Performance of Ultrasound as a Second Line Test to Serum Ca١٢٥ in Ovarian Cancer Screening in Postmenopausal Women

Nada Salih Amin* ,Asmaa Mohammed Abid**

ABSTRACT:

BACKGROUND:

Epithelial ovarian cancer is uncommon before ٤٠ years of age but the incidence then rises steeply until the mid sixth and seventh decades for which performance of transvaginal ultrasonography as a screening test for ovarian cancer in asymptomatic postmenopausal women with an elevated serum CA ١٢٥ had been performed.

OBJECTIVE:

Prospective ovarian cancer screening trial had been performed to estimate sensitivity, specifity and positive predictive value of different ultrasound criteria for detection of index cancer (e.g. primary invasive epithelial carcinoma of ovary) in postmenopausal women.

PATIENTS AND METHODS:

This study was carried out at the department of obstetrics and gynecology in AL-Yarmouk Teaching Hospital from October ٢٠٠٢ through October٢٠٠٣.The study included ١١٠ Postmenopausal women ≥ ٤٥ years, they underwent measurement of serum CA١٢٥.Women with CA ١٢٥ of ٣٠ IU/ml (or more) were recalled for an ultrasound examination.

RESULTS:

Of the ١١٠ women included in this study, ٩ women underwent ٣٠ scans during a follow up of one year. The sensitivity for detection of ovarian cancer of different ultrasound criteria was ١٠٠٪ for abnormal ovarian morphology, ١٠٠٪ for abnormal ovarian volume and ٥٠٪ for complex abnormal ovarian morphology. The highest specificity (١٠٠٪) and positive predictive value (١٠٠ %) was achieved by using complex abnormal ovarian morphology.

CONCLUSION:

A variety of ultrasound criteria had achieved high sensitivity, specificity and positive predictive value for ovarian cancer screening in postmenopausal women with an elevated CA ١٢٥. Ovarian morphology and ovarian volume used to interpret ultrasound had achieved increased sensitivity for ovarian cancer screening. While complex abnormal ovarian morphology had achieved increased in the specificity and the positive predictive value for ovarian cancer screening.

KEYWORDS: ovarian cancer, CA١٢٥, transvaginal ultrasound.

INTRODUCTION:

Ovarian cancer is a common solid tumour and is the leading cause of death from gynaecological cancer. It is a serious disease particularly in advanced stages with a course that is punctuated by frequent tumour recurrence and negative impact on quality and length of life. [١،٢،٣] Disease progression and patient decline is typically due to locoregional peritoneal dissemination and its consequence rather than due to visceral metastatic disease and this brings opportunities for therapy research that cannot be contemplated for other types of cancer. [١،٤،٥].

The current lifetime risk is ١ per ٤٨, the incidence being approximately ٢٢ per ١٠٠،٠٠٠ populations. Epithelial ovarian cancer is a disease of older women, the incidence peaking at the age of ٦٧. [١, ٢, ٦, ٧].

Numerous reproductive, environmental, and genetic risk factors have been associated with the development of ovarian cancer. The most important is a family history of breast or ovarian cancer, and approximately ٥ to ١٠ percent of patients have an inherited genetic predisposition. For the other ٩٠ to ٩٥ percent with no identifiable genetic link for their ovarian cancer, most risk factors are related to a pattern of uninterrupted

*Professor of Obstetrics and Gynaecology
College of Medicine Al-Mustansyria University
Obstetric and Gynecology AL-Yarmouk Teaching Hospital.
** Specialist Obstetrician&Gynaecologist
Department of Obstetrics &Gynaecology
AL-Yarmouk Teaching Hospital.

ovulatory cycles during the reproductive years. [٨،٩،١٠،١١،١٢،١٣]

Successful screening is defined as an intervention that results in reduction in the mortality of the screened population relative to the unscreened population. [١٤] CA١٢٥ is an antigen expressed by approximately ٨٠٪ of epithelial ovarian tumour, most frequently among serous and clear cell tumors with papillary and solid tubular growth pattern, but less frequently by mucinous tumour, tumours of cystic growth pattern and borderline malignancy. Serum CA١٢٥ levels have been shown to be useful in distinguishing malignant from benign pelvic masses. [١٥،١٦،١٧].Transabdominal and particularly transvaginal ultrasonography have been investigated extensively. Utilizing a morphological score, incorporating ovarian volume, wall structure, papillary vegitations, septation and cyst complexity, has proved useful in some screening programmes.Transvaginal ultrasound has better resolution than abdominal ultrasound and it can offer improved characterization of the size and morphology of the ovaries and ovarian masses. [١٨،١٩،٢٠] .

