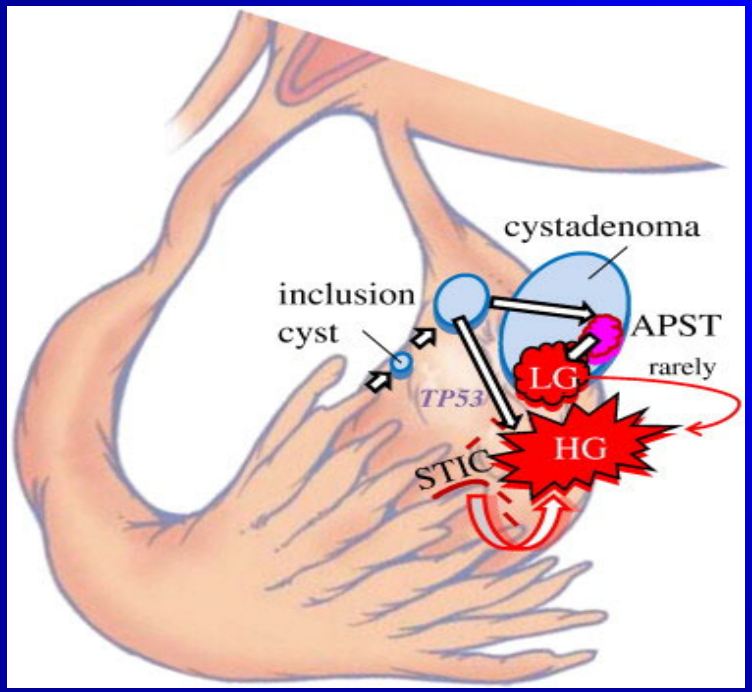
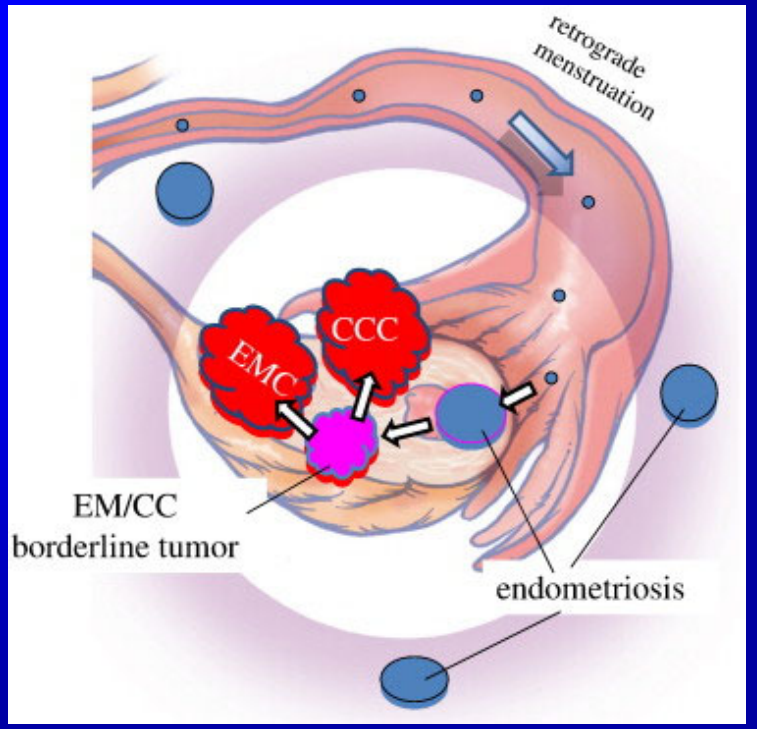

cystadenoma
inclusion
cyst
APST
rarely
LG
TP53
HG
STIC


retrograde
menstruation
EMC
CCC
EM/CC
borderline tumor
endometriosis

Risk factors in ovarian cancer

Risk factors		Protective factors	
Hereditary ($BRCA_1$, $BRCA_2$ status)	+++	Parity	+++
Nulliparity	+++	Oral contraceptives	+++
Late age at menopause	+	Early age at menopause	+
Endometriosis	+		
Read meat consumption	?	Vegetable consumption	?
Cosmetic talc use	?	Vitamin A, vitamin E	?
Fertility drug	?		
Hormone replacement therapy	?	Breastfeeding (nonmucinous)	?

