10.5005/jp-journals-10006-1571

ORIGINAL ARTICLE

Rethinking the Role of Serum Cancer Antigen 125 and Risk of Malignancy Index in Indian Women with Ovarian Masses: Newer Perspectives and Review of Literature

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ABSTRACT

Background: Demographic, socioeconomic, and cultural factors account for variation in global incidence trends of ovarian malignancy. Indian cancer registry statistics revealed equally wide interstate variations and prompted us to rethink on variations in screening techniques between different population groups. The present study was undertaken to verify the feasibility and effectiveness of Risk of Malignancy Index (RMI) and cancer antigen (CA) 125 in women residing in North India and place their screening results in the context of literature relevant to geographic and ethnic variations.

Materials and methods: The study is a retrospective review of patients attending a tertiary hospital in New Delhi between January 2009 and July 2011 with adnexal masses subsequently undergoing laparotomy. Information on demographic characteristics, ultrasound findings, menopausal status, CA-125, and histopathology was collected. The RMI scores were calculated and correlated with histopathological findings.

Results: Mean age of participants (n = 78) was 33.8 years with an average delay of 16 months before the presentation. Seventy-three tumors turned out to be ovarian in origin. Of these, 63 were benign and 16 malignant. The CA-125 (>35 IU) was used to predict the malignant nature of tumor, with sensitivity of 75%, specificity of 76.2%, positive predictive value of 47.4%, and negative predictive value of 91.4%. In contrast, RMI (>200) had improved sensitivity of 87.5%, specificity of 91.3%, positive predictive value of 73.6%, and negative predictive value of 96.5%.

Conclusion: The study demonstrated that CA-125 and RMI are feasible tools for distinguishing between benign and malignant ovarian masses for women residing in North India. Literature review revealed wide variation in performance of RMI in women living in the same geographic area and no correlations could be drawn due to paucity of data from different parts of the world. However, the ideology of individualized cut-offs for distinct ethnic and geographic groups needs additional research in future.

Keywords: Cancer antigen 125, Indian, Ovarian screening, Risk of malignancy index.

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How to cite this article: Malla VG, Tuteja A, Singh P. Rethinking the Role of Serum Cancer Antigen 125 and Risk of Malignancy Index in Indian Women with Ovarian Masses: Newer Perspectives and Review of Literature. J South Asian Feder Obst Gynae 2018;10(2):110-117.

Source of support: Nil

Conflict of interest: None

Date of received: 15 March 2018

Date of acceptance: 20 April 2018

Date of publication: July 2018

BACKGROUND

Ovarian malignancy is a prime cause of morbidity and mortality, especially in middle-aged women.[1] A total of 228,700 cases of ovarian cancer were reported worldwide in 2012, with 99,800 cases being diagnosed in developed countries, and 139,000 being diagnosed in less developed regions.[2] These statistics mirror the rising incidence of ovarian cancer in India, which is estimated to be 8% of all female cancers.[3] Demographic, socioeconomic, and cultural changes in India have led to increased longevity, delayed child bearing, decreased parity, and contributed to the ever-increasing patients of ovarian cancer.[4] In addition, Takiar et al[5] projected a 19.8% rise in ovarian cancers from 2010 to 2020. Thus, India with its increasing population and limited reporting of data has a large unestimated burden of disease.[6]

A detailed analysis of cancer registries in India highlights wide interstate variation in ovarian cancer rates.[7,8] In parallel, international demographics emphasize the differences in global incidence patterns and correlate them with environmental or cultural risk factors. Thus, etiological factors and incidence trends vary between geographical areas inhabited by unique ethnic groups.[2,9] This prompted us to rethink on the variations in screening modalities between different population groups.

