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"Genetic Mutations and Ovarian Cancer: Insights into Early Detection and Personalized Therapies"

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ABSTRACT: Ovarian cancer remains a leading cause of gynacologic cancer mortality, largely due to late stage diagnoses and limited treatment effectiveness. Recent advancements in gentic research have highted speciac mutations, particularly in BRCA1, BRCA2, and other DNA repair genes, as significant contributors to ovarian cancer risk. These discoveries present new opportunities for early detection and individualized treatment approaches. This review examines the roles of various genetic mutations associated with ovarian cancer susceptibility and progression, discussing their implications for diagnostic accuracy, risk assessment, and therapeutic intervention. Innovations in genomic testing, coupled with targeted therapies, offer promising strategies for high-risk individuals, particularly those with inherited mutations. Additionally, we explore the emerging role of poly(ADP-ribose) polymerase (PARP) inhibitors and other targeted treatments that exploit DNA repair deficiencies in tumor cells, enhancing personalized therapy outcomes. This overview underscores the importance of integrating genetic insights into clinical practice, aiming to improve early detection rates and expand personalized treatment options for ovarian cancer patients.

KEYWORDS:
1.Ovarian Cancer 2.Genetic Mutations 3.BRCA1/BRCA2 Mutations
4.HER2 Mutation5.TP53 Gene6.Early Detection7.Risk Factors
8.Genetic Testing9.Biomarkers10.Personalized Therapies
11.TargetedTherapy12.Immunotherapy13.Genomic Sequencing
14.Precision Medicine15.PARP Inhibitors

I. INTRODUCTION:

Ovarian cancer is one of the most deadly cancers affecting women worldwide, with a significant impact on both survival rates and quality of life. While the exact causes of ovarian cancer remain unclear, a growing body of research has highlighted the role of genetic mutations in its development. Mutations in certain genes, particularly those involved in DNA repair and cell growth, can contribute to the initiation and progression of ovarian cancer. Among the most well-known genetic mutations associated with ovarian cancer are those in the BRCA1 and BRCA2 genes, which are also linked to increased risks for breast cancer. Other mutations, such as those in the TP53 and KRAS genes, have also been implicated in the pathogenesis of ovarian tumors. Understanding these genetic mutations is crucial for developing targeted therapies, improving early detection methods, and offering personalized treatment options for patients. This introduction aims to explore the key geneticmutations associated with ovarian cancer and their implications for diagnosis, treatment, and prevention.

A significant number of gynecologic cancers in Canada can be prevented. Beyond risk factors that can be modified by lifestyle or HPV vaccination, a meaningful component of an individual's cancer risk can be attributed to hereditary predisposition or genetic susceptibility.

Individuals with proven hereditary cancer syndrome (HCS) have elevated lifetime rates of malignancy. It is estimated that one-fifth of ovarian cancers are hereditary in origin, with BRCA1 and BRCA2 genes being the largest contributor. Other HCS genes associated with increased ovarian cancer risk include Lynch Syndrome mismatch repair genes (MMR), TP53, RAD51C, RAD51D, BRIP1, and PALB2 . Women with BRCA1- or BRCA2-associated HCS have a lifetime risk of

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ovarian cancer between 17–44%. HCS genes associated with endometrial cancer include Lynch syndrome (MMR) and PTEN pathogenic variants. Cervical cancer is not considered a hereditary cancer, although mutations in immune response-related genes may be related to the ability to clear human papillomavirus infections . Vulvar cancer is related to human papillomavirus infection as well as TP53 . The full landscape of genetic variation in gynecological cancers has yet to be fully elucidated.

Advances in the fields of genomics, genetics, and hereditary cancer prevention offer new opportunities for women to quantify cancer risk and access effective prevention. It is now known, for example, that women with BRCA1 mutations have dramatically elevated risks of cancer (including ovarian (44%) and breast (71%) cancers and that high-risk surveillance and risk-reducing salpingo-oophorectomy (RRSO) decrease mortality by as much as 70%. It is important to note that effective screening still does not exist for ovarian cancer, and RRSO is the most effective prevention. Better identification of high-risk individuals and directed preventive care will decrease gynecologic incidence and mortality and help to build a more sustainable healthcare system.

