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Screening for Ovarian Cancer in Women

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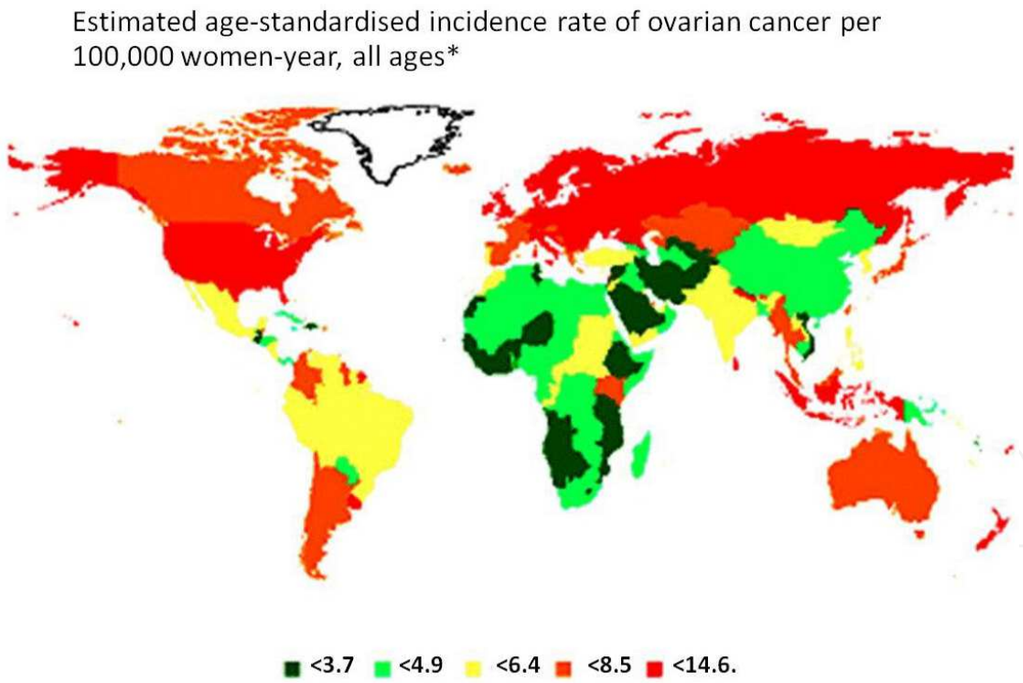
1. Introduction

Of all the gynecologic cancers, ovarian malignancy represents the greatest clinical challenge because it is difficult for early detection, difficult to cure, and it has the highest fatality to case ratio of all the gynecologic malignancies. Many studies have been tried to find a novel strategy on early detection of ovarian cancer. Ultimately, successful screening in asymptomatic women could increase cure rate and prolong survival among patients who have to live with ovarian cancer.



*Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM.
GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet].
Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr, accessed on day/month/year.

Fig. 1. Estimated age-standardised incidence rate per 100,000 women-year of ovarian cancer, all ages.

2. Epidemiology and impact

Higher than two hundred thousand women were diagnosed ovarian cancer in 2008 worldwide(Ferlay, Shin et al. 2010). As a result, more than one hundred and forty thousand women accounting for more than fifty percent fatality to case ratio died in this year. Major incidences are in Northern America and Europe. In Asia, higher trend of incidence grows significantly. Unfortunately, ovarian cancer remains mysterious for early detection and cure. Morbidity and mortality from ovarian cancer have been major burdens from the past to the present.

Region	**Ovarian cancer**		**Cervical cancer**		**Uterine cancer**	
	New cases	Death	New cases	Death	New cases	Death
World*	224,747	140,163	530,232	275,008	288,387	73,854
US**	21,990	15,460	12,710	4,290	46,470	8,120
Thailand***	1,384	-	6,954	-	745	-

*Ferlay, Shin et al. 2010
**American Cancer Society. Cancer Facts & Figures 2011. Atlanta: American Cancer Society; 2011.
***Attasara P, Srivatanakul, P, Sriplung, H. cancer incidence in Thailand. In: Khuhaprema T, Srivatanakul P, Attasara P, Sriplung H, Wiangnon S, Sumitsawan Y, editor. Cancer in Thailand 2001-2003 vol.V. 1st ed. Bangkok: Bangkok Medical Publisher. 2010: 3-76.

Table 1. Number of new cases and deaths from ovarian, cervical and uterine cancer in a year.