We decided to concentrate on CA-125 and RMI as they are commonly used and easily reproducible. The CA-125 is the most well-known and widely accepted tumor marker for ovarian cancer. The glycoprotein concentration (normal <35 IU/mL) values are raised in 30 to 50% of cases of early-stage ovarian cancer and 80% of women with advanced

ovarian malignancy. However, interpretation of CA-125 has to be done with caution.[10] The levels are elevated in 1% of healthy women, fluctuate during menstrual cycles, and are raised in many benign conditions like pelvic inflammatory disease, endometriosis, fibroid uterus, ulcerative colitis, liver cirrhosis, pleural, and pericardial effusion.[11]

Therefore, as an individual test, it is not sufficient for preoperative triage.[12] Various combined methods for evaluating the risk of ovarian cancer in women have been proposed and validated over the last two decades.[13] Risk of Malignancy Index was originally developed in 1990 and predicted the chance of cancer based on menopausal status, ultrasound, and CA-125.[14] A number of modifications to the RMI have been proposed improving the accuracy of score:

- RMI 1 = U × M × CA-125, where a total ultrasound score of 0 made U = 0, a score of 1 made U = 1, and a score of ≥ 2 made U = 3; premenopausal status made M = 1; and postmenopausal M = 3. The serum level of CA-125 was applied directly to the calculation.[14]
- RMI 2 = U × M × CA-125, where a total ultrasound score of 0 or 1 made U = 1, and a score of ≥ 2 made U = 4; premenopausal status made M = 1; and postmenopausal M = 4. The serum level of CA-125 was applied directly to the calculation.[15]
- RMI 3 = U × M × CA-125, where a total ultrasound score of 0 or 1 made U = 1, and a score of ≥ 2 made U = 3; premenopausal status made M = 1; and postmenopausal M = 3. The serum level of CA-125 was applied directly to the calculation.[16]
- RMI 4 = U × M × S (size in centimeters) × CA-125, where a total ultrasound score of 0 or 1 made U = 1, and a score of ≥ 2 made U = 4. Premenopausal status made M = 1 and postmenopausal status made M = 4. A tumor size (single greatest diameter) of <7 cm made S = 1, and ≥ 7 cm made S = 2. The serum level of CA-125 was applied directly to the calculation.[17]

Different versions of RMI have been validated retrospectively and prospectively in different clinical studies.[18] The Royal College of Obstetricians and Gynecologists (RCOG) suggests that a cut-off value of 200 demonstrates high degree of sensitivity and specificity for distinction between benign and malignant masses (sensitivity 51–90%, specificity 51–97%). In contrast, the IOTA group recommended an optimum cut-off value of 100 for clinical use.[12] Consequently, an ideal cut-off value of RMI for clinical application still needs to be assessed. Therefore, the present study was planned to retrospectively verify the effectiveness of RMI and CA-125 in distinguishing between benign and malignant ovarian masses, allowing local variations in CA-125 assays and ultrasound expertise in day-to-day practice. A relevant distinction from prior investigations will be our endeavor to focus the research on women residing in North India and place it in context of literature relevant to geographic and ethnic variations.

MATERIALS AND METHODS

We conducted a retrospective review of medical records of 78 women with pelvic masses admitted for surgery in Department of Obstetrics and Gynecology, Post Graduate Institute of Medical Education and Research and Dr. Ram Manohar Lal Hospital, New Delhi, India, between January 1, 2009 and July 31, 2011. No sample size calculation was performed due to the preliminary descriptive nature of this study. The hospital is a tertiary referral center in the national capital territory and its patients are typical of mixed ethnic groups residing in the northern parts of India. The referrals to the capital are dominated by the neighboring states of Haryana, Punjab, Rajasthan, Uttar Pradesh, and mountainous terrains of Uttarakhand and Himachal Pradesh. Despite having modern facilities, patients are consistently referred to the capital city in hope of modern treatments. Therefore, the study population is fairly representative of North Indian women.

The study was approved by the Institutional Ethical Committee. All women (age >30 years) having an adnexal mass planned for laparotomy were included in the study. Patients with incomplete medical records and those with preoperative histological diagnosis of malignant ovarian tumor were excluded from the study. Detailed clinical profile, including symptoms (local and systemic), duration of symptoms, and relevant history, was noted for each patient. Women were considered postmenopausal if they had at least 1 year of amenorrhea not related to other conditions or if they were 50 years old and had undergone a prior hysterectomy. All other women were considered premenopausal.

