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Prediction, Prevention, Prognostic and Personalized Therapy of Ovarian Cancer- Biomarkers and Precision Medicine

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Abstract

Ovarian cancer is one of the most common causes of death in women. Ovarian cancer is often diagnosed at an advanced stage, with survival rates dependent on the stage of the disease, while early stages are mostly asymptomatic. Early detection of this disease is one of the most important steps to promote a good prognosis for patients and an excellent response to drug treatment because genomic instability is one of the hallmarks of ovarian cancer. In an advanced stage, individual patients are treated with drugs that help control their growth, division, and spread. A new generation of technologies and biomarkers with targeted therapy are emerging rapidly, including microRNA, picoRNA, non-coding RNA and their tumor-intrinsic signaling pathways, angiogenesis, hormone receptors, and immune factors. Early detection is now possible thanks to some effective screening strategies. The ovarian cancer is divided into different clinical subtypes, and there is still a wide range of genetic and progressive diversity in each subtype. Once ovarian cancer is diagnosed at an advanced stage with different clinical subtypes, a new generation of treatments, such as targeted therapy, will become possible. Now, based on emerging biomarkers consisting of the DNA level (SNPs and epigenetics), RNA level (mRNA, microRNA, pico-RNA, non-coding RNA), and protein level, it is time to evaluate the early status and progression with the biomarkers related to an efficacy of the prevention and drug treatment for this type of disease.

Keywords: Precision medicine; Biomarker; Ovarian cancer; Prediction; Prevention; Prognostic management; and Personalized therapy.

Introduction

Ovarian cancer is one of the most common causes of death in women with survival rates related to the stage of the disease1-2. Ovarian cancer is often diagnosed at an advanced stage, while early stages are mostly asymptomatic. According to the literature, there are different subtypes of ovarian cancer based on the morphology of tumor cells, such as serous, mucinous (MC mucinous carcinoma), endometrioid (EC endometrioid carcinoma), clear cell, and squamous cell under histological subtype3-7. Although ovarian cancer is divided into different clinical subtypes, a wide range of genetic diversity can be detected for the subtypes. Early detection of the disease is one of the most important steps to improve good patient prognosis and reasonable response to drug treatment8-10. Early detection include DNA, RNA, and protein biomarkers, experimentally, such as SNPs, microRNA, pico-RNA, non-coding RNA and their tumor-intrinsic signaling pathways, angiogenesis and immune factors11-15. This paper will include the latest findings in ovarian

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cancer research to understand this disease better. Moreover, ovarian cancer has diverse genomic and molecular alterations of origin associated with different treatment approaches. Recent findings suggest that several ovarian cancers are found, early or advanced, with low-grade (LGSC, low-grade serous carcinoma) and high-grade malignancies (HGSC, high-grade serous carcinoma)16-17. WHO guidelines published in 1973 were the first attempt to systematically classify the many ovarian cancer subtypes based on architecture (microscopic tumor features) and cytology (the nature of the morphologically recognizable cell types and patterns). The latest version of the WHO classification of ovarian cancer published in 2014 demonstrated some new features, including the origin of OC tumor cells, pathophysiology (mechanisms of development and progression of ovarian cancer), pathological features, treatment response, and prognosis of different ovarian cancer subtypes18. The understanding of ovarian cancer has shown the importance of genetic defects for each primary histological type. According to the Research and Development (R&D) of genetics within ovarian cancer, a new generation of techniques can be used in biomarker detection with their treatments. Now, based on the numerous biomarkers, it is time to evaluate the status of prediction, prevention, prognostic management, and the efficacy of drug treatment for this disease. The manual will consist of four sections: (1) common biomarker for ovarian cancer, (2) the challenge of the common biomarker to detect ovarian cancer, (3) a new strategy for biomarkers related to tumorigenesis for prediction, prevention, prognostic and personalized therapy of tumor diseases, and (4) a new strategy for biomarker related to tumorigenesis for prediction, prevention, prognostic and personalized therapy of ovarian cancer.

