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Serum CA19.9 levels are commonly elevated in primary ovarian mucinous tumours but cannot be used to predict the histological subtype

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ABSTRACT

Aims CA19.9 is a monosialoganglioside secreted by mucinous tumours of the gastrointestinal tract, including the pancreas and biliary tree. Limited studies have shown that this tumour marker may also be elevated in primary ovarian mucinous neoplasms, but no study has assessed whether serum CA19.9 levels can be used to predict if a primary ovarian mucinous tumour is benign, borderline or malignant. The aim of this study was to correlate the serum CA19.9 level with the histological features in a large series of primary ovarian mucinous neoplasms.

Methods 144 cases of primary ovarian mucinous neoplasm (79 benign, 45 borderline and 20 malignant) were identified in which a preoperative serum CA19.9 level had been performed. The association between the serum levels and the histological subtype and a variety of other parameters was investigated. In a subset of cases, immunohistochemical staining for CA19.9 was performed on tumour blocks.

Results Serum CA19.9 levels were elevated in 27%, 38% and 40% of mucinous cystadenomas, borderline mucinous tumours and mucinous carcinomas, respectively. Markedly elevated levels of serum CA19.9 were observed in each group, with the highest serum CA19.9 measurements being noted in borderline mucinous tumours. There was no relationship between the serum CA19.9 level and whether the tumours were benign, borderline or malignant (Kruskal–Wallis test p value=0.32). A weak but statistically significant correlation was found between tumour maximum dimension and CA19.9 level (Spearman's rank correlation coefficient=0.17, p=0.04). In those cases in which CA19.9 immunohistochemistry was performed, all tumours showed positive staining for CA19.9, with 60% of these cases being associated with an elevated serum CA19.9 level.

Conclusion Preoperative CA19.9 levels cannot be used to predict whether a suspected ovarian mucinous tumour is benign, borderline or malignant. Markedly elevated serum levels (>1000 U/ml) may be found in benign mucinous neoplasms as well as in borderline and malignant tumours.

INTRODUCTION

Tumour markers are widely used in clinical practice. These are substances produced and released by neoplastic cells, or less commonly host cells, and their presence in serum or biological fluids acts as an indicator of the presence of a tumour[1]. CA125 is widely regarded as the most reliable and useful serum tumour marker of ovarian carcinoma.[2 3] It is of use in the investigation and management of a woman with an adnexal mass or disseminated peritoneal disease, and also in monitoring the response to chemotherapy and in follow-up of patients with known ovarian carcinoma. The role of CA125 as a screening tool in the diagnosis of ovarian malignancy is more controversial,[4] particularly as elevated serum levels can be present in benign conditions, such as pregnancy, endometriosis, pelvic inflammatory disease, ascites and non-gynaecological diseases. Elevated serum CA125 levels may also be present in non-gynaecological malignancies, particularly those with disseminated peritoneal disease. Although mild or moderate elevations in serum CA125 may be seen with other histological types of ovarian carcinoma, such as endometrioid or clear cell, markedly elevated levels are characteristic of serous carcinoma. Ovarian mucinous neoplasms are less frequently associated with an elevated serum CA125 than non-mucinous tumours[5] and levels are typically within the normal range or mildly elevated.[6 7] In most ovarian mucinous neoplasms with an elevated serum CA125, it is likely that the CA125 is secreted by reactive mesothelial cells, which are commonly seen in the omentum of patients with ovarian mucinous tumours, rather than by the tumour cells themselves since immunohistochemically the neoplastic cells are usually CA125 negative (W Glenn McCluggage, personal observations).

CA19.9 is a monosialoganglioside secreted by mucinous tumours of the gastrointestintal tract, including the pancreas and biliary tree.[8 9] Elevated serum levels are sometimes found in patients with an ovarian epithelial or germ cell tumour, in particular epithelial neoplasms of mucinous type, or germ cell tumours with a mucinous component.[9–16] Accordingly, in some institutions, CA19.9 has been incorporated as a tumour marker in a patient with an ovarian mass.