BRCAm carriers and lifetime risk of cancer

	BRCA1m	*BRCA2m*
-Risk for EOC	39-63%	10-27%

-Risk for BC 56-84% (similar for *BRCA1m* and *BRCA2m*)

20% (<40 years) 37% (50 years) 55% (60 years) >70% (> 70 years)

-Increased risk also for pancreatic cancer, UPSC and melanoma

EOC and OC: Collaborative reanalysis of data from 45 epidemiological studies

EOC

Study population: 23,257 women with EOC and 87,303 controls

Overall 7308 (31%) cases and 32,717 (37%) controls had ever used OC, for average durations among users of 4.4 and 5.0 years, respectively.

Duration of OC use (mean)	Cases/controls	RR	99% CI
Never	14703/51908	1.00	0.96–1.04
<1 year (0.4 years)	1492/6353	1.00	0.91–1.10
1–4 years (2.4 years)	2686/11329	0.78	0.73–0.83
5–9 years (6.8 years)	1562/7118	0.64	0.59–0.69
10–14 years (11.6 years)	655/3765	0.56	0.50–0.62
15 years or more (18.3 years)	247/1639	0.42	0.36–0.49

Beral 2008

Impact of progestin and estrogen potency in OC on ovarian cancer risk

Case-control study: 390 ovarian cancer patients

2865 controls (identified from CASH)

	OR* (95%CI)
Low-progestin potency OC	2.2 (1.3-3.9)