Common biomarker related to ovarian cancer

A biomarker is a biological feature that can be objectively measured and evaluated as an indicator of normal biological or pathological processes or responses to therapeutic intervention19-24. In precision medicine, a biomarker includes gene expression patterns such as levels of some specific proteins and mRNA in body fluids or tumor cells. Therefore, the updated utilization of technologies that can analyse nucleic acid and protein biomarkers is rapidly increasing25-26. Moreover, we are entering the era of precision medicine, so biomarkers have been used to identify molecular features that can be used for prediction, prevention, prognosis, and treatment, providing patients with maximizing the chance of success and minimal discomfort27-30. These molecules, called biomarkers, consist of the DNA level (SNPs and epigenetics), RNA level (mRNA, microRNA, pico-RNA, non-coding RNA), and protein level. In the manual, we focus on measuring expression levels and detecting DNA changes. Even if the molecules for the cell origin and pathogenesis from ovarian cancer remain unclear, pathogenic germline mutations, such as BRCA1 or BRCA2 genes, have been identified as significant risk factors for the development of ovarian cancer31. Here, firstly, are lists of the gene mutations with their specific cellular signalling pathways associated with ovarian cancer.

BRCA1 and BRCA2 Genes

Germline mutations in the BRCA1 and BRCA2 genes confer a high lifetime risk of ovarian cancer, which is the major genetic risk factor for the disease. The BRCA1 and BRCA2 genes are present in almost half of all families with ovarian cancer31, and both proteins play a role in the double-strand DNA break repair system. The BRCA1 gene is located on chromosome 11q21, containing 22 coding exons spanning 80 kb of genomic DNA, and has a 7.8 kb transcript that encodes an 1863 amino acid protein. The BRCA2 gene is located at 13q12-13 and consists of 26 coding exons spanning 70 kb of genomic DNA with an 11.4 kb transcript encoding a 3418 amino acid protein. Approximately 1.2% of women in the general population will develop ovarian cancer at some time in their lifetime.

In contrast, 39–44% of women who inherit a pathogenic BRCA1 variant and 11–17% of women who inherit a pathogenic BRCA2 variant will develop ovarian cancer by age 70–80 years32. The patient prognosis for BRCA1/2-related cancers depends on the stage of cancer diagnosis and the type of mutation; moreover, survival studies have shown conflicting information for individuals with germline BRCA1 or BRCA2 pathogenic variants compared with controls. Retrospective studies have demonstrated that heterozygosity for inherited BRCA pathogenic variants in patients with ovarian cancer is associated with a higher risk of developing ovarian cancer; the BRCA1 and BRCA2 genes encode proteins involved in DNA repair, tumors with alterations in both gene are susceptible to certain anticancer agents.

MMR genes

The mismatch repair (MMR) system is a group of functional families that repairs mutations during DNA replication or damage so that they play a crucial role in maintaining genome stability33. The MMR system is an integrated pathway at each stage. Seven MMR genes (mutL homolog 1, MLH1, mutL homolog 3 MLH3, mutS homolog 2, MSH2, mutS homolog 3, MSH3, mutS homolog 6, MSH6, increased postmeiotic segregation 1, PMS1, and increased post-meiotic segregation 1, PMS2) are involved in the human MMR system34. It is now known that the inactivation of MMR in human cells is associated with global genome instability, including microsatellite or DNA damage and predisposition to certain types of cancer. In ovarian cancer, MMR deficiency is the most common inherited cause of ovarian cancer after BRCA1 and BRCA2 mutations.