2.1 The incidence and prevalence of ovarian cancer including the stage distribution

World age-specific incidence rate of ovarian cancer was 6.3 per 100,000 women with a cumulative risk 0-74 year-old of 0.7 in 2008 (Ferlay, Shin et al. 2010). It does not seem to significant lower from the year 2002. The distant and regional stage distributions are higher than localized ovarian cancer in both developed and developing countries as shown in table 2. Overall five year survival rate in the SEER database is 45.9%(SEER).

Ovarian cancer distribution	**US***		**Thailand****	
	Percent of cases	5 year survival (%)	Percent of cases	5 year survival (%)
Localized	15	94	26	90
Regional	23	73	39	80
Distant	62	28	35	15-25

* American Cancer Society. Cancer Facts & Figures 2011. Atlanta: American Cancer Society; 2011.
**modified from Wilailak S. Epidemiologic report of gynecologic cancer in Thailand. J Gynecol Oncol. 2009;20: 81–83.

Table 2. The ovarian cancer distribution and percent of five-year survival.

2.2 The sequelae and impact of ovarian cancer

Eventually, ovarian cancer impacts on patients' survival and their quality of life. Suffering from gut obstruction and malnutrition, renal failure, liver failure, respiratory failure, severe chronic pain, infection and sepsis are expected during lifetime and at the end of life in women diagnosed with ovarian cancer. Impacts of ovarian cancer are direct from cancer and metastases and indirect from treatments and complications.

Direct sequelae from cancer and metastases

- Primary tumor: intractable pain
- Secondary tumor: Brain, Bone, Lung, Liver, KUB system, GI system, lymph nodes

Indirect sequelae from treatments and complications.

- Surgery: hemorrhage, internal organ injury, gut obstruction.
- Chemotherapy: Leukopenia, thrombocytopenia, sepsis, renal failure, cardiotoxicity, hypersensitivity reaction
- Molecular therapy: hypertension, bowel perforation.

3. Challenges of ovarian cancer

Challenges toward early ovarian cancer diagnosis could increase cure rate, prolong survival and delay suffering from cancer and decreased interventive complications.

3.1 Pre-Cancer lesion has not yet been identified

Ovarian cancer pathogenesis has been hypothesized, but it and also pre-cancerous lesion have not yet been identified.

3.2 Most cases are diagnosed in advanced stage

Asymptomatic women with intra-abdominal concealing of ovarian cancer are most likely having late ovarian cancer diagnosis. Eighty-five percent of patients with ovarian cancer are diagnosed when the cancer cells already metastases out of the ovary to the whole abdomen. Survival and prognosis directly relate to extent of disease. Asymptomatic or nonspecific symptoms always found in women with early ovarian cancer.

3.3 Symptoms are non-specific

Ninety percent of patients with ovarian cancer had non-specific symptoms which mostly were misdiagnosed and delayed proper treatments for some periods.

3.4 Difficulty in palpation by either patients or physicians

Women could not feel abdominal mass or even any abnormalities before the mass enlarged to beyond her pubic symphysis. Physicians could palpate any mass of ovarian cancer during pelvic examination.

3.5 Result of the treatment is poor in advanced stage

Contemporary standard primary treatment is surgery and adjuvant combined chemotherapy for early stages cancer. In advanced cancer, initially exploratory laparotomy with biopsy followed by palliative chemotherapy and/or secondary cytoreductive surgery or neo-adjuvant chemotherapy followed by primary cytoreductive surgery is decided depending on individualized patient. The most reliable prognosis depends on the residual tumor after every attempted surgery.

3.6 The present tumor markers are non-specific

Tumor markers are non-specific. Currently, CA125 is widely used as the most promising tool along with contemporary standard primary treatment. CA125 is a tumor-associated antigen which is detected in 80-85 percent of epithelial ovarian cancer. Only fifty percent of patients with FIGO stage I and 60% of patients with FIGO stage II has shown an increased CA125 level. Moreover, CA125 test has low specificity among women with reproductive age, pregnancy and benign diseases including myoma uteri, endometriosis, and pelvic infection. Data suggest that combined CA125 and transvaginal ultrasonography improved specificity for ovarian cancer screening.

4. Screening target population

Currently, there are no effective screening methods that could decrease mortality from ovarian cancer. They are evidences for ovarian cancer screening in both general and high risk population.