* high-progestin potency OC as referent group

Schildkaut 2002

Progesterone and EOC

PgR in normal epithelium

Progestins

↓

Upregulation of TGF-ß

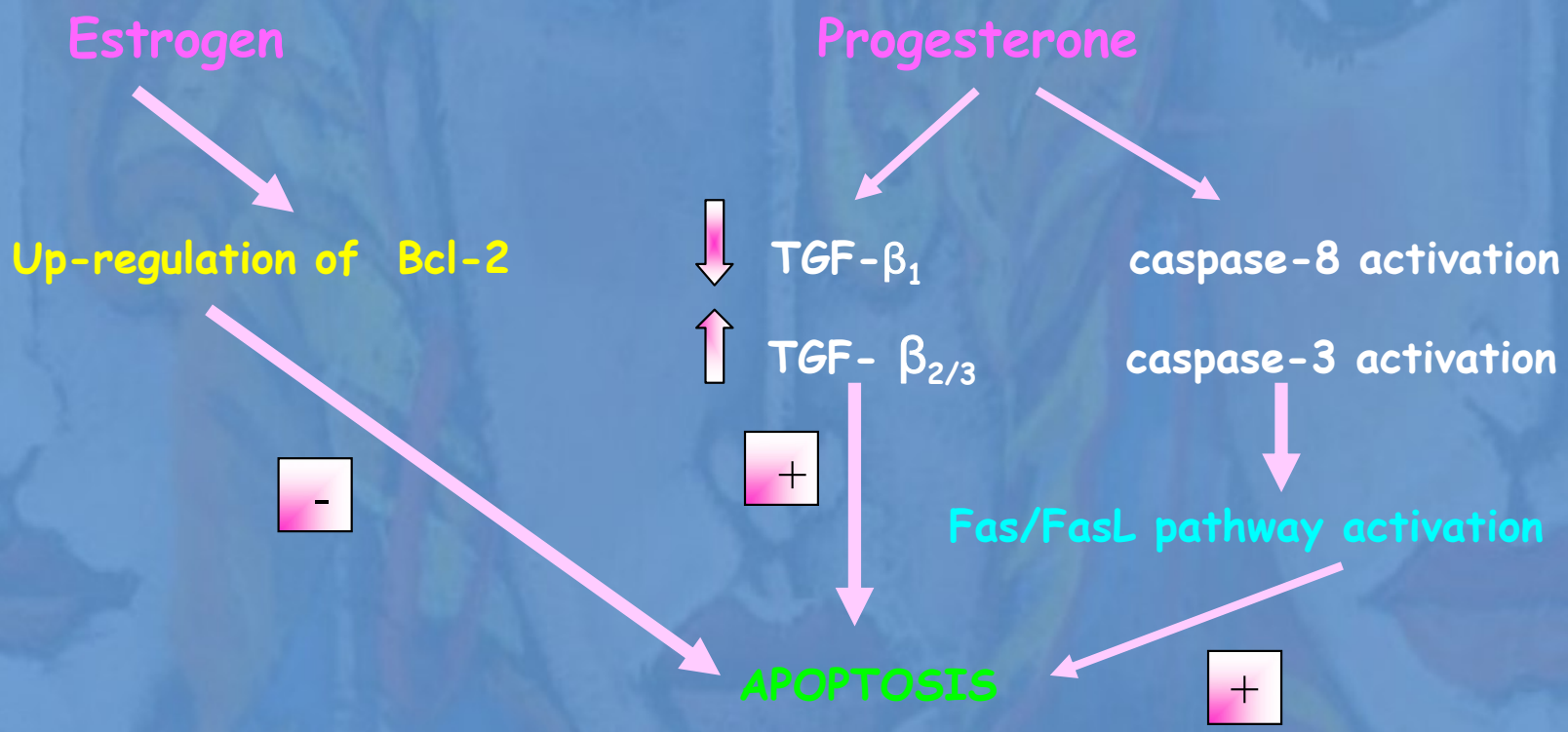
↓

Enhanced apoptosis in ovarian epithelium

Rodriquez 2002

A germline polymorphism variant in the hormone-binding domain of PgR is associated with 2-fold increased risk of EOC *(McKenna 1995)*

Estrogen and progesterone as modulators of apoptosis in ovarian epithelial cells



OC and EOC risk in $BRCA_1$ or $BRCA_2$ m carriers

- ✓ Canadian case-control study (207 with hereditary EOC; 161 of their sisters as controls)
- ✓ All pts were $BRCA_1$ (n.179) or $BRCA_2$ (n.28) m carriers
- ✓ Control women enrolled regardless of their mutational status

OC ever users	OR	95%
$BRCA_1$m carrier	0,5	0.3-0.9
$BRCA_2$m carrier	0.4	0.2-1.1
$BRCA_{1-2}$m carrier	0.5	(0.3-0.8)*

*Risk decreased with increasing duration of use (p for trend <0.001)

Narod 1998

Relationship between individual components of ovulatory cycles and risk of EOC among $BRCA_1$ and $BRCA_2$

Characteristic	Univariate RR (95%CI)	p	Multivariate RR (95%CI)	p
All subjects				
Parity	0.85 (0.79–0.91)	<0.0001	0.86 (0.79–0.93)	0.0003
Breastfeed, per year	0.86 (0.80–0.94)	0.0003	0.92 (0.84–1.00)	0.05
OC use, per year	0.95 (0.93–0.96)	<0.0001	0.94 (0.92–0.96)	<0.0001
Age at menopause, per year[2]	1.03 (1.01–1.05)	0.009	1.03 (1.00–1.05)	0.02

Kotsopolou, 2015

Relationship between individual components of ovulatory cycles and risk of EOC among $BRCA_1$ and $BRCA_2$

BRCA1 mutation carriers	Univariate	P value	Multivariate	P value
Parity	0.84 (0.78–0.91)	<0.0001	0.84 (0.76–0.93)	0.0005
Breastfeed, per year	0.88 (0.81–0.96)	0.004	0.95 (0.86–1.04)	0.27
OC use, per year	0.95 (0.93–0.97)	<0.0001	0.95 (0.92–0.97)	<0.0001
Age at menopause, per year[1]	1.04 (1.01–1.06)	0.003	1.03 (1.00–1.06)	0.01

Kotsopolou, 2015

Relationship between individual components of ovulatory cycles and risk of EOC among $BRCA_1$ and $BRCA_2$

BRCA2 mutation carriers	Univariate	P value	Multivariate	P value
Age at menarche, per year	1.05 (0.91–1.22)	0.51	1.04 (0.88–1.22)	0.64
Parity	0.88 (0.76–1.02)	0.10	0.91 (0.76–1.08)	0.28
Breastfeed, per year	0.76 (0.61–0.95)	0.01	0.77 (0.60–0.98)	0.03
OC use , per year	0.94 (0.91–0.97)	<0.0001	0.93 (0.90–0.97)	0.0005
Age at menopause, per year	1.00 (0.97–1.04)	0.85	1.01 (0.96–1.05)	0.85