Serum CA-125 levels (performed using electrochemiluminescence immunoassay) were measured preoperatively.[19] Ultrasonography was performed transvaginally by a 7.5 MHz transducer. A transabdominal repeat examination with a full bladder was obtained if a mass was found to be too large to be observed completely by vaginal route. A score was assigned for the following ultrasound features suggestive of malignancy: The presence of a multilocular cystic lesion, solid areas, bilateral lesions, ascites, and intraabdominal metastasis scored as one point for each. Thus, a total score (RMI 2) was calculated for each patient.[16]

The histopathological diagnosis was considered the gold standard for definite outcome.[17] When a borderline ovarian tumor was found, it was classified as malignant ovarian tumor.[20] Statistical analysis was performed using

Table 1: Histopathological classification and distribution of cases

Histopathological diagnosis	*n (%)*
Total benign cases	63 (79.5)
Serous cystadenoma	40 (51.2)
Mature teratoma	8 (10.2)
Endometrioma	8 (10.2)
Inclusion cyst	1 (1.2)
Xanthogranulomatous salpingooophoritis	1 (1.2)
Extra ovarian	5 (6.4)
Total malignant cases	16 (20.5)
Serous cystadenocarcinoma	10 (12.8)
Mucinous cystadenocarcinoma	3 (3.8)
Borderline malignant	2 (2.5)
Dysgerminoma	1 (1.2)

Statistical Package for the Social Sciences, version 20. Receiver operating characteristic (ROC) curves were used for evaluating the performance of serum CA-125 and RMI as predictive tests for malignancy. The best cut-off values of the models were calculated in consideration of sensitivity, specificity, positive predictive value, and negative predictive value.

RESULTS

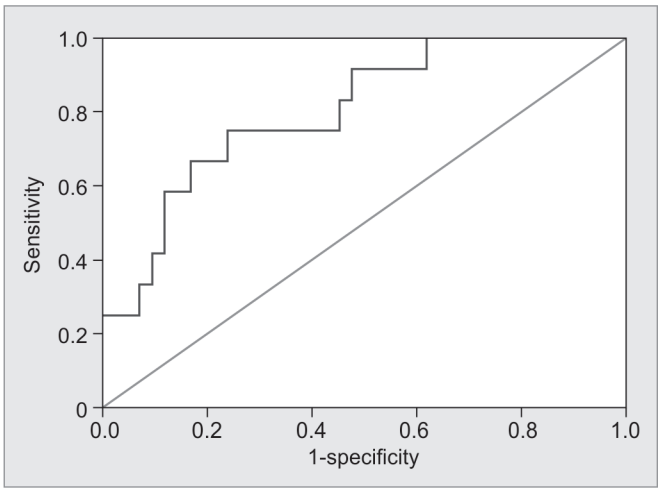
A total of 78 women were included in the analysis. The mean age of patients was 33.8 years. The most common symptom was pain, which was present in 65 (83%) women. The other symptoms ranged from menstrual complaints [45 women (58%)], lump abdomen [42 women (54%)], and other systemic complaints [52 women (66%)]. Further interviewing revealed that women had delayed presentation to the clinic even though they were symptomatic for more than 1 year (mean duration of symptoms was 16 months).

Table 2: Differences in age, menopausal status, CA-125, and RMI between benign and malignant pelvic masses

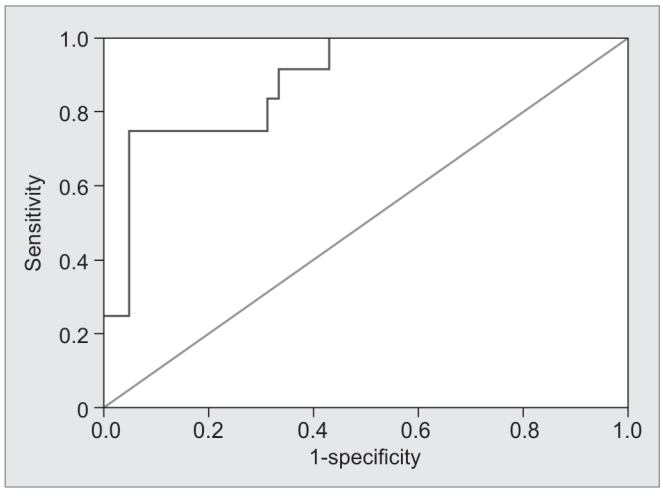
Variable	*Benign (n = 62)*	*Malignant (n = 16)*	*p-value*
Mean age (in years)	32.6	49.25	<0.005
Menopausal status			
Premenopausal (%)	89.06	10.93	<0.005
Postmenopausal (%)	38.4	61.6	<0.005
Mean CA-125 (IU/mL)	51.51	654	<0.005
Mean RMI score	134.6	3355	0.000