4.1 General population

Mass screening in asymptomatic and general risk population seems to be ineffective and associated with increased rates of surgery and patient anxiety(Fung, Bryson et al. 2004). Two large studies in Europe and Northern America (Menon, Gentry-Maharaj et al. 2009; Buys, Partridge et al. 2011) have shown currently data. The prostate, lung, colorectal and ovarian (PLCO) cancer screening randomized controlled trial was conducted in the United States. Asymptomatic women aged 55-74 years who had no previous diagnosis of lung, colorectal or ovarian cancer were recruited between 1993-2001. Thirty-nine thousand one hundred and five participants received annual screening with transvaginal ultrasounds for four years and CA125 blood tests for six years. On comparison, Thirty-nine thousand one hundred and eleven participants received usual medical care. The positive predictive value was only 23.5%. Sixty percent of invasive cancers would not have been detected by the screening. Only 21 percent of the participants, who were detected cancer by the screening, were stage I/II. It was shown that women who were screened for ovarian cancer with annual transvaginal ultrasound and CA125 blood test had not reduced ovarian cancer mortality. In addition, the screening increased invasive medical procedures and associated harms (Buys, Partridge et al. 2011).

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) was studied between 2001-2005 (Menon, Gentry-Maharaj et al. 2009). Post-menopausal women aged 50—74 years were randomly assigned to no treatment (control; n=101 359); annual CA125 screening with transvaginal ultrasound scan as a second-line test (multimodal screening [MMS]; n=50 640); or annual screening with transvaginal ultrasound (USS; n=50 639) alone in a 2:1:1 ratio (Menon, Gentry-Maharaj et al. 2009).

Forty-two women with the annual CA125 screening and transvaginal ultrasound scan and 45 women with annual transvaginal ultrasound were detected primary ovarian and tubal cancers including 28 borderline tumors (eight MMS, 20 USS). 28 (16 MMS, 12 USS) of 58 (48·3%) of the invasive cancers were stage I/II, with no difference in stage distribution between the groups. For primary invasive epithelial ovarian and tubal cancers, the sensitivity, specificity, and positive-predictive values were 89·5%, 99·8%, and 35·1% for MMS, and 75·0%, 98·2%, and 2·8% for USS, respectively. Specificity was higher in the annual CA125 screening with transvaginal ultrasound scan than in the annual screening with transvaginal ultrasound alone group, resulting in lower rates of repeat testing and

surgery. The screening strategies might be feasible. However, the results of ongoing screening are awaited to determine the effect of the screening on mortality from ovarian cancer (Menon, Gentry-Maharaj et al. 2009).

4.2 Increased-risk population

Prevalence of ovarian cancer is higher in high risk population. Positive family history of specific cancers, menopause and having adnexal mass are higher probabilities for ovarian cancer. Screening benefits should be more pronounced and encourage. In addition, screening by gynecologic oncologists is feasible and cost effective.

4.2.1 Menopause

Senescence is significantly caused genetic aberration inducing cancer. Postmenopause are high risk for ovarian cancer (Hensley, Robson et al. 2003).

4.2.2 Positive family history

Women with certain family histories have higher risks of ovarian cancer than general population. Ten percent of women with epithelial ovarian cancer have mutations in the BRCA1 and BRCA2 genes with located on chromosome 17 and 13 respectively. Lynch II syndrome is a less common genetic cause of ovarian cancer and endometrial cancer, which is known as the hereditary nonpolyposis colorectal cancer syndrome (HNPCC syndrome). There is a very limited benefit, of screening even in high-risk women with BRCA1 and BRCA2 mutation carriers (Hermsen, Olivier et al. 2007; Woodward, Sleightholme et al. 2007). In addition, annual gynecological screening is unlikely to reduce mortality in women with BRCA1 and BRCA2 mutation carriers (Hogg and Friedlander 2004; Hermsen, Olivier et al. 2007).

4.2.3 Having adnexal mass

Malignant ovarian masses are pathological diagnosed. Occasionally, it is possible to differentiate benign from malignant tumors on the basis of history and physical examination findings.