Kotsopolou, 2015

Prophylactic surgery for reduding EOC risk

- Patients with BRCA 1-2m (bilateral salpingo-oophorectomy [BSO], bilateral salpingectomy [BS] and BS with delayed oophorectomy [BSDO])
- Patients with Lynch syndrome

BSO in BRCA mutation carriers

BSO : decreases EOC risk by 85%-95%

decreases BC risk by 53%-68%

removes occult cancer in 2-18% of women

induces significant menopausal symptoms

increases risk for osteoporosis

increased risk for CHD (women <50 years)

Roccas WA Lancet Oncology 2006; Metcalfe KA Open Med 2007; Finch A Maturitas 2011; Finch A. Womens Health 2012

BSO and oncologic risk

BSO should be performed at 35-40 years in *BRCA1m* carriers after completing their family, and delayed until 45-50 years in *BRCA2m* carriers

-It is debated whether concomitant HT should be included so as

i) To completely excise the interstitial component of Fallopian tubes

ii) to reduce the risk of endometrial pathology in women taking TAM

iii) to use estrogen-only replacement therapy (eliminating progestogens)

Sigal BM, Cancer Epidemiol Biomarkers Prev 2012;
ACOG Practice Bulletin, Obstet Gynecol 2008

Prophylactic BSO and BS

- ✓ In women at increased EOC risk, BSO is the only intervention that has been shown to decrease EOC mortality and is the standard of care
- ✓ BS proposed as alternative option in BRCAm carriers in their forties, with definitive oophorectomy performed at 50-52 years (No available data)
- ✓ In a study on 2281 *BRCA$_1$*m and 1038 *BRCA$_2$*m carriers, tubal ligation was associated with HR for EOC = 0.43 (95% CI, 0.24–0.75)
- ✓ PSDO for high-risk premenopausal women within clinical trials

Oliver Perez MR Surg Oncol. 2015; Swanson CL. Curr Treat Options Oncol. 2016

NCT01907789

PSDO observational prospective cohort study

Premenopausal BRCA1-2m carriers (age : 30-48 years)

Aim of study: to compare

i)Screening (physical examination, CA125, HE4, TV-US every 6 months),

ii)BSO

iii)BSDO

Estimated Enrollment: 80

Lynch Syndrome: prophylactic surgery

- ✓ Autosomal dominant familial cancer risk syndrome (gMMRm) associated with increased risk of colorectal, endometrial, and ovarian cancer
- ✓ Gynecological screening (from 30–35 years): gynecologic examination, TV-US, endometrial biopsy and *CA* 125 assay
- ✓ Prophylactic HT +BSO after completion of childbearing may be offered
- ✓ Schmeler reported 2 pts who underwent HT + BSO and who had PPC 12 and 8 years later. Unknown magnitude of the risk, but pts counseled

Schmeler KM N Engl J Med. 2006; Schmeler KM. Obstet Gynecol. 2010

Effect of screening on EOC mortality in PLCO cancer screening trial

Randomized trial involving 10 centers across the US (1993-2011) that recruited 78.216 women aged 55-74 years

RANDOM

Intervention group:	Usual care
Annual screening with CA125 for 6 years and TV-US for 4 years	no annual screening (usual medical care)

All women followed up to 13 years (median =12.4, range=10.9-13.0)

Buys 2011

Effect of screening on EOC mortality in PLCO cancer screening trial

	Intervention arm (n. 39.105)	Usual care (n. 39.111)	RR	95% CI
Diagnosis of OC	212 (5.7 per 10,000 person-years)	176 (4.7 per 10,000 person-years)	1.21	0.99-1.48
Death from OC	118 (3.1 per 10,000 person-years)	100 (2.6 per 10,000 person-years)	1.18	0.82-1.71

Buys 2011

Effect of screening on EOC mortality in PLCO cancer screening trial

Of 3285 women with FP results, 1080 underwent surgery (32.9% for oophorectomy).

