SCREENING FOR OVARIAN CANCER

DR MACİT ARVAS

Ovarian cancer is the leading cause of death from gynecologic malignancy

In 2008, ovarian cancer was the seventh common cancer in women worldwide

There were 225,500 new cases of ovarian cancer worldwide.

The risk of ovarian cancer is increased when there is a family history

Odds ratio of 3.1 for developing ovarian cancer in women with one first- or second-degree relative with the disorder

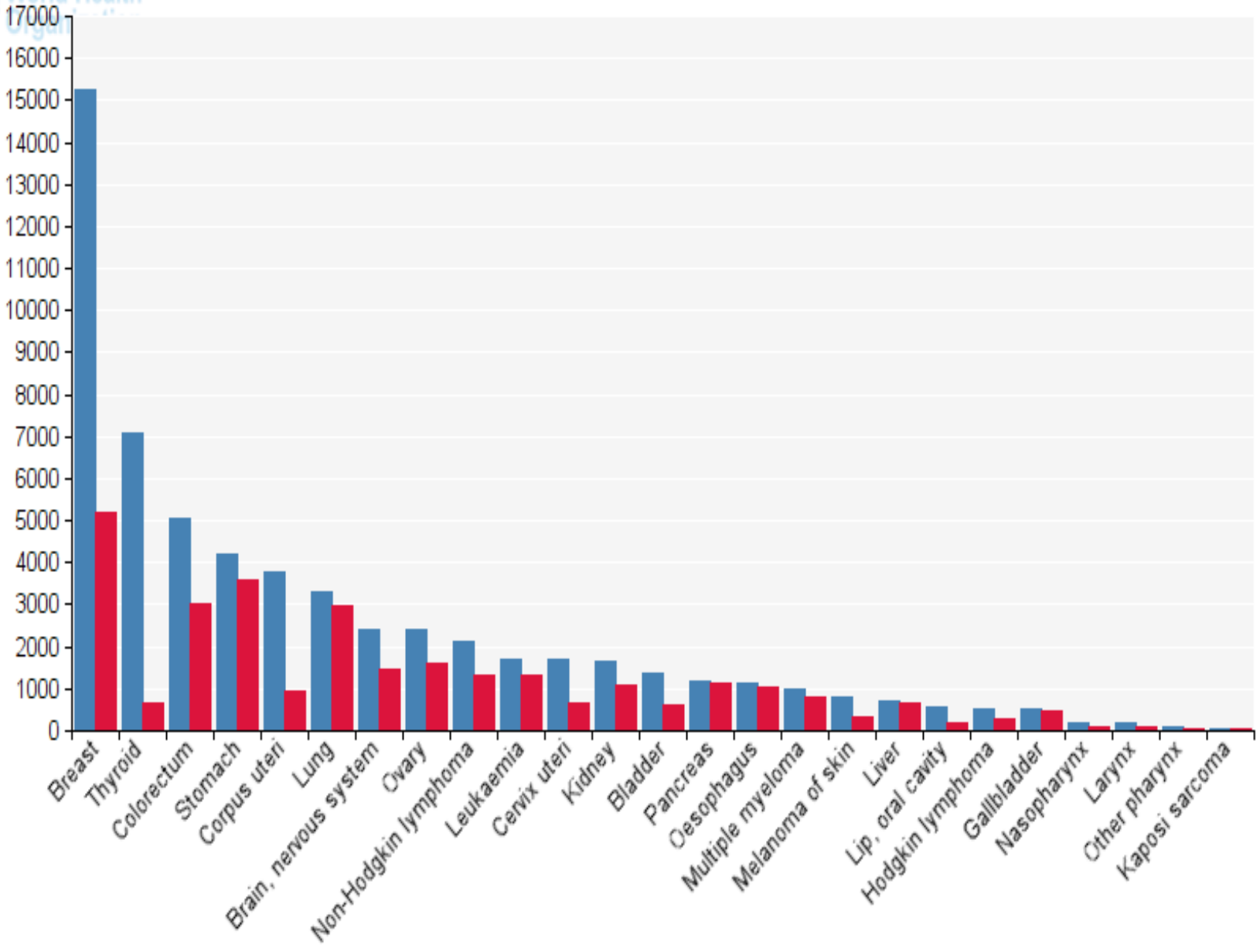
It was estimated that a family history of ovarian cancer in one relative increased the lifetime probability of ovarian cancer in a 35-year-old woman from 1.6 to 5.0 percent.

In contrast, women with hereditary ovarian cancer syndromes have a lifetime probability of ovarian cancer of 25 to 50 % .

International Agency for Research on Cancer

World Health Organization

Turkey: Female, all ages

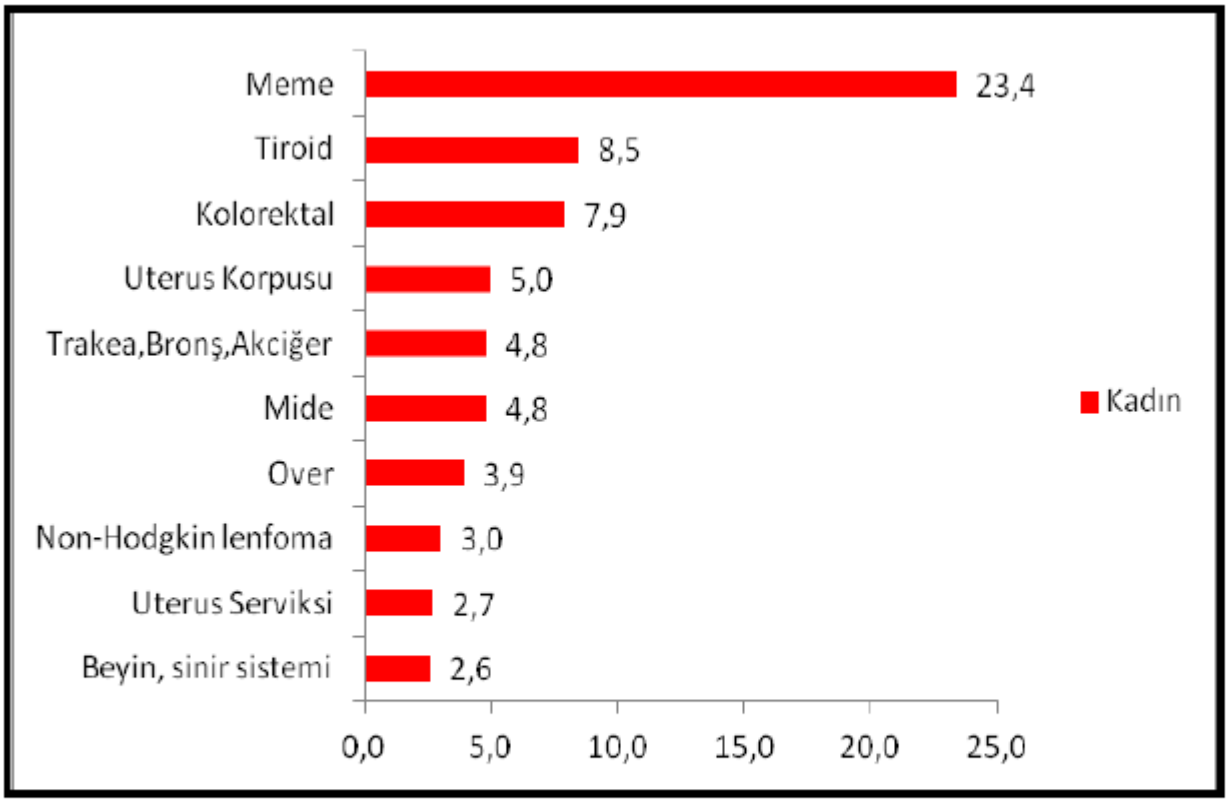


Incidence

Mortality

GLOBOCAN 2012 (IARC) (18.4.2014)