AIM OF THE STUDY:

To estimate sensitivity, specifity and positive predictive value of different ultrasound criteria for detection of index cancer (e.g. primary invasive epithelial carcinoma of ovary) in ovarian cancer screening in postmenopausal women.

PATIENTS AND METHODS:

This is a prospective outpatient study from October ٢٠٠٢ to October ٢٠٠٣ for one- hundred and ten women from Baghdad. It had been done at AL-Yarmouk Teaching Hospital. Eligibility for the study was limited to women resident in Baghdad who were aged ٤٥ years or older and who were naturally post menopausal (one year or more amenorrhea i.e. at least one elapsed year since the last menstrual period) or artificially post menopausal due to hysterectomy with ovarian conservation. Exclusion criteria were history of bilateral oophorectomy or ovarian cancer. All women had been informed about the uncertain impact of screening for ovarian cancer. Approval was obtained from the local ethics committee and all women gave written consent. At first patient's evaluation was done including history and examination. Then primary screening was measurement of serum CA١٢٥. Venous blood samples were obtained from each woman and collected in heparinazed or EDTA tubes. For measuring CA١٢٥, we used VIDAS CA١٢٥ II Kits, which is an automated quantitative test for use on the VIDAS analyzer for measurement of OC١٢٥ antigenetic determinant in human serum or plasma using ELFA technique (Enzyme Linked Fluorescents Assay).Women with CA١٢٥ of ٣٠ IU/ml (or more) were recalled for an ultrasonography. Ultrasonography was performed using a transabdominal approach for single (unmarried) women and, transvaginal ultrasound for married women. Subsequently ٧ women were randomized to CA ١٢٥ screening every ٣ months. The ovaries were scanned transabdominaly in the transverse and longitudinal sector scanner using ٣,٥ MHZ transducer. Most of women were scanned transvaginally in the lithotomic position and had an empty bladder with ٥-٧,٥ MHZ transvaginal probe. Irrespective to the mode of scanning, the ovaries were observed above the internal iliac arteries, the intention was to measure the diameter of each ovary in three planes and to document ovarian morphology. Ovarian volume was calculated using the formula for an ovoid. The volume of the entire lesion calculated from the diameters in the three perpendicular planes according to the formula for a prolate ellipsoid (Π / ٦ × D١ × D٢ × D٣). D١; The maximum teraservers diameter. D٢; The antero posterior diameter. D٣; The longitudinal diameter. One observer (consultant radiologist) performed all the scans. Ovarian morphology was regarded as normal if the ovary was of uniform hypoechogenecity and smooth outline. Abnormal ovarian morphology was sub classified as simple cyst (single, thin walled, anechoic cyst with no septa or papillary projections) or complex (abnormal ovarian morphology other than simple cyst; presence of papillary projections or solid areas).

The interpretation and management protocol following ultrasound was as follows:
١. Normal Scan: A. Ovarian volume < ٨,٨ ml with normal morphology (uniform hypoechgenecity and smooth outline) or B. Ovaries not visualized but no pelvic abnormality apparent. Repeat CA١٢٥ estimation every three months for a year.
٢. Equivocal scan: ovarian volume < ٨,٨ ml and abnormal morphology: repeat scans at intervals of ٦ weeks until a scan could be classified as normal or abnormal.
٣. Abnormal scan: ovaries volume ٨,٨ ml or more, irrespective of ovarian morphology: referred to a gynecologist for assessment and advice. Surgical management including surgical intervention as explorative lapratomy was at the discretion of the specialist receiving the referral.

An episode was defined as a single or series of scans initiated by a raised CA١٢٥ and ending in referral for a gynecological opinion or return to CA١٢٥ screening. Study participants underwent a maximum of four CA١٢٥ screens and hence a maximum of four episodes was possible per women. For analysis, each scan episode was classified on the basis of last scan result in to normal, equivocal or abnormal. Sensitivity, specificity and positive predictive value for detection of index cancer were calculated.