To find carriers of BRCA only after a cancer diagnosis should be considered a failure of cancer prevention. Optimally, effective health systems would identify unaffected women with BRCA or other HCS, offering prophylactic interventions before the onset of disease. Although personalized prevention has been lifesaving in the management of individual cases one patient at a time, the promise of genetics and genomics has not yet been delivered in the domain of public/population health. There is a need to reconcile the disparity between knowledge and health policy.

Types of Genetically Mutated Ovarian Cancers:

1. BRCA1 and BRCA2 Mutated Ovarian Cancer

- **Mutation Type:** Inherited (germline) or acquired (somatic) mutations.
- **Cancer Type:** High-grade serous ovarian carcinoma (HGSOC).
- **Impact:** These mutations impair DNA repair through the homologous recombination pathway, increasing the risk of ovarian and breast cancers.
- **Treatment Note:**Tumors often respond well to **PARP inhibitors** (e.g., olaparib).

2. TP53 Mutated Ovarian Cancer

- **Mutation Type:** Almost universal in HGSOC (~95% of cases).
- **Cancer Type:** High-grade serous carcinoma.
- **Impact:** TP53 is a tumor suppressor gene; mutations here lead to uncontrolled cell division.
- **Clinical Note:** Often associated with aggressive tumorbehavior.

3. KRAS Mutated Ovarian Cancer

- **Mutation Type:** Common in low-grade serous and mucinous ovarian cancers.
- **Cancer Type:** Low-grade serous, mucinous carcinoma.
- **Impact:** KRAS mutations activate signaling pathways that promote cancer cell growth.
- **Therapeutic Note:** These tumors are usually **chemoresistant** and may require targeted therapy.

4. PIK3CA Mutated Ovarian Cancer

- **Mutation Type:** Common in endometrioid and clear cell ovarian carcinomas.
- **Cancer Type:** Endometrioid, clear cell carcinoma.
- **Impact:** Activates the PI3K/AKT/mTOR pathway, promoting cell survival and growth.
- **Targeting:** PI3K inhibitors are being explored in clinical trials.

5. ARID1A Mutated Ovarian Cancer

- **Mutation Type:** Frequently seen in clear cell and endometrioid carcinomas.
- **Cancer Type:** Clear cell, endometrioid carcinoma.
- **Impact:** Loss of ARID1A leads to epigenetic dysregulation and promotes tumorigenesis.
- **Relevance:** May be used to develop targeted therapies in the future.

6. Mismatch Repair Deficiency (MMRd) / Lynch Syndrome

- **Mutation Type:** Germline mutations in MLH1, MSH2, MSH6, PMS2 genes.
- **Cancer Type:** Endometrioid ovarian cancer.
- **Impact:** Leads to microsatellite instability (MSI) and defective DNA repair.
- **Treatment Note:** Patients may respond to **immunotherapy** (e.g., PD-1 inhibitors).

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1. BRCA1 and BRCA2 Mutated Ovarian Cancer

Ovarian cancer can be classified based on tumour origin into epithelial (~90% of all cases [1]), sex cord/stromal and germ cell. The epithelial cases differentiate into five main histological subtypes ("histotypes"), including high-grade serous carcinomas (HGSC), which is the most frequent subtype [2], low-grade serous carcinomas (LGSC), mucinous, endometrioid and clear cell ovarian cancers.

Several genes have been associated with increased risk of ovarian cancer, including BRCA1 and BRCA2 [6], PALB2, BRIP1 [7], RAD51C and RAD51D , with the largest percentage of cases (10-15%) being attributable to germline pathogenic variants in BRCA1 or BRCA2. Previous findings have suggested that the distribution of ovarian cancer histopathology subtypes differs in germline BRCA1 and BRCA2 pathogenic variant carriers, compared to non-carriers, with a similar distribution associated with pathogenic variants for the two genes.

