Clinical implementation of novel diagnostic biomarkers for epithelial ovarian cancer - can we improve diagnosis

Akademisk avhandling
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att officiellt förvaras i Hörsal Arvid Carlsson, Academicum Medicinaregatan 3, den 24 april, klockan 09.00

av Maria Lycke

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Avhandlingen baseras på följande delarbeten
I. Lycke M, Kristjansdottir B, Sundfeldt K A multicenter clinical trial validating the performance of HE4, CA125, risk of ovarian malignancy algorithm and risk of malignancy index Gynecol Oncol 2018;151:159-165; doi:10.1016/j.ygyno.2018.08.025


III. Lycke M, Ulfvenborg B, Lauesgaard J, Kristjansdottir B, Sundfeldt K Consideration should be given smoking, endometriosis, renal function (eGFR) and age when interpreting CA125 and HE4 in ovarian tumor diagnostics, 2020. Manuscript

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Abstract

Background: Epithelial ovarian cancer (EOC) is the most lethal gynecologic cancer. The 5-year survival is about 30%, a consequence of failure to establish early diagnosis due to unspecific symptoms. The biomarker serum CA125 and transvaginal ultrasound are used as the “gold standards” for assessing ovarian cysts and pelvic tumors of unknown origin, but early diagnosis is still not achieved and specificity is low. Increased knowledge of EOC specific mutations has revised our understanding of ovarian cancer etiology and heterogeneity. Rare tumor mutations can be detected in liquid biopsies from different compartments.

Aims: To investigate established EOC biomarkers and algorithms in an unselected population of women with ovarian cysts/pelvic tumors. To compare and combine established and new biomarkers and algorithms to improve differential diagnosis of EOC (Paper I-III). To explore new ways for early detection of gynecologic cancer, from circulating tumor DNA (ctDNA) and somatic mutations, by mutation specific analysis in liquid biopsies from the genital tract and plasma (Paper IV).

Methods: A prospective multicenter trial (Paper I-III) was conducted and we also participated in an international multicenter trial (Paper IV) with the aim to improve diagnostic accuracy of EOC and to find new screening methods. Serum was collected for analysis of the biomarkers CA125 and HE4. Risk of Malignancy Index (RMI), Risk of Ovarian Malignancy Algorithm (ROMA) and new algorithms were explored. Patient and tumor characteristics were recorded at time for inclusion and evaluated by multivariate regression analysis (Paper I-III). Liquid biopsies were collected from genital tract thin-prep liquids and plasma. Corresponding formalin fixed and paraffin imbedded tissue biopsies were retrieved from the pathology repository and analyzed with a multiplex PCR based barcoding of DNA for mutation detection using next generation sequencing (PapSEEK) for rare mutations (Paper IV).

Results: Paper I: At recommended cut-off >35, CA125 achieved highest sensitivity (SN) for both pre- and postmenopausal women (SN 95.7%; 92.0%), but low specificity (SP) in both pre- and postmenopausal women (SP 59.6%; 79.5%). HE4 was inferior compared to CA125 in SN but increased in diagnostic performance with highest SP (Pre-M 90.9%; Post-M 92.1%). RMI and ROMA were identical in their predictive ability. Paper II: Three new algorithms were tested and found to perform better than RMI, ROMA or CA125 alone (GOT-1, GOT-2, GOT-3). The addition of HE4 to CA125 or RMI increased SP without hampering SN. Paper III: Smoking, heart- or kidney failure and endometriosis should be considered when evaluating CA125 and HE4 levels in women assessed for an ovarian cyst/pelvic tumor of unknown origin. Paper IV: The PapSEEK technique showed impressively high SP (98.6% cervical; 100% endometrial), and when cervical sampling was combined with plasma ctDNA analysis, SN for ovarian cancer was 63%, with retained SP of 100%.

Conclusion: CA125 was superior to HE4 to identify women with ovarian cancer and HE4 was superior to CA125 to identify the benign lesions, in this unselected population of women with an ovarian cyst/pelvic mass. Addition of HE4 to CA125 increased diagnostic accuracy and decreased false positives. We suggest that HE4 should be incorporated for the differential diagnosis of women with ovarian cysts/pelvic tumors of unknown origin to decrease unnecessary oophorectomies. It is possible to detect somatic mutations and ctDNA from ovarian cancer in plasma, cervical- and endometrial liquid biopsies with high SP. This thesis demonstrate the potential of a protein and gene mutation-based diagnostic test to detect EOC. With improved technique, this might be a potential test for ovarian cancer screening, in the future.

Keywords: Ovarian neoplasms, EOC, diagnosis, protein biomarkers, CA125, HE4, Algorithms, RMI, ROMA, NGS, rare mutations, liquid biopsies, screening

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