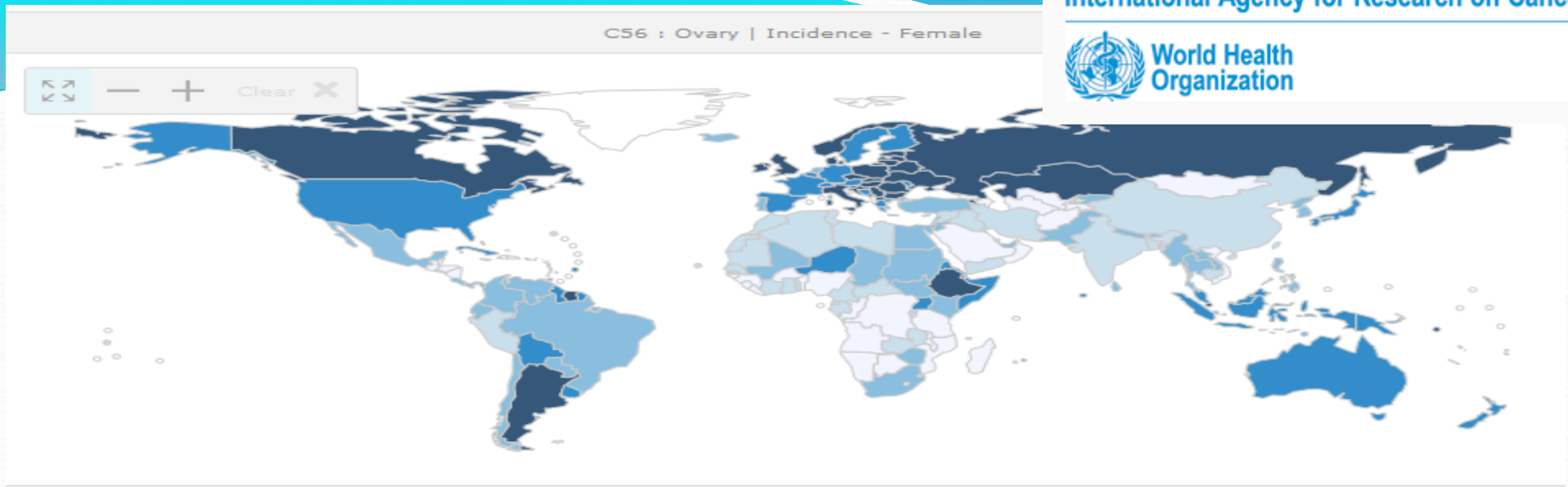
Şekil 7. Kadınlarda En Sık Görülen İlk 10 Kanserin Yaşa Göre Standardize Edilmiş Hızlarının Dağılımları (Birleşik Veri Tabanı, 2009) (Dünya Standart Nüfusu, 100.000 Kişide)

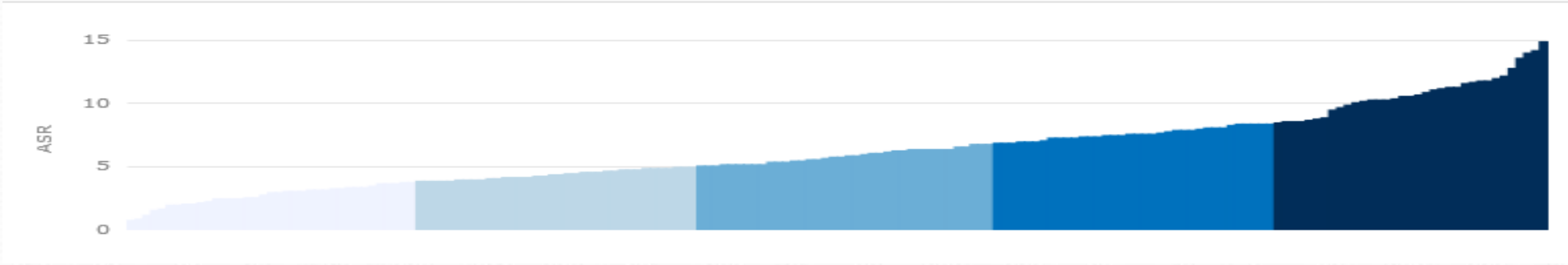


Şekil 9. Tüm Yaş Gruplarındaki Kadınlarda En Sık Görülen Bazı Kanserlerin Bu Grup İçindeki Yüzde Dağılımları (Birleşik Veri Tabanı, 2009)