RESULTS:

One- hundred and ten asymptomatic postmenopausal women were included in this prospective study. All women were attending to the outpatient clinic at AL-Yarmouk Teaching Hospital for period of one year. A characteristic of women included in this study is shown as following:

Table ١: The general characteristics of the study group (n=١١٠).

Characteristic	Minimum	Maximum	Mean	SD	N
Age in years	٤٥	٧١	٥٣,١	٦,١	١١٠
Body weight (Kg)	٥٦	١٠٢	٨٠,٤	٩,٨	١١٠
Body height (cm)	١٥٠	١٨٠	١٦٠,٥	٥,٩	١١٠
BMI (Body Mass Index) (Kg/m٢)	١٨	٤٢	٣١,٣	٤,٣	١١٠
Age at menarche (years)	١١	١٦	١٢,٧	١,١	١١٠
Age at menopause (years)	٤٢	٥٣	٤٧,٢	٢,٩	١١٠
Parity	٠	١٤	٥,٣	٣,٨	١١٠
Abortion	٠	٣	٠,٣	٠,٦	١١٠
Age at first delivery (years)	١٤	٣٢	٢٠	٤	٩٩
Age at last delivery (years)	٢٠	٤١	٣٢,٦	٤,٤	٩٩

Table ٢: shows that history of ovarian cyst was associated with an obviously higher rate of ovarian tumour (٥٠٪) compared to those with a negative history of ovarian cyst (٠٪).Similar conclusion was observed with the history of unilateral oophorectomy (٤٠٪) for those with positive history versus (٠٪) for those with negative history. Family history of ovarian tumour and colorectal cancer had no obvious relation with the risk of ovarian tumour for the women in this study, only a positive history of breast cancer slightly increased the risk of ovarian tumour.

Table ٢: The rate (risk) of having ovarian tumour by selected variable.

	Ovarian tumour (benign and malignant)					
	Negative		Positive		Total	
	N	%	N	%	N	%
Tubal ligation						
Negative	٩٧	٩٩	١	١	٩٨	١٠٠
Positive	١١	٩١,٧	١	٨,٣	١٢	١٠٠
Family history of ovarian tumour						
Negative	١٠٥	٩٨,١	٢	١,٩	١٠٧	١٠٠
Positive	٣	١٠٠	٠	٠	٣	١٠٠
Family history of breast Ca						
Negative	١٠١	٩٩	١	١	١٠٢	١٠٠
Positive	٧	٨٧,٥	١	١٢,٥	٨	١٠٠
Family history of Colorectal Ca						
Negative	١٠٦	٩٨,١	٢	١,٩	١٠٨	١٠٠
Positive	٢	١٠٠	٠	٠	٢	١٠٠
History of ovarian cyst						

Negative	١٠٦	١٠٠	٠	٠	١٠٦	١٠٠
Positive	٢	٥٠	٢	٥٠	٤	١٠٠
History of unilateral oophorectomy						
Negative	١٠٥	١٠٠	٠	٠	١٠٥	١٠٠
Positive	٣	٦٠	٢	٤٠	٥	١٠٠
Serum Ca١٢٥ (iu/ml)-Baseline reading						
Normal	١٠١	١٠٠	٠	٠	١٠١	١٠٠
Abnormal	٧	٧٧,٨	٢	٢٢,٢	٩	١٠٠

Table٣:shows that ٩ women had developed an elevated CA ١٢٥,they underwent ٣٠ scans during a follow up of one year, a further ٢ patients with a CA١٢٥≥ ٣٠ IU /ml were not included as they declined a scan (n = ٢). Those women with an elevated CA١٢٥ underwent transvaginal ultrasound scanning. Two women underwent surgical investigation and they had an ovarian tumour.Three women had fibroids by ultrasound scan and two women had persistent simple ovarian cysts by ultrasound scan, following gynaecological referral elected not to have surgery.

Table٣: The follow up values of serum CA١٢٥ and ovarian volume measured by ultrasound in nine postmenopausal females with an abnormally high baseline value of serum CA١٢٥.

