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Contribution of ROMA index towards the primar diagnosis of ovarian cancer

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Abstract

Preoperative distinction between benign and malignant pelvic mass plays an important role in treatment planning ultimately based on the patient's survival rate and quality of life.

The ROMA (Risk of Ovarian Malignancy Algorithm) predictor uses a combination of HE4 (Human Epididymis protein 4) and CA125 to assess the risk of ovarian epithelial cancer (EOC) in women with established pelvic mass.

It represents a useful algorithm with significant diagnostic value in detecting ovarian epithelial processes in postmenopausal women, but not in premenopausal patients.

In addition, the very high specificity of HE4 in distinguishing endometriosis and benign ovarian cysts from EOC is emphasized.

As in the case of Ca 125 is not a clinical means of utilizing population control (screening test). Increased can be found in other clinical cases, a condition that requires thorough clinical laboratory testing and accurate differential diagnosis.

Aim of this study reflects the determination of usefulness of ROMA marker in the preoperative categorization of patients with ovarian processes at high and low risk for ovarian epithelial carcinoma (EOC).

Criteria for excluding these studies are established malignancy in both the minor pelvis and the systemic circulation, as well as the existence of systemic diseases.

Keywords: *Epithelial ovarian cancer, Roma Index, Ca-125, HE4*

Introduction

Ovarian cancer consists the most lethal cancer among gynecological cancers in women of pre-and most of all postmenopausal age.

During last decade, estimated annual death incidence 151,905 worldwide. and 238,719 cases respectively. *[1]*

Many predisposition factors affect the prognosis survival rate and the imaging depiction of the lesion.

Age of the patient, staging of the lesion, grading, histologic type, lymph node infiltration and most of all size of the tumor. *(Table I.)*

Overall prognosis of ovarian cancer is strongly associated with stage of the lesion. 5-year survival prognosis estimates about 46%, reaching very poor standards. *[2]*

Survival rate about 70% especially for stages I and II, between 20 and 40% for stages III and IV respectively. *[3]*

In order to establish preoperative tools for detection of CIN lesion, we must understand the pathophysiologic mechanism of this pathogenic route.

Ovarian cancer is a nonspecific term for a variety of tumors that involve the ovary. Ovarian cancers can be classified into *three large groups: epithelial, germ cell,*

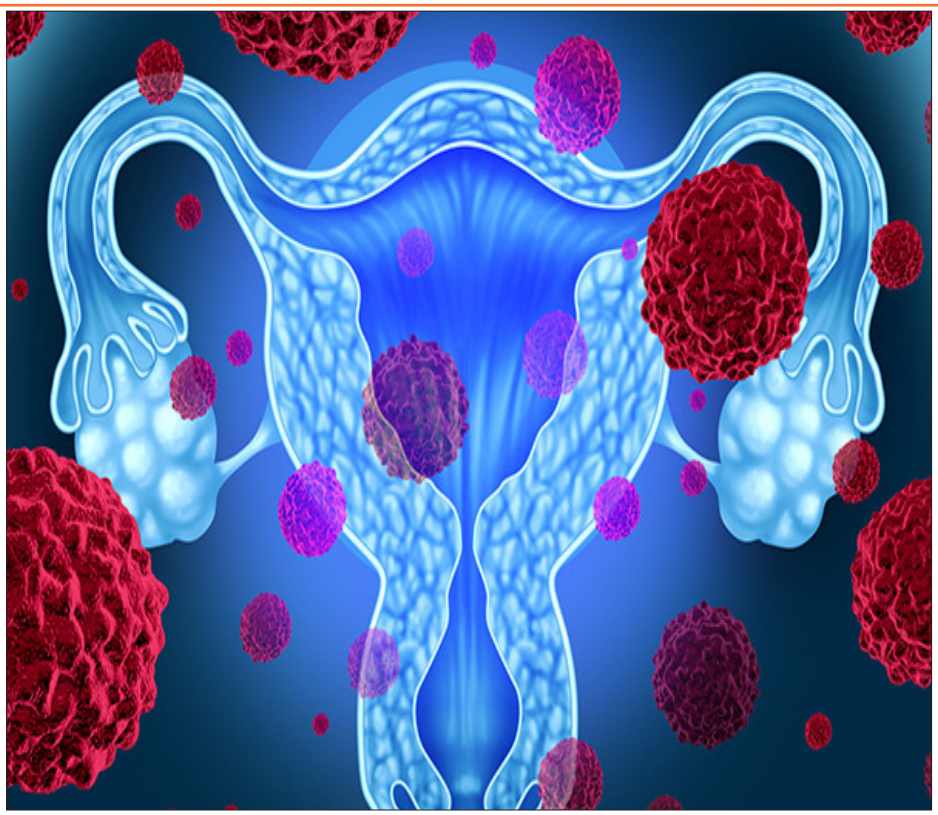
and specialized stromal cell tumors. The vast majority of ovarian cancers are epithelial ovarian cancers (EOCs). *The most common histological subtypes of epithelial ovarian carcinomas are serous (68-71%), endometroid (9-11%), clear cell (12-13%), mucinous (3%), transitional (1%), and mixed histologies (6%). [4]*

