Title Page

Importance of serial CA125 pattern rather than absolute cut-offs in detection of asymptomatic ovarian cancer in women at increased risk.

*James Dilley MRCOG[1], *Ranjit Manchanda MRCOG[12], Michelle Johnson MSc[1], Adam N. Rosenthal PhD[1], Sue Gessler PhD [1], Usha Menon FRCOG[1]

[1]Department of Women's Cancer, EGA Institute for Women's Health, University College London, 149 Tottenham Court Road, London W1T 7NF, UK;

[2]Department Gynaecological Oncology, Barts and the London Hospital, London, UK;

*Joint

Corresponding Author

Mr James Dilley

Gynaecological Cancer Research Centre, EGA Institute for Women's Health,

First floor, Maple House,

149 Tottenham Court Road, London W1T 7NF

Email j.dilley@ucl.ac.uk

Tel: +44(0)2034472108

Fax- +44(0)2034472129

KEYWORDS: CA125, ovarian screening, family history, cancer risk, ovarian cancer, primary peritoneal cancer, diverticulitis

SYNOPSIS: Assessment based on change in serial CA125 values rather than absolute cut-off would have allowed earlier diagnosis of invasive epithelial ovarian cancer.

Word Count 392

A 45-year old presented to our familial gynaecological cancer clinic. Her family-history of cancer did not fulfil criteria used in clinic or the national UK Familial Ovarian Cancer Screening Study (UKFOCSS for high-risk patients. She had no living affected relatives and was not eligible for BRCA1/2 testing. Hence, she was ineligible for risk-reducing salpingo-oophorectomy (RRSO) or 4-monthly screening on UKFOCSS. Given her family-history and wishes, annual screening (annual Ca125 and Trans-vaginal Ultrasound (TVUS) was arranged. She had a history of diverticulitis. Her Ca125 remained normal (30U/ml cut-off) in 2008 (12U/ml) and 2009 (24U/ml) and rose to 176U/ml in July-2010 (Fig-1). Her TVUS remained normal throughout. In July-2010 she gave a 7-month history of worsening constipation, bloating, urinary frequency and left sided pain. Repeat Ca125 was 233U/ml; TVUS showed only thickening of the left fallopian tube and colonoscopy was consistent with diverticular disease. .CT scan in August-2010 showed widespread abdomino-pelvic peritoneal and omental disease. Omental biopsy confirmed diagnosis of poorly-differentiated serous carcinoma of ovarian/peritoneal origin. Genetic testing following diagnosis showed no mutations in the BRCA1/2 genes. Retrospective analysis of Ca125 values using the Risk of Ovarian Cancer Algorithm (ROCA)(1) used in screening trials would have classified her as being at ‘high-intermediate’ risk

which would have triggered repeat Ca125 and imaging in 4 weeks in July 2009, twelve months before diagnosis (Fig-1).

Our case highlights important issues facing patients and clinicians managing women with family-history of breast and/or ovarian cancer. The only effective clinical option is RRSO but currently it is recommended only in BRCA1/2 mutation carriers or women with a high-risk family-history. In those with a family-history suggestive of lesser levels of risk, the available options are symptom awareness (2) and screening, both of which are of questionable efficacy. Our experience emphasises the importance of serial CA125 profile. ROCA use when compared to a fixed cut-off doubled the number of screen-detected invasive epithelial OC in the general population UK Collaborative Trial of Ovarian Cancer Screening.(3) The PEB longitudinal algorithm has also been shown on modelling to identify ovarian cancer earlier (4). Even using a simple doubling rule may have led to an earlier diagnosis. Reliance on an absolute CA125 cut-off or normal pelvic TVUS in the context of rising marker levels is inadequate. This is immediately relevant to clinicians who offer adhoc screening to high-risk patients who are unwilling to consider risk-reducing surgery.

Conflict of Interest Statement

UM owns stocks in Abcodia, Ltd., a UCL company with an interest in ROCA and ovarian cancer screening. The other authors declare no conflict of interest.

Contribution to authorship

JD, RM, ANR, MJ and UM drafted the report. MJ, RM, ANR, SG, UM were involved in the clinical care of the patient. All authors contributed to and approved this manuscript.

Patient Consent

Written consent to publish was obtained from the patient

References

1. Skates SJ, Menon U, MacDonald N et al. Calculation of the Risk of Ovarian Cancer From Serial CA-125 Values for Preclinical Detection in Postmenopausal Women. J Clin Oncol. 2003;15(21):206–10.

2. Rossing M a, Wicklund KG, Cushing-Haugen KL, Weiss NS. Predictive value of symptoms for early detection of ovarian cancer. Journal of the National Cancer Institute. 2010. p. 222–9.

3. Menon U, Ryan A, Kalsi J, Gentry-Maharaj A, Dawnay A, Habib M, et al. Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. J Clin Oncol. 2015;

4. Drescher CW, Shah C, Thorpe J, O'Briant K, Anderson GL, Berg CD, et al. Longitudinal screening algorithm that incorporates change over time in CA125 levels identifies ovarian cancer earlier than a single-threshold rule. J Clin Oncol. 2013;31(3):387–92.