Screening and Prevention for Gynecologic Cancers

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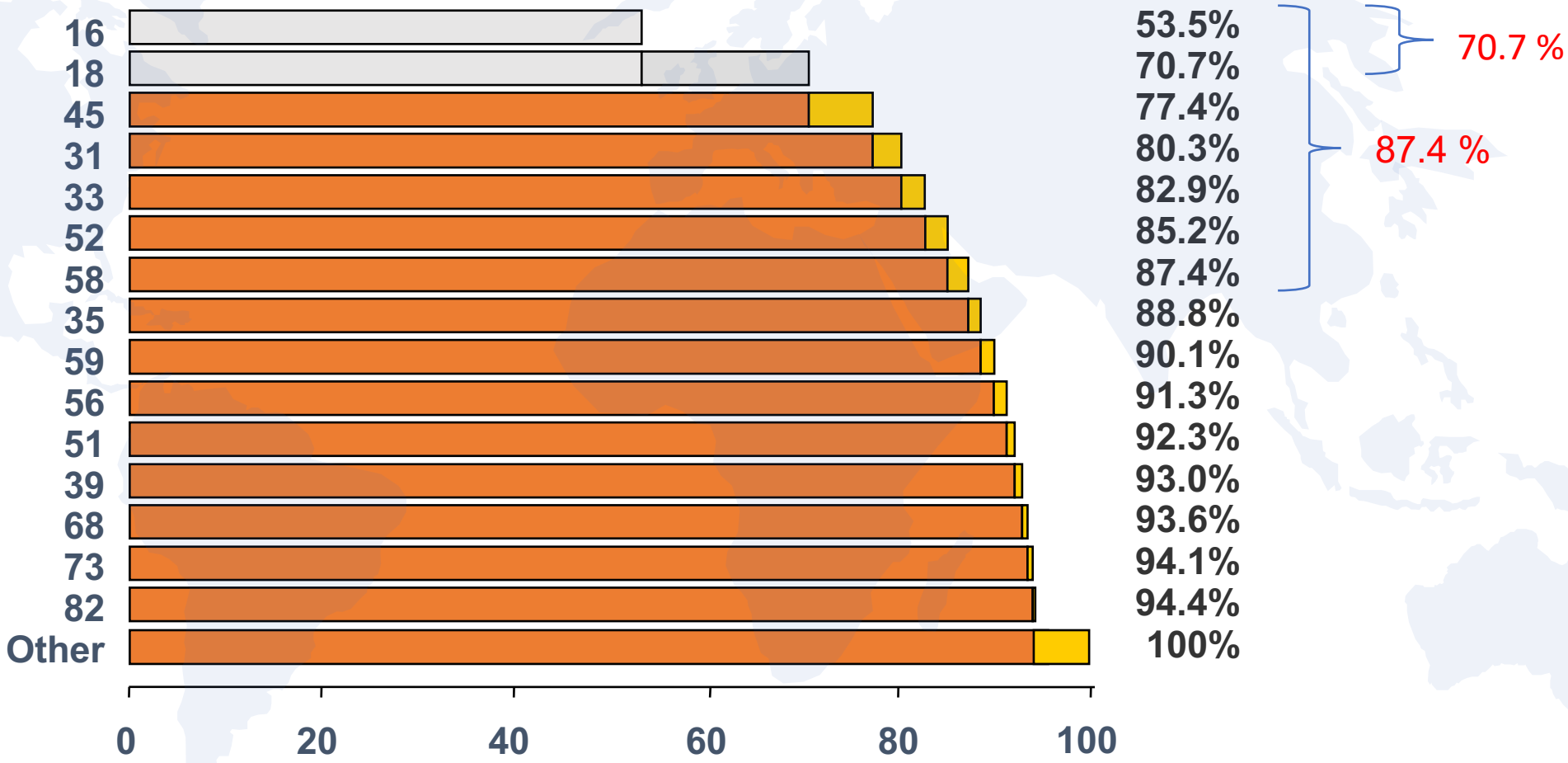
CERVİCAL CANCER

Epidemiology and Risk factors

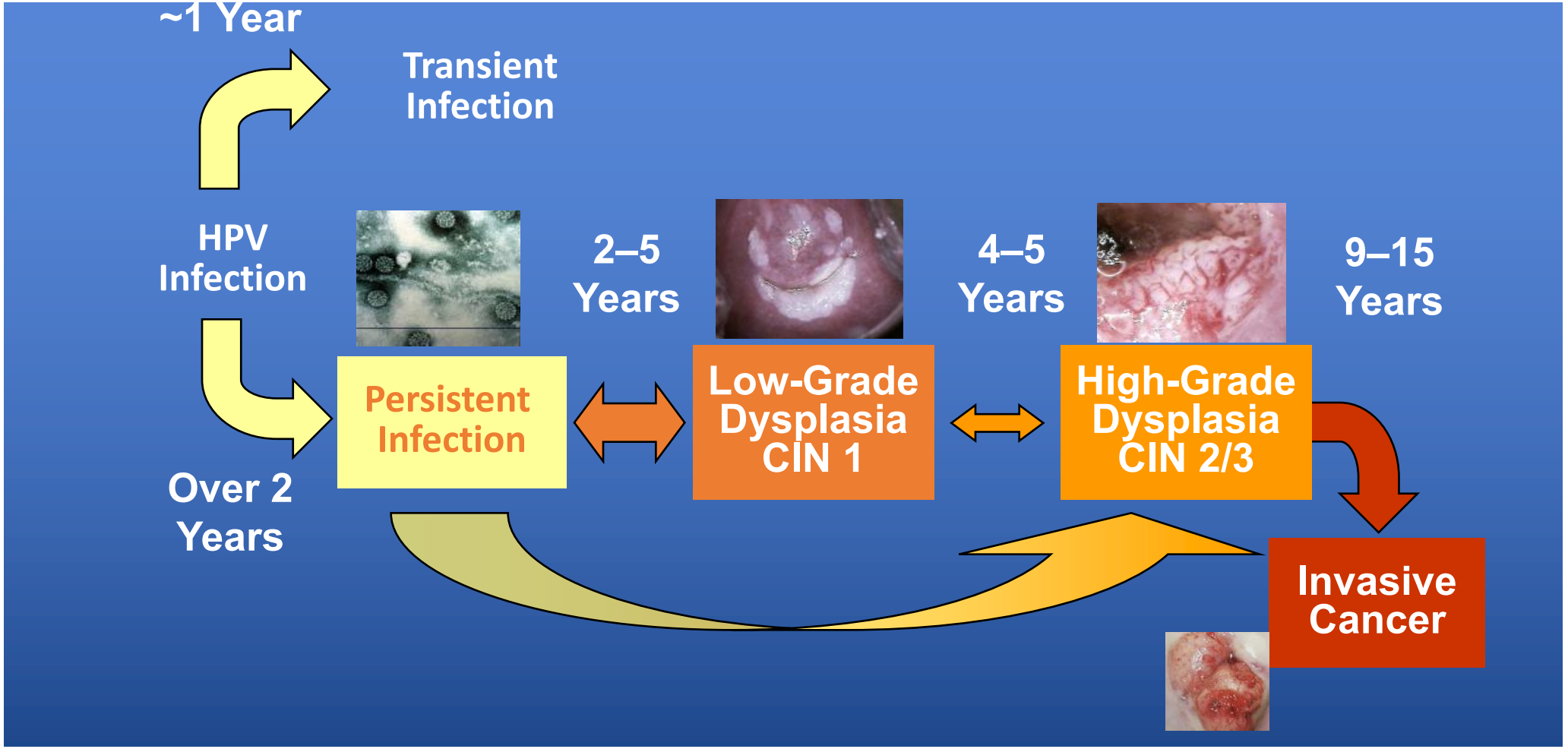
- Human papillomavirus (HPV) infection is the causal agent of cervical cancer
- Lifetime probability of developing cervical cancer is 1:128
- The mean age for cervical cancer is 47 years
- < 50 % of the cases are less than 35 years-old (Fertility sparing surgery)
- ***Risk factors***: young age at first intercourse, multiple sexual partners, cigarette smoking, high parity and low socioeconomic status.
- The initiating event in cervical dysplasia and carcinogenesis is infection with HPV