Of note, only 73 patients had tumors of ovarian origin. The remaining five patients had intraoperative surprises consisting of three mesenteric cysts, one appendicular tumor, and one large subserosal fibroid. After surgical resection and histopathological examination, 16 patients had malignant and 63 had benign diseases. The detailed description of tumor histology is mentioned in Table 1. Statistically significant differences were found regarding age, menopausal status, ultrasound score, serum CA-125 and RMI between the groups with benign and malignant pathology (Table 2).

In the ROC curve evaluation, CA-125 levels and RMI were found to be relevant predictors of malignancy (Graphs 1 and 2). The sensitivity, specificity, positive predictive value, and negative predictive value of CA-125 and RMI at the prevalidated cut-off values are depicted in Table 3. By using a cut-off level of 35, serum CA-125 had a sensitivity of 75%, specificity of 76.2%, positive predictive value of 47.4%, and negative predictive value of 91.4%. In contrast, RMI had a sensitivity of 87.5%, specificity of 91.3%, positive predictive value of 73.6%, and negative predictive value of 96.5%.



Graph 1: Receiver operating characteristic curve depicting the relationship between sensitivity and specificity of serum levels of CA-125 in the discrimination of malignant and benign pelvic masses



Graph 2: Receiver operating characteristic curve depicting the relationship between sensitivity and specificity of RMI for discrimination between benign and malignant pelvic masses. Area under curve = 0.94

Table 3: Comparative performance of serum CA-125 and RMI scores in predicting benign and malignant pelvic masses

Criteria	*Sensitivity (%)*	*Specificity (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*	*p-value*
CA-125 (cut-off 35 IU/mL)	75	76.2	47.4	91.4	<0.05
RMI (cut-off 200)	87.5	91.3	73.6	96.5	0.00

RMI scores (p-value = 0.000) were better predictors of malignancy than CA-125

Hence, serum CA-125 levels failed to predict nearly one-fourth of the pelvic masses correctly and the retrospective corelation highlighted a false-positive rate of 24.1% and a false-negative rate of 25%. In comparison, RMI had significantly better predictive accuracy with a false-positive rate of 8.6% and a false-negative rate of 12.5%. Among the various histological types, serous cystadenoma accounted for most false-positive and mucinous cystadenocarcinoma was underlying most false-negative cases. This difference did not reach any statistical significance due to the small sample size of the study population.

DISCUSSION

Approximately 20% of women will develop a pelvic mass in their lifetime.[21] Ovarian pathology is responsible for 70% pelvic masses found at exploratory laparotomy on patients with preoperative diagnosis of adnexal masses not attributable to fibroids.[22] However, there is no effective screening method to timely detect cancer and improve clinical outcome. Subsequently, majority of women (60%) present with advanced disease and poor prognosis. The 5-year survival rate in all cases is 29% with median survival being 14 months only.[4,5,23] Survival in women with ovarian cancer is not only dependent on the stage of disease but also on the treating surgeon and the treatment facility.[24,25] There is a statistically significant difference in the 5-year survival rates between patients being treated by high-volume physicians who perform surgery frequently, administer correct chemotherapy, and deliver appropriate treatment to ovarian cancer patients vis-à-vis low-volume physicians.[26]

Despite the clear benefits of referral to gynecologic oncologists, more than 50% of patients are not referred to higher centers and lack preoperative triaging.[27,28] For triage, epidemiological and genetic risk factors, evaluation of clinical signs and symptoms with careful selection, and interpretation of diagnostic tests should be individualized to each clinical context.[29] For this reason, it is imperative to ascertain the variations of commonly used screening modalities for distinct ethnic groups which share common genetic backgrounds, cultural traditions, reproductive beliefs, and dietary practices.