	Baseline reading	Second reading-after ٣ months		Third reading-after ٦ months	Fourth reading-after ٩ months
Serum CA١٢٥					
Uterine fibroid	٣٠	٣٥		٣٠	٣٠
٢	٣٥	٣٢		٣٠	٣٢
Benign ovarian tumour	١٠٠				
Uterine fibroid	٣٤	٣٠		٣٠	٣٠
٥	٣٥	٣٥		٤٠	٣٣
Malignant ovarian tumour	٢٠٠				
٧	٤٠	٣٥		٣٥	٣٥
٨	٣٣	٤٠		٣٥	٣٥
٩	٤٥	٤٨		٤٥	٤٥
Ovarian volume					
Uterine fibroid	٥	٥		٤,٥	٤
٢	٥	٤		٤	٤
Benign ovarian tumour	١٠				
Uterine fibroid	٥	٤		٤	٤
٥	٤,٤	٥		٥	٥
Malignant ovarian tumour	٩				
٧	٦,٣	٦		٦	٦
٨	٣	٣,٥		٣	٣
٩	٥	٤,٨		٤,٩	٤,٩

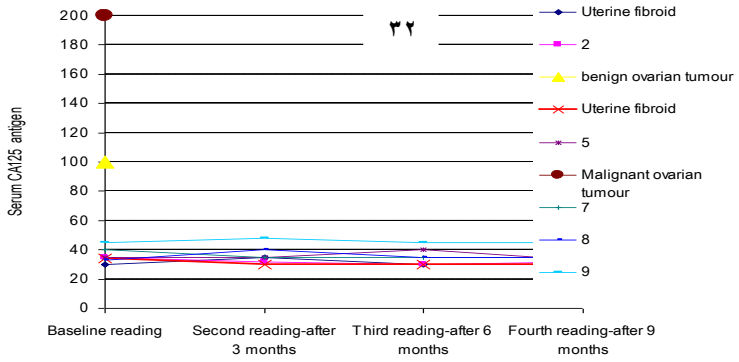

Figure ١: Line graph showing the follow up values of serum Ca١٢٥ for the nine postmenopausal females with an abnormally high baseline value, most results had stationary value.

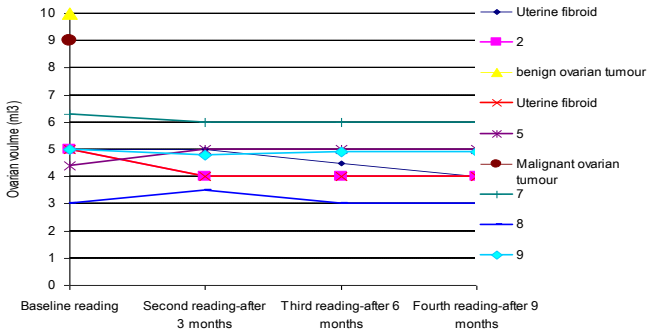

Figure ٢: Line graph showing the follow up values of ovarian volume by ultrasound for the nine postmenopausal females with an abnormally high baseline value of serum CA١٢٥, most results had stationary value.

Table ٤: shows that an elevated serum CA١٢٥ IU/ml had achieved sensitivity of ١٠٠٪ and positive predictive value of ٢٢,٢٪.While an abnormal ovarian volume and abnormal ovarian morphology achieved higher sensitivity (١٠٠٪) than complex abnormal ovarian morphology (٥٠٪).The highest specificity (١٠٠٪) and positive predictive value (١٠٠٪) was achieved by using complex abnormal ovarian morphology. The positive predictive value achieved by using complex abnormal ovarian morphology (١٠٠٪) was significantly higher than that achieved by abnormal ovarian morphology (٦٦,٧٪) or abnormal ovarian volume (٥٠٪).

Table ٤ :Test validity parameters of CA١٢٥ and ٣ ultrasound criteria in the diagnosis of women with ovarian tumour in the study group.