Relative contribution of hpv types to cervical cancer: All World Regions Combined



Muñoz N., Bosch FX., et al, IJC 2004

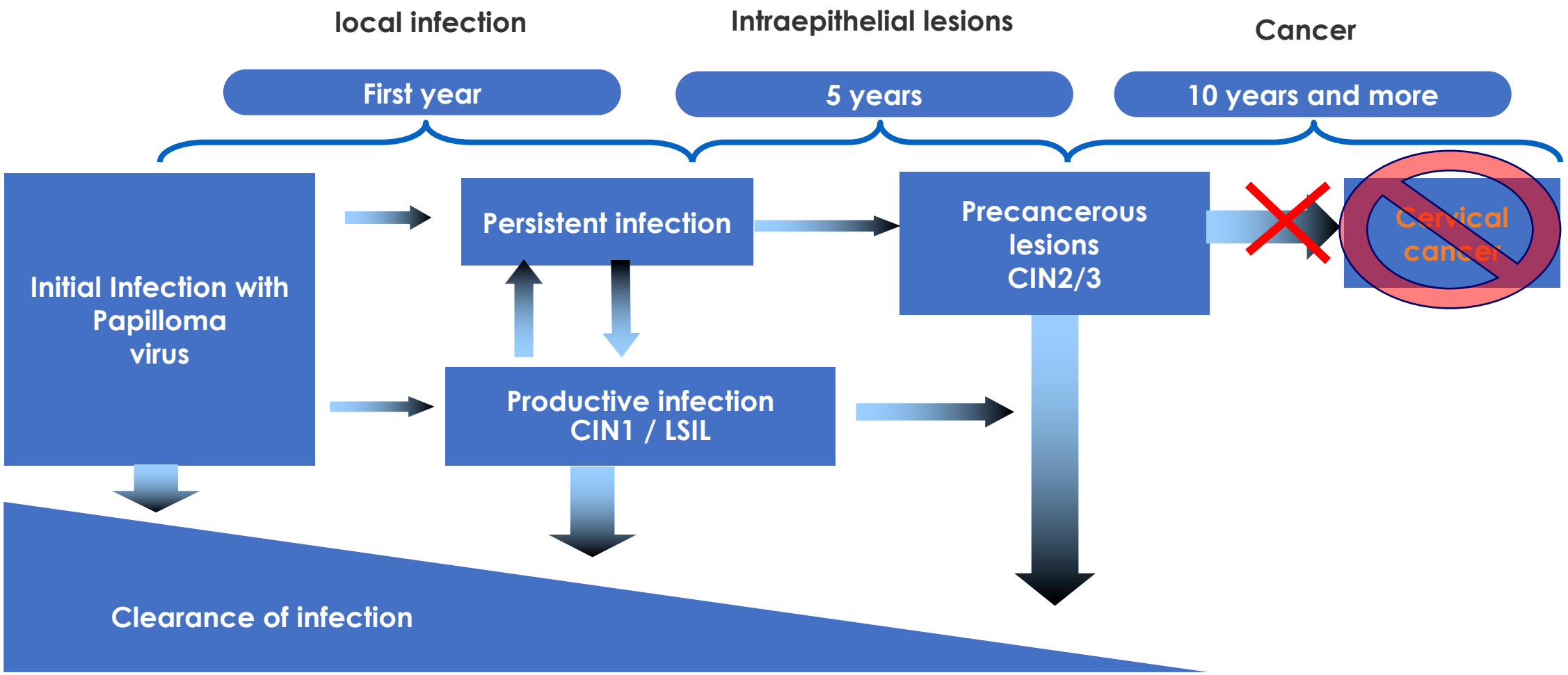
Natural History of Cervical Cancer



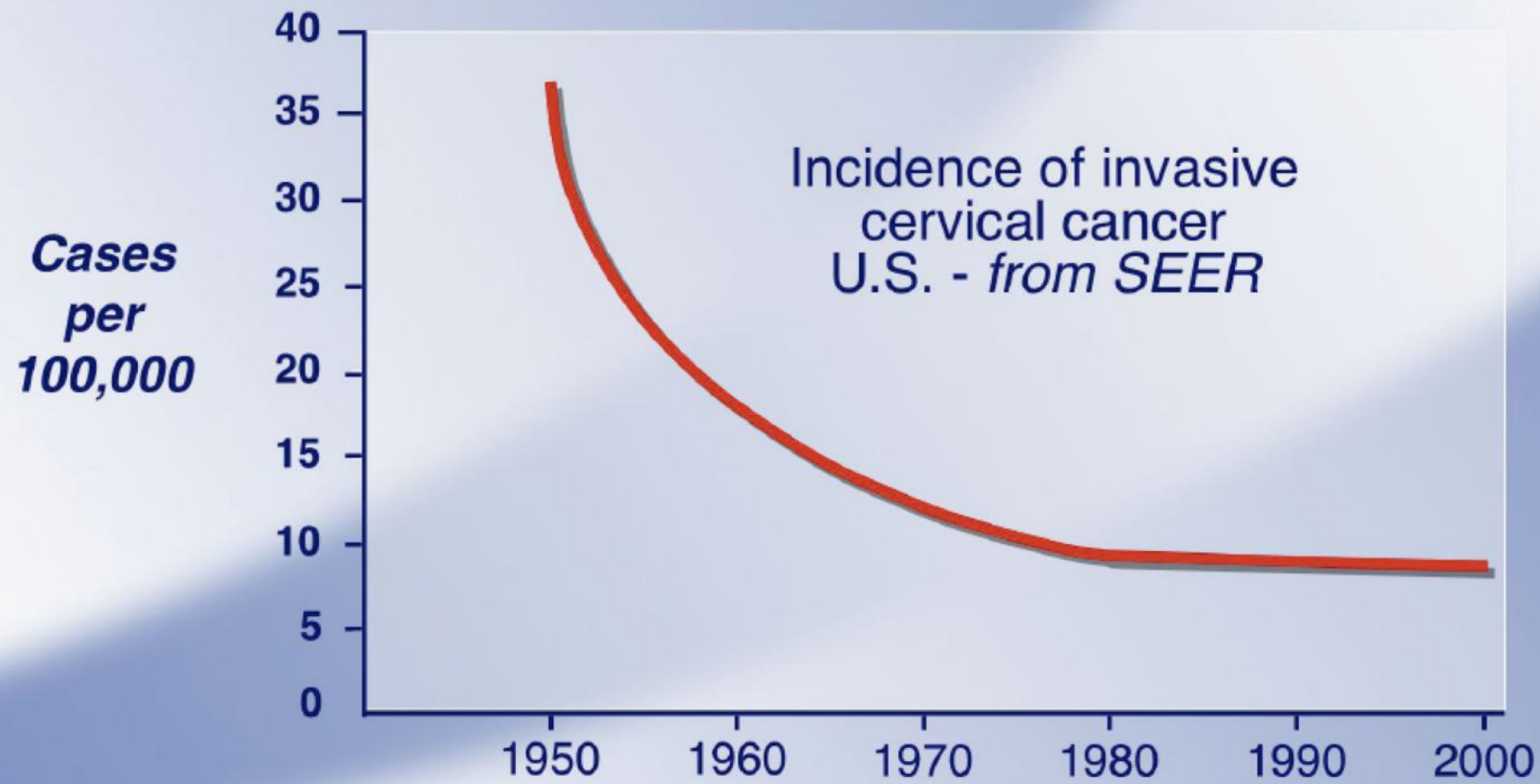
What is the objective of screening?