Our study validates the use of CA-125 and RMI for North Indian women and emphasizes that both of these would be excellent screening tools dependent on availability. For appropriate triage and referral, all tiers of health care workers can be trained to interpret the results and make timely referrals to tertiary care centers. Clearly, serum CA-125 levels at a cut-off value of 35 IU/mL have a positive correlation with malignant histopathological findings with nearly similar sensitivity 75% and specificity 76.2%, but noticeably low positive predictive value of 47.41% and high negative predictive value of 91.4%. In remote areas, where sonographic facilities are limited, serum samples could be collected and transported to tertiary centers for measurement of CA-125 levels. Although the false-positive and false-negative rates are high, serial levels could be researched further to improve the positive predictive value of the test.

Next, RMI cut-off of above 200 revealed an improved sensitivity (87.5%), specificity (91.3%), positive predictive value (73.6%), and negative predictive value (96.5%) when compared with CA-125. If all strata of health care professional learn to interpret ultrasound images and reports along with CA-125 and calculate RMI, the false-negative rate would decline to half (24.1–12.5%) and false-positive rate to one-fourth of the previous rate (25–8.6%). The performance of RMI recognized in the present study is comparable to researchers in other parts of the world. Research articles reviewed in Table 4 distinctly bring forth high negative predictive values and sensitivity of RMI all over the globe with frequently low positive predictive value. To the best of authors' knowledge, it is the first attempt to understand distinct patterns and cut-offs in communities populating different countries. However, there is a markedly wide variation in the performance of RMI (cut-off 200) in scientists working in the same geographical area. We believe that these differences may be attributed to lack of sufficient information on participant composition in the populations under study. Further, no discernible correlations were apparent in the detection capabilities of RMI in the same region or in-between regions. This may be explained by relatively small sample size in the observation studies. Moreover, imaging modalities have advanced over years effecting the sensitivity and specificity of sonographic parameters and eventually influencing the consistency in reporting from 1990 to 2017. Nevertheless, all researchers verified that RMI is a feasible tool useful all over the world.

Despite a promising performance of RMI at a cut-off of 200, some authors have shifted their focus to selecting a different cut-off for RMI (125–265). However, lowering the cut-off to 125 or elevating it to 265 did not bring any distinct improvement in the performance of RMI (Table 5).

Table 4: Diversity of performance of RMI in different population groups (RMI cut-off 200)

	Population under study	*Author*	*Year*	*n*	*Sensitivity (%)*	*Specificity (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*
Asian region								
	India	Manjunath et al[30]	2001	152	73	91	93	67
		Rao[31]	2014	90	84	89	93	71
		Javdekar and Maitra[32]	2015	58	70.5	87.8	70.5	87.8
		Chopra et al[33]	2015	100	96.7	84	85.5	67.7
		D'Almeida and Rao[34]	2015	300	60	92	60	92
		Vasudevan et al[35]	2016	102	83.33	88.46	68.96	94.52
		Kumari et al[36]	2017	65	77.27	64.28	53.12	84.37
	Nepal	Pariyar[37]	2008	70	85	88	–	–
	Pakistan	Irshad and Irshad[38]	2013	36	91.3	76.9	87.5	83.3
		Aziz and Najmi[39]	2015	283	53.8	92.2	52.2	92.5
	Thailand	Leelahakorn et al[20]	2005	175	88.6	90.7	70.5	97
		Moolthiya W et al[40]	2009	209	70.6	83.9	75	80
	China	Ma et al[41]	2003	140	87.3	84.4	82.1	89
	Japan	Yamamoto et al[42]	2014	296	81.1	89.6	72.3	93.4
Middle Eastern region								
	Jordan	Obeidat et al[43]	2004	100	90	89	96	78
	Turkey	Ulusoy et al[44]	2007	296	71.7	80.5	67.3	83.6
	Qatar	Mohammed et al[45]	2014	172	80.7	93.1	70	96
	Oman	Al-Musalhi et al[46]	2015	361	57	81	38	90
	Iran	Karimi-Zarchi et al[47]	2015	200	66.66	82.75	72.22	87.68
Scandinavian region								
	Norway	Tingulstad et al[15]	1996	173	71	96	89	88
	Norway	Tingulstad et al[16]	1999	365	71	92	69	92
	Denmark	Andersen et al[48]	2003	180	70.6	87.7	66.1	89.8
	Denmark	Håkansson et al[49]	2012	1159	92	82	62	97
	The Netherlands	Geomini et al[18]	2009	116	78	87	–	–
	The Netherlands	Van den Akker et al[50]	2010	548	81	85	48	96
	Finland	Niemi et al[51]	2017	100	71.9	80.3	63.9	85.5
United Kingdom and Europe								
	Britain (London)	Jacobs et al[14]	1990	143	85.4	96.6		
	Britain (London)	Davies et al[52]	1993	124	87	89		
	Britain	Bailey et al[53]	2006	182	88.5	–	86.8	–
	Scotland	Harry et al[54]	2009	142	94	70	50	97
	Italy	Morgante et al[55]	1999	124	58	95	78	87
Other countries								
	Serbia	Terzic et al[56]	2011	81	83.33	94.12	89.29	90.57

