AMJ Australasian Medical Journal [AMJ 2017;10(5):375–380]

CA 19-9 is more useful than CA 125 in the diagnosis of ovarian malignancy, and can truly differentiate the histological subtypes of the ovarian tumours

Abidullah Khan, Iqbal Haider, Maimoona Ayub, and Majid Khan

Khyber Teaching Hospital (KTH), Peshawar, Pakistan

RESEARCH

Please cite this paper as: Khan A, Haider I, Ayub M and Tahir AA. CA 19-9 is more useful than CA 125 in the diagnosis of ovarian malignancy, and can truly differentiate the histological subtypes of the ovarian tumours. AMJ 2017;10(5):375–380.
https://doi.org/10.21767/AMJ.2016.2815

Corresponding Author:
Dr Abidullah Khan
Deaprtment of Medicine
Khyber Teaching Hospital
25000-Peshawar, Pakistan
Email: dr.abidk@yahoo.com

ABSTRACT

Background

CA 125 is a tumour marker; commonly, used for screening ovarian malignancy. However, recent studies have proven a limited role for CA 125 as a diagnostic marker for ovarian cancer. Nevertheless; recently, a limited number of studies have demonstrated a role for CA 19-9 in the diagnosis and prognosis of malignant ovarian tumours.

Aims

To evaluate the utility of CA 19-9 in the workup of suspected ovarian malignancy.

Methods

In this observational study, on the basis of histopathology reports of ovarian tumours, 45 patients were equally divided into three different groups namely; benign, borderline and malignant. All the patients had their serum CA 125 and CA 19-9 measured preoperatively. The data was analysed using SPSS version 16. One-way ANOVA with Turkey HSD, independent sample t-test and chi squared tests were run for the statistical analysis.

Results

Serum CA 125 does not predict the type of ovarian histopathology in a suspected ovarian malignancy, $p>0.05$. However, CA 19-9 is the highest in malignant (M=168.27±48.78, $p<0.001$), higher in borderline (M=42.92±34.08, $p<0.001$) and the lowest in benign (M=23.93±24.96, $p<0.001$) ovarian mass lesions respectively.

Conclusion

CA 19-9 is a better tumour marker in the diagnosis of suspected ovarian malignancy. Moreover, CA 19-9 can truly predict the histological subtype of the underlying ovarian tumour.

Key Words

Ovarian tumour, CA 125, CA 19-9, gynaecologic malignancy, tumour markers

What this study adds:

1. What is known about this subject?

CA 125 is a serologic marker for the workup of ovarian malignancy. Furthermore, CA 19-9 has been found to be elevated in non-pancreatic tumours as well.

2. What new information is offered in this study?

This study focuses on the usefulness of CA 19-9 as a diagnostic tumour marker for ovarian malignancy and is being compared with CA 125.

3. What are the implications for research, policy, or practice?

This study will provide basis for further studies on CA 19-9. Moreover, it may be a practice changing step in the screening and diagnosis of ovarian tumours.

Background

The glycoprotein tumour marker, CA 19-9 is used in the diagnosis of various gastrointestinal neoplasms. Moreover, CA 19-9 plays a crucial role in predicting prognosis of

colorectal, pancreatic, and biliary tract malignancies. However, it is more specific tumour marker for pancreatic malignancy.[1-6] Apart from its diagnostic and prognostic role in gastrointestinal malignancies; there is evidence that CA 19-9 is also elevated in non-gut neoplasms like dermoid cysts and even non-neoplastic inflammatory conditions like inflammatory bowel disease, liver cirrhosis, cystic fibrosis and so forth.[7,8] The usefulness of CA 19-9 in the diagnosis of ovarian malignancies has rarely been studied.[9,10]

Although, CA 125 has been used for years in the diagnosis and prognosis of ovarian malignancy; however, the charm of CA 125 in the diagnosis of ovarian cancer is declining. The reasons are that, CA 125 is also elevated in a variety of other non-ovarian conditions namely; pregnancy, endometriosis, pelvic inflammatory disease and so forth. Moreover, a number of researchers observed that CA 125 was not elevated in most primary ovarian mucinous neoplasms. Because of the non-specificity of CA 125 in truly predicting ovarian cancer, many gynaecologists and oncologists recommend the use of CA 19-9 as a preoperative marker in the workup of an ovarian mass, but the evidence is still scarce.[8,11-15]

We conducted this observational study to define the true roles of both, CA 19-9 and CA 125 in the diagnosis of ovarian neoplasm, as well as in predicting the histological type of the underlying ovarian tumour.