- To reduce morbidity/mortality from cervical cancer
  - Not to find abnormal Paps or CIN
  - Not to find HPV infections

Screening: secondary prevention



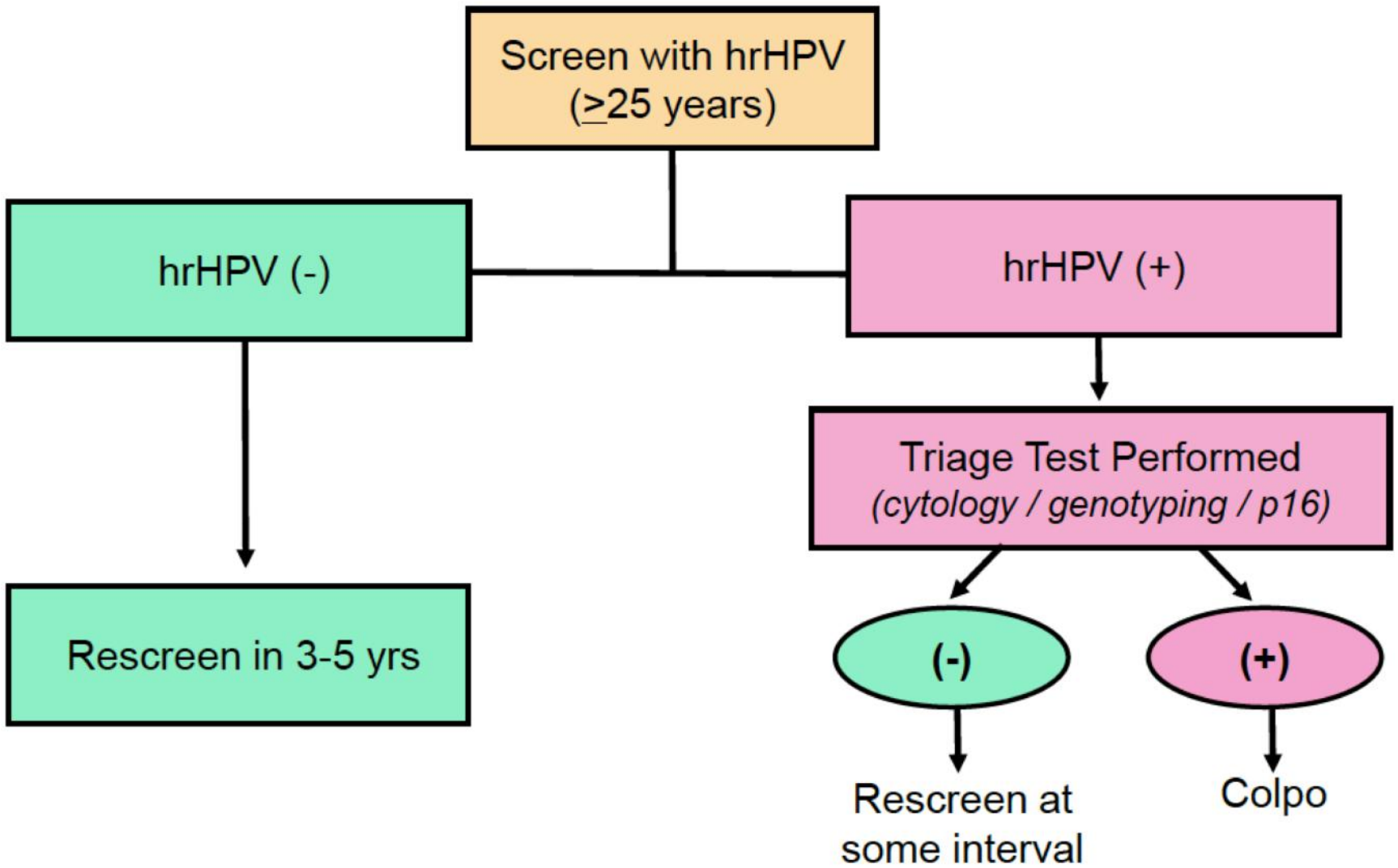
Impact of Cervical Cytology in U.S.



Primary HPV screening

- Screening tests (**cervical Pap smear, HPV**) identify an existing pre-invasive cervical lesion
- Pap smear (ie cytology) has been the mainstay of cervical screening for past 60 years
- However, increased awareness of **limitations of cytology:**
  - Interpretation subjective, potential sources of error (lesion not sampled, abnormal cells may not be transferred, preservation of cells may be inadequate, may be reading errors)
  - Single Pap low sensitivity (44-65%)
  - Poor in preventing adenocarcinoma
  - Poor PPV – unnecessary colposcopy
  - Requires at least 3 yearly repeats
- Key clinical question that has informed change is the reduction in the burden of CIN3 and cervical cancer incidence and mortality by the combination of hrHPV testing and cytology (60-70% greater efficacy than cytology alone)