	Ovarian tumour (benign and malignant)					Malignant ovarian tumour				
	Negative	Positive	Total			Negative	Positive	Total		
Serum Ca١٢٥ (iu/ml)				Sensitivity=	١٠٠				Sensitivity=	١٠٠
Normal	١٠١	٠	١٠١	Specificity=	٩٣,٥	١٠١	٠	١٠١	Specificity=	٩٢,٧
Abnormal	٧	٢	٩	PPV=	٢٢,٢	٨	١	٩	PPV=	١١,١
Total	١٠٨	٢	١١٠			١٠٩	١	١١٠		
Ovarian volume (ml^3)				Sensitivity=	١٠٠				Sensitivity=	١٠٠
Normal	١٠٦	٠	١٠٦	Specificity=	٩٨,١	١٠٦	٠	١٠٦	Specificity=	٩٧,٢
Abnormal	٢	٢	٤	PPV=	٥٠,٠	٣	١	٤	PPV=	٢٥,٠
Total	١٠٨	٢	١١٠			١٠٩	١	١١٠		
Abnormal ovarian morphology				Sensitivity=	١٠٠				Sensitivity=	١٠٠
Negative	١٠٧	٠	١٠٧	Specificity=	٩٩,١	١٠٧	٠	١٠٧	Specificity=	٩٨,٢
Positive	١	٢	٣	PPV=	٦٦,٧	٢	١	٣	PPV=	٣٣,٣
Total	١٠٨	٢	١١٠			١٠٩	١	١١٠		

Complex abnormal ovarian morphology				Sensitivity=	٥٠,٠				Sensitivity=	٠,٠
Negative	١٠٨	١	١٠٩	Specificity=	١٠٠	١٠٨	١	١٠٩	Specificity=	٩٩,١
Positive	٠	١	١	PPV=	١٠٠	١	٠	١	PPV=	٠,٠
Total	١٠٨	٢	١١٠			١٠٩	١	١١٠		
Result of baseline scan				Sensitivity=	١٠٠				Sensitivity=	١٠٠
Normal	١٠٦	٠	١٠٦	Specificity=	٩٨,١	١٠٦	٠	١٠٦	Specificity=	٩٧,٢
Abnormal	٢	٢	٤	PPV=	٥٠,٠	٣	١	٤	PPV=	٢٥,٠
Total	١٠٨	٢	١١٠			١٠٩	١	١١٠		

Table ٥: shows description of another way to increase the low specifity and positive predictive value of CA١٢٥, this is by considering the criteria for diagnosis positive only in the presence of another positive ultrasound criteria. A combination of ٢ criteria (elevated CA١٢٥ and abnormal ovarian volume) or ٣ criteria elevated (elevated CA١٢٥, abnormal ovarian volume and abnormal ovarian morphology) had achieved sensitivity of ١٠٠٪, specifity of ١٠٠٪ and positive predictive value of ١٠٠٪.Since CA١٢٥ had achieved sensitivity of ١٠٠٪, it can detect all possible cases with out come of interest and it can limit the use of ultrasound parameter to those with an elevated CA١٢٥only.

Table ٥: Validity parameters for combination of tests or criteria.

		Malignant ovarian tumour					Ovarian tumour (benign and malignant)			
		Total	Positive	Negative			Total	Positive	Negative	
١٠٠	Sensitivity =				١٠٠	Sensitivity =			Serum Ca١٢٥ (iu/ml)	
٩٢,٧	Specificity =	١٠١	٠	١٠١	٣,٥	Specificity =٩	١٠١	٠	١٠١	Normal
١١,١	PPV=	٩	١	٨	٢,٢	ppv=٢	٩	٢	٧	Abnormal
		١١٠	١	١٠٩			١١٠	٢	١٠٨	Total
١٠٠	Sensitivity =				١٠٠	Sensitivity =			A combination of ٢ criteria (CA١٢٥ and Abnormal ovarian volume)	
٩٩,١	Specificity =	١٠٨	٠	١٠٨	١٠٠	Specificity =	١٠٨	٠	١٠٨	Negative (any negative)
٥٠,٠	PPV=	٢	١	١	١٠٠	PPV=	٢	٢	٠	Positive (Both positive)
		١١٠	١	١٠٩			١١٠	٢	١٠٨	Total
١٠٠	Sensitivity =				١٠٠	Sensitivity =			A combination of ٣ criteria (CA١٢٥, Abnormal ovarian volume and abnormal ovarian morphology)	
٩٩,١	Specificity =	١٠٨	٠	١٠٨	١٠٠	Specificity =	١٠٨	٠	١٠٨	Negative (any negative)
٥٠,٠	PPV=	٢	١	١	١٠٠	PPV=	٢	٢	٠	Positive (all ٣ positive)
		١١٠	١	١٠٩			١١٠	٢	١٠٨	Total