Primary mucinous neoplasms of the ovary represent a diverse group of tumours, from a histogenetic viewpoint and from a morphological viewpoint. They can be subdivided into two distinct histogenetic types: namely the much more common intestinal (or non-specific) type and the less common Müllerian (or endocervical) type. Within these two categories, ovarian mucinous tumours constitute a spectrum and are further subdivided into benign mucinous cystadenoma, borderline mucinous tumour (mucinous tumour of low malignant potential) and mucinous carcinoma.[17–26]

While in many institutions, CA19.9 is used as a preoperative tumour marker in the investigation of a patient with an ovarian mass, to date there have been few studies that have investigated whether serum levels correlate with the histological subtype of mucinous neoplasm. This study aims to address

this issue and to establish if there is a correlation between the serum CA19.9 level and (i) whether the mucinous tumour is benign, borderline or malignant, and (ii) a variety of other clinical and pathological parameters including tumour size and the menopausal status of the patient. In a subset of cases, the tumour was stained with CA19.9 to investigate whether there is a correlation between the serum CA19.9 level and the immunohistochemical staining pattern.

METHODS

Cases of primary ovarian mucinous tumour diagnosed between 2004 and 2008 were retrieved from the archives of the four pathology departments in Northern Ireland, UK, by performing a computer search using the appropriate SNOMED codes. Those cases in which preoperative serum CA19.9 measurements were available are included in the study. All serum tumour assays were performed in the Clinical Chemistry department of Belfast City Hospital Cancer Centre. CA19.9 was measured on the Abbott Axsym (Abbott UK, Maidenhead, UK) system until September 2006 and thereafter on the Abbott Architect by the CA19.9 XR assay. Serum CA19.9 of 0–37 U/ml was taken as within the normal range. The pathology reports were reviewed and parameters recorded were the patient age, the menopausal status (for the purposes of the study, age 50 years or less was taken as premenopausal and age >50 years as postmenopausal), the maximum tumour dimension, the histogenetic type (intestinal or Müllerian), whether the tumour was benign, borderline or malignant, and the International Federation of Gynecology and Obstetrics (FIGO) stage. All cases were discussed at a gynaecological oncology multidisciplinary meeting and all neoplasms confirmed as ovarian primaries.

Cases were excluded from the study if there was a prior or concurrent diagnosis of a second primary malignancy. Cases were also excluded if there was another histological type of primary ovarian epithelial tumour, either borderline or malignant. Cases in which a mucinous neoplasm occurred in association with a mature cystic teratoma or a Brenner tumour (both known associations) were included in the study. The presence of other benign lesions, either in the ovary or in other resected tissues, was recorded, but did not preclude a case from inclusion.

In 10 cases, immunohistochemical staining for CA19.9 had been performed at the time of reporting of the case. In these cases, the immunostained slide was reviewed, and staining of the mucinous epithelial component was categorised as negative, focally positive (<50% of tumour staining) or diffusely positive (≥50% of tumour staining).

Statistical analysis

The significance of differences in serum CA19.9 levels between the histological subtypes of tumour (benign, borderline and malignant) was determined using a Kruskal–Wallis test. Spearman's Rank correlation was used to evaluate the relationship between tumour size and serum CA19.9, and between patient age and serum CA19.9. Student t test was used to compare the menopausal status of the patients and the serum CA19.9 level. A p value of less than 0.05 was regarded as significant. There were too few cases of Müllerian-type mucinous neoplasm to statistically evaluate the relationship between histogenetic type and the serum CA19.9 level.

RESULTS

Three hundred and ninety-three cases of primary ovarian mucinous neoplasm were identified from the pathology archives. Of these, 178 had a preoperative serum CA19.9 level performed. One hundred and forty-four cases fulfilled the criteria for inclusion in the final analysis (79 benign, 45 borderline and 20 malignant). The surgical procedure performed was variable and ranged from ovarian cystectomy to hysterectomy, bilateral salpingoophorectomy and omentectomy.

Benign mucinous cystadenoma

Patient and tumour characteristics

Seventy-nine cases of benign mucinous cystadenoma met the inclusion criteria. The age of the patients ranged from 14 years to 81 years (mean 49 years, median 50 years). Thirty-six patients were postmenopausal and 43 were premenopausal. The maximum tumour dimension was available in 77/79 cases; in the other two cases the cyst was received piecemeal. The maximum tumour diameter ranged from 4 cm to 38 cm (mean 16 cm, median 17 cm). As expected, all tumours were FIGO stage I. Benign mucinous cystadenomas are not generally classified into intestinal and Müllerian types, and so these are not further subdivided. Additional pathology was a coexistent Brenner tumour in the same ovary (n=4), adenomyosis (n=4), features of torsion (n=2), serous cystadenoma in the contralateral ovary (n=2), endometriosis (n=2), dermoid cyst (n=4; same ovary in two cases, contralateral ovary in one case, and both ovaries in one case) and an isolated vasculitis (n=1).