Earlier work also suggests that germline BRCA1 and BRCA2 pathogenic variants are unlikely to be found in patients with tumours of mucinous histology (0 to 4% . Borderline tumours, a separate entity of non-invasive epithelial ovarian cancers, are also characterised by a low frequency of BRCA1 and BRCA2 germline pathogenic variants.

BRCA1 and BRCA2 genetic testing applied for the identification of high-risk individuals will often (5–10%) identify variants of uncertain significance (VUS)

Data collection and selection criteria

An overview of the data collection process is shown in Fig. 1, where the selection and exclusion criteria are stated. In this study, data from ovarian cancer cases were collected (ovarian epithelium, primary peritoneum or fallopian tubes as primary sites) from reported germline BRCA1 and BRCA2 pathogenic or likely pathogenic variant carriers and individuals who tested negative for germline BRCA1 and BRCA2 (likely) pathogenic variants (non-carriers), with known histology information. Variant class (pathogenic or likely pathogenic) was based on the classification assigned by contributing sources at the time of collection.

Clinicopathological characteristics

The assembled dataset consisted of 10,373 ovarian cancer cases, including 2044 germline BRCA1 carriers, 761 germline BRCA2 carriers and 7568 non-carriers (based on germline testing) (Supplementary Table S2). Patient clinicopathological characteristics are shown in Table 1. The most frequent histotype was HGSC (70.9%), followed by endometrioid (9.7%), clear cell (6.3%), LGSC (4.9%), 'other' (4.7%), and mucinous (3.5%) histotypes.

In this multicentre study, we evaluated the association of ovarian tumour histology with germline BRCA1 and BRCA2 pathogenic variant status. We aimed to standardise the application of this evidence in clinical variant curation using the ACMG/AMP classification system, to inform future VUS interpretation in BRCA1 and BRCA2.

In this study, ovarian cancer histological subtypes were evaluated as predictors of BRCA1 and BRCA2 pathogenic variant status. We also provided refined LR estimates for the association of ovarian cancer histology in combination with other tumour and patient

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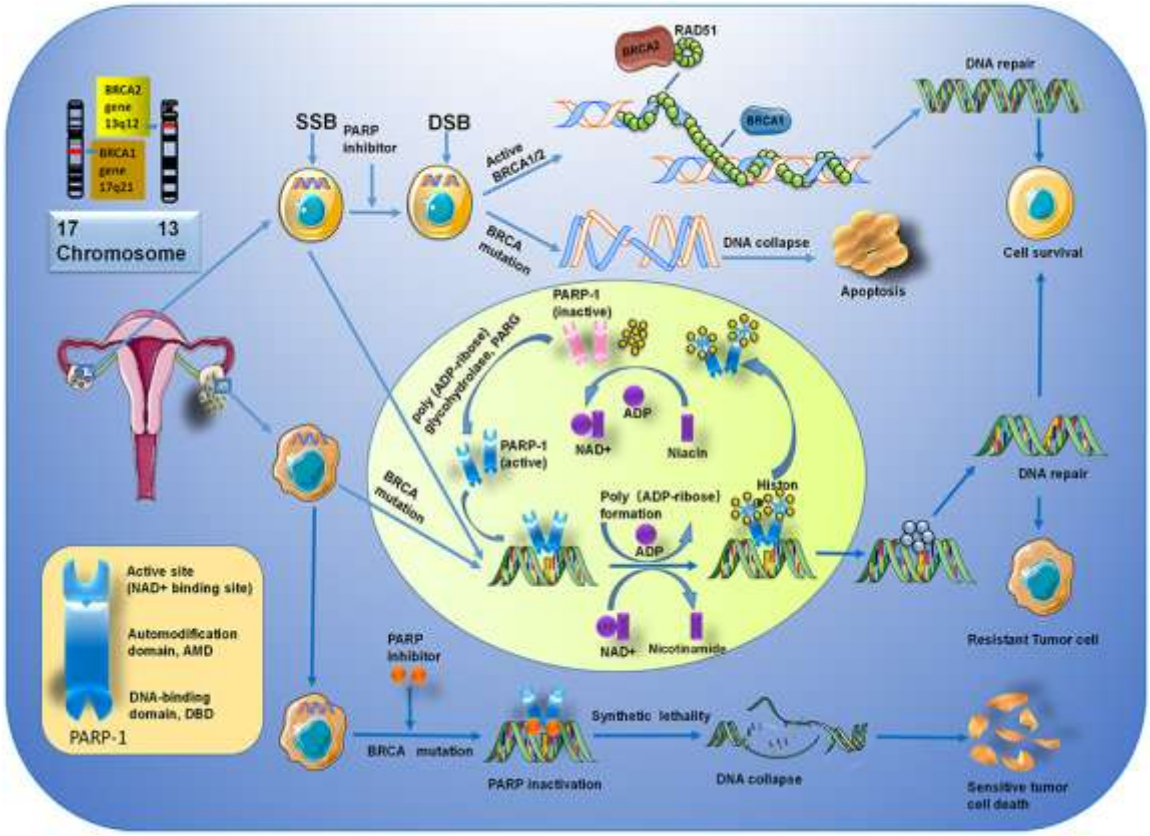
characteristics. Overall, we provide evidence for the incorporation of the derived LR estimates in variant classification to improve the interpretation of VUS identified in the BRCA1 and BRCA2, and thereby inform carrier clinical management.