International Agency for Research on Cancer

World Health Organization



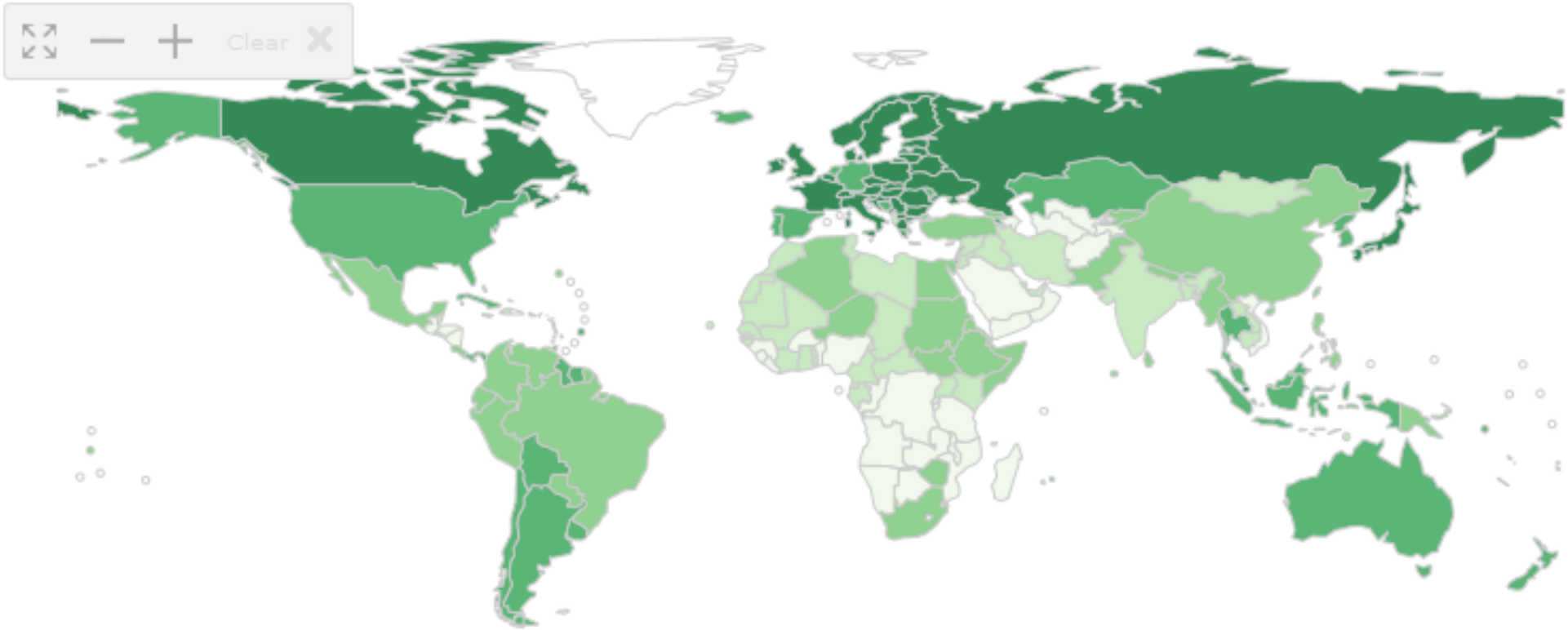


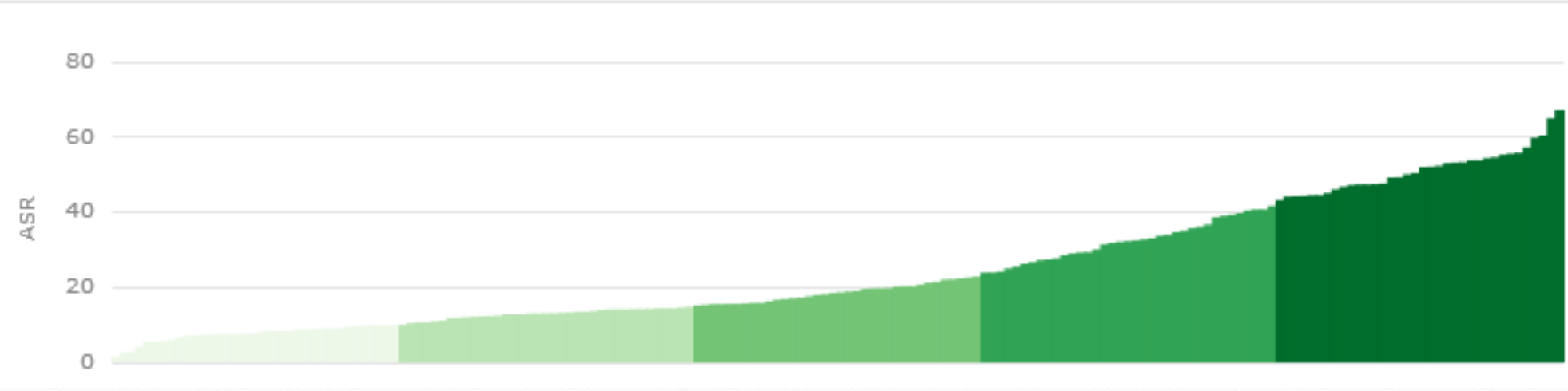
Metric	Country	Count	ASR/P	ASR comparison	
C56 : Ovary					
Incidence - Female	Turkey	2,400	6.3	0	15
Mortality - Female	Turkey	1,588	4.2	1	9.8
Prevalence (5yr) - Female	Turkey	5,816	20.8	1	67

International Agency for Research on Cancer

World Health Organization

C56 : Ovary | Prevalence (5yr) - Female



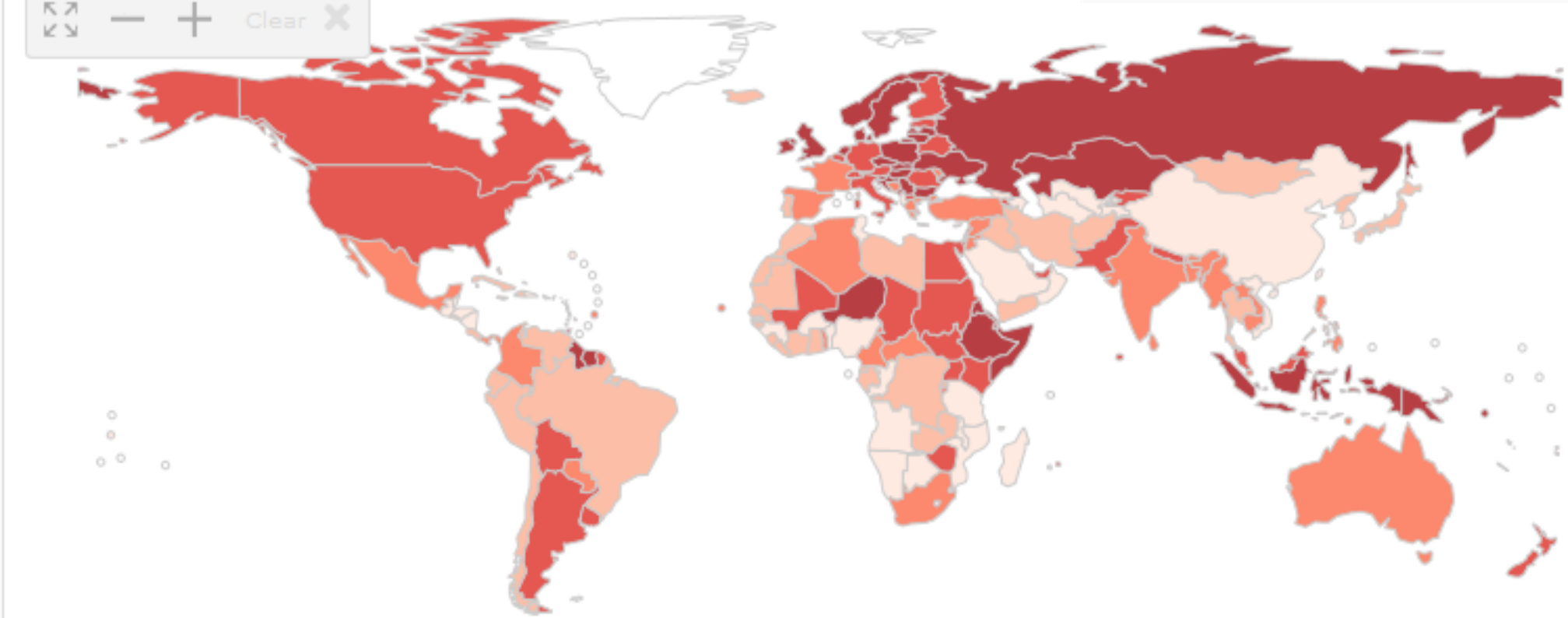


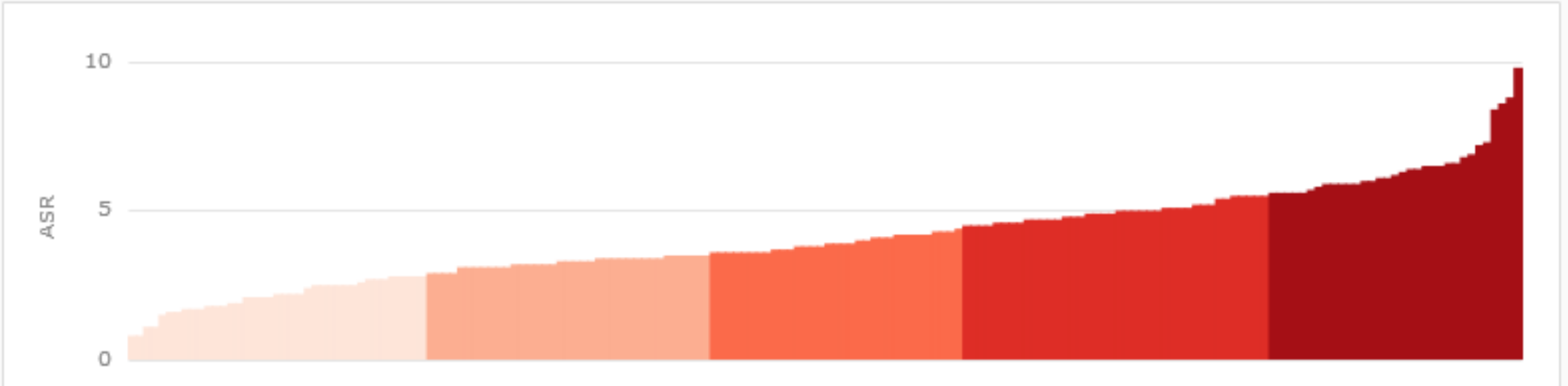
International Agency for Research on Cancer

World Health Organization

C56 : Ovary | Mortality - Female

Clear





GLOBOCAN 2012

Cancer Incidence, Mortality and Prevalence Worldwide

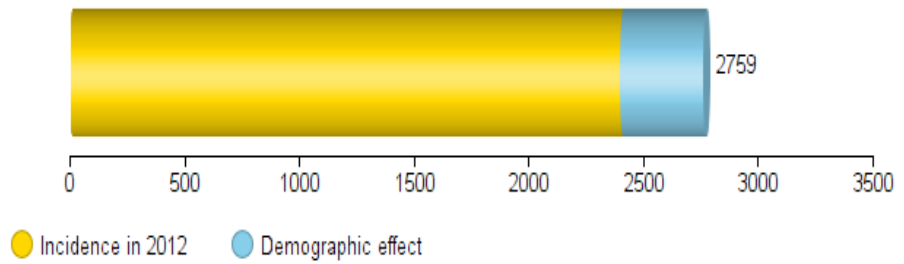
Turkey
Ovary

Year	Estimated number of new cancers (all ages)	Male	Female	Both sexes
2012		-	2400	-
	ages < 65	-	1749	-
	ages >= 65	-	651	-
2015		-	2759	-
	ages < 65	-	1901	-
	ages >= 65	-	858	-
	Demographic change	-	359	-
	ages < 65	-	152	-
	ages >= 65	-	207	-

GLOBOCAN 2012 (IARC) - 18.4.2014

Population forecasts were extracted from the *United Nations, World Population prospects, the 2012 revision.*
Numbers are computed using age-specific rates and corresponding populations for 10 age-groups.