Of these, 163 women (15%) experienced a total of 222 distinct major complications (20.6 complications per 100 surgical procedures)

Table 5. Major Complications Associated With Diagnostic Evaluation for Ovarian Cancer

	No. (%)		
	Intervention Group		Cancer Cases in Usual Care Group (n = 176)[b]
	No Cancer, Surgical Follow-up (n = 1080)[a]	Cancer (n = 212)[b]	
Women with complications	163 (15)	95 (45)	91 (52)
Total complications[c]	**222** (100)	**140** (100)	**143** (100)
Infection	89 (40)	32 (23)	37 (26)
Direct surgical	63 (28)	69 (49)	61 (43)
Cardiovascular or pulmonary	31 (14)	26 (19)	27 (19)
Other	39 (18)	13 (9)	18 (12)

[a] Includes only women who had a false-positive screening result for ovarian cancer during the screening phase of the trial.
[b] Includes women diagnosed with cancer during the screening phase or follow-up.
[c] Some women had more than 1 complication.

Buys 2011

OC screening and mortality in the UK Collaborative Trial Of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

From 2001 to 2005, 202.638 women aged 50–74 years with anaverage OC risk (from 13 centers in England, Wales, and Northern Ireland) were randomized (1:1:2 ratio):

i.annual multimodal screening [MMS] with serum CA125 (algorithm,ROCA) (n. 50.640)

ii.annual TV-US screening [USS) (n. 50.624)

iii.no screening (n. 101,299)

Jacobs, 2016

OC screening and mortality in the UK Collaborative Trial Of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Primary analysis (Cox proportional hazards model)

Mortality reduction over years 0-14

a) 15% (95% CI = -3 to 30; p=0.10) with MMS

b) 11% (95% CI =-7 to 27; p=0.21) with USS

Jacobs, 2016

OC screening and mortality in the UK Collaborative Trial Of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Prespecified analysis of OC death of MMS vs no screening (prevalent cases excluded)

Years	Average mortality reduction
0-14	20% (-2 to 40)
0-7	8% (-27 to 43)
7-14	28%* (-3 to 49) (p=0.021)

* long-term effect of MMS screening program

Jacobs, 2016

Improving quality and decreasing cost in gynecologic oncology care.
Society of gynecologic oncology (SGO) recommendations for clinical practice.

RECOMMENDATIONS

•Do not perform Pap tests of the vaginal cuff in patients with a history of endometrial cancer.

•Do not perform colposcopy for low grade Pap in women with a history of cervical cancer.

•Avoid routine imaging for cancer surveillance in asymptomatic women with gynecologic cancer, specifically ovarian, endometrial, cervical, vulvar and vaginal cancer.

•Do not screen women at low risk for ovarian cancer with US , CA-125 or other biomarkers.

•Do not delay basic palliative care for women with advanced or relapsed gynecologic cancer, do refer to a palliative care specialist when needed, and avoid unnecessary treatments at life's end.

Rimel BJ 2015

NCCN GUIDELINES VERSION 4.2017 . OVARIAN CANCER

The literature does not support routine screening for OC in the general population, and routine screening is not currently recommended by any professional society

Clarke-Pearson DL, 2009; Brown DL, 2010; Schorge JO, 2010; Hartge P, 2010; Buys SS, 2011; Nolen BM, 2012; Moyer VA, 2012; Gentry-Maharaj A, 2012; Rimel BJ, 2015; Smith RA, 2015

Some physicians follow high-risk women (BRCA mutations, family hystory) using CA125 and TV-US (*Smith RA, 2015*)
Prospective validation of these tests remains elusive

GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries

New Cases and Deaths for 36 Cancers and All Cancers Combined in 2018

CANCER SITE	NO. OF NEW CASES (% OF ALL SITES)	NO. OF DEATHS (% OF ALL SITES)
Breast	2,088,849 (11.6)	626,679 (6.6)
Cervix uteri	569,847 (3.2)	311,365 (3.3)
Corpus uteri	382,069 (2.1)	89,929 (0.9)
Ovary	295,414 (1.6)	184,799 (1.9)
Vulva	44,235 (0.2)	15,222 (0.2)
Vagina	17,600 (0.1)	8,062 (0.1)

Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

Endometrial carcinoma

	Type-1	Type-2
Histology	Endometrioid	Non endometrioid
Origin	Atypical hyperplasia	Intraepithelial carcinoma
Endocrine status	Estrogen-dependent	Estrogen-independent
P53-status	Wild-type	Mutated
Prognosis	Good	Poor

Type-1 (endometrioid) EC

Risk factors

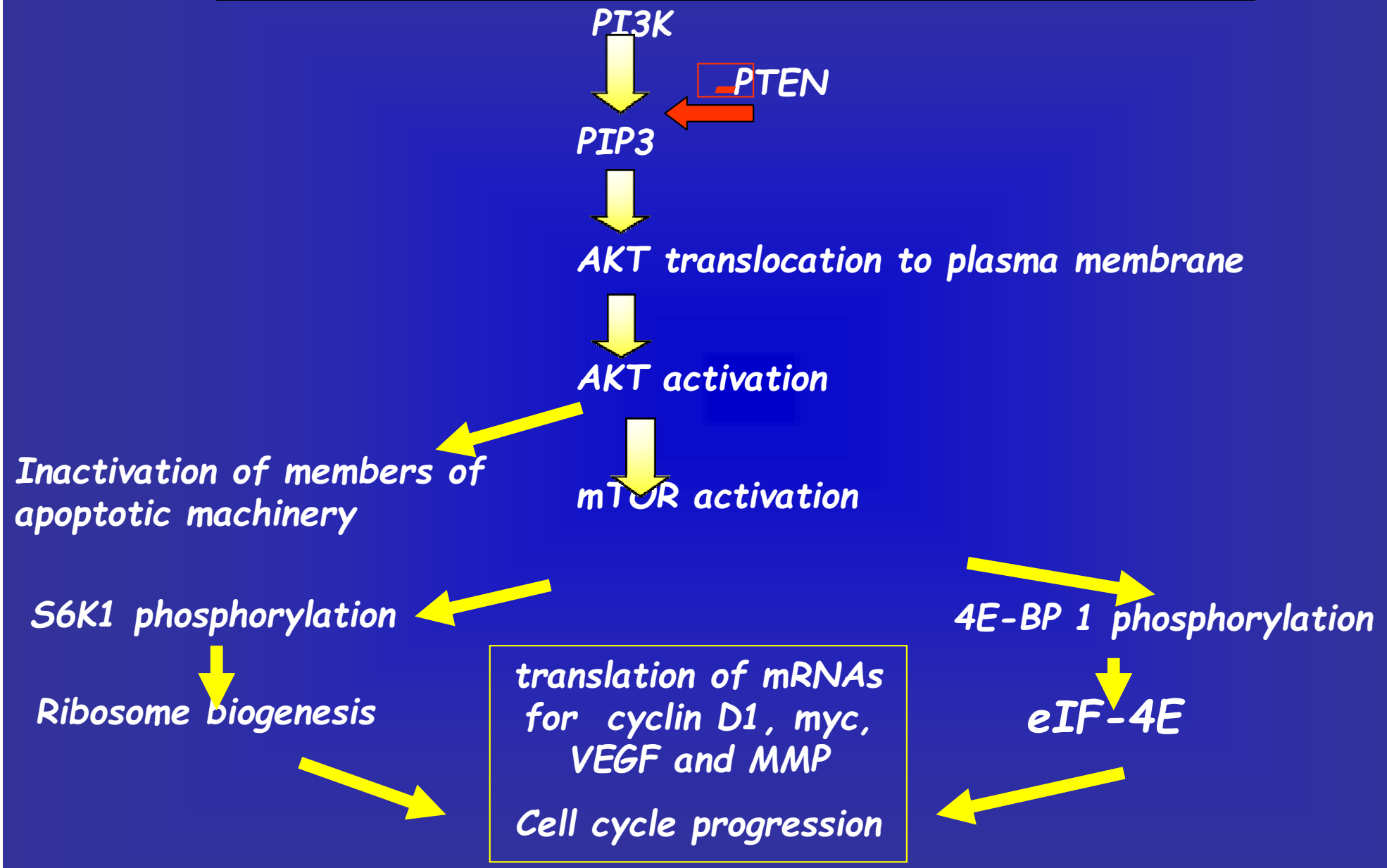
- Early menarche
- Late menopause
- Nulliparity
- Infertility
- PCO
- Lynch-II Syndrome
- Diabetes
- Hypertension
- Unopposed ERT
- TAM
- Obesity