2. TP53 Mutated Ovarian Cancer

Genomic sequencing analyses of a variety of human cancers have revealed that massive mutations of cancer-relevant genes are the major alterations in cancerous cells, and their mutation frequencies or rates are highly associated with the development, progression, metastasis, and drug resistance of cancers as well as their clinical outcomes and prognosis.

This essay will review the most recent progress in understanding the role of TP53 mutations in development, progression, and metastasis of EOC, and discuss the potential of TP53 mutations as diagnostic and prognostic biomarkers as well as therapeutic targets for EOC.Functions and mutations of p53

p53 is a nuclear transcriptional regulator that participates in multiple cellular processes. By binding to DNA, p53 controls the expression of hundreds of target genes in order to maintain homeostasis and genome integrity. p53 can activate DNA repair proteins when DNA has sustained damage, arrest cell growth by holding the cell cycle at the G1/S transition, allowing DNA repair, and initiate apoptosis if DNA damage proves to be irreparable.

Because of its essential role in tumor suppression, p53 is unsurprisingly found to be frequently mutated in cancer, as more than 50% of all types of human cancers have TP53 mutations. Over 36,000 TP53 mutations have been reported, and approximately 80% of p53 mutations are missense mutations with amino acid substitutions

TP53 mutations are the most common genetic events that occur at a single gene in sporadic human EOC.

Role of p53 mutations in cause and development of EOC

The causes of human cancer are diverse, but malignant transformation is invariably caused by genetic alterations that lead to malfunction of the cell cycle and disruption of cell death.

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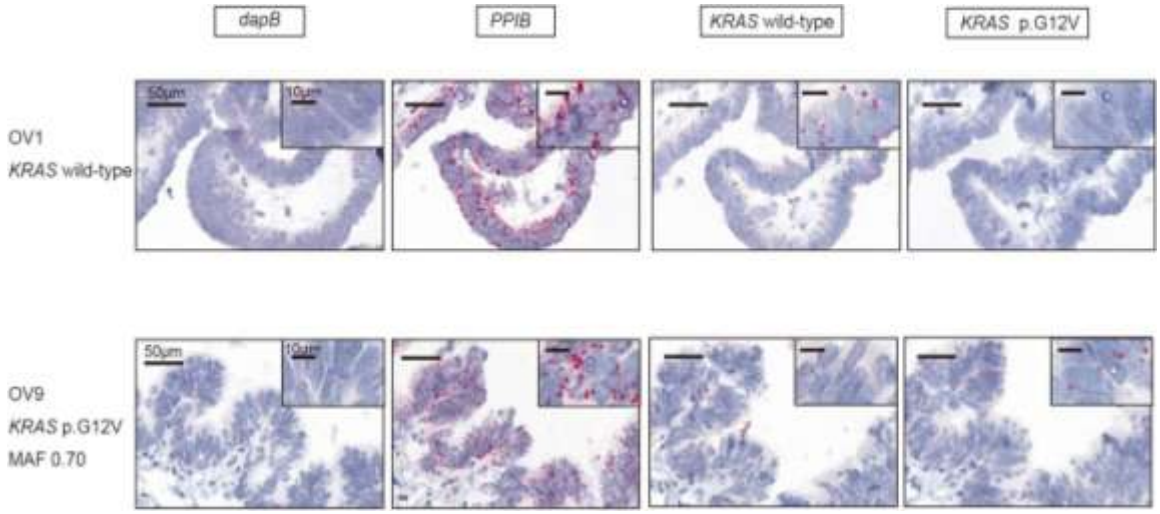
TP53 mutations occur early in tumor evolution and may be driver events in ovarian carcinogenesis.