Turkey
Ovary
Number of new cancers in 2015 (all ages)



GLOBOCAN 2012

Cancer Incidence, Mortality and Prevalence Worldwide

Turkey
Ovary

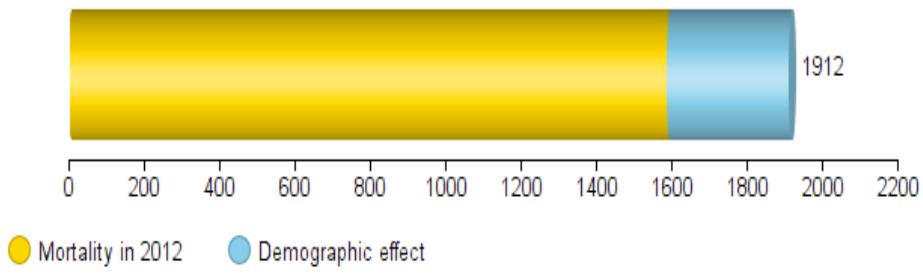
Year	Estimated number of cancer deaths (all ages)	Male	Female	Both sexes
2012		-	1588	-
	ages < 65	-	903	-
	ages >= 65	-	685	-
2015		-	1912	-
	ages < 65	-	1004	-
	ages >= 65	-	908	-
	Demographic change	-	324	-
	ages < 65	-	101	-
	ages >= 65	-	223	-

GLOBOCAN 2012 (IARC) - 18.4.2014

Population forecasts were extracted from the *United Nations, World Population prospects, the 2012 revision.*
Numbers are computed using age-specific rates and corresponding populations for 10 age-groups.

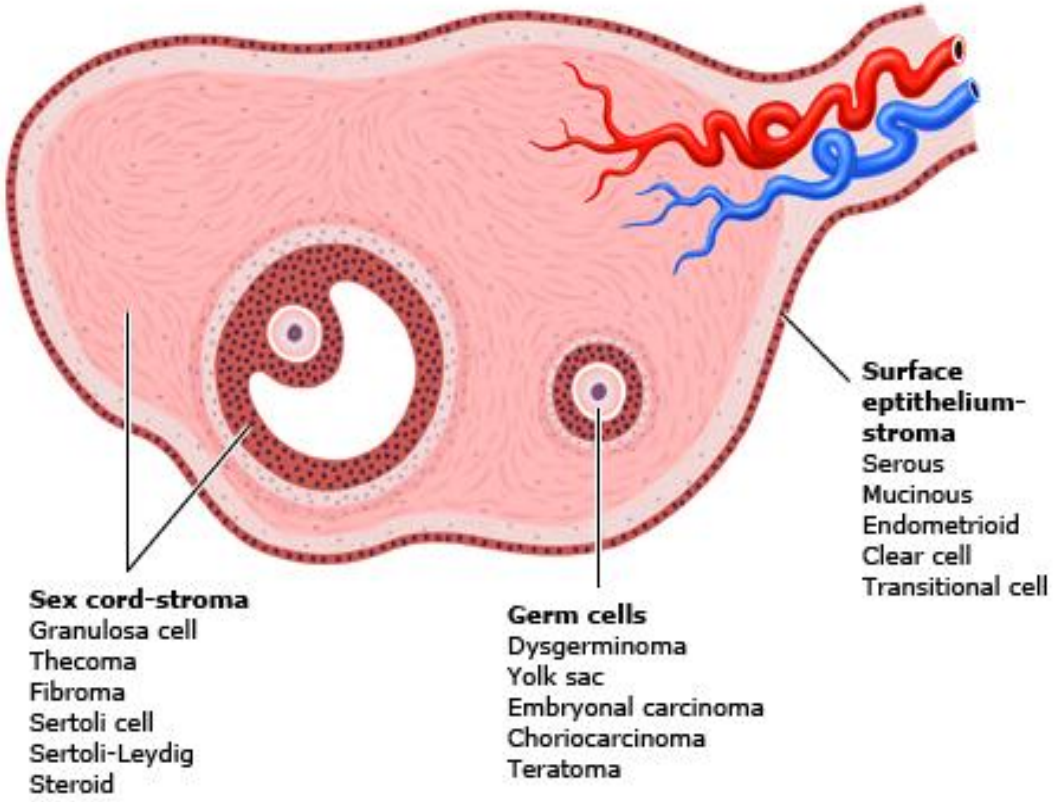
International Agency for Research on Cancer

World Health Organization



GLOBOCAN 2012 (IARC) (18.4.2014)

Origins of ovarian tumors



Some epithelial ovarian carcinomas may originate in the fallopian tube epithelium.

Ovarian cancer symptoms consensus statement

Historically, ovarian cancer was called the "silent killer" because symptoms were not thought to develop until the chance of cure was poor. However, recent studies have shown this term is untrue and that the following symptoms are much more likely to occur in women with ovarian cancer than in women in the general population. **These symptoms include**[1,2]:

- Bloating
- Pelvic or abdominal pain
- Difficulty eating or feeling full quickly
- Urinary symptoms (urgency or frequency)

Women with ovarian cancer report that symptoms are persistent and represent a change from normal for their bodies. The frequency and/or number of such symptoms are key factors in the diagnosis of ovarian cancer [3]. Several studies show that even early stage ovarian cancer can produce these symptoms[2-6].

Women who have these symptoms almost daily for more than a few weeks should see their doctor, preferably a gynecologist. Prompt medical evaluation may lead to detection at the earliest possible stage of the disease. Early stage diagnosis is associated with an improved prognosis.

Several other symptoms have been commonly reported by women with ovarian cancer[2-5]. These symptoms include fatigue, indigestion, back pain, pain with intercourse, constipation, and menstrual irregularities. However, these other symptoms are not as useful in identifying ovarian cancer because they are also found in equal frequency in women in the general population who do not have ovarian cancer[1].

Familial ovarian cancer syndromes are uncommon, accounting for 5 to 10 % of ovarian cancer cases.

These hereditary syndromes include:

- Breast-ovarian cancer syndrome (usually associated with a BRCA1 or BRCA2 mutation)

- The Lynch II syndrome (cancers of colon, breast, endometrium, and ovary with hereditary nonpolyposis colorectal cancer or HNPCC)

Women with Lynch syndrome have a lifetime risk of ovarian cancer that is 3 to 14 % (compared with 1.8 % in the general population) and develop ovarian cancer at an earlier age than the general population

Weitzel JN, et al. JAMA 2007; 297:2587.
Smith SA, et al. Gynecol Oncol 2001; 83:586.
Lynch HT et al. Am J Med 1986; 81:1073.

The breast-ovarian cancer syndrome is the most common hereditary ovarian syndrome.

Most of these families have germ-line mutations in one of the breast cancer susceptibility genes, BRCA1 or BRCA2.

In the United States, carriers of BRCA mutations are rare in the general population (1 in 300 or fewer),

Among persons of Ashkenazi Jewish descent the prevalence is estimated to be 2 %.

The absolute risk of developing ovarian cancer over a lifetime associated with the presence of a BRCA1 mutation is 35 to 45 %, while it is less for those with BRCA2 mutations (15 to 25 %)

Khoury-Collado F, Bombard AT. Hereditary breast and ovarian cancer: what the primary care physician should know. Obstet Gynecol Surv 2004; 59:537.