TableI. *FIGO staging for cancer of the ovary, fallopian tube and peritoneum*

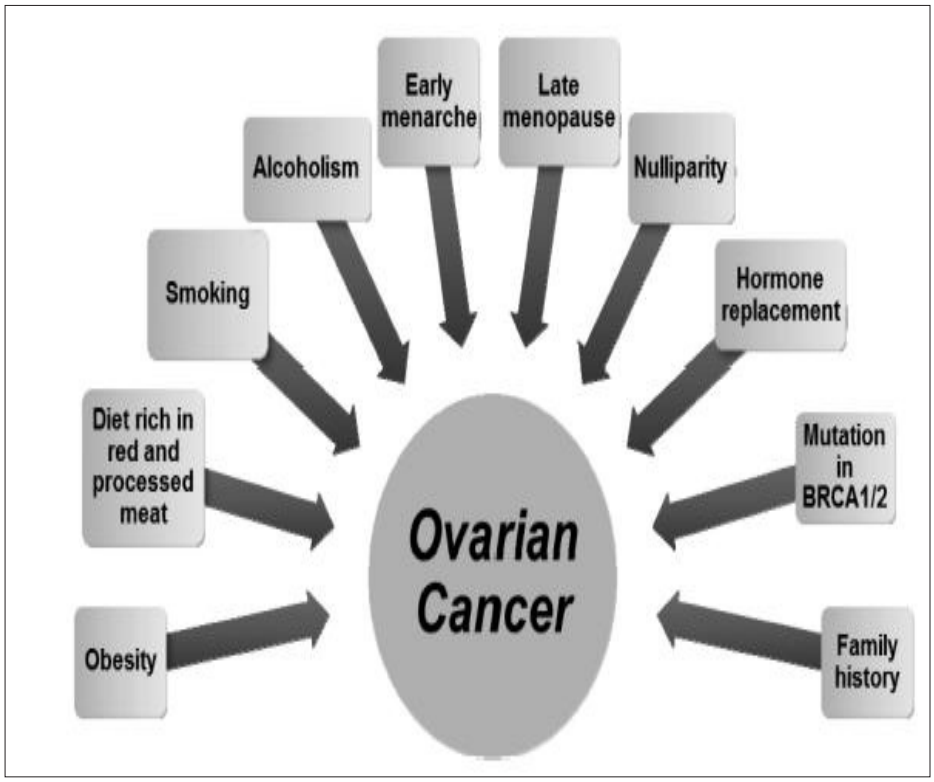
FIGO STAGING CRITERIA FOR CANCER OF THE OVARY, FALLOPIAN TUBE, AND PERITONEUM

Stage I	**Tumor limited to the ovaries or fallopian tubes**
I A	Tumor limited to one ovary (capsule intact) or fallopian tube No tumor on the external surface of the ovary or fallopian tube No malignant cells in ascites or peritoneal washings
I B	Tumor limited to both ovaries (capsules intact) or fallopian tubes No tumor on the external surface of the ovaries or fallopian tubes No malignant cells in ascites or peritoneal washings
I C	Tumor limited to one or both ovaries or fallopian tubes, with any of the following: Stage IC1: Surgical spill Stage IC2: Capsule ruptured before surgery, or tumor on ovarian or fallopian tube surface Stage IC3: Malignant cells in the ascites or peritoneal washings
Stage II	**Tumor involves one or both ovaries or fallopian tubes, with pelvic extension (below pelvic brim) or primary peritoneal cancer.**
II A	Extension and/or implants on the uterus and/or ovaries and/or fallopian tubes
II B	Extension to other pelvic intraperitoneal tissues
Stage III	**Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes**
III A1	Positive (cytologically or histologically proven) retroperitoneal lymph nodes only Stage IIIA1(i) Metastasis up to 10 mm in greatest dimension Stage IIIA1(ii) Metastasis more than 10 mm in greatest dimension
III A2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
III B	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
III C	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes. Stage IIIC includes extension of tumor to the capsule of liver and spleen without parenchymal involvement of either organ.
Stage IV	**Distant metastasis, excluding peritoneal metastases**
IV A	Pleural effusion with positive cytology
IV B	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Exploring, understanding and focusing on the pathogenic path, it is more feasible to establish such *preoperative markers. (Figure I.)*