HPV as the Initial Screening Test



Guideline Recommendations

Figure 2. Clinical Summary: Screening for Cervical Cancer

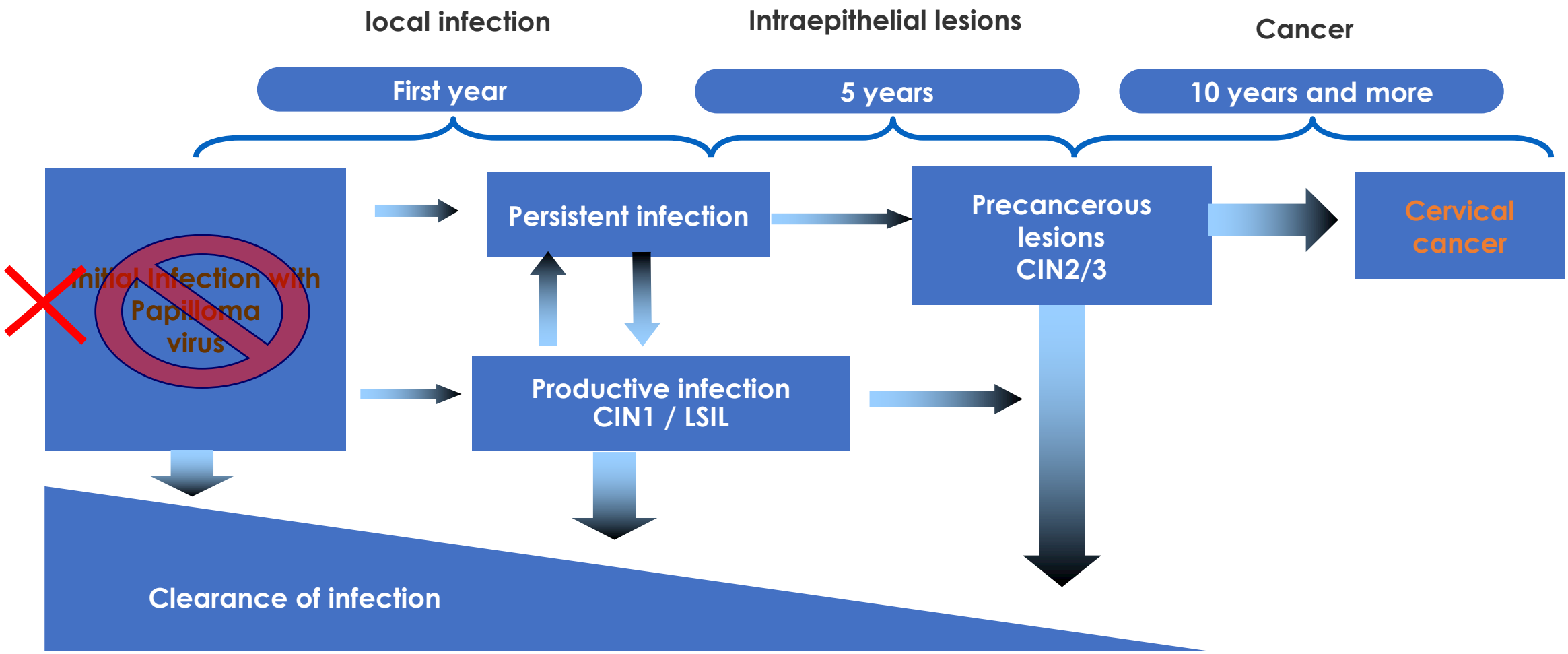
Population	Women aged 21 to 29 years	Women aged 30 to 65 years	Women younger than 21 years, women older than 65 years with adequate prior screening, and women who have had a hysterectomy
Recommendation	Screen for cervical cancer every 3 years with cytology alone. Grade: A	Screen for cervical cancer every 3 years with cytology alone, every 5 years with hrHPV testing alone, or every 5 years with cotesting. Grade: A	Do not screen for cervical cancer. Grade: D

Dual Prevention

- We now have two powerful technologies to dramatically reduce cervical cancer incidence:
  - **Screening for HPV infection**
  - **Immunisation against HPV**
- Success will depend on using *both* technologies together to achieve effective coverage in all groups
- This will require better technologies, better guidelines, better information systems and better partnerships with all communities

-

Vaccination: Primary Prevention



HPV Vaccines

	Girls	Boys	Age
Cervarix (16,18)	Cervix, Vulva, Vagina	No indication	> 9 years
Gardasil (6,11,16,18)	Cervix, Vulva, Vagina, Anal, Genital Warts	Anal, Genital Warts	> 9 years
9vHPV (6,11,16,18,31,33,45,52,58)	Not available in Turkey		

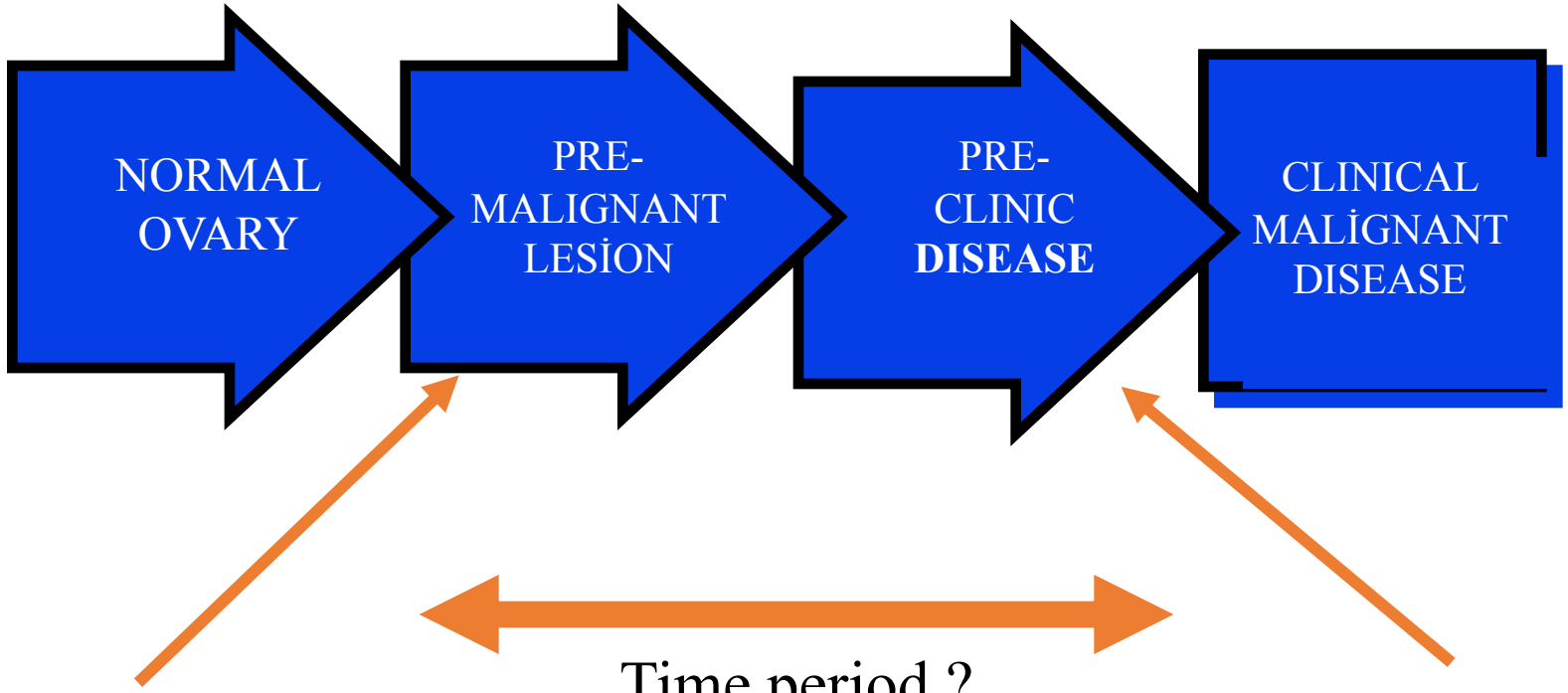
Current Cervical Cancer Screening Programme

- Screening Test: **Pap smear**
- Target Age Group: **30-65 years**
- Screening Interval: **5 years**
- **Population based screening** through KETEMs (free of charge) + **Opportunistic screening**
- EU Quality guidelines are implemented with on site monitorization and evaluation
- KETEMs have consultant Ob&Gyn specialist in addition to other experts. If smear is abnormal, these consultations, treatment after screenings and follow up of patients are free fo charge without any strict referral rules

OVARIAN CANCER
Prevalence and Burden

- Ovarian cancer is the fifth most common cause of cancer death in US women and the leading cause of gynecologic cancer deaths despite having low incidence.
- Approximately 22440 ovarian cancer cases and 14080 deaths are estimated to occur in 2017.
- Incidence 11.4 cases per 100.000 women.
- Mortality rate 7.4 per 100.000 women.
- The majority of women diagnosed with ovarian cancer are over age 45 (88%), with a median age of diagnosis of 63 years.