The risk of ovarian cancer appears to be decreased in women with a history of:

- Pregnancy
- Use of oral contraceptive pills
- Breastfeeding
- Tubal ligation or hysterectomy

The risk of ovarian cancer may be increased in patients with a history of:

- Infertility
- Endometriosis
- Perimenopausal or postmenopausal hormone therapy

Large meta-analysis and cohort studies have found that *fertility treatment does not independently increase ovarian cancer risk*.

Bristow RE,. Fertil Steril 1996; 66:499.
Brinton LA, et alObstet Gynecol 2004; 103:1194.

Risk factors for ovarian cancer

	Relative risk	Lifetime probability, percent[1]
General population	1.0	1.4[1]
BRCA1 gene mutation		35 to 46[2]
BRCA2 gene mutation		13 to 23[2]
Lynch syndrome (hereditary nonpolyposis colon cancer)		3 to 14[3]
Family history of ovarian cancer (with negative testing for a familial ovarian cancer syndrome)	Uncertain[4]	
Infertility	2.67[5]	
Polycystic ovarian syndrome	2.52[6]	
Endometriosis (increase in risk of clear cell, endometrioid, or low grade serous carcinomas)	2.04 to 3.05[7]	
Cigarette smoking (increase in risk of mucinous carcinoma)	2.1[8]	
Intrauterine device	1.76[9]	
Past use of oral contraceptives	0.73[10]	
Past breast feeding (for >12 months)	0.72[11]	
Tubal ligation	0.69[12]	
Previous pregnancy	0.6	

References:
1. *http://seer.cancer.gov/statfacts/html/ovary.html.*
2. *Chen S, Parmigiani G. J Clin Oncol 2007; 25:1329.*

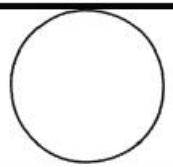
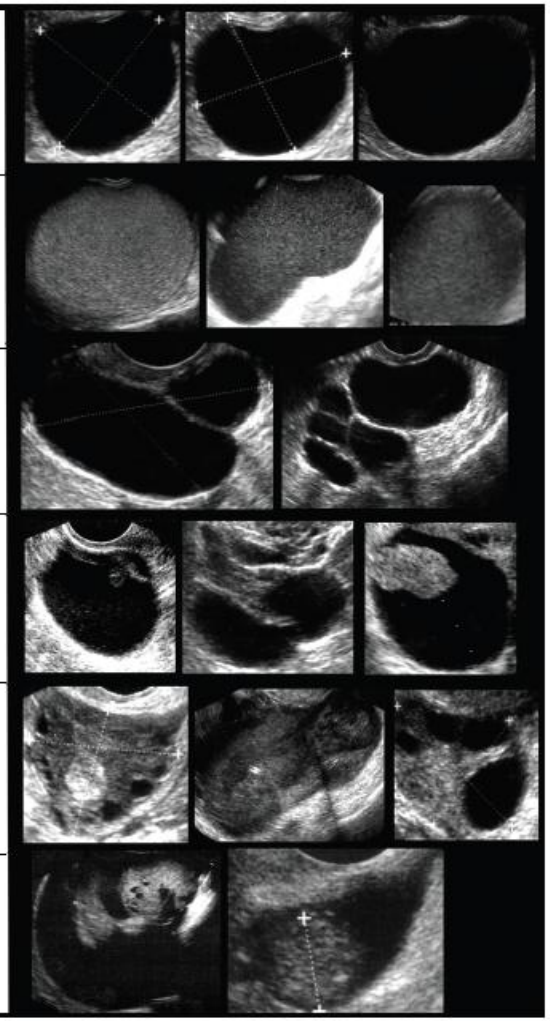
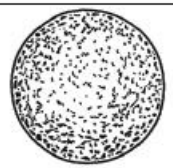
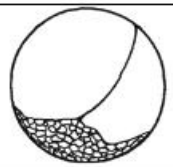
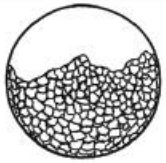
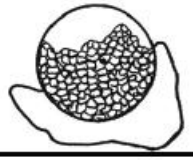
0	Benign simple cyst		
1	Benign hemorrhagic cyst		
2	Benign cyst with septation(s)		
3	Malignancy with papillary projections		
4	Malignancy with solid components		
5	Solid malignancy with ascites		

Figure 1 Sonographic images of benign and malignant ovarian morphology. Numeric representation of increasing morphologic complexity is noted in the first column.

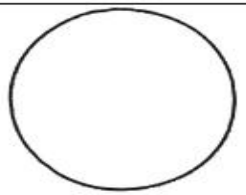
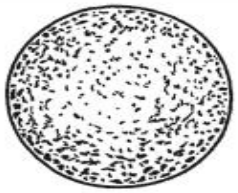
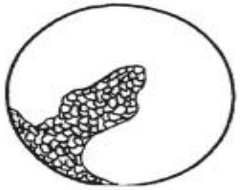
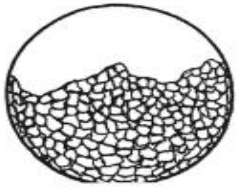
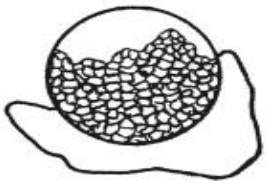
	Tumor volume	Tumor structure
0	<10 cm^3	
1	10–50 cm^3	
2	>50–100 cm^3	
3	>100–200 cm^3	
4	>200–500 cm^3	
5	>500 cm^3	

Figure 2 The University of Kentucky Ovarian Tumor Morphology Index.

Screening for Ovarian Cancer

- *There is **no evidence*** that screening for Ovarian Cancer leads to earlier detection or improved survival…
- Nonetheless, the following *have been* or *are being used*
  - TVS
  - CA125
  - Multimodal
  - Symptoms
  - Biomarkers
  - Microbubble contarst agent with TVUS
  - Radiologic Imagine studies

Cancer antigen 125 (CA 125)

Use of cancer antigen 125 (CA 125) as a biomarker for EOC was first described in 1983.

CA 125 is currently the most widely used biomarker for EOC and it is approved by the US Food and Drug Association (FDA) for monitoring response to therapy in women with known EOC.

CA 125 is often used off-label for evaluation of an adnexal mass alone or combined with other serum biomarkers and/or pelvic ultrasound

The CA 125 antigen is a large transmembrane glycoprotein derived from both coelomic (pericardium, pleura, peritoneum) and müllerian (fallopian tubal, endometrial, endocervical) epithelia .

CA 125

The normal values for the two assays are:

CA 125: ≤35 U/mL
CA 125 II: <20 U/mL

Serum CA 125 values are elevated in approximately 50 % of women with early stage disease and in over 80 % of women with advanced ovarian cancer .

However, CA 125 levels are elevated in approximately 1 % of healthy women and fluctuate during the menstrual cycle.

Nonetheless, a prospective study of asymptomatic postmenopausal women found that an elevated CA 125 concentration (≥30 U/mL) was a powerful predictor of subsequent ovarian cancer risk (RR 35.9 at one year and 14.3 at five years) .

Zuckerman E, et al Am J Gastroenterol 1999; 94:1613.
Devarbhavi H, et al. Mayo Clin Proc 2002; 77:538.
Sjövall K. Gynecol Oncol 2002; 85:175.
Johnson CC, et al. Gynecol Oncol 2008; 110:383.