DISCUSION:

This is a detailed study of ultrasound findings in asymptomatic postmenopausal women with an elevated serum CA١٢٥.The findings have important clinical implications and are valuable for the design of future ovarian cancer screening trials. The performance of ultrasound in the prospective study was encouraging and a variety of ultrasound criteria achieved an acceptable positive predictive value. In this study, strict application of the study criteria (ovarian volume ≥٨,٨-ml) without clinical input would have resulted in surgical referral following ٣٠ scan episodes, with a sensitivity of ١٠٠٪, specificity of ٩٨,١٪ and a positive predictive value of ٥٠٪. While in the other study done by Usha Menon, ovarian volume criteria of ultrasound resulted in surgical referral following ٨٠ scan episodes, with sensitivity of ٨٩,٥٪, specificity of ٩٣,٧٥٪ and a positive predictive value of ٢١٪. The cause may be attributed to the small number of positive findings in this study[٢] .

Using of abnormal ovarian morphology as the

discriminating criterion in this study had achieved sensitivity of ١٠٠٪ with minimal changes in the specificity of ٩٩,١٪ and increased in the positive predictive value of ٦٦,٧٪. While in the other study done by Usha Menon, using of abnormal ovarian morphology increased the sensitivity to ١٠٠٪ with minimal change in specifity (٩٣,٩٥٪) and positive predictive value (٢٣,٧٥٪) but this improvement did not reach statically significance. The use of complex abnormal ovarian morphology in this study further increased the specificity of (١٠٠٪) and positive predictive value of (١٠٠٪), this is the same as in the study done by Usha Menon[٢] . (Specifity increased to ٩٧,٣٢٪ and positive predictive value increased to ٣٧,٢١٪). Using of complex abnormal ovarian morphology in this study, the sensitivity fell to ٥٠٪, while in the other study done by Usha Menon, [٢] the sensitivity fell to ٨٤٪. This may be attributable to the lower resolution of the older generation transabdominal scanning technique used in the early part of the other study, compared with the transvaginal approach that used in this study. This is consistent with the observation that five of the ١٢ ovarian cancers detected on the primary transabdominal ultrasound screening in the study by Campbell et al. were found to have simple morphology on scan, while none of the ovarian cancers detected by transvaginal scanning in the more recent ultrasound screening trials had simple morphology[٢١] . Clearly, a variety of ultrasound criteria had achieved high sensitivity and positive predictive value for ovarian tumour in women with an elevated CA ١٢٥.The balance of evidence suggested that ovarian morphology and ovarian volume was the most sensitive criteria. Even larger studies are needed to definitively establish the criterion with the best performance characteristics.

In this study, the primary test involved a serum CA ١٢٥; women with an elevated serum CA ١٢٥ are assessed by an ultrasound examination which incorporated both ovarian morphology and ovarian volume, with the major emphasis on morphology. On the basis of our analysis reported here, the uses of ultrasound assessment as a secondary test will maintain the sensitivity of the CA ١٢٥ (١٠٠٪) and enable the overall screening programme to achieve a high positive predictive value

CONCLUSION:

A variety of ultrasound criteria had achieved high sensitivity, specificity and positive predictive value for ovarian cancer screening in postmenopausal women with an elevated CA ١٢٥. Ovarian morphology and ovarian volume used to interpret ultrasound had achieved increased sensitivity for ovarian cancer screening. While complex abnormal ovarian morphology had achieved increased in the specificity and the positive predictive value for ovarian cancer screening. This screening strategy seems to be acceptable and feasible; however these results justify a larger trial among the general population of postmenopausal women.

REFERENCES:

١. D.Keith Edmonds. Benign diseases of the vagina, cervix and ovary. Dewhurst's Textbook of Obstetrics and Gynaecology for post graduates, ٧th edition ٢٠٠٧; ٦٠٦.

٢. .Usha Menon, A. Talaat, David H. Oram. Ultrasound screening for ovarian cancer, B.J.O.G ٢٠٠٠;١٠٧:١٦٥-٦٩.