3. Kirsten Rat Sarcoma Viral Oncogene Homologue (KRAS) and Signal Transmission

3.1. Structure of KRAS

The KRAS gene belongs to the RAS oncogene family, which possesses two distinct human isoforms: neuroblastoma and Harvey rat sarcoma viral oncogene (NRAS and HRAS). Barbacid and Weinberg discovered a gene from human bladder cancer in carcinoma cells in 1982. The HRAS gene, identified from the short arm of chromosome 11 (11p15.1–11p15.3), has been subsequently demonstrated to be the human homolog of RAS genes .

RAS is a variety of membrane-bounded regulatory proteins (G protein) primarily attached to guanine nucleotides, which is associated with the guanosine triphosphatase family (GTPases) . The function of RAS is to act as a binary switch between guanosine diphosphate (GDP) and triphosphate (GTP), which mediates essential signal transmission through receptors on the membrane to the intracellular molecule. Because of the intrinsic GTPase activity, it further hydrolyzes the GTP to GDP, and KRAS commonly attaches to the GDP in its inactive form . The KRAS-GDP complex shows less affinity for GDP in the presence of guanine nucleotide exchange factors (GEFs) after cellular stimulation and the interactions between epidermal growth factor (EGF) and its receptor (EGFR). This process promotes the exchange of GDP to GTP within the protein, utilizing higher intracellular concentrations of GTP (about 10-fold) and its greater binding affinity relative..



Advances in New Strategies in Targeting P53 for Ovarian Cancer Treatment

Currently, most reports emphasize that mutations of P53 are associated with progression and prognosis of OC.[23,28,29] Mutated p53 protein is an effective target for tumor-specific therapies because of its absence on normal tissue. Consequently, we focus on reviewing the attempts which have been made to exploit P53 as a target to treat ovarian cancer.

Restoring Mutant P53 to WT-P53 Function

Firstly, restoring function of p53 protein could make efficient eradication of tumors in liver carcinomas, sarcomas, and OC.Several small molecules have been considered to be able to reverse the oncogenic function of mutant P53. P53 re-activation and induction of massive apoptosis (PRIMA-1, also known as APR-017) and PRIMA-1Met (also known as APR-246) are widely studied, and have been confirmed to induce apoptosis and inhibit tumor growth by refolding and restoring of WT P53 function (Figure 2).