5. General characteristics of a good cancer screening

Screening for ovarian cancer is a method for secondary prevention by early detection followed with definite treatment. Efficacy screening depends on 5 factors including incidence of disease, effective early treatment, available cost effectiveness method and adequate population target. Impact of ovarian cancer burden and surgically and adjuvant chemotherapeutic effective early treatments are significantly propagated the development of a good ovarian cancer screening. There are general characteristics to consider.

a. High sensitivity, specificity and predictive value

Accuracy for screening is necessary. Ideally, a good cancer screening for ovarian cancer could decrease mortality rate significantly. As this result, it could detect ovarian cancer among women who have the cancer. It could discrete non-ovarian cancer women among truly non-ovarian cancer women. Moreover, the test should be accurate on the results of the tests, it means that truly non-ovarian cancer women would be among negative tests' women and truly asymptomatic women with ovarian cancer would be among positive tests' women. More than 75 percent sensitivity and more than 99 percent specificity of the most effective test is required

to achieve a positive predictive value of 10 percent(Moore, MacLaughlan et al. 2010). These mean ten operations of each case of ovarian cancer detected.

b. Safe

Safety set as a priority for mass screening in asymptomatic women.

c. Simple

Simple method screening which is easy and noninvasive is suitable to coverage the target population.

d. Inexpensive

Cost of the screening should be paid on attention other than its effectiveness. Cost could be one of the obstacles to be refused and ignore from the target population.

6. The aim of ovarian cancer screening is an attempt to detect early-stage asymptomatic individuals

6.1 Tools for ovarian cancer screening

Beyond pelvic examination, various tools are proposed including tumor markers, ultrasonography and abdominal imaging.

6.2 Tumor markers

The most extensively evaluated and available tumor marker currently is Cancer Antigen 125 (CA125). It has been firstly introduced as OC125 since 1981(Bast, Feeney et al. 1981). Up to eighty percent of patients with advanced epithelial ovarian cancer had high CA125 levels during diagnosis. However, only 50 percent of patients at early staged ovarian cancer were found higher levels than serum thresholds. Low specificity and variable levels of CA125 resulted in low accurate for screening. Many benign gynecologic and medical conditions compromised the specificity. However, CA125 remains valuable for follow up in women with epithelial ovarian cancer who have ever had high CA125 level.

6.3 Imaging

6.3.1 Ultrasonography

Utrasonographic results could discriminate patients with ovarian malignancy including bilaterality, large cystic structure, any solid lesions (as shown in picture 1), and papillary vegetation on the cyst wall or ascites. Accuracy of ultrasonography is still low for detecting ovarian cancer.

6.3.2 Computerized tomography (CT), Magnetic resonance imaging (MRI)

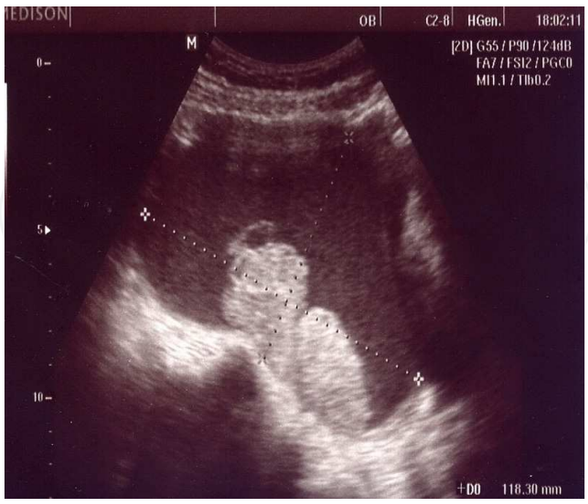
High false positive rate for detecting ovarian cancer using imaging technology have been reports. Individualized patients who should have benefits from the imaging should be judged by their physicians.

7. Single modality of screening or multiple modalities

7.1 Single/multiple tumor markers

Various types of tumor markers have been study both early staged and late staged of ovarian cancer (Table 3)(Rein, Gupta et al. 2011). High serum levels of HE4, Osteopontin, Mesothelin, B7-H4, Prostatin and VEGF were found in both early staged and late staged

ovarian cancer. A number of tumor markers were detected only in late staged of cancer as shown in table 3.



Picture 1. Transabdominal ultrasonography of 44 year-old, single woman with palpable pelvic mass has shown mixed solid cystic mass sized 11.8 cm. Postoperative pathologic diagnosed clear cell adenocarcinoma of ovary, FIGO stage IC.