Borderline mucinous tumour

Patient and tumour characteristics

Forty-five cases of borderline mucinous tumour met the inclusion criteria. The age of the patients ranged from 18 years to 80 years (mean 47 years, median 45 years). Fifteen patients were postmenopausal and 30 premenopausal. The maximum tumour dimension was recorded in all cases and ranged from 2.2 cm to 33 cm (mean 20 cm, median 20 cm). The cyst capsule was recorded as intact in 19 cases and deficient in 22 cases. In four cases, there was no record as to the integrity of the capsule on gross examination. All cases were FIGO stage I. In four cases, the borderline tumour was Müllerian in type, and the others were of intestinal-type. Additional pathology was adenomyosis (n=1), endometriosis (n=2), atypical endometrial hyperplasia (n=1), serous cystadenoma in the contralateral ovary (n=1), and Brenner tumour in the same ovary (n=2).

Mucinous carcinoma

Patient and tumour characteristics

Twenty cases of primary ovarian mucinous carcinoma met the inclusion criteria. The age of the patients ranged from 27 years to 75 years (mean 52 years, median 51 years). Ten patients were postmenopausal and 10 were premenopausal. The maximum tumour dimension was recorded in 19 cases and ranged from 11 cm to 35 cm (mean 19 cm, median 17 cm). The tumour capsule was recorded as intact in six cases and deficient in 10 cases. In four cases, there was no record as to the integrity of the capsule on gross examination. Nineteen cases were FIGO stage I and one was FIGO stage IIIB. A diagnosis of Müllerian-type mucinous carcinoma was made in two cases and the others were of intestinal type. Additional pathology was Brenner tumour in the same ovary (n=1), benign mucinous cystadenoma in the contralateral ovary (n=1), and dermoid cyst in the same ovary (n=1).

Correlation between serum CA19.9 level and histological subtype

Table 1 summarises the serum CA19.9 levels in the various tumour subtypes (ie, benign, borderline and malignant). The mean, median and interquartile ranges for serum CA19.9 levels are also given. On statistical analysis, there was no evidence of

Table 1 Serum CA19.9 levels in histological subtypes of primary ovarian mucinous tumour

Tumour subtype	No. of cases	No. of cases above normal value* (%)	Range of CA19.9 levels (U/ml)	Mean serum CA19.9 level (U/ml)	Serum level (percentiles)		
					25th percentile (U/ml)	50th percentile (median) (U/ml)	75th percentile (U/ml)
Benign	79	21 (27%)	<2–4447	158	6.0	13.0	52.0
Borderline	45	17 (38%)	<1–153 216	6151	5.0	13.0	179.0
Malignant	20	8 (40%)	<1–22 109	1714	8.8	25.0	378.3

p=0.32 (Kruskal–Wallis Test).
*Normal CA19.9=0–37 U/ml.

a significant relationship between tumour type and serum CA19.9 level (Kruskal–Wallis test p value=0.32).

Correlation between serum CA19.9 level and tumour size

The mean and median maximum tumour dimensions for benign, borderline and malignant mucinous neoplasm are stated above. A weak correlation was observed between maximum tumour dimension and serum CA19.9 level when all tumour sizes were analysed in combination with size as a continuous variable (Spearman's rank correlation coefficient=0.17, p=0.04). A similar correlation was observed within the benign group when maximum tumour dimension was assessed for each individual tumour subtype (Spearman's rank coefficient=0.28, p=0.02). There was no evidence of a correlation within the borderline (Spearman's rank correlation coefficient=0.06, p=0.71) or malignant groups (Spearman's rank correlation coefficient=−0.03, p=0.91).

Correlation between serum CA19.9 level and menopausal status

The mean serum CA19.9 level in the premenopausal patients (n=83) was 2730 U/ml and in the postmenopausal patients was 1572 U/ml (n=61). There was no statistically significant difference between the two groups (p=0.62).