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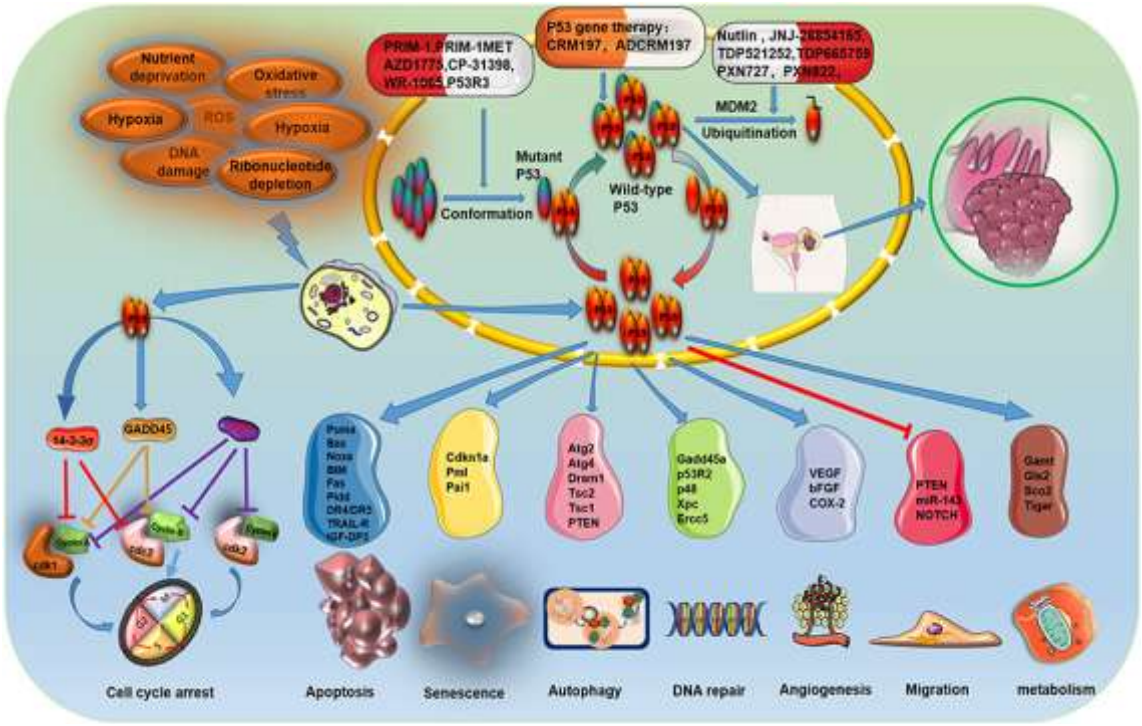

Figure 2 Cellular functions of P53 in ovarian cancer. P53 is activated to regulate the expression downstream genes to induce a series of cellular responses, such as cell cycle arrest, apoptosis, senescence, autophagy, DNA repair, angiogenesis, migration and metabolism in different types of extracellular and intracellular stress (eg, nutrient deprivation, telomere erosion, hypoxia, DNA damage, ribosomal stress, and oncogene activation). The primary treatment strategy for patients with ovarian cancer with P53 mutations is focused on restoring WT-P53 function to mutant P53, Blocking the interaction of WT P53 with MDM2/MDM4, and gene therapy with P53.

Blocking the Interaction of WT-P53 with MDM2/MDM4

Not all of tumors contain P53 mutations. In some tumors that retain WT-P53 function, the retained protein can lose function by interaction with MDM2/MDM4. So, blocking the interaction of WT-P53 with MDM2/MDM4 is a worthy strategy for targeting P53. MDM2 and MDM4 are major negative regulators of P53 and tightly control P53 activity. MDM2/MDM4, which are the downstream target genes, precisely block P53 degradation by preventing the binding of WT-P53. Especially MDM2, which is a transcriptional target and a negative regulator of P53, is phosphorylated and activated by AKT. The MDM2 inhibitor can restore P53 function or activate the expression of P53-dependent DNA repair genes to lead to tumor growth inhibition and induct apoptosis.

The diagnosis of Lynch syndrome (LS) in endometrial cancer (EC) is crucial for counseling and cancer surveillance of patients and their relatives. LS is a highly penetrant, hereditary, cancer-prone syndrome caused by germline variants in the DNA mismatch repair (MMR) genes: mutL homologue 1 (MLH1), mutS homologue 2 (MSH2), mutS homologue 6 (MSH6), or postmeiotic segregation increased 2 (PMS2).

4.Mismatch Repair Deficiency (MMRd) / Lynch Syndrome

Standard screening of endometrial cancer (EC) for Lynch syndrome (LS) is gaining traction; however, the prognostic impact of an underlying hereditary etiology is unknown.

After MMR-immunohistochemistry, MLH1-promoter methylation testing, and next-generation sequencing, tumors were classified into 3 groups according to the molecular cause of their MMRd-EC. Kaplan-Meier method, log-rank test, and Cox model were used for survival analysis.The diagnosis of Lynch syndrome (LS) in endometrial cancer (EC) is crucial for counseling and cancer surveillance of patients and their relatives.