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CHEK2 gene

CHEK2 is a tumor suppressor gene located on human chromosome 22 (22q12.1) with a length of 54 kb (chr22: 28,687,743–28,742,422; reverse strand; GRCh38) 35. The most expressed transcript variant 1 (NM_007194/ ENST00000404276.6) encodes an mRNA consisting of 15 exons in which the translation start site is located in exon 2. The CHEK2 gene encodes a protein kinase that is activated in response to DNA damage and has been demonstrated to interact with BRCA1 to promote cell survival after DNA damage. The role of CHEK2 mutations in ovarian cancer carcinogenesis is well known. In particular, the missense variant of CHEK2 I157T is significantly associated with ovarian cystadenomas, ovarian marginal tumors, and low-grade invasive cancers, but not high-grade ovarian cancers.

PTEN gene

PTEN is one of the most frequently mutated genes (13%) in the four most common cancers in women (breast, ovarian, endometrial, and cervical cancers). PTEN mutations can coexist and lead to aberrant activation of the PI3K/Akt/ mTOR pathway so that the combination of PTEN mutations and KRAS mutations in the ovary induces aggressive and metastatic endometrioid ovarian cancer36. PTEN is a tumor suppressor gene located on chromosome 10 (cytogenetic location 10q23.3) that is variably mutated and/or deleted in a variety of human cancers. In many ovarian cancers, the frequency of loss of heterozygosity (LOH) of PTEN flanking and internal markers is 30% to 50%, and the frequency of somatic PTEN mutations is <10%.

TRKs gene

Tropomyosin receptor kinases (TRKs) are receptors in the tyrosine kinase family that are activated by neurotrophins (a family of nerve growth factors) 37. Three members of the TRK family have been described: TRKA, TRKB, and TRKC encoded by neurotrophic tropomyosin receptor kinase 1 (NTRK1), NTRK2, and NTRK3, respectively. The NTRK1, 2, and 3 genes encode a family of tyrosine kinase receptors that play an active role in neural development. All rearrangements result in constitutive activation of these proteins. NTRK rearrangements have been reported in a range of solid and hematological tumors with varying frequencies. These recent findings present diagnostic and therapeutic challenges. The U.S. Food and Drug Administration (FDA) recently approved a selective neurotrophic tyrosine receptor kinase (NTRK) inhibitor, larotrectinib. In parallel, the development of multi-kinase inhibitors that are active against tumors harboring TRK fusions is also underway. Chromosomal translocations involving the NTRK1, NTRK2, and NTRK3 genes result in constitutive activation and aberrant expression of TRK kinases in multiple cancer types.

p53 gene

A mutation in the p53 gene, also known as the TP53 gene, can cause cancer cells to grow and spread in the body38. The p53 gene is a tumor suppressor gene that stops tumors from forming by arresting the cell cycle and repairing DNA. When P53 mutated, the p53 protein loses its tumor suppressive functions and can gain oncogenic functions so that P53 help cells grow and survive. These mutations are the most common acquired mutations in cancer and have been found in over 50% of human malignancies.

RAD51, BRIP1, and PALB2 gene

In some studies, BRIP1, PALB2, and RAD51C were sequenced for mutations associated with breast and ovarian cancer risk39 due to their role in the double-strand break repair pathway and their close association with BRCA1 and BRCA2.

Some rare genetic syndrome

Certain rare genetic syndromes, including Lynch syndrome and Lee-Fraumeni syndrome, also have significantly increased risk of ovarian cancer. Lynch syndrome is most commonly associated with mutations in the MLH1 or MSH2 genes40, whereas Li-Fraumeni syndrome is caused by germline mutations in the p53 gene38.