Table 5: Changing performance of RMI using different cut-off values (ranging from 100 to 265)

Population under study	*Author*	*RMI cut-off*	*Year*	*n*	*Sensitivity (%)*	*Specificity (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*
Pakistan	Asif et al[57]	125	2004	100	87	88	–	–
India	Arun-Muthuvel and Jaya[58]	150	2014	467	84	97	–	–
Turkey	Simsek et al[59]	163.5	2014	569	74.7	96.2	94	82.6
Iran	Ashrafgangooei and Rezaeezadeh[60]	238	2011	151	89.5	96.2	77	98
Germany	Enakpene et al[61]	250	2008	302	88.2	74.3	71.3	90
Turkey	Yavuzcan et al[62]	250	2013	153	75	93.2	88	75
Pakistan	Aziz and Najmi[39]	250	2015	283	54.05	93.4	55	93
India	Yelikar et al[63]	250	2016	102	85.71	85.07	75	91.9
Iran	Bouzari et al[64]	265	2011	182	91.3	88	52	98.5

It is more important to draw the ideology of this argument and explore different cut-off levels for different ethnic groups residing in particular geographic locales. This will require dedicated documentation and publication of RMI values from gyne-oncology centers across the world. Further, statistical input from experts can help define ideal RMI cut-offs for each population.

Based on the review, it is definite that we need to find answers to questions, such as: Are tumor markers dependent on genetic makeup? Is it possible that tumor characteristics depend on geographic areas? Do we need to develop specific screening guidelines based on ethnicity or domicile? Do groups with high-risk behaviors need different RMI cut-offs for early detection? At the moment, there is paucity of data to comment anything substantial in relation to any of these questions.

We acknowledge that the research has three pertinent limitations. Firstly, we have analyzed data from 78 women, which is a small sample size but it definitely adds to the growing pool of data from the Indian subcontinent. Secondly, although the research findings were comparable to previous studies from different parts of the world, we have grouped all our patients under a single umbrella of "North Indian" women. We aim to delve deeper and draw definite patterns in distinctive geographic or ethnic groups which reside in northern parts of India, as we collect and analyze more data in our ongoing study. Thirdly, the review of world literature is limited as articles in languages other than English are not included due to limited funding for translation.

CONCLUSION AND FUTURE PROSPECTS

The debate on the ideal screening method is ongoing, and despite many tools and algorithms, there is no consensus in the best possible technique for clinical practice. In future, the focus needs to be shifted away from the best screening tool to the development of individual cut-offs for homogenous populations. So far, no studies have specifically concentrated on stratification of screening tool cut-offs customized to distinctive ethnic groups. To add to this dilemma, we could not draw any conclusions from figures obtained from all over the world. However, we anticipate that due to our emphasis on commonly used screening tools, our findings have strong potential to influence clinical practice and encourage gynecologists from different countries to document data pertaining to RMI and CA-125. In the future, meticulous documentation of CA-125 and RMI scores will help to formulate robust evidence-based cut-off values for every ethnic and geographical group.

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