FigI. *Etiology and Pathophysiology of ovarian cancer. Med Page Today*

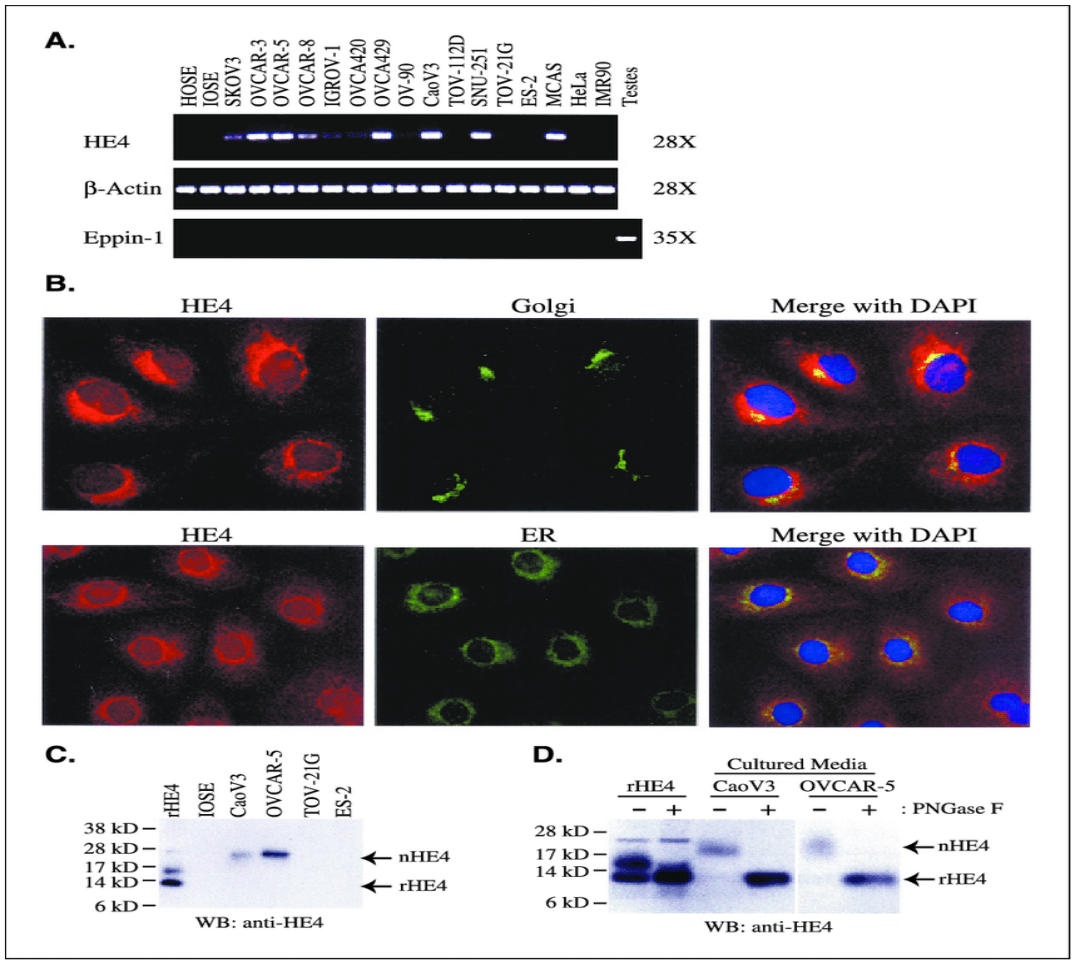


FigII. *Risk factors associated to ovarian cancer. Abbreviations: BRCA, breast cancer. Jammal-M, Lima-C, Murta E, Nomelini S. Is Ovarian Cancer Prevention Currently Still a recommendation of Our Grandparents? Rev. Bras. Gynecol. Obstet. vol.39 no.12 Rio de Janeiro Dec. 2017*

Despite low sensitivity and specificity of ovarian cancer screening methods and need to develop new early diagnostic methods, gynecological examination, ultrasound, and monitoring of a panel of systemic tumor markers represent approaches that are currently considered reasonable for obtaining an early diagnosis of ovarian neoplasia. [5]

New markers focusing on the primary detection of ovarian masses and especially in ovarian malignancies consists the *ROMA Index (Risk of Ovarian Malignancy Algorithm).*

The ROMA (Risk of Ovarian Malignancy Algorithm) predictor uses a combination of HE4 (Human Epididymis protein 4) and CA125 to assess the risk of ovarian epithelial cancer (EOC) in women with established pelvic mass.