The challenge to detect the common biomarkers within ovarian cancer

Now, although DNA level (SNPs and epigenetics), RNA level (mRNA, microRNA, pico-RNA, non-coding RNA), and protein are largely emerging to measure ovarian cancer, there are not feasible biomarkers to use all prediction, prevention, prognosis, and treatment with ovarian cancer. In expression levels such as protein biomarkers (CA125) has been used as the primary ovarian cancer marker for the past four decades. Research indicated that ovarian cancer in stages I and II using CA125 as a diagnostic biomarker has not improved patients' survival, so screening average-risk asymptomatic women with CA125 is not recommended by any professional society. After several clinical research, only point-of-care testing has the potential for effective longitudinal screening and quick monitoring of ovarian cancer patients during and after treatment. Now, only small parts such as CA125 can be used for screening in recommendation, ovarian cancer41. At the DNA level, in order to study early periods to detect ovarian cancer, although a lot of clinical scientists are going to study the feasible detection of early ovarian cancer, their results of detection are arguing. For example, the Ovarian Cancer Association Consortium selected seven candidate SNPs to study the relationship between SNPs and ovarian cancer. The seven candidates' genes included F31I (rs2273535) in AURKA, N372H (rs144848) in BRCA2, rs2854344 in intron 17 of RB1, rs2811712 in the 5′ flanking CDKN2A, rs523349

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in the 3′ UTR of SRD5A2, D302H (rs1045485) in CASP8, and L10P (rs1982073) in TGFB1. To study SNPs related to ovarian cancer, about forty association coordination members have reported that SNPs confer differential ovarian cancer risk when cases are stratified by histologic subtype according to selected 4,624 invasive epithelial ovarian cancer cases and 8,113 non-Hispanic white controls. Their research found KRAS gene mutations in mucinous ovarian cancer, whereas germline BRCA1 and BRCA2 mutations predispose to serous ovarian cancer. Moreover, they did not find evidence of an effect for any SNP when stratifying invasive ovarian cancer by histologic subtype. When they analysed cases of borderline ovarian cancer, they found a marginal association for rs1045485 in CASP8. False-positive results were also obtained because of hidden population stratification. The International Consortium study of ovarian cancer concluded that these genes with SNPs did not have a significant effect on ovarian cancer risk42. In other parts, such as epigenetics, microRNA, picoRNA, non-coding RNA are largely emerging to detect ovarian cancer, there are not feasible biomarkers to use for prediction, prevention, prognosis, and treatment of ovarian cancer.

A new strategy for biomarkers related to tumorigenesis

To discover specific biomarkers to study tumor prediction, prevention, prognosis, and treatment, some clinical scientists have begun to focus on a new strategy to address the issue. That is the "genetic profile to study tumorigenesis" as Figure 1.

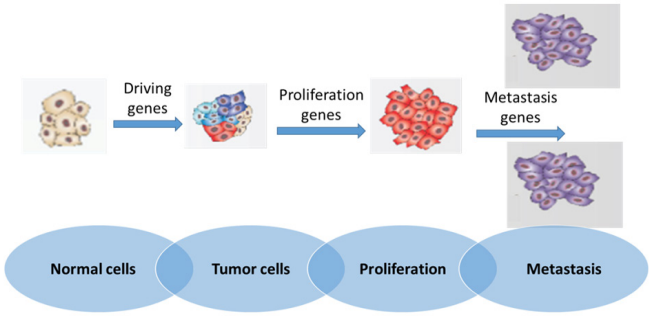

Figure 1: Tumorigenesis and tumor development

Background

As Figure 1, cancer development goes through a process called tumorigenesis: it starts with subtle changes in the genome or genetics, such as changes in driver genes. Over time, the accumulation of driver gene changes will produce changes in tumor proliferation genes and then cause changes in tumor metastasis genes. The tumorigenesis may also occur in some other form, such as chromosome instability (breakage and rearrangement) after the human body is exposed to radiation or contact with genotoxic chemicals or infection caused by carcinogenic microorganisms43.