Tumor markers*	
Early staged	Advanced and late-staged
HE4	HE4
Osteopontin	Osteopontin
Mesothelin	Mesothelin
B7-H4	B7-H4
Prostasin	Prostasin
VEGF	VEGF
IGFBP-3	IGFBP-3
RASSF1A	RASSF1A
BRCA1	BRCA1
LPA	LPA
IL-6, IL-8	Haptoglobin
Eosinophil-derived neurotoxin and COOH-osteopontin fragments	M-CSF
OVX1	Sat2-Chr1, Satα
APOA1 and transthyretin	MCJ
	P53

*modified from Rein BJ, Gupta S, Dada R, Safi J, Michener C, Agarwal A. Potential markers for detection and monitoring of ovarian cancer. J Oncol 2011;2011: 475983. (Rein, Gupta et al. 2011)

Table 3. The tumor markers detect during early staged and late staged of ovarian cancer.

Human epididymis protein 4 (HE4) is elevated in ovarian cancer, especially endometrioid adenocarcinoma and serous cystadenocarcinoma (Scholler, Crawford et al. 2006).
Osteopontin is a glycoprotein and secreted from vascular endothelial cells and osteoblasts. It has an ability to inhibit apoptosis and correlates with metastasis(Denhardt and Noda 1998).
Mesothelin expresses on the surface of mesothelial cells. It is overexpressed in ovarian cancer, mesotheliomas and pancreatic cancer (Hassan, Remaley et al. 2006).
B7-H4 over expressed in T-cells and ovarian cancer including serous cystadenocarcinoma, endometrioid adenocarcinoma and clear cell carcinoma. Its levels were elevated 45% of patients with early stage ovarian cancer (Simon, Zhuo et al. 2006).
Hepatoglobin originated from the liver. It has been shown expression in ascetic fluid and serum of patients with ovarian cancer. Higher levels of hepatoglobin have been associated with poor prognosis(Zhao, Annamalai et al. 2007). The levels also decreased during chemotherapy.
CA125 is only promising tumor marker currently, but it is low specificity. In combination with CA125, other serum tumor markers have been evaluated to improve the accuracy with some limitations (Visintin, Feng et al. 2008; Amonkar, Bertenshaw et al. 2009; Nosov, Su et al. 2009). The study in 2008 evaluated various combinations of 9 markers including CA125, HE4, SMRP, CA72-4, Osteopontin, ERBB2, Inhibin, Activin, and EGFR. Dual marker combination of CA125 and HE4 had a greater sensitivity than either marker alone (Moore, Brown et al. 2008). However, the dual markers are limited in detecting epithelial ovarian cancer of mucinous cell type. Human epididymis protein4 (HE4) has equivalent sensitivities to CA125 for detecting malignancy in women with pelvic masses (Shah, Lowe et al. 2009). In addition, HE4 has greater specificity in premenopausal women due to it does not influence by benign gynecologic conditions. Contrary, another study has shown that in combination of HE4 and CA125 test was no benefit in clinical practice(Jacob, Meier et al. 2011). HE4 is going on studies for ovarian cancer screening.

7.2 The risk of malignancy index (RMI)

The risk of malignancy index (RMI) was introduced for discriminating ovarian cancer from other ovarian mass (Jacobs, Oram et al. 1990). The RMI score is calculated from menstruation status, ultrasonographic result and CA125 level. RMI cut-off level of 200 has 85% sensitivity and 97% specificity to identify ovarian cancer.
RMI indices followed by Histoscanning study, a novel computer aided diagnostic tool, were assessed in 199 women with adnexa masses. A cutoff RMI value of 250 resulted in 74% sensitivity and 86% specificity. The RMI indices with cutoff values between 105-2100 followed by Histoscanning study improved diagnostic accuracy in women with adnexal masses with 88% sensitivity and 95% specificity (Vaes, Manchanda et al. 2011).

7.3 Risk of malignancy algorithm (ROMA)

The risk of malignancy algorithm (ROMA) is a scoring system in combination of CA125 and HE4 which shows excellent diagnostic performance for the detection of epithelial ovarian cancer in post-menopausal women presenting with pelvic mass (Montagnana, Danese et al. 2011).
Using ROMA, 389 women with pelvic mass were measured serum levels of HE4 and CA125 preoperatively. A cutoff of 12.5% for pre-menopausal patients had 67.5% sensitivity and 87.9% specificity. A cutoff of 14.4% for postmenopausal patients had 90.8% sensitivity and 66.3% specificity. However, HE4 and ROMA did not increase the detection of ovarian cancer comparing to CA125 alone (Van Gorp, Cadron et al. 2011).