EC: molecular alterations

Type 1	Type2
PTEN mutation	p53 mutation
PI3K mutation	p16 inactivation
MMR defects	Low E-cadherin expression
MSI	Her-2/neu overexpression
β-catenin mutation	STK15 amplification
K-Ras mutation	LOH

Lax 2000; Prat 2001, 2007; Moreno-Bueno ,2002, 2003 ; Matias-Guiu 2001; Koul, 2002; Holcomb, 2002; Santin, 2005; Gadducci 2006; Doll, 2008 Catasus , 2008; Llobet, et al. 2009 ; Yalta, 2009

PTEN-PI3K-AKT-mTOR pathway



Characteristic of four genomic classes of endometrioid and serous EC

	POLE (ultramutated)	MSI (hypermutated)	Copy-number low (endometrioid)	Copy-number high (serous-like)
Copy-number aberrations	Low	Low	Low	High
MSI/MLH1 methyl ation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Mutation rate	Very high (232 × 10^{-6}mutations/Mb)	High (18 × 10^{-6}mutations/Mb)	Low (2·9 × 10^{-6}mutations/Mb)	Low (2·3 × 10^{-6}mutations/Mb)
Genes commonly mutated (prevalence)	POLE (100%) PTEN (94%) PIK3CA (71%) PIK3R1 (65%) FBXW7 (82%) ARID1A (76%) KRAS (53%) ARID5B (47%)	PTEN (88%) RPL22 (37%) KRAS (35%) PIK3CA (54%) PIK3R1 (40%) ARID1A (37%)	PTEN (77%) CTNNB1 (52%) PIK3CA (53%) PIK3R1 (33%) ARID1A (42%)	TP53 (92%) PPP2R1A (22%) PIK3CA (47%)
Histological type	Endometrioid	Endometrioid	Endometrioid	Serous, endometrioid, and mixed serous and endometrioid
Tumour grade	Mixed (grades 1–3)	Mixed (grades 1–3)	Grades 1 and 2	Grade 3
Progression-free survival	Good	Intermediate	Intermediate	Poor

Prognostic signficance of POLE ε mutations in EC

✓ POLE ε mutations: 6.1% of 788 ECs enrolled in PORTEC-1 and-2 trials

✓ POLE ε-mutated: less relapses (6.2% vs 14.1%) and deaths (2.3% vs 9.7%)

Among the 109 G3 ECs

	POLE ε-mutated	POLE ε-wt
Tumor recurrence	0/15 (0%)	29/94 (30.9%)

POLE ε mutations: Better PFS at multivariate analysis (HR=0.11, 95% CI= 0.001- 0.84)

Church DN et. 2014

Association of POLE ε-mutated and MSI EC with neoantigen load, TILs, and PD1/PD-L1expression

Materials: tumor samples from 63 patients with EC

	Neoantigen Load		
	Median	(range)	p value
POLE ε ultramutated	8342	(628- 20440)	
MSI hypermutated	541	(146-8063)	0.001
MSS tumors	70.5	(7-1877)	<0.001

POLE ε ultramutated+/MSI: higher CD8+ TILs (P <0.001) vs MMS

Howitt et al. 2015

Association of POLE ε -mutated and MSI EC with neoantigen load, TILs, and PD-1/PD-L1 expression

- PD-1 overexpressed in TILs ($p < 0.001$) and peritumoral lymphocytes ($p < 0.001$) of POLE ε ultramutated and MSI ECs
- POLE ε ultramutated and MSI ECs: high neoantigen loads and high number of TILs, counterbalanced by PD-1/ PD-L1 overexpression
- Strong rationale for testing immune check-point inhibitors

Howitt et al. 2015

Comparison of classification of EC

	Bokhman	WHO	The Cancer Genome Atlas
Basis	Clinical and epidemiological features	Histological features	Genome-wide genomic characterisation
Categories	Type I	Endometrioid	POLE (ultramutated), MSI (hypermutated) Copy-number low (endometrioid)
	Type II	Serous Clear cell	Copy-number high (serous-like)