LS is a highly penetrant, hereditary, cancer-prone syndrome caused by germline variants in the DNA mismatch repair (MMR) genes: mutL homologue 1 (MLH1), mutS homologue 2 (MSH2), mutS

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homologue 6 (MSH6), or postmeiotic segregation increased 2 (PMS2).

Tumor triage by MMR-immunohistochemistry (IHC) and/or MSI analysis in combination with targeted MLH1-methylation testing can identify patients with LS. The Proportion of Endometrial Tumours Associated Lynch Syndrome study showed that IHC-based triage is most accurate, whereas clinical selection based on age and family history were imprecise predictors

Table 1. Summary of select population-based genetic testing studies involving gynecological cancers.

Reference	Population	Genetic Testing	Main Findings
Metcalfe 2010 [7] Metcalfe 2013 [40]	AJ * women 25–80 y Ontario, Canada (n = 2082)	- Three BRCA1/2 AJ - founder mutations -	High level of interest in testing among AJ women Many individuals with mutations would not have been eligible for testing under current guidelines ~1% of AJ women carry a BRCA mutation
Manchada 2015 [41] Manchada 2020 [42]	Randomized controlled trial of AJ women/men (n = 1034) >18 y in Northern London	- Three BRCA1/2 AJ founder mutations -	Population-based testing did not adversely affect long-term psychological wellbeing or quality of life compared to family-history based BRCA testing Population-based testing could identify up to 150% additional BRCA carriers
Narod 2021 [44] The Screen Project	Canadians >18 y, open recruitment (n = 1269)	BRCA1/2 mutations -	2.4% carrier rate for a pathogenic BRCA mutation
Grzymski 2020 [8] Healthy Nevada Project	Population-based cohort <18 y (n = 26,906)	BRCA1/2, MLH1, MSH2, - MSH6, PMS2 -	1.33% carrier rate for pathogenic variants 90% of carriers had not been previously identified

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Rowley 2019 [9] Lifepool Australia	Women without cancer 50–74 y (n = 5908)	- BRCA1/2, PALB2, ATM, CDH1, PTEN, STK11, - TP53, BRIP1, RAD51C/D -	0.64% of women carried a pathogenic variant Genetic testing was well accepted The majority of carriers would not have met existing family history testing eligibility
Hu 2021 [43]	Breast cancer (n = 32,247) Controls (n = 32,544)	ATM, BARD1, BRCA1/2, CDH1, CHEK2, NF1, - PALB2, PTEN, RAD51C/D, TP53	1.63% of controls had pathogenic variants
Gabai-kapara 2014 [45]	Population-based cohort of AJ men (n = 8195)	BRCA1/2 -	2.17% pathogenic variant prevalence
Dorling 2021 [39]	Breast cancer (n = 66,466) Controls (n = 53,461)	- 35 gene panel	2.0% of European controls had a pathogenic variant in breast-cancer associated gene

* AJ: Ashkenazi Jewish.

Heterogeneity in ovarian cancer:

Ovarian cancer is a type of cancer that starts in the ovaries, which are part of the female reproductive system and responsible for producing eggs and hormones like estrogen and progesterone. It is often challenging to detect early, as symptoms can be vague, such as bloating, pelvic pain, and changes in appetite. Most ovarian cancers are classified as epithelial, meaning they arise from the cells on the surface of the ovary, but there are also less common types that start in egg-producing cells or supporting tissue.

Risk factors include age (mainly affecting women over 50), family history of ovarian or breast cancer, genetic mutations (such as BRCA1 and BRCA2), and certain lifestyle factors. Early detection can be difficult, but advanced imaging, blood tests (like CA-125), and genetic testing can help in diagnosis and risk assessment. Treatment typically involves surgery and chemotherapy, with newer therapies such as targeted therapy and immunotherapy also showing promise.