CA19.9 IMMUNOHISTOCHEMICAL STAINING AND COMPARISON WITH SERUM CA19.9 LEVEL

Ten cases (two borderline, eight malignant) were stained with CA19.9 and all were positive. Focal staining was present in four cases, all of which were mucinous carcinomas. The remaining cases, including both borderline tumours, exhibited diffuse staining. The serum CA19.9 level in the two borderline cases was 4 U/ml and 20 U/ml. The serum CA19.9 level in the four mucinous carcinomas that showed focal staining for CA19.9 ranged from <1 U/ml to 2752 U/ml. The serum CA19.9 level in the four mucinous carcinomas showing diffuse positive staining ranged from 22 U/ml to 6632 U/ml. Four cases (two borderline, two malignant) had a normal serum CA19.9 level despite showing positive immunohistochemical staining. Figure 1 shows an example of an ovarian mucinous carcinoma staining diffusely for CA19.9.

DISCUSSION

CA19.9 is a sialylated oligosaccharide recognised by a monoclonal antibody originally developed against a human colorectal carcinoma cell line.[27] High rates of serum detection were initially demonstrated in patients with colonic and pancreatic cancer.[28 29] Subsequent studies have shown an increased serum CA19.9 in up to 51% of patients with ovarian cancer, with levels being most frequently elevated in ovarian mucinous neoplasms.[30] That increased serum CA19.9 levels may occur in ovarian mucinous neoplasms is not surprising given that the majority of these exhibit intestinal differentiation.[17 20] While the differentiation between intestinal and Müllerian type mucinous neoplasms is usually restricted to borderline and malignant subtypes, it is clear that many benign ovarian mucinous neoplasms also exhibit intestinal differentiation. The pathological distinction between an intestinal and a Müllerian mucinous neoplasm has been extensively discussed previously[17 20] and we make the point that intestinal differentiation is not always apparent morphologically in the form of goblet cells. Many intestinal-type mucinous neoplasms do not contain goblet cells but rather their mucin histochemical profile is akin to that of gastric or pancreaticobiliary epithelium.[31]

Previous studies have shown that elevated serum CA19.9 is predictive that an ovarian neoplasm is mucinous in type, but until now no study has determined if serum CA19.9 levels can be used to predict whether a primary ovarian mucinous neoplasm is benign, borderline or malignant. This would be clinically useful since it is often suspected on radiological examination that an ovarian mass is mucinous in type, since these neoplasms are usually large and unilateral. If serum CA19.9 levels could predict whether a likely mucinous tumour was benign, borderline or malignant, this could allow for full surgical staging, including lymphadenectomy, to be performed at initial surgery. Our study shows that the percentage of neoplasms associated with an elevated serum CA19.9 increases from benign through borderline to malignant. However, there was no statistically significant difference between the mean or median serum levels when comparing these three groups. The highest individual serum levels were seen in tumours that were borderline on histology. A notable finding was that 27% of benign mucinous tumours were associated with an elevated preoperative serum CA19.9 level, and in one

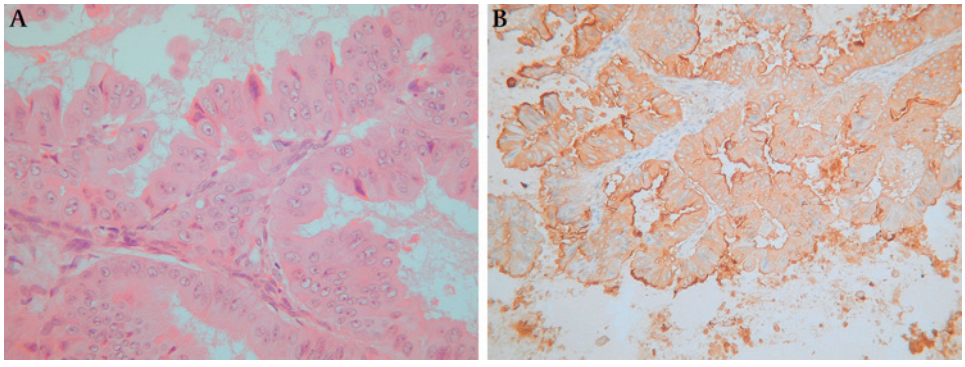

Figure 1 Mucinous ovarian carcinoma of intestinal type (A), exhibiting diffuse immunoreactivity for CA19.9 (B).