Natural History of Ovarian Cancer



Screening for Ovarian Cancer

Difficulties:

- Intraperitoneal localization of ovaries
- Absence of precursor lesions
- Unknown preclinic stage time period
- Multisentric primary tumour

Rationale of Screening

- The high mortality and low 5-year survival among all women diagnosed with ovarian cancer is largely due to challenges detecting the disease at an early stage.
- Only 15 percent of cases are diagnosed at the local stage, when 5-year survival is favorable at 92 percent. Over 60 percent of cases are diagnosed after the cancer has distant metastases. With distant spread, the 5-year survival drops to 29 percent.
- Thus, **screening for early-stage disease** has been a focus of research.

Screening strategies

- Bimanual pelvic examination
- CA 125
- Transvaginal Ultrasound
- Other biomarkers and the use of alternative imaging strategies

Screening for Ovarian Cancer
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Table 3. Effects of Ovarian Cancer Screening on Ovarian Cancer Mortality (Key Question 1)[a,b]

Source	Screening Method	No. Analyzed		Ovarian Cancer Deaths, No. (%)		Ovarian Cancer Mortality per 10 000 Person-Years		Between-Group Difference in Mortality
		Screening Group	Control Group	Intervention	Control	Intervention	Control	
UKCTOCS,[31] 2016	CA-125 ROCA	50 624	101 299	160 (0.32)	358 (0.35)	2.9	3.3	HR, 0.89 (95% CI, 0.74-1.08); $P = .23$[c]
	TVU	50 623	101 299	163 (0.32)	358 (0.35)	3.0	3.3	HR, 0.91 (95% CI, 0.76-1.09); $P = .31$[c]
PLCO,[21] 2011	CA-125 + TVU	34 253	34 304	118 (0.34)	100 (0.29)	3.1	2.6	Rate ratio, 1.18 (95% CI, 0.82-1.71); P = NR[d]
UK Pilot,[33] 1999[e]	CA-125	10 958	10 977	9 (0.08)	18 (0.16)	NR	NR	Relative risk, 0.50 (95% CI, 0.22-1.11); $P = .08$[f]

Henderson JT, Jama 2018

Screening related Harms (PLCO Trial)

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 SS, Jama 2011

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Ovarian Cancer
US Preventive Services Task Force
Recommendation Statement

- The USPSTF found adequate evidence that screening with transvaginal ultrasound, testing for the serum tumor marker cancer antigen 125 (CA-125), or a combination of both does not reduce ovarian cancer mortality.

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

SGO
Society of Gynecologic Oncology

ACOG COMMITTEE OPINION

Number 716 • September 2017

(Replaces Committee Opinion Number 477, March 2011)

The Role of the Obstetrician–Gynecologist in the Early Detection of Epithelial Ovarian Cancer in Women at Average Risk

Neither ultrasonography nor measurement of tumor markers has demonstrated the sensitivity, specificity, and PPV necessary to justify use for early detection of ovarian cancer in women at average risk.

Ovarian cancer screening tests and early detection tests, such as those using the **Risk of Ovarian Cancer Algorithm** and laboratory panels of multiple tumor markers, are being marketed directly to women. At this time, there is insufficient evidence to support the use of any of these tests or algorithms for the early detection of ovarian cancer in average-risk women.

Ovarian Cancer

High risk group

1. Hereditary ovarian cancer syndromes (14 % of all OvCa)

1. **Hereditary Breast and ovarian cancer syndrome** (BRCA 1- BRCA 2)

2. **Lynch syndrome** (MLH1, MSH2, MSH6 and PMS2) (**0.5-2 %** of all ovarian cancers)

HNPCC + [ovarian cancer (increased risk of OvCA in **8-15 %** of carriers)
endometrial cancer (increased risk of EC in **15-30 %** of carriers)
pancreas cancer]

2. Familial ovarian cancers (2-10 %)

Family history of ovarian cancer

High-risk population

Organization	Routine Screening	Screening Method	Frequency of Screening	Surgical Treatment
American College of Obstetricians and Gynecologists (ACOG) Society of Gynecologic Oncology (SGO)	Routine screening generally not recommended. Short term surveillance until RRSO is reasonable	Transvaginal ultrasound (TVUS) or CA 125	Starting at age 30–35, or 5–10 years earlier than family member's age at time of diagnosis	Risk reducing salpingo-oophorectomy (RRSO) at age 35–40 for BRCA1, at age 40–45 for BRCA2
National Comprehensive Cancer Network (NCCN)	Routine screening not recommended	TVUS or CA 125	Case-by case basis beginning at age 30–35	RRSO at age 35–40 or at completion of childbearing. May delay until age 40–45 for BRCA2 if patient has had a bilateral mastectomy
US Preventative Services Task Force (USPSTF)	No recommendations in high risk population			

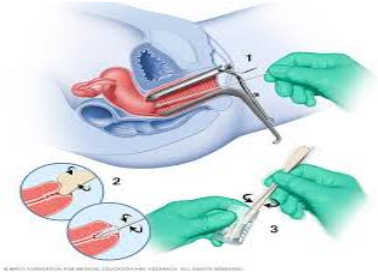
Prevention

- **The use of oral contraceptives** (estimated 20 percent decrease in the risk of ovarian cancer for every 5 years of use)
- **Parity** also has a protective effect with estimates of a 30-40 percent decrease in the risk of cancer associated with a fırst pregnancy and 10 to 15 percent decrease in each subsequent pregnancy
- **Breastfeeding** is also associated with decreased risk
- **Risk-reducing surgery (BSO);** The risk reduction conferred, however is not 100 percent and has been associated with side effects and potential risks including: early menopause, osteoporosis, cardiovascular disease and increased overall mortality
- **Bilateral salpingectomy**
- **Tubal ligation and hysterectomy**

ENDOMETRİAL CANCER

- Endometrial cancer is the fifth most common cancer in women
  (4.8% of cancers in women)
- In 2012 around 320 000 new cases of endometrial cancer were diagnosed worldwide.
- The highest incidences in 2012 are estimated in the USA and Canada ; 19.1/100 000
- Projections show that the number of cases will increase to 42.1 per 100 000 in 2030
- Cumulative risk ; 1 %
- ACS (2017) : 61 380 new cases
  10 920 deaths
- 14 % of cases are diagnosed in premenopausal women
- 5% of whom are younger than 40 years
- Early diagnosis more than 80 %
- 5 year survival is 97 % in early stage, 85 % in all stages

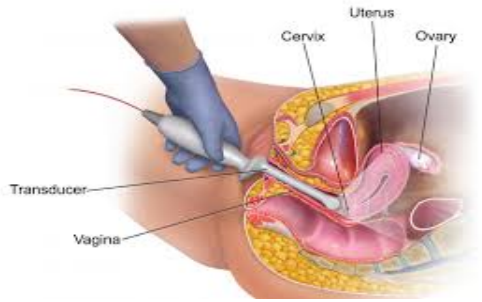
Possible Screening tools

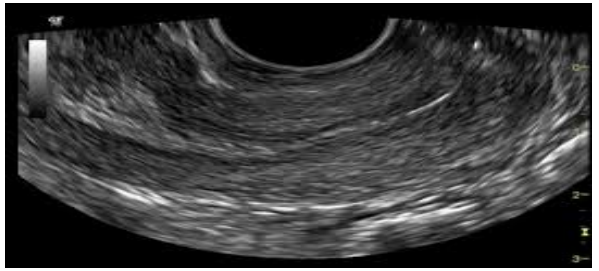


- **Pap-smear :** Sensitivity 40 to 55%

- **Transvaginal sonography:**

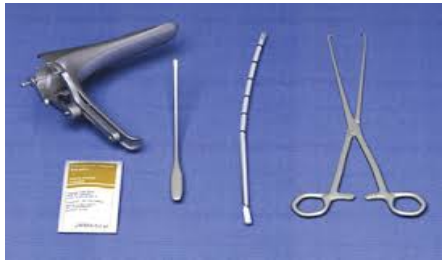
  -Sensitivity and specificity are low
  - Non-invasive

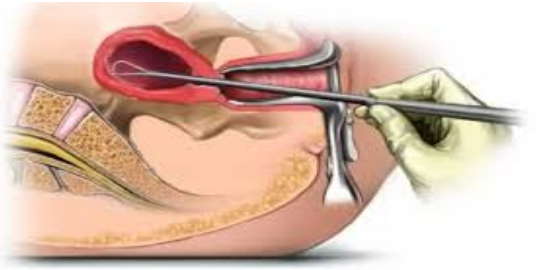




- No discriminative **serum biomarker**

- **Endometrial biopsy** (pipelle, D&C or Hysteroscopy) is a sensitive and specific test, but it is invasive and increases costs.