Method

This cross sectional study was conducted on 45 patients, aging 18–70 years, in the departments of medicine and obstetrics & gynaecology of Khyber Teaching Hospital Peshawar, Pakistan, between January 2015 and October 2016. The study was approved by the ethics review committee of our hospital and informed written consent was obtained from every participant.

The study design was prospective and observational. The inclusion criteria included; 1) Female patients, 2) age limit 18–70 years, 3) trans abdominal and/or transvaginal ultrasound proven mass lesion/s within any or both the ovaries, and 4) patients who were candidates for excision of the mass lesion/s in the ovaries or at least for laparoscopic or open biopsy.

All the patients who did not fulfil the above criteria were excluded from the study. Similarly, those with suspected or confirmed pelvic inflammatory disease (PID), endometriosis, adenomyosis, any gynaecologic neoplasm in organs other than the ovaries, endometrial thickening on trans-vaginal ultrasound, and vulval mass lesions were excluded. Furthermore, patients with suspicion of any neoplastic or non-neoplastic pancreatic lesions, gut malignancy, inflammatory bowel disease, liver cirrhosis and so forth were also excluded from the study.

All the patients who fulfilled the inclusion criteria were worked up with detailed clinical evaluation and relevant investigations, to assess their suitability for inclusion in the final study. A total of 200 patients were assessed initially; however, only 45 satisfied the strict inclusion/exclusion criteria and were thus the final subjects of the study.

On the basis of histopathology reports of the excised ovaries or biopsy of the ovarian mass, all the 45 patients were divided in three equal groups; 1) benign lesions, 2) borderline lesions, and 3) malignant lesions. All these patients had their serum CA 125 and serum CA 19-9 measured, three days before the biopsy or the operation.

All the data was collected on a structured questionnaire; specifically, designed for this purpose. The questionnaire had a combination of closed and open ended questions, and included information regarding demography, clinical findings, histopathology report, and CA 125/ CA 19-9 levels.

All the data was stored and analysed by SPSS version 16. Percentages and frequencies were determined for qualitative variables like marital status, ethnic background and so forth. Means and standard deviations were measured for quantitative variables like age, parity, CA 125 and CA 19-9 levels and so forth. Finally, one-way ANOVA was run to compare the means of CA 125 and CA 19-9 in the three groups; namely, benign, borderline and malignant ovarian lesions. Post-hoc analysis was done by using Turkey HSD. Chi-squared and independent sample t-tests were also applied.

Results

Mean age of all the participants was 46.36±6.44. Only 13 per cent of the participants were unmarried in the benign ovarian group. In the borderline ovarian group, 33 per cent of the patients were unmarried. However, none was unmarried in the group with proven ovarian malignancy. A brief overview of other demographic data is given (table 1 and 2).

The mean values of CA 125 in each of the histopathologically proven benign, borderline and malignant ovarian mass were 58.90±34.42, 73.00±49.78, and 60.47±47.06respectively. Although, the values of CA 125

were numerically higher in the borderline and malignant subgroups than in the benign group, the difference was not significant, $p>0.05$.

In order to compare means of the three groups, one-way ANOVA was run. The assumption of normality was satisfied (kurtosis=-0.75, skewness=0.55). Moreover, the assumption of homogeneity of variance was tenable [Levene (2,42)=2.90, $p>0.05$]. The results of one one-way ANOVA did not show any statistically significant difference in mean CA 125 levels across the three different histopathologic ovarian groups [F (2)=0.36, $p>0.05$]. Thus, there was enough evidence to conclude that, CA 125 value does not differ significantly, with a change in the ovarian histopathology from benign to malignant.