Conditions associated with an elevated serum CA 125 concentration

Gynecologic malignancies
Epithelial ovarian, fallopian tube, and primary peritoneal cancers
Endometrial cancer
Benign gynecologic conditions
Benign ovarian neoplasms
Functional ovarian cysts
Endometriosis
Meig syndrome
Adenomyosis
Uterine leiomyomas
Pelvic inflammatory disease
Ovarian hyperstimulation
Pregnancy
Menstruation

Nongynecologic conditions
Cirrhosis and other liver disease
Ascites
Colitis
Diverticulitis
Appendicular abscess
Tuberculosis peritonitis
Pancreatitis
Pleural effusion
Pulmonary embolism
Pneumonia
Cystic fibrosis
Heart failure
Myocardiopathy
Myocardial infarction
Pericardial disease
Renal insufficiency
Urinary tract infection
Recent surgery
Systemic lupus erythematosus
Sarcoidosis
Nongynecologic cancers
Breast
Colon
Liver
Gallbladder
Pancreas
Lung
Hematologic malignancies

Data from:
1. *Buamah P. J Surg Oncol 2000; 75:264.*
2. *Miralles C, et. al. Ann Surg Oncol 2003; 10:150.*
3. *Moss EL, et al. J Clin Pathol 2005; 58:308.*

Other tumor markers

- **Human Epididymis Protein 4 (HE4)**

HE4 is an antigen derived from human epididymis protein, a product of the WFDC2 gene that is overexpressed in patients with serous and endometrioid ovarian carcinoma

The human epididymis protein 4 (HE4) assay was approved by the FDA in 2008

Appears to have similar sensitivity to CA 125 when comparing serum from ovarian cancer cases to healthy controls,

A higher sensitivity when comparing ovarian cancer cases to benign gynecologic disease

Assay is approved for monitoring women with ovarian cancer for disease recurrence or progression, but not for screening.

Shah CA, Lowe KA, Paley P, et al. Influence of ovarian cancer risk status on the diagnostic performance of the serum biomarkers mesothelin, HE4, and CA125. Cancer Epidemiol Biomarkers Prev 2009; 18:1365.

Biomarker panels and multimodal tests

OVA1

OVA1 is a test that includes five serum biomarkers.

It was approved by the FDA in 2009 to further assess the likelihood of malignancy in women who are planning to have surgery for an adnexal mass.

The OVA1 test incorporates five proteins

Two are up-regulated **(CA 125 II, beta 2 microglobulin)** and three down-regulated **(transferrin, transthyretin, apolipoprotein A1)**.

Premenopausal women

Low probability of malignancy: OVA1 <5.0

High probability of malignancy: OVA1 ≥5.0

Postmenopausal women

Low probability of malignancy: OVA1 <4.4

High probability of malignancy: OVA1 ≥4.4

Risk of Malignancy Algorithm (ROMA)

Includes CA 125 and HE4.

It was approved by the FDA in 2011 to further assess the likelihood of malignancy in women who are planning to have surgery for an adnexal mass.

ROMA is available internationally.

ROMA score is then reported:

Premenopausal women: High risk of malignancy ≥13.1 %

Postmenopausal women: High risk of malignancy ≥27.7 %

Menopausal status is determined by clinician report.

Risk of Malignancy Index (RMI)

Originally developed in 1990

Combines serum CA 125, pelvic ultrasound, and menopausal status

Index score to predict the risk of ovarian cancer in women with an adnexal mass .

The RMI is primarily used in the United Kingdom, and the calculation for RMI I is included in the
United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines

RMI I is a product of the ultrasound scan score (U), menopausal status (M), and serum CA 125 level (RMI I = U x M x CA 125). The NICE guidelines advise that all women with an RMI I score of ≥200 should be referred to a specialist.

SERUM BIOMARKERS

- One study evaluated **serum biomarkers using multiplex immunoassays** in 2031 healthy women

1067 women with early and late stage ovarian cancers, benign pelvic tumors, or breast, colorectal, or lung cancer .

A four-marker panel (CA 125, HE4, CEA, and VCAM-1) had the highest diagnostic power, with 86 % sensitivity for early-stage ovarian cancer at 98 % specificity.

These results, while requiring validation, suggest that combinations of biomarkers may provide improved detection as the first step in a multimodal screening protocol.

Moore RG, McMeekin DS, Brown AK, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol 2009; 112:40.

Randomized Trial for Kentucky University

The University of Kentucky Ovarian Cancer Screening Trial (UKOCS)

since 1987, and has enrolled 41,413 women.

all women over the age of 50 years and women above 25 years of age with a documented family history of ovarian cancer.

Control population of women from the same geographic area, receiving the same treatment protocols, at the same hospital, over the same time period who did not receive screening.

van Nagell JR Jr, et al. Obstet Gynecol 2011; 118:1212.

Randomized Trial for Kentucky University

In this screening trial, all women with an abnormality on TVS are evaluated and treated according to a standard protocol.

Women with an abnormal screen have a repeat screen in 4 weeks.

If the repeat screen is abnormal, a serum Ca-125 is obtained, Doppler analysis of tumor blood flow is performed, and tumor morphology indexing is completed .

An ovarian tumor is at high risk for malignancy, laparoscopic tumor removal is performed as soon as possible

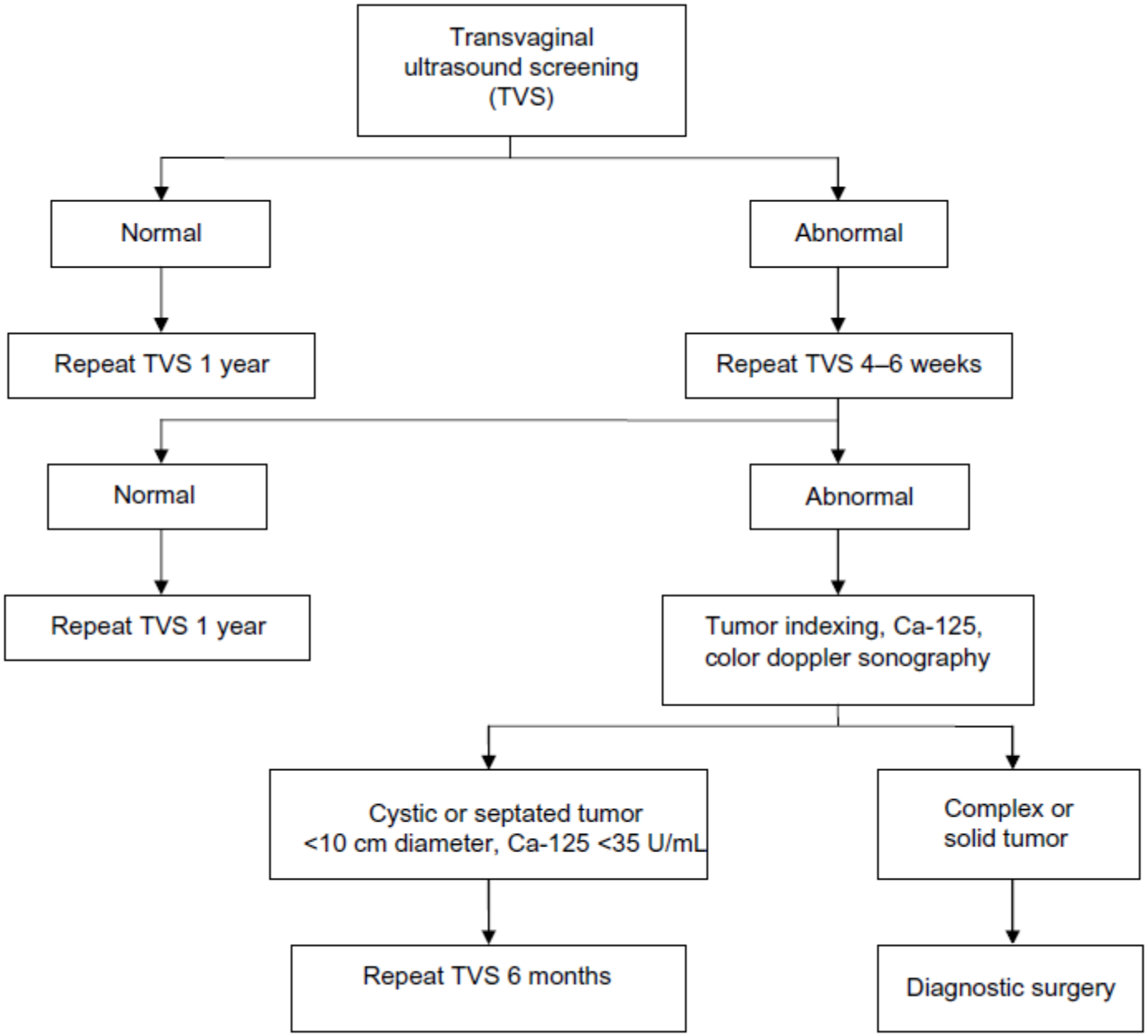


Figure 3 Evaluation algorithm for women enrolled in the University of Kentucky Ovarian Cancer Screening Trial.