Endometrial cancer screening

- No effective screening tool
- 90 % of the cases symptomatic (abnormal bleeding)
- When symptomatic is still often confined to uterus, effective therapy is available with high survival rate (not late for diagnosis).
- ACS does not recommend any screening for endometrial carcinoma, only suggests informing women at average or increased risk at the onset of menopause about risks and symptoms (in particular, unexpected bleeding and spotting)

Women using Tamoxifen

- Although the primary therapeutic effect of tamoxifen is derived from its antiestrogenic properties, this agent also has **modest estrogenic activity for endometrium.**
- Slight **increase in endometrial cancer risk** (1.26/1000 versus 0.58/1000 patient years), risk is dose and time dependent
- Endometrial biopsy if any abnormal bleeding
- Routine endometrial sampling has not proved
- Women taking tamoxifen should be informed about the risks of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas.
- Encouraged to promptly report any abnormal vaginal symptoms, including bloody discharge, spotting, staining, or leukorrhea.

Hereditary non-poliposis colorectal cancer (HNPCC)

- **5-25 %** of endometrial cancers are related to high-risk germline mutations which are characterized by early onset of disease before age 40 years.
- Germline mutations in one of the mismatch repair genes

  (MLH1 (54 %), MSH2 (21%), MSH6 (16%), PMS2)
- At least **1.8%** of all endometrial cancer patients have Lynch syndrome

Hereditary non-poliposis colorectal cancer (HNPCC)

- Lynch sydrome genetic mutation carrier status.
- The substantial likelihood of being a mutation carrier (ie, a mutation is known to be present in the family).
- The absence of genetic testing results in families with suspected autosomal dominant predisposition to colon cancer.

- Annual endometrial biopsy starting at age 30-35 or 5-10 years prior to the earliest diagnosis of endometrial cancer in the family.

- Potential benefits, harms and limitations of testing for EC

Prevention

- **<u>Chemoprevention:</u>**

  Oral contraceptives

  50% decrease in risk of endometrial cancer

- **<u>Risk-reducing surgery:</u>**

  NCCN recommends ’’**Hysterectomy and bilateral salpingo-oophorectomy** should be offered to women who have completed child bearing and carry *MLH1*, *MSH2* or *MSH6* mutations older than 35 years

Thank You For Your Attention

TURKISH SOCIETY OF MEDICAL ONCOLOGY
In pursuit of science for life...

Turkish Society of Medical Oncology

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&
3rd INTERNATIONAL CONGRESS ON ONCOLOGICAL SCIENCES

27 November - 1 December 2019
Regnum Carya Convention Center
Antalya, Turkey

Risk factors

Average risk

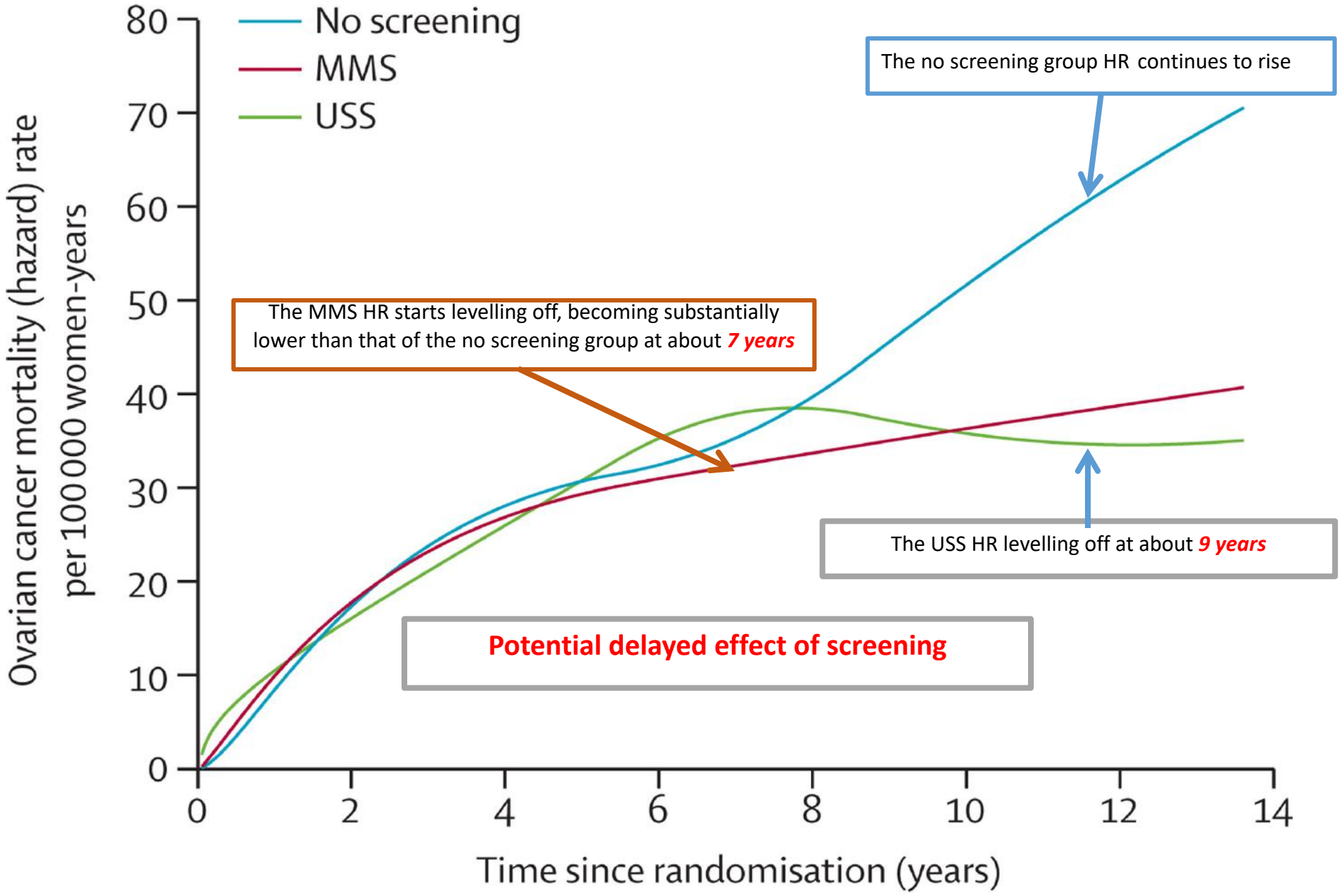
Increased Risk :