The World Health Organization's 2022 report shows that cancer become the "world's number one killer"44. In order to fight against cancer, the World Health Organization has proposed two important tasks: to understand the carcinogenic mechanism to achieve early detection and prevention of tumors and to further develop personalized treatment for precision treatment to solve the treatment of advanced tumors. In the last century, people have made outstanding achievements in studying the cellular and molecular mechanism framework of cancer occurrence, development, and metastasis from single genes and single chromosome changes by screening individual genes in cancer45. A new turning point in cancer research appeared in the late 1990s. After the Human Genome Project was initially conducted in 2003, the Cancer Genome Research Project was launched to identify somatically acquired sequence variations and mutations, thereby identifying specific genes that are critical in human cancer. For example, the International Cancer Genome Consortium (ICGC) was established in 2008. ICGC provides collaborative and comprehensive information on all mutations in 50 cancers, including copy number changes, insertions, and deletions46. To date, many cancer genome and epigenetics studies have sequenced a range of cancer types and helped us gain an unprecedented understanding of the molecular mechanisms behind the complexity of tumor biology. Now, the goal is to define the initiation of cancer as the set of all drivers in genomics that lead to the emergence of malignant transformation. Moreover, the driver gene resides in non-coding RNA molecules (or piRNA, microRNA, long non-coding RNA).

Developing a clinical analysis and diagnosis of precision medicine is necessary to prevent and treat this disease effectively. We aim to fill the gap in the current clinical diagnosis and clinical management related to biomarkers for diagnosis and personalized treatment. This will (1) establish precise clinical prevention and treatment methods for early-stage tumors and (2) develop individualized clinical management of precision treatment, thereby solving the issues of individualized clinical treatment for advanced tumors.

A successful example of the new strategy

According to the WHO strategy to address the issues called tumorigenesis and discover “driver genes”-“tumor proliferation genes”-“tumor metastasis genes” for tumor development related to prediction, prevention, prognostic, and personalized therapy, two clinical modules have achieved great results: tumorigenesis for colorectal cancer (CRC) and tumorigenesis for leukemia which we have involved in about 20 years47-55.

As Figure 2 shown and discussed above, cancer development will probably go through (1) subtle changes in genetics, such as driver genes; over time, the accumulation of driver gene changes will produce changes in tumor proliferation genes and then cause changes in tumor metastasis

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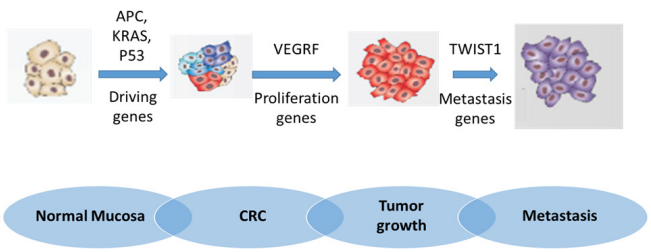

Figure 2: CRC Tumorigenesis and biomarkers

genes. As shown in Figure 2, CRC can cause a change of driver genes (APC, KRAS, and P53) into tumor proliferation genes (VEGFR) and then tumor metastasis genes (TWIST1). (2) The tumorigenesis also occurs in other forms, such as chromosome instability (breakage and rearrangement). In a further study, the tumorigenesis can occur from the chromosome level by more complex, namely chromosomal instability (CIN), CpG island methylator phenotype (CIMP), and microsatellite instability (MSI). After scientists' efforts, new evidence set up a bridge between chromosomal instability and biomarker change. The classical CIN pathway begins with acquiring mutations in adenomatous polyposis coli (APC), followed by mutational activation of the oncogene KRAS and inactivation of the tumor suppressor gene TP53. Aneuploidy and loss of heterozygosity (LOH) are significant factors in CIN tumors, which not only account for the majority of sporadic tumors but also involve familial adenomatous polyposis cases associated with germline mutations in the APC gene. The CIMP pathway is characterized by hyper-methylation of the promoters of various tumor suppressor genes, most importantly MGMT and MLH1. This hyper-methylation is often associated with BRAF mutations and microsatellite instability. The MSI pathway involves the inactivation of genetic alterations in short repeat sequences. Hyper-methylation of MMR genes may lead to MSI. This mechanism is often associated with the CIMP pathway. MSI tumors are often associated with the proximal colon, are poorly differentiated, but have a better prognosis56. These three mechanisms frequently overlap in CRC tumorigenesis into as Figure 2.