In order, to assess the mean values of CA 19-9 across the three groups of ovarian mass lesions; namely, benign, borderline and malignant, one-way ANOVA was applied. The assumptions of normality and homogeneity of variance were tested, and were found tenable [kurtosis=-0.40, skewness=0.84, Levene (2,42)=3.22, $p>0.05$]. The results of one-way ANOVA showed that, the blood CA 19-9 was the highest in malignant ovarian lesions (N=15, M=168.27±48.78, $p<0.05$), higher in the borderline ovarian tumours (N=15, M=42.92±34.08, $p<0.05$) and the lowest in the histopathologically benign looking ovarian mass lesions (N=15, M=23.93±24.96, $p<0.05$). Furthermore, there was a statistically significant difference in CA 19-9 levels across the three study groups; [F (2)=66.45, $p<0.001$]. Thus, there was strong evidence to suggest that, more the malignant looking ovarian mass, higher the CA 19-9 level will be. Post-Hoc analysis via Turkey HSD revealed that the biggest difference in CA 19-9 levels was seen between the malignant and borderline or benign ovarian groups ($p<0.001$). However, there was no statistically significant difference between the benign or borderline ovarian tumours ($p>0.05$).

Finally, CA 125 and CA 19-9 were analysed with respect to menopausal status by using independent sample's t-test. The results showed that, CA 125 was lower in postmenopausal ladies than the premenopausal women at a statistically significant level, t(43)=2.21, P=0.03, (Table 3). Similarly, the histological type of ovarian tumour was stratified with respect to the menopausal status of the participants by using chi-square test which demonstrated the predominance of benign or borderline histology in the premenopausal ladies than the postmenopausal women who had a predominant malignant histology (Table 4).

Discussion

CA 19-9 is a tumour marker, mainly secreted by gastrointestinal adenocarcinomas. However, it is frequently expressed in ovarian mucinous neoplasms also. It is noteworthy that; although, CA 19-9 is a well-recognized diagnostic marker in various types of gastrointestinal adenocarcinomas, there have been limited studies on the role of CA 19-9 as a diagnostic marker in various ovarian mucinous tumours.[10,15] Therefore, we conducted this study to evaluate the utility of CA 19-9 as a tumour marker in ovarian tumours.

On the basis of histogenetic background, primary mucinous tumours of the ovaries can be split into two distinct sub-types: the commoner intestinal type and the rarer Müllerian (or endocervical) type.[10] It is therefore understandable that, CA 125, which is primarily secreted by the less common Mullerian subtype of the ovarian mucinous neoplasms, cannot be a true and major representative of the vast majority of ovarian mucinous tumours, which are chiefly, the intestinal subtype.[16] Furthermore, primary mucinous tumours of the ovaries are subdivided into benign, borderline or malignant tumours, pathologically.[16] However, it must be noted that up to 75 per cent of the ovarian mucinous tumours are benign. According to the model explaining ovarian carcinogenesis, Type 1 ovarian tumours include low-grade, relatively less aggressive neoplasms like serous, mucinous, endometrioid, transitional cell carcinomas and so forth. At the time of diagnosis, such tumours, are frequently limited to the ovary and have a relatively stable genome. In contrast, ovarian tumours in the type-2 category, because of their inborn genetic instability, are usually high-grade and aggressive and include serous carcinomas, undifferentiated carcinomas, and so forth.[17-20]

Magnetic resonance imaging (MRI) of the ovaries can be useful in differentiating the different subtypes of ovarian mass lesions and at times, can precisely, be indicative of the behaviour of the tumours, for example to regard them as less aggressive, low grade or more aggressive and high grade lesions.[21] However, considering less cost-effectiveness and lack of widespread availability of MRI; especially, in the developing world like Pakistan, its true role is still questionable. Furthermore, serum CA 125 level, a typical tumour marker usually used for the screening of ovarian malignancy, is often not elevated in various mucinous and non-mucinous ovarian tumours. Considering the limitations of the usefulness of CA 125, as the best marker of ovarian malignancy, confirmation with CA 19-9 is recommended by different authorities.[22-23] Our study

demonstrated that, CA 19-9 is often elevated in ovarian tumours and is better than CA 125 in predicting the underlying histological subtype of the ovarian tumour. In our study, we observed that, CA 19-9 had a strong positive association with a malignant change within the ovarian tumours, as the highest values of CA 19-9 were encountered in patients with malignant tumours than those with borderline or benign ovarian mass lesions.