case a massive elevation at 4447 U/ml was recorded. A similar markedly elevated CA19.9 level has been reported previously in a benign mucinous cystadenoma.[16] This contradicts other reports that suggest that CA19.9 levels greater than 1000 U/ml are almost always associated with a malignant tumour.[32] Thirty-eight per cent of borderline mucinous tumours were associated with an elevated CA19.9 in our study. This number is comparable to two other studies that have observed an elevated serum CA19.9 level in 40.9% and 45% of mucinous borderline tumours.[14 33] In our study, we found 40% of ovarian mucinous carcinomas to be associated with an elevated serum CA19.9 level. This is at variance with other studies that have reported an elevated CA19.9 level in between 76.9% and 83.3% of ovarian mucinous carcinomas.[5 13] These latter studies included larger numbers of mucinous carcinoma than our study. In one of these studies, 12 of 30 mucinous carcinomas were FIGO stage II or greater.[13] This is unusual for primary ovarian mucinous carcinomas, which are almost always stage I, and suggests to us that some of the neoplasms in that study might represent secondary carcinomas. Only one case of mucinous carcinoma in our study was higher than stage I. All our cases were discussed at a gynaecological oncology multidisciplinary meeting and the possibility of a secondary neoplasm excluded by a combination of clinical, radiological and pathological parameters. While an objective of our study was to investigate whether there was a correlation between tumour stage and serum CA19.9, obviously no meaningful analysis could be performed since there was only a single case of advanced stage ovarian mucinous carcinoma.

The very high serum CA19.9 levels observed in a small number of borderline mucinous tumours skewed the mean data in our series. By assessing the median serum CA19.9 levels across the study groups, it can be seen that serum levels were highest in the malignant group, but these median values still fell within the normal range.

It is well recognised that primary ovarian mucinous tumours are heterogeneous neoplasms in which areas that are morphologically benign, borderline and malignant commonly coexist in an individual tumour. It is also well established that there is a continuum from benign to borderline to malignant; in other words mucinous cystadenomas may evolve to a borderline tumour, which may in turn give rise to an invasive carcinoma.[18 20 22 34 35] Extensive pathological sampling is therefore required when evaluating ovarian mucinous neoplasms in order to avoid missing a small area of malignancy. Theoretically in our series, foci of invasion could have been missed in the individual benign and borderline mucinous tumours with markedly elevated serum CA19.9. However, we feel this is unlikely and it is clear that markedly elevated CA19.9 levels may occur in benign, borderline and malignant primary ovarian mucinous neoplasms.

It has been reported previously that serum CA19.9 levels may correlate to some extent with the size of an ovarian mucinous borderline tumour.[33] In our series, there was a weak but statistically significant correlation between maximum tumour dimension when considering all cases together and serum CA19.9. A weak correlation was also found between maximum tumour dimension and CA19.9 level in benign mucinous cystadenomas, but there was no evidence of such an association in the borderline and malignant groups. It is likely that the overall correlation reflects the relationship observed within the benign group, as more benign neoplasms were included in our study. As CA19.9 is directly produced by tumour cells, it would be expected that some correlation would exist between serum levels and size. However, substances produced by tumour cells are not necessarily released into the serum.[8 36] Furthermore, increased tumour size does not necessarily equate with an increased amount of constituent epithelium, since many of these neoplasms are predominantly cystic, with an epithelial component accounting for only a minor proportion of the tumour.

There was no demonstrable relationship the between menopausal status of the patients and the serum CA19.9 level. Similarly, no relationship was observed when age was considered as a continuous variable. While there may be little theoretical basis to expect such a relationship, we have identified no other studies that have attempted to address this point.

As discussed, mucinous ovarian tumours can be divided into the much more common intestinal type and the relatively rare Müllerian type. This distinction was initially made in borderline tumours[23] but has more recently been described in carcinomas.[19 25 37] A total of six Müllerian-type mucinous tumours were included in our study (four borderline, two malignant). Elevated serum CA19.9 levels were observed in one borderline and one malignant Müllerian neoplasm but given the small number of these tumours in our study, it is not appropriate to attempt to draw any meaningful conclusion.

