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Ovarian Cancer Biomarkers: Current Trends in Translational Research for Early Detection

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The role of translational research in current therapeutic implementations and public health applications is evolving in promising directions, particularly in association with novel biomarker discoveries. Translational medicine embodies multidisciplinary aspects ranging from basic science to drug discovery. Collaborative efforts between hospitals, academic institutions, and industrial research laboratories are inevitable for improving patient care and clinical outcomes [1]. The development of specific biomarkers for companion diagnostic and prognostic applications and for predicting clinical outcomes is driving translational and personalized medicine. Rapid developments in multiple -omics research are making it possible to improve cancer outcomes through early diagnosis, personalized therapy, and better prognosis [2]. Effective bioinformatics and electronic medical record initiatives are essential to this effort. Despite these advances, the best method to reduce mortality of human diseases is to maintain early screening and identify preventive measures.

Ovarian cancer is a deadly disease, in part because women often do not experience clinical symptoms that would induce them to visit the clinic. By the time the patient experiences uncomfortable symptoms, the cancer has frequently reached an advanced stage. Ovarian cancer has the highest death rate of all gynecological malignancies, and although the mortality rate has decreased by 1.9% every year from 2004-2008, ovarian cancer still accounts for 3% of all cancers among women. Every year more than 15,000 deaths are expected in United States and about 140,000 worldwide [3]. The anatomical location of the ovaries deep down the pelvis makes it difficult to detect abnormalities until the tumor becomes enlarged or metastasized. Similarly, ovaries become dysfunctional after menopause and abnormalities are not likely to be detected in the early stages. Translational research advances aim to detect ovarian cancer in early stages by monitoring molecular changes that develop during onset of disease [4]. Assays for identification and validation of early detection biomarkers can be performed on patient samples including blood, urine and other body fluids, and tissues. It is not practical to focus on tissue biomarkers for early detection because in the absence of symptoms women with early stage ovarian cancer have no reason to visit the clinic other than routine OB/Gyn care. It is unlikely that an invasive surgical procedure (e.g., laparoscopy) will be used for routine screening of ovary or nearby tissues. The practical approach to early detection of incipient ovarian cancer is to screen biomarkers that can be detected in bodily fluids. Common FDA approved molecular biomarkers currently used in ovarian cancer screening are CA 125 and HE4. These markers in combination are currently available in the clinic to discovered ovarian cancer in various stages. Because ovarian cancer is life threatening and is the most aggressive neoplastic disease in women, markers for its detection must achieve high specificity and sensitive. However, CA125 lacks both specificity and sensitivity, and use of HE4 alone does not often meet this clinical standard [5].

Potential biomarkers can be identified and extracted using a bioinformatics-based approach. Putative hits can be validated by testing on procured biospecimens from patients. It is essential that biomarkers be validated using high-quality clinical samples from tissue repositories. A recent review by Sarojini et al. discussed the potential of KLK6/7, GSTT1, PRSS8, FOLR1, ALDH1A1, miRNAs, Mesothelin, Osteopontin, and YKL-40 in early detection of ovarian malignancies [5]. Although CA 125 is still considered the gold standard biomarker for ovarian cancer, fluctuations in CA 125 levels associated with menstrual cycle, pregnancy, and benign conditions such as liver cirrhosis, endometriosis, and peritonitis undermine its significance as a single biomarker for early detection. Thus, since no single biomarker can provide all necessary information regarding diagnosis and therapy, focus has shifted to use of panels of biomarkers with higher sensitivity and specificity. As one example, serum HE4 was found to yield higher specificity and sensitivity when used in combination with CA 125 than when used alone as a single biomarker [6]. The FDA has approved the use of HE4 for monitoring relapse or progression of epithelial ovarian carcinoma. Similarly, expression of mesothelin is elevated in epithelial ovarian cancer, and it is known to enhance the migration and metastasis of cancer cells, suggesting its potential as a biomarker [7]. KLK6 and 7 can also be considered as early detection biomarkers for ovarian cancer as higher expression levels of these proteins were noted in serum samples of papillary serous and serous subtypes of ovarian carcinoma. Thus, the analysis of the human serum proteome suggested better candidates for detecting ovarian cancer in early stages, and their use has improved the five year survival rate more than 90%. Another benefit of using serum biomarkers for early detection is the convenience for patients, since a blood draw is only minimally invasive. Patients are more willing to provide blood than tissue or other specimens for translational research. The availability of samples is critical to the translational research effort to evaluate these biomarkers for their utility in reducing the morbidity and mortality of ovarian cancer worldwide.