The mechanism behind elevation of CA 19-9 in various ovarian cysts has been documented. In one study, the presence of CA 19-9 in the mucosal lining of the bronchi, and mature cystic teratoma was demonstrated, by using immunohistochemical staining. It was suggested that, leakage of CA 19-9 from the tumour into the blood is probably, the mechanism behind high levels of CA 19-9 in the blood of those with ovarian malignancy.[24] Emin et al. suggested a role for the tumour size. They observed that, larger the ovarian tumour, higher the serum CA 19-9 will be. Although, we did not study the relationship between tumour size and the blood CA 19-9, we found a significant association between tumour histology and the serum CA 19-9 levels. It must be noted that, there is scarcity of published evidence of the usefulness of CA 19-9, as a crucial preoperative screening tool in ovarian cancer. In a sharp contrast to our results, a retrospective study by Paul et al., failed to reveal a significant relationship between serum CA 19-9 elevation and histologic subtype of the primary mucinous tumours of the ovary.[10]

We recommend further studies to evaluate the role of CA 19-9, as a marker of diagnosis and prognosis in suspected ovarian malignancy. Furthermore, larger sample size must be incorporated in any future studies, to better understand the usefulness of CA 19-9 in patients with ovarian mass lesions.

Conclusion

Preoperative CA 19-9 level, can truly predict the histological subtype of the underlying ovarian tumour. Moreover, CA 19-9 has the highest, intermediate and lowest blood values in malignant, borderline and benign tumours of the ovaries respectively. In contrast to CA 19-9, preoperative serum CA 125 does not suggest the histological nature of the ovarian mass lesion.

References

1. Pavai S, Yap SF. The clinical significance of elevated levels of serum CA 19-9. Med J Malaysia.2003;58:667–72.
2. Scharl A, Crombach G, Vierbuchen M, et al. Antigen CA 19-9: presence in mucosa of nondiseased mullerian duct derivatives and marker for differentiation in their carcinomas. Obstet Gynecol. 1991;77:580–85.
3. Dede M, Gungor S, Yenen MC, et al. CA19-9 may have clinical significance in mature cystic teratomas of the ovary. Int J Gynecol Cancer. 2006;16:189–93
4. Wang WS, Lin JK, Chiou TJ, et al. CA19-9 as the most significant prognostic indicator of metastatic colorectal cancer. Hepatogastroenterology. 2002;49:160–64.
5. Ni XG, Bai XF, Mao YL, et al. The clinical value of serum CEA, CA19-9, and CA242 in the diagnosis and prognosis of pancreatic cancer. Eur J Surg Oncol. 2005;31:164–69.
6. Fong ZV, Winter JM. Biomarkers in pancreatic cancer: diagnostic, prognostic, and predictive. Cancer J.2012;18:530–38. http://emedicine.medscape.com/article/2087513-overview#a2
7. Cho H, Kyung MS. Serum CA19-9 as a Predictor of Malignancy in Primary Ovarian Mucinous Tumors: A Matched Case-Control Study. Medical Science Monitor : International Medical Journal of Experimental and Clinical Research. 2014;20:1334-1339. doi:10.12659/MSM.890954.
8. Kyung MS, Choi JS, Hong SH, et al. Elevated CA 19-9 levels in mature cystic teratoma of the ovary. Int J Biol Markers. 2009;24:52–56
9. Kelly PJ, Archbold P, Price JH, et al. Serum CA19.9 levels are commonly elevated in primary ovarian mucinous tumours but cannot be used to predict the histological subtype. J Clin Pathol. 2010;63:169–73.
10. Bast RC, Jr, Klug TL, St John E, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med. 1983;309:883–87.
11. Gadducci A, Ferdeghini M, Prontera C, et al. The concomitant determination of different tumor markers in patients with epithelial ovarian cancer and benign ovarian masses: relevance for differential diagnosis. Gynecol Oncol. 1992;44:147–55.
12. Zorn KK, Tian C, McGuire WP, et al. The prognostic value of pretreatment CA 125 in patients with advanced ovarian carcinoma: a Gynecologic Oncology Group study. Cancer. 2009;115:1028–35.
13. Lu D, Kuhn E, Bristow RE, et al. Comparison of candidate serologic markers for type I and type II ovarian cancer. Gynecol Oncol. 2011;122:560–66.
14. Rosen DG, Wang L, Atkinson JN, et al. Potential markers that complement expression of CA125 in epithelial ovarian cancer. Gynecol Oncol. 2005;99:267–77.
15. Hart WR. Mucinous tumors of the ovary: a review. Int J Gynecol Pathol. 2005;24:4–25