Older Age (more than 55)
Exposure to endogenous and exogenous estrogens
Obesity, HT
Diabetes,
Early age at menarche
Nulliparity
Late-onset menopause
Use of Tamoxifen
Infertility
Failure of ovulate

Very High Risk :

Herediter non-polipozis kolorektal kanser (HNPCC)

UKCTOCS: the Kaplan-Meier cumulative death rates

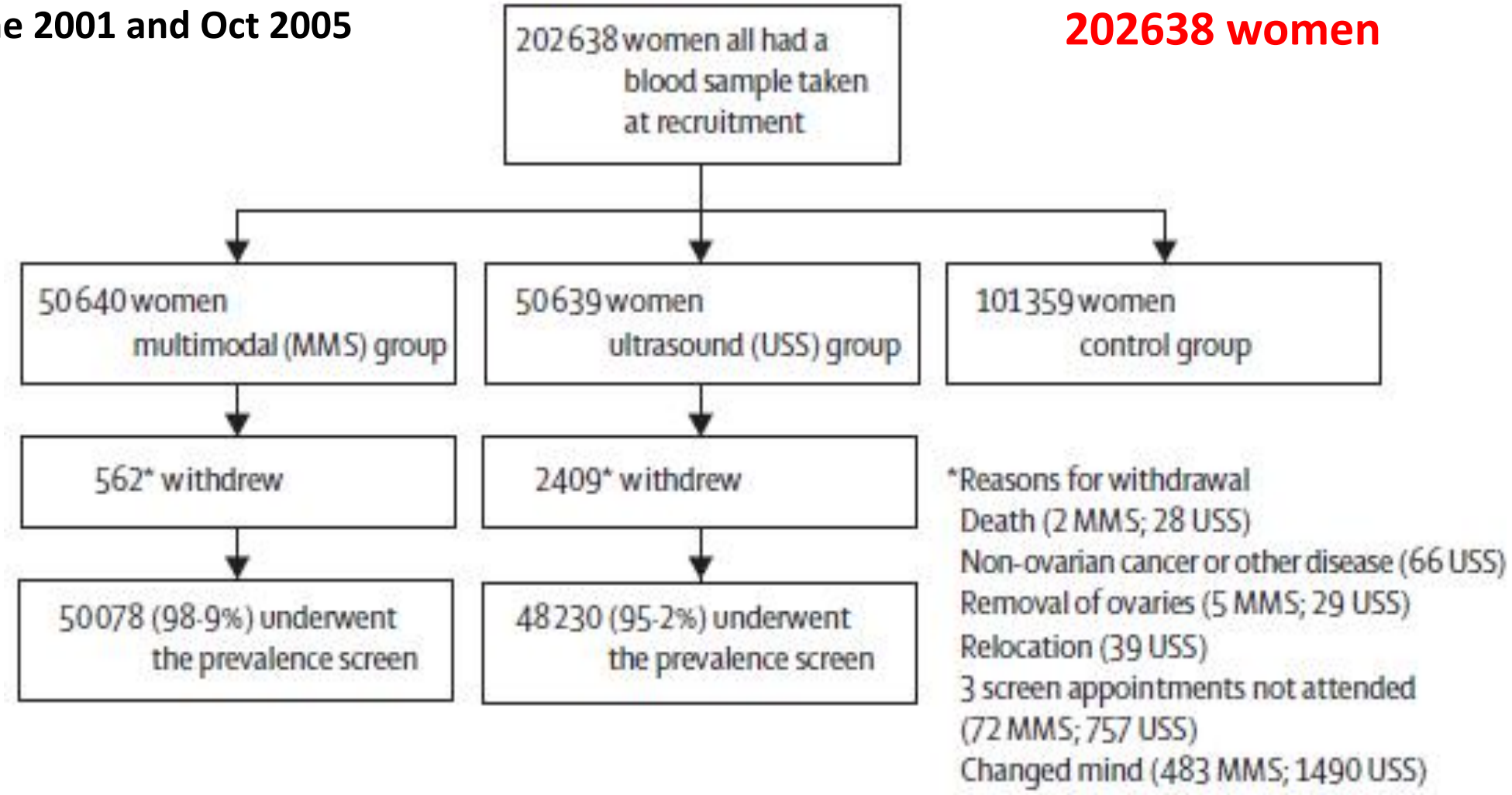


Jacobs I et al, Lancet Dec 17 2015 **http://dx.doi.org/10.1016/ S0140-6736(15)01224-6**

Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomized controlled trial

Between June 2001 and Oct 2005

202638 women



Effect of Screening on Ovarian Cancer Mortality
The Prostate, Lung, Colorectal and Ovarian **(PLCO)** Cancer Screening Randomized Controlled Trial

- Randomized controlled trial of 78216 women.
- Aged 55 to 74 years
- Annual screening with **Ca 125 and TVUSG** (n: 39105)
- Usual Care (n: 39111)
- 10 screening centers across the United States
- Between November 1993 and July 2001
- Participants were followed up for a maximum of 13 years for cancer diagnoses and death until February 28, 2010

Buys SS, Jama 2011

PAP SMEAR

Secretuar phase in premenopausal period

Postmenopausal period

} **Endometrial cells not seen.**

Asymptomatic, postmenopausal women with endometrial cells on pap-test should be sampled by endometrial biopsy

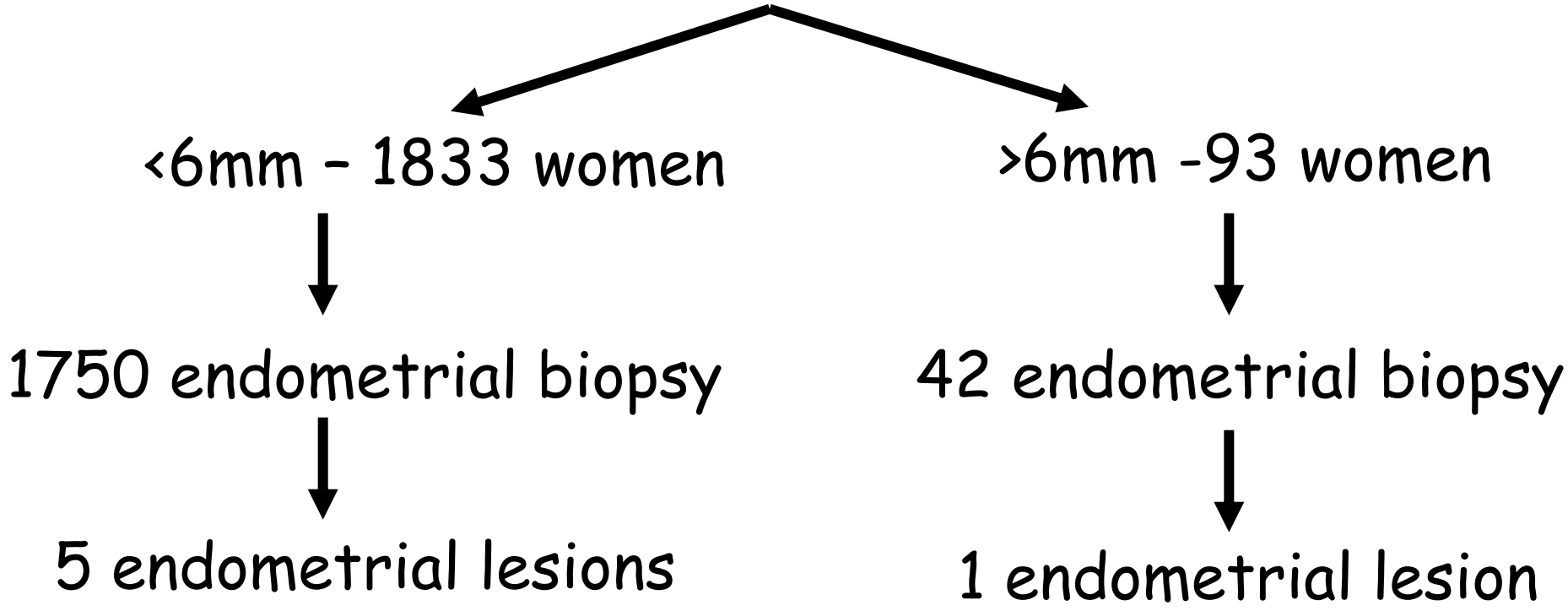
(6 % EC, 13 % EH).