Translational research and concurrent development of sophisticated computer technology and statistical methods has generated many tools that have increased the sensitivity of CA 125 for diagnosis and therapy of ovarian cancer. ROCA (Risk of Ovarian Cancer Algorithm) is an example of a computerized algorithm which incorporates and stratifies age-specific risk of ovarian cancer using the CA 125 profile of the individual. In pre-clinical detection, ROCA improves the sensitivity of CA 125 up to 86%. If, for example, an individual's CA 125 level shows an increasing trend with age, ROCA can be used to predict whether that individual is or is not at higher risk for developing ovarian cancer. ROCA scores triage women into low risk, high risk, and intermediate risk. The analysis is used in referral for further procedures such as TVS

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(Trans vaginal Sonography), or evaluation of CA125 levels [8]. Another important FDA approved test used for detecting ovarian cancer is OVA1, which incorporates measurements of five proteins CA125-II, apolipoprotein A1, transthyretin, beta 2 microglobulin, and transferrin. OvaCalc software is used for interpreting the results, and a score (Ova1 score) is provided, which accounts for the menopausal status of the individual [9]. Similarly, another detection tool incorporating serum levels of HE4 and CA125 for improving diagnosis of ovarian cancer from benign pelvic masses has been developed. This method (ROMA – Risk of Ovarian Malignancy Algorithm) can also be useful in the early stages, and identifies patients as high risk or low risk based on a ROMA score calculated from a predictive index [10].

Genetic and epigenetic biomarkers also play important roles in early detection, diagnosis, and therapy of ovarian cancer. The acquired and accumulated DNA sequence variations in developing cancer cells induce them to proliferate, metastasize, and express drug resistance. Mutations associated with increased ovarian cancer risk include mutations in *BRCA1, BRCA2*, and *Rad51D.* Similarly, serous ovarian cancer stages II and IV are associated with mutations in *TP53, RB1, NF1, FAT3, CS\MD3, GABRA6, CDK12, BRAF,* and *KRAS* [11]. In non-epithelial ovarian cancers, mutations in *DICER1* occur frequently. Combinations of genetic, epigenetic, and molecular biomarkers in concert with computer technology are poised to drive current and future therapeutic options for ovarian cancer toward the realization of early detection and individualized therapy. To meet future challenges, and to achieve the potential benefits accruing from translational research and individualized therapy in ovarian cancer, support should be provided in areas of tissue procurement and banking, identification and evaluation of molecular biomarkers, and in clinical trials based on laboratory observations. Participation of individuals and patients is critical for the translational research effort in conducting surveys and clinical trials based on the results of laboratory findings. The introduction of molecular biomarkers promises to lead to appropriate, individualized drug therapy based on individual biomarker analysis, and, combined with genetic and epigenetic profiling, better patient outcome.

In conclusion, identification and evaluation of novel and robust biomarkers, coupled with their successful implementation through clinical trials, could significantly improve the overall survival rate in ovarian cancer patients. Serum biomarkers for early detection are widely being used in current practice in combination with CA125. Harmonization across biobanks is required to ensure the availability of tissues and other biospecimens for health innovations in cancer research [12]. These efforts will be critical in the validation of more relevant biomarkers, will increase productivity, and will ensure that personalized medicine develops along a faster, more targeted trajectory.

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