On comparison, the dual markers using HE4 and CA125, calculated a ROMA value were evaluated preoperatively (Moore, Jabre-Raughley et al. 2010). This study used the following predictive probability algorithm (ROMA):

Premenopausal Predictive index (PI) = -12+2.38*LN (HE4) +0.0626*LN (CA125)
Postmenopausal Predictive index (PI) = -8.09+1.04*LN (HE4) +0.732*LN (CA125)
Predicted probability = exp (PI)/ [1+exp (PI)]

The following equation was used to calculate RMI:

RMI = U X M X serum CA125

Where
U = 0 for imaging score of 0
U = 1 for imaging score of 1
U = 3 for imaging score of 2-5
M = 1 if premenopausal
M = 3 if postmenopausal

It shows significant higher sensitivity for detecting epithelial ovarian cancer than RMI as shown in figure 5 (Moore, Jabre-Raughley et al. 2010).

Group	**Sensitivity (%)**			**Positive predictive value (%)**		**Negative predictive value (%)**	
	ROMA	RMI	Pretest *P* value	ROMA	RMI	ROMA	RMI
Benign vs. EOC and LMP	89.0	80.7	0.0113	62.3	59.7	93.6	89.3
Benign vs. EOC stage I-IV	94.3	84.6	0.0029	59.8	56.8	97.1	92.5
Benign vs. EOC stage I-II	85.3	64.7	0.0000	27.1	21.8	97.9	95.1
Benign vs. EOC stage III-IV	98.8	93.0	0.0350	52.1	50.3	99.6	97.5

*modified from Moore. Comparison of a novel multiple marker assay versus the RMI. Am J Obstet Gynecol 2010.

Table 4. The sensitivity, positive predictive value and negative predictive value between Risk of Ovarian Malignancy Algorithm (ROMA) and Risk of Malignancy Index (RMI) of benign tumor and epithelial ovarian cancer (EOC) stage I-IV at a set specificity of 75%. LMP= low malignant potential.

Receiver operating characteristic (ROC) analysis of individual tumor markers and their combinations were evaluated and summarized(Jacob, Meier et al. 2011). HE4 performed best 83.3% sensitivity and 84.6% specificity. Whereas ROMA were 85.4% sensitivity and 85.6% specificity (Table 4).

Tumor markers and their combinations	Borderline tumors and cancer group versus non-malignant group		
	AUC	Sensitivity (%)	Specificity (%)
HE4	0.89	83.3	84.6
CA125	0.87	60.4	91.3
CA125*HE4	0.90	70.8	94.2
ROMA	0.90	85.4	85.6
RMIHE4	0.93	79.1	86.5
RMICA125	0.95	66.7	97.1
RMICA125*HE4	0.95	75.0	98.1

*modified from Jacob F, Meier M, Caduff R, et al. No benefit from combining HE4 and CA125 as ovarian tumor markers in a clinical setting. Gynecol Oncol 2011;121(3): 487-91. (Jacob, Meier et al. 2011)

Table 5. The AUC, sensitivity and specificity of individual tumor markers and their combinations between borderline tumors and cancer group versus non-malignant group.

8. Economic evaluation: Cost effectiveness analysis

During economic crisis around the world, the cost effectiveness should be evaluated. It is estimated the cost-effectiveness of different screening strategies using a stochastic simulation model (Skates and Singer 1991). On prediction, a multimodel strategy would cost 51,000 US dollars per year of life saved. Therefore, it would be potentially cost-effective for ovarian cancer screening (Sfakianos and Havrilesky 2011).

9. Conclusion and recommendations

In conclusion, screening for ovarian cancer would be emerged as a promising strategy to increase cure rate, prolong survival and decrease morbidities in the future. Further evaluations for ovarian cancer screening and early detection should be encouraged. Understanding preclinical ovarian cancer and development of novel effective strategy could lead for early detection, ultimately it will decrease incidence and mortality from ovarian cancer.

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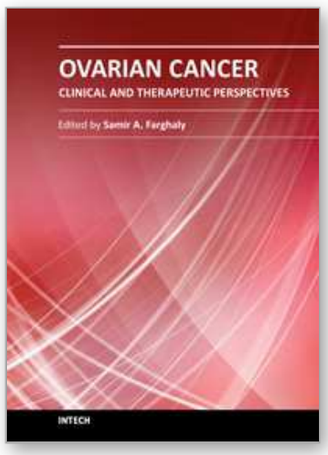

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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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