A new strategy for biomarkers related to OC tumorigenesis

OC characteristics

Ovarian cancer, which is different from CRC and leukemia as discussed above, is a heterogenetic disease with distinct subtypes57. Now, five subtypes of ovarian cancer rely on the morphology of tumor cells such as serous, mucinous, endometrioid, clear cell, and squamous cell under the histological subtype. Because OC is divided into five subtypes, a wide range of genetic diversity can be detected for the subtypes, so OC tumorigenesis is more difficult than those from CRC and leukemia. Fortunately, DNA, RNA, and protein biomarkers from OC are quickly emerging, such as new SNP and epigenetics, microRNA, pico-RNA, non-coding RNA, and some new proteins, the discovery of biomarkers and Research and Development (R&D) of the techniques is playing an important role to study OC biomarkers related with OC tumorigenesis.

OC biomarkers for OC tumorigenesis

As Table-1 and Fig-3, DNA level (SNP and epigenetics), RNA level (microRNA, picoRNA, non-coding RNA), and protein have largely been researched in ovarian cancer.

Table 1: New Biomarkers for OC

No.	Types	Examples
DNA	SNPs and epigenetics	miR-1246 and miR-150-5p
RNA	mRNA	Ca125, C5a, HE4
	microRNA	miR-1282, miR-224-5P
	Pico-RNA	piR-52297
	non-coding RNA	LOC101927151
Protein	Blood or body fluid	Ca125

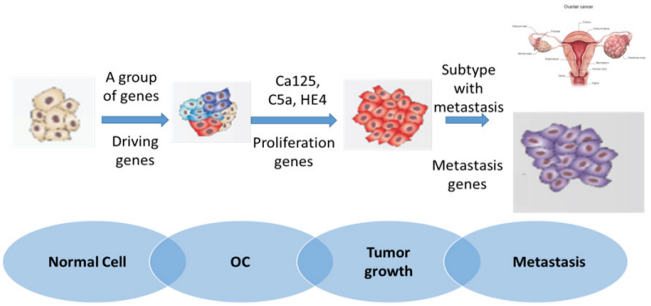

Figure 3: OC Tumorigenesis and OC development

DNA level

DNA level can be applied to some tumor diseases for physicians to define what genomics and genetic change makes the patient susceptible to his disease or anticipates which medical prevention and treatments. Recent developments in clinical research have enabled physicians to understand the causes and mechanisms of some diseases related to genomic profiles analyzed by genome-wide association studies (GWAS) for single nucleotide polymorphisms (SNP) of different prevention and treatment58. Targeted therapy is the second advanced module that interferes with specific targeted molecules needed for some diseases, such as carcinogenesis and tumor growth.

Although these DNA sequences of tumor suppressor gene and oncogene with their aberrant changes are extensively studied in tumor disease, some genetic changes are not involved in encoded DNA sequence rather than result from external or environmental factors with a gene switch on

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and off. The term 'epigenetics' regarding aberrant tumor suppressor gene and oncogene changes emerged in the 1990s. Currently, epigenetics is focusing on DNA methylation and histone modification for the study of tumorigenesis and clinical analysis for therapeutic targeting of tumor prevention and treatment59.

RNA level

As we know, each individual has a unique variation in personal transcriptome, even if some of the unique variations from a person have no impact on their health, behaviors, or adaptation to the environment.

A message RNA (mRNA) alteration that was discovered in clinical specimens has largely been reported in clinical applications60. To develop the new field, personalized medicine will apply some new technologies for a patient's specimen, such as mRNA, to lead to discovering unique variations. Moreover, an RNA-seq can show RNA expression involved with some unknown specific tumor biomarkers, and therefore, RNA-sequencing (RNA-seq) can provide a broader understanding of an individual of tumorigenesis61.