16. Shih Ie M, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol. 2004;164:1511–18.
17. Koshiyama M, Matsumura N, Konishi I. Recent concepts of ovarian carcinogenesis: type I and type II. Biomed Res Int. 2014;2014:934261.
18. Kurman RJ, Shih Ie M. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer – shifting the paradigm. Hum Pathol. 2011;42(7):918–31
19. Santin AD, Zhan F, Bellone S, et al. Gene expression profiles in primary ovarian serous papillary tumors and normal ovarian epithelium: identification of candidate molecular markers for ovarian cancer diagnosis and therapy. Int J Cancer. 2004;112:14–25
20. Bazot M, Haouy D, Darai E, et al. Is MRI a useful tool to distinguish between serous and mucinous borderline ovarian tumours? Clin Radiol. 2013;68:e1–8
21. Donaldson ES, Van Nagell JR, Pursell S, et al. Multiple biochemical markers in patients with gynecologic malignancies. Cancer. 1980;45:948–53.
22. Karaferic A, Jovanovic D, Jelic S. Expression of HER2/neu, estrogen and progesterone receptors, CA 125 and CA19-9 on cancer cell membrane in patients with serous and mucinous carcinoma of the ovary. J BUON. 2009;14:635–39.
23. Ito K. CA19-9 in mature cystic teratoma. Tohoku J Exp Med. 1994;172:133–38.
24. Emin U, Tayfun G, Cantekin I, et al. Tumor markers in mature cystic teratomas of the ovary. Arch Gynecol Obstet. 2009;279:145–47.

ACKNOWLEDGEMENTS

We are thankful to the laboratory service of our hospital for their help. We are grateful to all the participants included in the study.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

None

ETHICS COMMITTEE APPROVAL

This study was approved by the Ethics Review Committee of Khyber Teaching Hospital/Khyber Medical College, Peshawar, Pakistan. An informed written consent was obtained from every participant of this study.

Table 1: Combined demographic data and CA 125/CA 19-9 values in all the 45 participants

Variable	Value	Standard Deviation
Age (years)	46.36	6.44
Weight (kilogram)	48.22	5.28
Height (foot)	5.09	0.52
Parity	2.71	1.80
CA 125 (IU/ml)	64.11	43.90
CA 19-9 (IU/ml)	78.40	74.31

Table 2: Group wise demographic data and values of tumour markers, CA 125 and CA 19-9

Group	CA 125 (IU/ml)	CA 19-9 (IU/ml)	Age (years)	Parity	Weight (Kg)	Height (feet)
Benign	58.87±34.42	23.93± 24.96	45.13± 6.30	2.80± 1.86	49.27± 4.11	5.06± 0.45
Borderline	73± 49.78	42.93± 34.08	44.93± 7.49	2.33± 1.75	49.93± 6.97	5.13± 0.64
Malignant	60.47± 47.06	168.27± 48.78	49± 4.79	3± 1.81	45.47± 3.09	4.93± 0.45

Table 3: Stratification of tumour makers with respect to menopausal status by using independent sample's t-test

Variable	Premenopausal		Postmenopausal	
	Mean	SD	Mean	SD
CA 125(IU/L)	76.40	49.20	49.00	31.00
CA 19-9(IU/L)	57.30	61.10	105.00	82.30
P value	<0.05		<0.05	

Table 4: Stratification of ovarian histology with respect to menopausal status by using chi- square test

	Premenopausal (n=25)		Postmenopausal (n=20)		P value
	Number	Percentage	Number	Percentage	
Benign	10	40%	5	25%	0.10
Borderline	10	40%	5	25%	
Malignant	5	20%	10	50%	
Total	25	100%	20	100%	