Elevated serum CA19.9 levels are encountered in a range of benign and malignant conditions, both gynaecological and non-gynaecological.[9] With respect to benign ovarian neoplasms, elevated levels are sometimes seen with dermoid cysts (mature cystic teratomas).[11] Approximately 3–5% of ovarian mucinous tumours occur in association with a dermoid cyst,[38] and it is probable that elevated CA19.9 levels reflect the presence of mucinous epithelium within these lesions. In our series, several mucinous neoplasms (four benign, one malignant) were associated with a dermoid cyst. Serum CA19.9 levels in the benign cases ranged from 9 U/ml to 96 U/ml; the serum CA19.9 level was 20 U/ml in the single malignant case. There is also a known association between Brenner tumour and an ovarian mucinous neoplasm[17]; seven such cases were included in this study (four benign, two borderline, one malignant). A single case report has described an elevated serum CA19.9 level in association with a Brenner tumour.[39] In our study, only one mucinous cystadenoma in association with a Brenner tumour was associated with an elevated serum CA19.9.

Increased serum CA19.9 levels have been documented in patients with malignancies of the stomach, colorectum, pancreas, lung and liver. Elevated levels have also been described in benign conditions of the hepatobiliary tract, and in renal failure, systemic lupus erythematosis and pneumonia.[9] In our series, patients presented with symptoms relating to the presence of an adnexal mass. Only clinical information provided on the pathology request form was used to assess eligibility for inclusion in the study and those who had a history of another malignancy were excluded. We cannot exclude the possibility that some patients had one or more of the non-gynaecological conditions described and this is a potential source of error in this study.

Immunohistochemical staining for CA19.9 was performed on 10 cases (two borderline, eight malignant) in our study. Sixty per cent of cases, including the two borderline tumours, exhibited diffuse positive staining for CA19.9; the remaining cases showed focal staining. Fifty per cent and 33% of the cases that showed focal and diffuse positivity for CA19.9, respectively, were associated with an elevated serum CA19.9. This supports the theory that substances secreted by tumour cells are not necessarily released into the blood.[8] The number of cases on which CA19.9 immunohistochemistry was undertaken is very small and it would be interesting to perform this in a larger number of cases.

CA125, a murine monoclonal immunoglobulin raised to a cell line derived from ovarian serous adenocarcinoma, is one of the most

Take-home messages

- The serum CA19.9 is elevated in a significant percentage of primary ovarian mucinous tumours.
- There is no association between the serum CA19.9 level and the morphological subtype of primary ovarian mucinous neoplasm.
- There is a weak association between maximum tumour dimension and the serum CA19.9 level.

widely used serum tumour markers in clinical practice.[1 40] CA125 is less frequently elevated in mucinous ovarian tumours when compared with serous neoplasms.[41] Although the results are not presented, serum CA125 levels were available for many of the cases included in our study. Elevated serum levels (>35 U/ml) were found in 25%, 58% and 70% of cases of benign, borderline and malignant mucinous neoplasm, respectively. The range of serum CA125 levels was 4–855 U/ml in benign mucinous cystadenomas, 2–2011 U/ml in borderline mucinous tumours, and 10–3016 U/ml in mucinous carcinomas. Immunohistochemical expression of CA125 is uncommon in ovarian mucinous tumours.[8] It is likely that the elevated serum CA125 level in primary ovarian mucinous neoplasms is attributable to CA125 production by reactive mesothelial cells within the peritoneum and omentum. Histologically, the omentum in primary ovarian mucinous neoplasms often contains collections of reactive mesothelial cells (W Glenn McCluggage, personal observations) that are immunohistochemically CA125 positive. This is likely because primary ovarian mucinous neoplasms are typically large and result in mesothelial cell proliferation as a direct pressure effect.

CONCLUSION

In the investigation of a patient with an ovarian mass it has been shown previously that an elevated serum CA19.9 level is predictive of a mucinous neoplasm. This study adds to the current literature by illustrating that serum CA19.9 levels do not correlate with the histological subtype of a primary ovarian mucinous tumour; in other words, the serum level cannot be used to predict whether an ovarian mucinous neoplasm is benign, borderline or malignant. Markedly elevated serum CA19.9 levels can be seen with benign, borderline or malignant ovarian mucinous neoplasms. A weak correlation exists between tumour size and increased serum CA19.9 levels.

Competing interests None.

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