A microRNA (miRNA) alteration discovered in clinical specimens has largely been reported to clinical application. Now many miRNAs alterations have been uncovered to associate with tumor disease and tumorigenesis62. Clinically, detecting miRNA profiles has been increasingly applied to predict prognosis and monitor clinical response to treat tumor diseases and classify tumor diseases about tumor disease and tumorigenesis. Table 1 includes OC for miRNA change.

Long non-coding RNAs (lncRNAs) 63 are a group of longer than 200 nucleotides, the largest and most diverse cell transcripts. lncRNAs demonstrated some unique characteristics, such as lower quantity, higher tissue specificity, higher stage specificity, and higher cell subtype specificity. The current evidence from tumor diseases suggests that lncRNAs are a crucial regulatory RNA present in tumor cells, and therefore, their alterations are associated with tumorigenesis and tumor diseases.

Protein level

Clinical protein measurement and proteomic techniques contributed to OC protein biomarker detection, for example, ELISA and Western blot to detect CD125. More genes related to metastasis 64 are shown in Table 2.

Table 2: Biomarkers relate to OC metastasis

Subtypes	Metastasis biomarkers
High-Grade serous carcinoma	P53, BRCA1/2
Clear Cell	ARID1A, PIK3CA, CTNNB1, PPP2R1A, MSI
Endometriod	ARID1A, PIK3CA, CTNNB1, PPP2R1A, MSI
Low-Grade serous carcinoma	KRAS, BRAF
Mucinous	KRAS, HER2

Proteomic techniques consist of protein microarray (microarray proteomics) and mass spectrometry 65. Although most proteomics information for cancer diseases is still unknown, a technological mechanism to detect the proteomic variation is the ubiquitous aneuploidy in cancer, which is defined as an imbalanced chromosomal content. Another proteomics change is defective protein structure in cancers. Mutations in cancer-associated genes can produce defective protein structures, and therefore, these defects can cause the affinity between protein-protein interactions66. These proteomic detections for tissue samples can early determine the presence of tumor disease for personnel information. Therefore, clinical proteomics will be most useful for the diagnosis of diseases, monitoring the therapeutic effect, and improving treatment for individual patients.

OC tumorigenesis for precision medicine

According to the update strategy, discover "driver genes,"-"tumor proliferation genes,"-and "tumor metastasis genes" for tumor development related to prediction, prevention, prognostic, and personalized therapy. Once we study five subtypes of ovarian cancer with different biomarkers in DNA level (SNP and epigenetics), RNA level (microRNA, picoRNA, non-coding RNA), and protein level in individual subjects, we can define personalized prevention in the early periods and select personalized therapy for advanced periods as Fig-4.

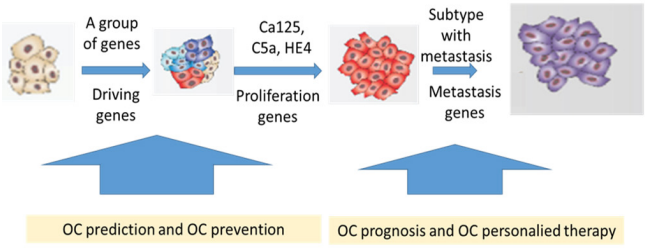

Figure 4: Biomarkers related with precision medicine

Conclusion

Most ovarian cancer can be diagnosed at an advanced stage, while early stages are mostly asymptomatic. Early detection is one of the most important steps to promote a good patient prognosis and an excellent response to drug treatment. Because a new generation of technology can be used for a discovery of the new biomarkers, an early detection is now possible for effectively screening strategies. Moreover, a new generation of targeted molecules will be largely discovered to specific targeting the new biomarkers. It is time to set up the new strategy for biomarkers related to a new generation of prevention and treatment for ovarian cancer.

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Author contributions

XHH and JL contributed equally to the work, JQ, GRY and PTS participating XHH working, YFZ working in experiments under BL and BL conceived and designed the experiments.

Competing interest's Statement

The authors declare competing non- financial interests.

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