Randomized Trial for Kentucky University

To date, 53 primary epithelial ovarian malignancies have been detected in the UKOCS trial

68% of which were limited to the ovary or pelvis (stage I or II disease).

Twelve women developed ovarian cancer within 12 months of a normal screen (interval cancers).

Ovarian cancers were diagnosed by screening had earlier-stage disease at detection (68% stage I or II disease) than those who did not receive screening (27% stage I or II disease, *P*,0.01).

In addition, there was a substage shift within stage III in that more women in the screening group had stage IIIA disease

Randomized Trial for Kentucky University

Specitivity for EOC; 98,5 % and PPV: 8,9 %

Number need to surgery for per ovarian cancer : 11,1

47 ovarian cancer were found with screening and 70 % of cancers were Stage 1-2.

5 year survival in ovarian cancer patients; **SCREENED WOMEN; 84,6** % , NOT SCREENED WOMEN 53,7 %

van Nagell JR Jr, et al. Obstet Gynecol 2011; 118:1212.

Multimodal screening

Three large randomized trials have evaluated combination screening with serum CA 125 and ultrasonography

One trial has reported final data and two are ongoing

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial in the United States - *Completed*

UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) Trial- *ongoing*

Japan Trial - *ongoing*

UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) Trial

The largest ongoing ovarian screening trial is the UK Collaborative Trial of Ovarian Cancer Screening (UKC-TOCS)

In this trial, a total of 202,638 postmenopausal women ages 50–74 years were randomly assigned

- no treatment (n=101,359)
- annual Ca-125 screening with TVS as a second-line test (n=50,078),
- annual screening with TVS alone (n=48,230)

An abnormal scan was defined as the presence of complex morphology in one or both ovaries,

a simple cyst 60 cm3 in volume, or ascites.

Menon U, et al. Lancet Oncol 2009; 10:327.

UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) Trial

A woman with an abnormal primary screen had a repeat ultrasound examination in 6–8 weeks,

if the repeat scan was abnormal, she was referred for clinical assessment.

Clinical assessment included a serum Ca-125, repeat TVS, Doppler studies, and computed tomography/magnetic resonance imaging scans of the abdomen and pelvis.

Of the 48,230 women who underwent ultrasound alone 2,774 (5.7%) were classified as abnormal and had a repeat scan.

There was a persisting ovarian abnormality on the repeat scan in 1,824 women.

Menon U, et al. Lancet Oncol 2009; 10:327.

UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) Trial

These women then underwent clinical assessment, and 845 (1.8%) had surgery.

42 of these women had malignant neoplasms of the ovary, 23 of which were borderline tumors.

The ratio of surgeries to screen detected cancers in the ultrasound-alone arm of this trial was 18.8 to 1.

50 % of primary invasive ovarian or tubal malignancies detected by ultrasound screening alone had stage I or II disease versus 26% in the control cases detected clinically,

Screening produced a significant increase in the detection of early stage ovarian malignancy.

Menon U, et al. Lancet Oncol 2009; 10:327.

UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) Trial

In the multimodality-screening arm of this trial, ultrasound was performed only in women whose Ca-125 values placed them in an intermediate or high risk for ovarian cancer.

Of the 50,078 women in the multimodality-screening arm,

409 (0.8%) had TVS, and 97 underwent surgery after clinical assessment.

34 patients had ovarian cancer, 16 of whom (47%) had stage I or II disease.

The ratio of surgeries to screen-detected cancers in this arm of the trial was 2.8 to 1.

The UKC-TOCS trial is ongoing, and the effect of screening on ovarian cancer mortality will be published after data analysis is complete.

Menon U, et al. Lancet Oncol 2009; 10:327.

UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

The sensitivity, specificity, and PPV were 89.4, 99.8, and 43.3 % respectively for all primary ovarian and tubal cancers and 89.5, 99.8, and 35.1 % for primary invasive cancer.

Additional testing was required in 8.7 % (4355) of the MMS participants and surgery was performed in 0.2 % (97).

Specificity was **significantly greater** for MMS compared to TVUS.

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO)

78,216 women aged 55–74 years

annual screening with TVS and serum Ca-125 for 4 years or their usual gynecologic care

considered abnormal included:

an ovarian cyst volume .10 cm3,

any solid area or papillary projection extending into the cavity of a cystic ovarian tumor of any size,

any mixed (solid and cystic) component within a cystic ovarian tumor.

Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 2011; 305:2295.

●Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO)

Evaluated cancer mortality as the primary outcome in 68,557 postmenopausal women (aged 55 to 74 years)

Screening with both CA 125 and transvaginal ultrasound

Secondary outcomes were incidence of ovarian cancer, cancer stage at diagnosis, complications from screening, and all-cause mortality.

At baseline the prevalence (initial) screening of 28,816 women found 1740 with either an abnormal CA 125 or ultrasound, and 34 had both .

Nearly one in three women who had a positive screening test underwent surgery .

Among 570 women who had surgery, 29 tumors were found, of which 20 were invasive (90 % of these stage III or IV).

Buys SS, et al. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. Am J Obstet Gynecol 2005; 193:1630.

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO)

Women in the intervention group received annual screening with CA 125 for six years and transvaginal ultrasound for four years.

Positive screening rates for CA 125 ranged from 1.4 to 1.8 % during the six rounds from 2.9 to 4.6 % during the four ultrasound rounds.

Ovarian cancer was detected in 212 women (5.7 per 10,000 person-years) in the screening group 176 women (4.7 per 10,000 person-years) in the usual care group.

Buys SS, et al. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. Am J Obstet Gynecol 2005; 193:1630.

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO)

17 ovarian tumors of low malignant potential were detected

71 % of women whose ovarian cancers were detected by TVS alone

stage I or II disease, but the PPV of TVS varied from only 0.7% to 1.6% for each year of the trial,

the ratio of surgeries to screen-detected ovarian cancers was 19.5 to 1.

There was no evidence of a shift to earlier stage disease associated with screening in this trial,

survival rates were similar in the screening and usual-care arms.

Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 2011; 305:2295.

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO)

There was **no difference** in the stage of ovarian cancer, with advanced disease (stage III or IV) in 77 %of the cancers in the intervention group and 78 % in the usual care group.

Both the incidence of ovarian cancer and the mortality rate were **nonsignificant between groups** (RR 1.21, 95% CI 0.99-1.48 and 1.18, CI 0.91-1.54, respectively).

Excluding deaths from ovarian, colorectal, and lung cancer, **all-cause mortality was similar in both groups** (2924 intervention deaths and 2914 control deaths).

Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 2011; 305:2295.

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO)

False-positive results were found in 3285 women and 1080 underwent surgical follow-up.

15 % of women who had surgery for a false-positive finding

experienced at least **one serious complication**.

Thus, screening **did not reduce mortality**,

and there was evidence that false-positive findings led to some harm.

In addition, more cancers were diagnosed in the intervention group (212) than the usual care group (176), raising the possibility of overdiagnosis.

Buys SS, et al. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. Am J Obstet Gynecol 2005; 193:1630.

JAPAN STUDY

The multicenter ovarian cancer screening trial in Japan

28 prospective randomized trial conducted between 1985 and 1999 in which asymptomatic postmenopausal women

Women in the screening arm received an annual pelvic examination, an annual pelvic ultrasound, and a serum Ca-125.

JAPAN STUDY

In a randomized controlled trial

83,000 postmenopausal women in Japan,

42,000 women were invited to participate in annual screening with pelvic ultrasound and CA 125 .