٣. Sankaranarayanan R, Ferlay J: Worldwide burden of gynaecological cancer: the size of the problem. Best Pract Res Clin Obstet Gynaecol ٢٠٠٦;٢٠:٢٠٧.

٤. Boyle P & Ferlay J (٢٠٠٥) Cancer incidence and mortality in Europe, ٢٠٠٤;*Ann Oncol* ١٦ :٤٨١–٨٨.

٥. Parkin DM, *et al*. (٢٠٠٥) Global cancer statistics, ٢٠٠٢;*CA Cancer J Clin* ٥٥:٧٤–١٠٨.

٦. Quirk JT, Natarajan N: Ovarian cancer incidence in the United States, ١٩٩٢–١٩٩٩. Gynecol Oncol ٢٠٠٥;٩٧:٥١٩.

٧. Jemal A, Siegel R, Ward E, et al: Cancer statistics, ٢٠٠٧. CA Cancer J Clin ٢٠٠٧;٥٧:٤٣.

٨. Purdie DM, Bain CJ, Siskind V, et al: Ovulation and risk of epithelial ovarian cancer. Int J Cancer٢٠٠٣;١٠٤:٢٢٨.

٩. Greer JB, *et al*. Short-term oral contraceptive use and the risk of epithelial ovarian cancer. *Am J Epidemiol* ٢٠٠٥;١٦٢: ٦٦–٧٢.

١٠. Ness RB Endometriosis and ovarian cancer: thoughts on shared pathophysiology. *Am J Obstet Gynecol* ١٢٠٠٣;٨٩:٢٨٠–٩٤.

١١. Sogaard M, KjaerSK & GaytherS ovarian cancer and genetic susceptibility in relation to the BRCA١ and BRCA٢ genes. Occurrence, clinical importance and intervention Acta *Obstet Gynecol Scand* ٢٠٠٦;٨٥:٩٣–١٠٥.

١٢. Baldwin RL, *et al*. BRCA١ promoter region hypermethylation in ovarian carcinoma: apopulation-based study. *Cancer Res* ٢٠٠٠;٦٠:٥٣٢٩–٣٣.

١٣. Riman T, Dickman PW, Nilsson S, et al: Risk factors for invasive epithelial ovarian cancer: Results from a Swedish case-control study. Am J Epidemiol ٢٠٠٢;١٥٦:٣٦٣.

١٤. Sharma A & Menon U Screening for gynaecological cancers. *Eur J Surg Oncol* ٢٠٠٦.

١٥. American College of Obstetricians and Gynecologists: The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer. ACOG committee opinion no, ٢٠٠٢. Obstet Gynecol;١٠٠:١٤١٣.

١٦. Skates SJ, Menon U, MacDonald N, et al. Calculation of the risk of ovarian cancer from serial CA-١٢٥ values for preclinical detection in postmenopausal women. *J Clin Oncol* ٢٠٠٣; ٢١(١٠ suppl):٢٠٦–٢١٠.

١٧. Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* ٢٠٠٢; ٣٥٩:٥٧٢–٥٧٧.

١٨. van Nagell JR Jr, DePriest PD, Reedy MB, et al. The efficacy of transvaginal sonographic screening in asymptomatic women at risk for ovarian cancer. *Gynecol Oncol* ٢٠٠٠; ٧٧(٣):٣٥٠–٣٥٦.

١٩. Ueland FR, DePriest PD, Pavlik EJ, et al. Preoperative differentiation of malignant from benign ovarian tumors: the efficacy of morphology indexing and Doppler flow sonography. *Gynecol Oncol* ٢٠٠٣; ٩١ (١): ٤٦ –٥٠.

٢٠. Togashi K. Ovarian cancer: the clinical role of US, CT, and MRI. *Eur Radiol* ٢٠٠٣; ١٣(suppl ٤): L٨٧-L١٠٤

٢١. . Stuart Campbell, Vijay Bhan, Patrik Royston, Malcolml I White head, William P Collins, Transabdominal ultrasound screening for early ovarian cancer. B.M.J. ١٩٨٩, Vol ٢٩٩, ٢ December: ١٣٦٣-٦٦.