CA125 and Ovarian Cancer

Subjects: Oncology

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The tumour biomarker CA125 has been used as a biomarker for ovarian cancer detection and progression.

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1. CA125

Tumour biomarkers have played an essential role in the detection and management of ovarian cancer. Numerous ovarian cancer biomarkers have been the subject of extensive and intensive studies. Among these biomarkers, Cancer Antigen 125 (CA125), also referred to as Carbohydrate Antigen 125, has played the most significant role in screening, detecting, and managing ovarian cancer for the last four decades[1]. CA125 is a high molecular weight mucinous glycoprotein found on the surface of ovarian cancer cells. This antigen is then shed and quantified in serum samples of ovarian cancer patients. Serum CA125 levels are elevated in 50% of early-stage tumours, which are mostly type I ovarian cancers and 92% of advanced-stage tumours, which are mostly type II ovarian cancers[2][3]. However, due to the low incidence of ovarian cancer, screening average-risk women with CA125 results in a considerable number of false positives[4].

Bast and colleagues first described CA125 in 1981 by developing a monoclonal antibody (OC125) against this antigen[5]. A radioimmunoassay was developed in 1983 to detect CA125 in serum using the 35 U/mL threshold. About 80% of patients with ovarian cancer exhibited elevated CA125 levels measured using this assay, while only 1% of healthy women in the study had elevated CA125 levels beyond 35 U/mL[6]. The upper limit of 35 U/mL has not changed since the first report.

Further analysis revealed that CA125 is a large glycoprotein with variable weights due to variation in glycosylation[7]. The amino acid analysis showed that CA125 has a high serine, threonine, and proline content seen in mucin-like molecules[8]. Partial cDNA for the CA125 protein component was cloned in 2001 by Yin and Lloyd. Consequently, CA125 was found to be an epitope on a glycoprotein encoded by the MUC16 gene, located on the short arm of chromosome 19, at 19p13.3. Furthermore, MUC16 has multiple epitopes recognized by different antibodies[7]. Specifically, CA125 has two main antigenic domains, separately binding OC125-like antibodies (group A) and M11-like antibodies (group B)[3][9]. CA125II is another heterologous assay that replaced the original CA125 assay. CA125II uses both M11 on the solid phase and OC125 as a probe and has less intraassay variation[10][11].

CA125, an epitope on the MUC16 molecule, has multiple physiological functions. MUC16 is a large glycoprotein with 22,152 core amino acids and a molecular mass of ~2.5 MDa. MUC16 contains a significant O- and N-linked glycosylated portion with a potential mass of ~20 MDa. It has distinct domains including, the amino-terminal, 60 tandem repeats of 156 amino acids, a transmembrane domain, and a cytoplasmic tail of 32 amino acids rich in tyrosine, threonine, and serine residues used for possible phosphorylation. This molecule is involved in ovarian tumorigenesis and metastasis[12].

Biomarker-based diagnosis of ovarian cancer with CA125

Biomarkers identify circulating tumour elements, proteins overexpressed by tumours, or components of the immune response to the tumour in body fluids such as blood and urine[13]. An ideal screening serum tumour marker has sufficient specificity and sensitivity to reach a positive predictive value (PPV) of 10% analogous to 1 cancer diagnosed out of 10 positive test results. There are two strategies for improving the PPV of screening tests. One approach is changing the screening population from asymptomatic women to symptomatic women who will have a higher frequency of ovarian cancer. The other approach is increasing the cutoff point for reducing false-positive results. Due to the low prevalence of ovarian cancer, the ideal screening test must have a sensitivity above 75% and a specificity of at least 99.6%[14][15][16][17]. In general, tumour biomarkers become clinically significant upon an accurate prediction of the disease at screening, management, and follow up phases of treatment. Currently, no single ovarian cancer biomarker performs well in all three phases.

Understanding the variation between subtypes of ovarian cancer is an important factor for the development of useful biomarkers. CA125 expression varies between different subtypes of ovarian cancer. HGSC and endometroid ovarian cancers have a higher expression of CA125 compared to other subtypes[18]. Generally, serous tumours have higher CA125 concentrations, and mucinous ovarian cancers have the lowest[11]. Likewise, type I and II tumours have different CA125 expression patterns. Patients with type I ovarian cancer are usually younger and are more frequently diagnosed in the asymptomatic early stages. Similarly, multiple studies have shown significantly higher CA125 levels in type II patients than patients with type I tumours[19][20][21][22][23][24][25][26] . Type II tumours account for 75% of ovarian carcinomas and 90% of ovarian cancer mortality[27]. In a study by Lu et al. on 14 ovarian cancer serologic markers, CA125 showed the highest discriminatory power for type II tumours compared to healthy controls[28]. Therefore, CA125 is a great screening candidate for the aggressive subtype (Type II) of ovarian cancer.

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