FigIII. *HE4 is overexpressed and secreted as a glycoprotein by ovarian carcinoma cells.* ***A,*** *expression of HE4 was determined by semiquantitative RT-PCR. Normal OSE (HOSE) and IOSE RNA served as negative controls for HE4 expression. Expression of h-actin served as a loading control. Eppin-1 is another WAP gene located on chromosome 20q13 (Fig. 1A). Right, number of PCR cycles. HE4 is overexpressed by most ovarian carcinoma cells lines and is absent in HeLa and IMR90 cells.* ***B,*** *HE4 is localized to the perinuclear Golgi apparatus and endoplasmic reticulum (ER). Immunofluorescence localization of HE4 in SKOV-3 cells revealed a perinuclear pattern that partially colocalized with the 58K Golgi protein and Grp78, an ER marker. Images were merged with 4V ,6-diamidino-2-phenylindole to show the nucleus. Similar results were obtained in CaoV3 and OVCAR-5 cells.* ***C****, HE4 is secreted by ovarian cancer cells. Conditioned medium from IOSE, CaoV3, OVCAR-5, TOV-21G, and ES-2 cells was concentrated and analyzed by Western blot for HE4. Secreted HE4 migrates as a higher molecular weight species compared with recombinant HE4.* ***D,*** *secreted HE4 is N-glycosylated. Cultured medium was incubated with PNGase* ***F,*** *a DE glycosylation enzyme. Western blot analysis of the migration of the recombinant glycosylated HE4 and the HE4 secreted by CaoV3 and OVCAR5 cells comigrate with unmodified recombinant HE4 after enzymatic DE glycosylation. Experiments were repeated at least three independent times. Drapkin R, Von Horsten H, Mock S. Cancer Research 65(6):2162-9*

Discussion

Contemporary imaging depiction of ovarian cancer consists transvaginal ultrasound and serum measurement of *Ca 125.*

Unfortunately, this particular method reflects insufficient specificity, especially in women before menopause.

Among the wide range of potential biomarkers, the scientific utility of *HE4* has been conducted from many researchers globally. *[6]*

Carbohydrate Antigen 125 (Ca 125) represents a mucin-type glycoprotein, produced by the MUC16 gene and associated with the cellular membrane.

This biomarker usually increases in many clinical conditions, including gestation, endometriosis, ovarian mass and many others.

Human Epididymis Protein 4 (HE4) consists a new biomarker, coding for the WAR proteins located in the chromosome 20q12-13.1. *[7]*