Montz, Gynecol Oncol 2001

TV USG

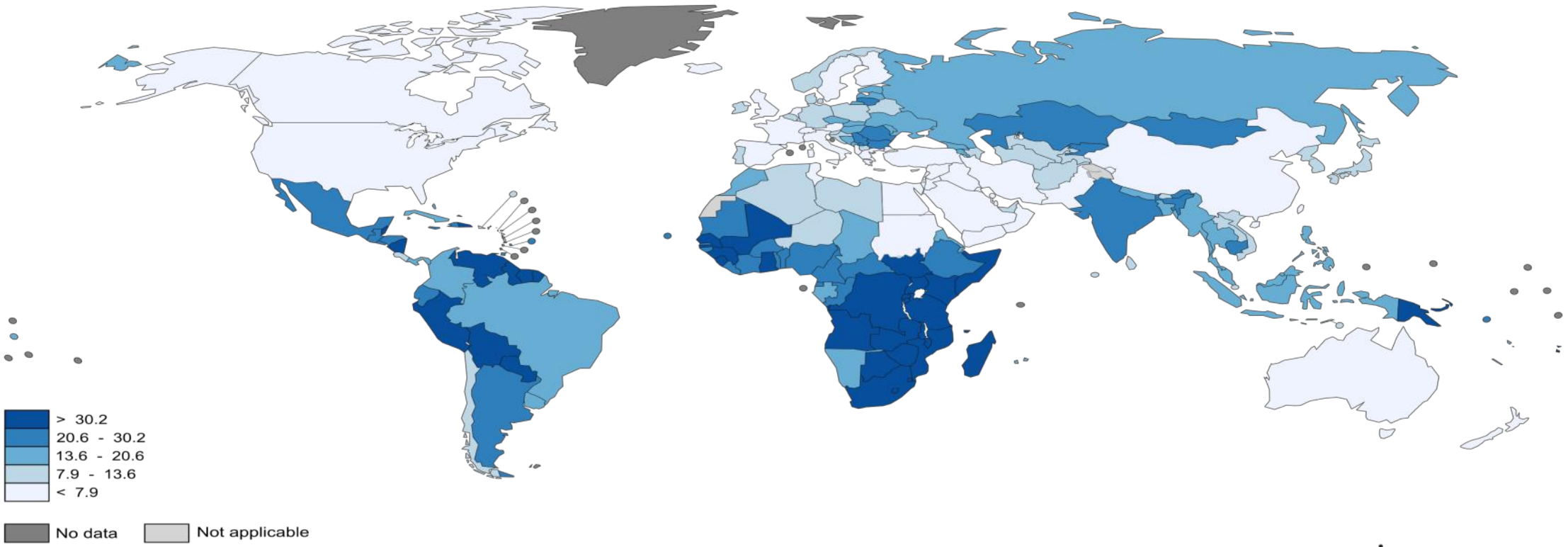
Fleischer, Am J Obstet Gynecol 2001
Double blinded, placebo controlled
1926 asymptomatic postmenopausal women

Endometrial thickness



Sensitivity %17, PPV %2

Global Cervical Cancer Incidence, 2012



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

Risk Factors for Ovarian cancer

Risk factors	RR	Risk for ovarian cancer (Lifetime) (%)
No risk factors	**1.0**	**1.2**
Ailesel over kanser sendromu	Unknown	**50**
1 veya 2. derece yakınında bir over kanseri	**3.1**	**3.7**
2 or 3 family members with ovarian cancer	**4.6**	**5.5**
OC use	**0.65**	**0.8**
Pregnancy	**0.5**	**0.6**

Meme-Over Kanser Sendromu

- **BRCA 1: Kromozom 17q21**
- **BRCA 2: Kromozom 13q12-13**
- **Erken yaş: <45**

Ailesel Over Kanseri

Artmış Risk

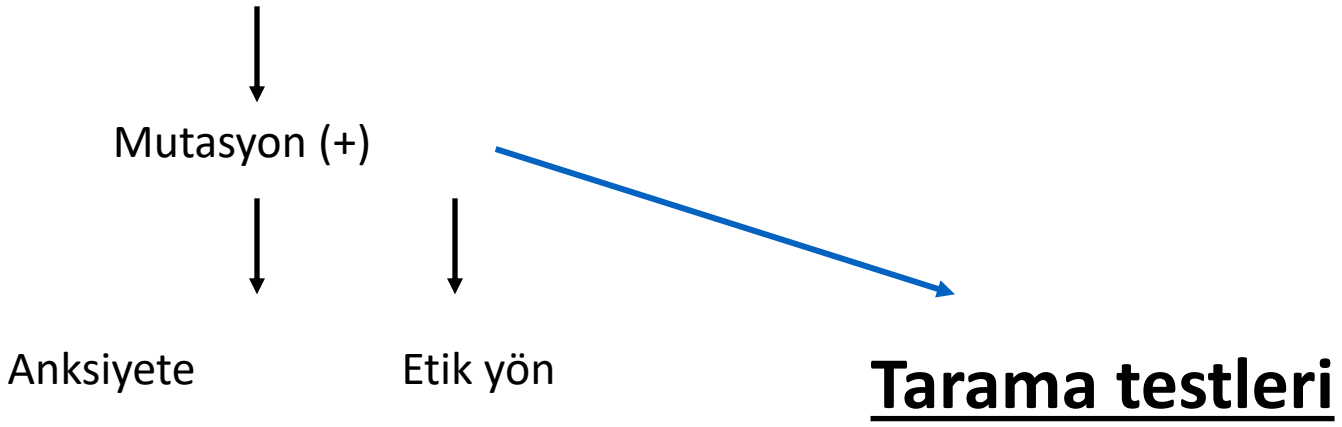
- Life time risk: %2-10
- Birinci derece yakınında birden fazla over kanseri hikayesi olmayanlar
  - Tarama ?
  - Cerrahi ?

Yüksek Risk

- Life time risk: %10 ve ↑
- Birinci derece yakınında 2 veya daha fazla over kanseri hikayesi olanlar

Yüksek Riskli Olguların Yönetimi

- **Doğru anamnez**
- **Genetik analiz** → Mutasyon (-) → Düşük risk grubuna



Yüksek Riskli Olguların Yönetimi

- **Tarama**
  - **Ailedeki en geç hastalık başlama yaşından 5 yıl önce**
  - **CA 125, ultrasound**
- **Kemoprofilaksi**
  - **Oral kontraseptif (?)**
- **Cerrahi: Tartışmalı**