There was no significant difference in the detection of ovarian cancer, at an average follow-up of 9.2 years, between patients who received screening (27 cases) and control patients (32 cases).

There was a **non-significant** trend toward earlier-stage disease in the screened group.

Thirty-three surgeries were performed to detect each case of ovarian cancer.

Kobayashi H, Yamada Y, Sado T, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int J Gynecol Cancer 2008; 18:414.

JAPAN STUDY

Ultrasound findings were classified .,

1) normal ovary, largest diameter ,4 cm with normal morphology,

2) benign impression, ovarian length 4 cm with simple morphology,

3) malignant impression, ovarian length 4 cm with complex morphology.

A total of 103 patients thought to be at high risk for ovarian cancer on the basis of ultrasound findings

64 underwent surgery.

JAPAN STUDY

20 patients were found to have primary ovarian cancer, and 10 had metastatic disease to the ovary.

63% of ovarian cancer patients detected by screening had stage I disease versus 38% in the control arm.

optimal tumor debulking was achieved more frequently in women whose ovarian cancer was detected by screening.

Assessment of the long-term effect of screening on ovarian cancer mortality is presently in progress.

Table 2 Ovarian cancer screening trials utilizing transvaginal sonography

Screening trial	Years	Control group	Study design	Screening test(s)	Number screened/ detected	Invasive cancers	Stages I and II	Stages III and IV	Stage shift	Survival benefit
PLCO (USA)[26]	1993–2001	(+)	Randomized control	Ultrasound Ca-125	34,253	212	47 (22%)	163 (77%)	(–)	(–)
UKC-TOCS (UK)[27]	2001–2005	(+)	Randomized control	Ultrasound Ca-125	50,078	34	47%	53%	(+)	Analysis pending
				Ultrasound alone	48,230	24	50%	50%	(+)	Analysis pending
Multicenter (Japan)[28]	1985–1999	(+)	Randomized control	Ultrasound Ca-125	41,688	27	67%	33%	(+)	Analysis pending
University of Kentucky (USA)[29]	1987–2013	(+)	Population control	Ultrasound	41,413	53	68%	32%	(+)	(+)

Abbreviations: PLCO, Prostate, Lung, Colorectal and Ovarian; UKC-TOCS, UK Collaborative Trial of Ovarian Cancer Screening.

High-risk women

Randomized trials of screening for women with a familial ovarian cancer syndrome are not likely to be performed, clinicians, would not accept assignment to a no screening arm.

Therefore, prospective cohort studies provide the available data regarding the impact of screening for this population.

Risk assessment criteria for inherited breast-ovarian ovarian cancer syndome, combining several guidelines

Non-Jewish families
Any of the following:
One case of breast cancer ≤40 yo in a FDR or SDR*
One FDR or SDR with breast and ovarian cancer, at any age
Two or more cases of breast cancer in FDRs or SDRs if one is diagnosed at ≤50 years old, or is bilateral
One FDR or SDR with breast cancer at ≤50 years old, or bilateral and one FDR or SDR with ovarian cancer
Three cases of breast and ovarian cancer (at least one case of ovarian cancer) in FDRs and SDRs
Two cases of ovarian cancer in FDRs and SDRs
One case of male breast cancer in an FDR or SDR if another FDR or SDR has (male or female) breast or ovarian cancer
Jewish families
Any of the following:
One or more cases of breast cancer ≤50 years old in an FDR or SDR
One or more cases of ovarian cancer at any age in a FDR or SDR
One or more FDRs or SDRs with breast cancer at any age, if another FDR or SDR has breast and/or ovarian cancer at any age
One or more cases of male breast cancer in an FDR or SDR

* FDR: first-degree relative; SDR: second-degree relative.

Adapted from: Hampel H, et al. J Med Genet 2004; 41:81.

●United Kingdom Familial Ovarian Cancer Screen Study (UK FOCSS),

Largest cohort study

3563 women with a familial ovarian cancer syndrome (estimated minimum lifetime risk of 10 %) who had declined or deferred risk reducing salpingo-oophorectomy (RRSO),

participants were screened annually for a mean of 3.2 years with a combination of transvaginal ultrasound and CA-125 .

The reported sensitivity for the detection of incident ovarian cancer/fallopian tube cancer was 81.0 to 87.5 %,

Depending on whether occult cancers detected at the time of RRSO (end of the study period) were classified as false negative or true positive.

The positive predictive value of incident screening was **25.5 %,** which exceeds the threshold of 10 % considered **necessary for ovarian cancer screening.**

Four women underwent surgery for each case of detected cancer.

Rosenthal AN, Fraser L, Manchanda R, et al. Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. J Clin Oncol 2013; 31:49.

United Kingdom Familial Ovarian Cancer Screen Study (UK FOCSS)

Additionally, the Risk of Ovarian Cancer algorithm used in the UKCTOCS will be incorporated into the next phase of this study for determining and following up abnormal results.

Although RRSO remains the only reliable method of decreasing mortality from ovarian cancer in this high-risk population,

This study suggests that screening may have the potential to somewhat reduce risk for women who wish to maintain their childbearing potential until they are ready to undergo surgery.

PLCO trial results for high-risk women .

Women who underwent screening (n = 28,460) were stratified for risk by personal and family history:

average risk (no history breast or ovarian cancer),

moderate risk (one first-degree relative with breast cancer),

high risk (family history of ovarian cancer, ≥ two relatives with breast cancer, or personal history of breast cancer).

After three post-baseline screening exams, the positive predictive value for abnormal screening results was 2.8 % in the highest-risk group.

Lack of clear benefit from intensive surveillance programs in women at high risk due to genetic predisposition

Experts to advocate other interventions to reduce risk in this population, including use of the **oral contraceptive pill** and **prophylactic salpingo-oophorectomy.**

High-risk family history

Women who are found to have BRCA1 and/or BRCA2 mutations and/or Lynch syndrome **should discuss risk-reducing surgery,**

Protocols in clinical use for surveillance of such women include combinations of

pelvic examinations,
CA 125 and other tumor marker measurements,
vaginal ultrasonography,
color Doppler imaging.

Even though evidence for screening effectiveness has not been demonstrated, the **decision to screen** this patient population is based on their **very high lifetime risk** of ovarian cancer.

High-risk family history

The optimal screening protocol, or frequency for screening, has not been determined.

In the absence of randomized trials,

American College of Obstetricians and Gynecologists (ACOG)

National Comprehensive Cancer Network (NCCN)

recommend screening women with BRCA mutations,

starting at age 30 to 35 years or 5 to 10 years before the earliest diagnosis in a family member, using a combination of serum CA 125 and transvaginal ultrasound every 6 to 12 months

www.cancer.gov/cancertopics/pdq/screening/ovarian/healthprofessional/allpages (Accessed on August 24, 2009).
American College of Obstetricians and Gynecologists, ACOG Committee on Practice Bulletins--Gynecology, ACOG Committee on Genetics, Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. Obstet Gynecol 2009; 113:957.
National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology.
http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (Accessed on April 01, 2014).
www.ahrq/gov/clinic/3rduspstf/ovariancan/ovcanrs.htm (Accessed on August 24, 2009).
http://www.uspreventiveservicestaskforce.org/uspstf12/ovarian/ovarartaddend.htm (Accessed on June 26, 2012).
Moyer VA, U.S. Preventive Services Task Force. Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med 2012; 157:900

RECOMMENDATIONS

North American expert groups
US Preventive Services Task Force (USPSTF)
The Society of Gynecologic Oncology (SGO)
American College of Obstetricians and Gynecologists (ACOG)
Canadian Task Force on the Periodic Health Examination

NO routine screening for ovarian cancer in asymptomatic women.

Hereditary ovarian cancer syndromes;

SGO and the National Comprehensive Cancer Network (NCCN) recommend screening

every six months with CA 125 and TVUS beginning between the ages of 30 and 35 years

OR 5 to 10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family

The National Cancer Institute (NCI); there is not sufficient evidence to support screening for ovarian cancer in any population, including women at increased risk