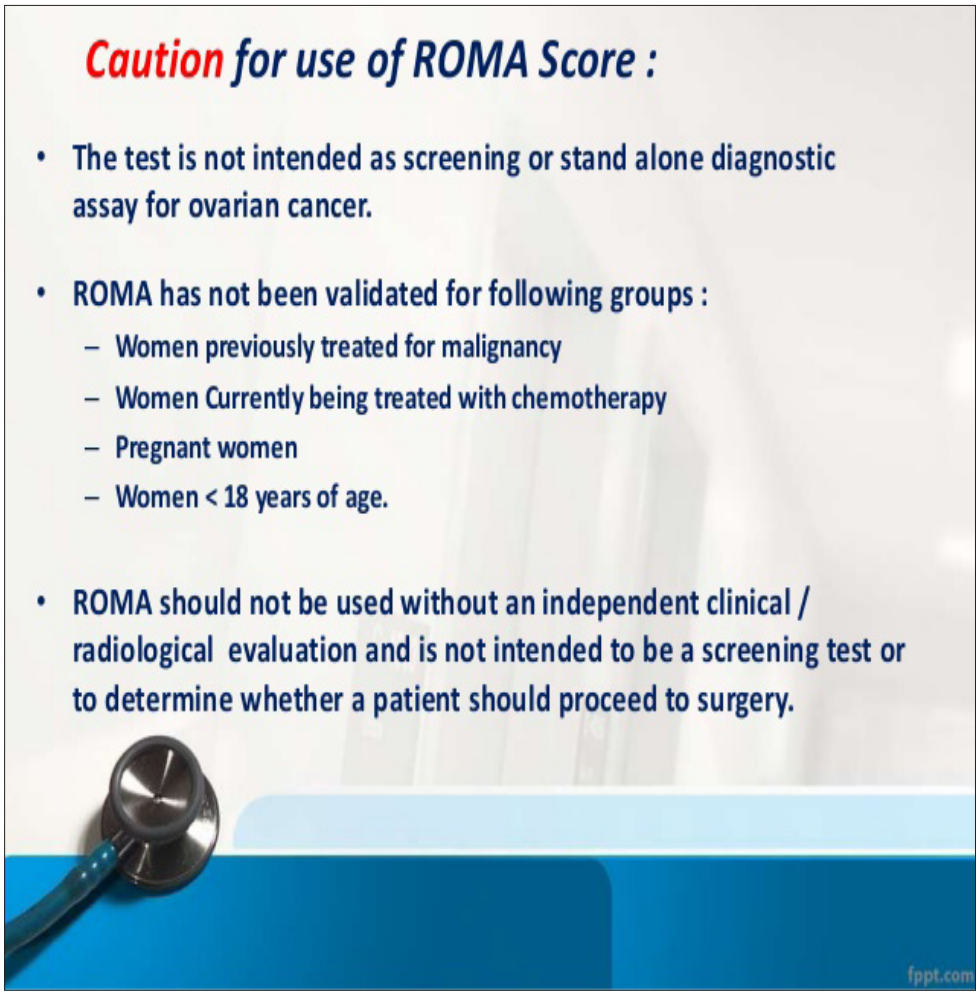
Many conducted studies, as scientific examples from current bibliography, depict isolation of *HE4* from anatomic area of epididymis, reflection an important role in the procedure of sperm maturation. *[8]*

Additionally, body mass index and smoking consuming are strongly associated with interpretation of HE4. *[9]*

Assiduous detection of all predisposition factors can lead to calculate significant parameters concerning *Ca 125, HE4 and ROMA Index.*

Specificity, sensitivity, positive and negative prognostic value, overall survival and most of quality of patient's life consist ultimate goal concerning therapeutic mapping of *ROMA Index* in benign and malignant adnexal tumors.

We must never mention specific exclusions criteria concerning ROMA Index measuring. *(Figure IV.)*



FigIV. *Exclusions criteria regarding ROMA Index*

Throughout current conducted studies *ROMA Index* remains a controversial entity, focusing on scientific and experimental status, not taking place as screening method tool regarding primary detection of adnexal benign or malignant masses.

Statistical analysis of *ROMA Index* establishes the potential capability of primary diagnosis. *(Table II.)* This statistical classification divides *ROMA Index* in *low- and high grade*, leading to further evaluation. *[10]*

TableII. *Statistical measuring of ROMA Index 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; 112:40-6*

Before menopause: PI=-12.0 +2.38x LN [HE4] +0.026Xln [Ca125]
After menopause: PI= -0.89+1.04x LN[HE4] +0.732Xln[Ca125]
ROMA value (%)=e PI / [1+e PI] x 100%
PI: predictive value
LN: natural logarithm
e: base of natural algorithm

Cut off value for *Ca 125 was 35 U/ml* as manufacture recommendation and cut off value for *HE4 was 70 pmol/L.*

ROMA Index for high risk premenopausal and postmenopausal women was measured 13,1% and 27,7% respectively. *[10]*

For all statistical comparisons, a p-value < 0.050 was accepted as statically significant.

Summarizing all recent conducted studies, we can finally reach at significant conclusions, regarding the primary diagnosis and treatment of adnexal benign and malignant masses.

Ca125, without doubt depicts higher specific compared to ROMA and HE4 especially in postmenopausal women.

Hence, HE4 and ROMA Index reveal a high specificity and although they are less sensitive than Ca125 in premenopausal women, they were of comparable sensitivity in postmenopausal women in addition to their higher specific. [11]

Focusing on the high sensitivity of CA 125 and specificity of *HE4, a panel of both tests using algorithms such as ROMA reflects a well promising procedure.*

Conclusion

Main objective of our study remained an assiduous depiction and well understanding of contribution *of ROMA Index* concerning the proper preoperative diagnosis of adnexal benign and malignant masses.

Many authors declare this measuring controversial, well others insist regarding their scientific significance.

Multidisciplinary approach is always mandatory. Assiduous atomic history, detailed clinical examination and laboratory evaluation establish ultimate therapeutic approach.

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