Ovarian cancer metastasis and organ tropism for the adipose-rich omentum:

Ovarian cancer is characterized by rapid proliferative growth, peritoneal disseminated metastasis, and malignant ascites within the intraperitoneal cavity. The biological mechanisms that regulate ovarian cancer metastasis are distinctive and notably different from the classic mechanisms of hematogenous metastasis that frequently occurs in most solid cancers. In certain cancers, such as breast, lung, liver, colorectal, and prostate cancers, the metastatic cascade represents a multifaceted process that includes local invasion, intravasation, survival in circulation, extravasation, and metastatic colonization at distant metastatic sites. Thereby, cancer cells frequently encounter with a number of environmentally grueling challenges. In ovarian cancer, peritoneal disseminated metastasis seems to be easier because of the lack of anatomical barriers around the primary ovarian cancer in the milieu of the peritoneal cavity. Upon successful detachment from primary tumor, ovarian cancer cells can survive by forming multicellular spheroids with some stromal components, which float in the specific microenvironment of ascitic fluid, and then metastasize predominantly to the omentum and peritoneum via a direct mechanism. This phenomenon leads to multiple disseminated tumors within the intraperitoneal cavity.

In the metastatic process, the phenomenon wherein cells of particular types of cancer preferentially colonize only a

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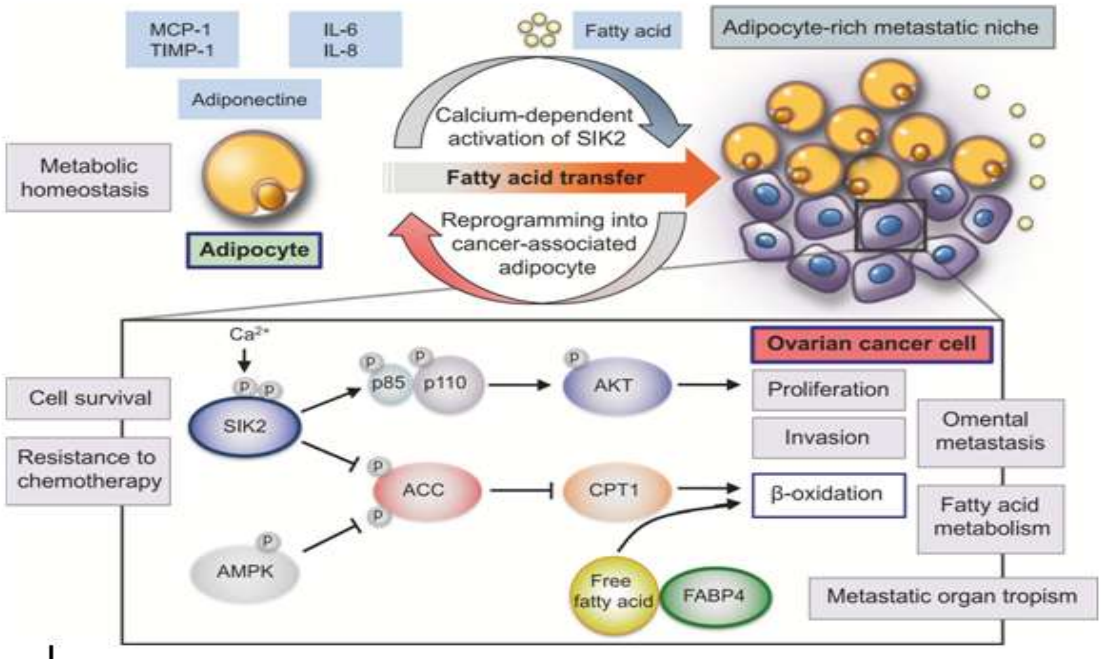

Fig. 1 Adipocytes represent a central player in the creation of the metabolic tumor microenvironment in the omentum during ovarian cancer metastasis. Adipocytes are reprogrammed into cancerassociated adipocytes by cancer-derived mediators. These activated adipocytes release a wealth of lipids and various adipokines, including IL-6, IL-8, MCP-1, and TIMP-1, which contribute to the establishment of the omental metastatic niche for ovarian cancer. FABP4, which is an intracellular chaperone for free fatty acids, regulates lipolysis in adipocytes and β-oxidation in ovarian cancer cells, and plays a crucial role in the interaction of ovarian cancer cells with adipocytes, promoting omental metastasis. In addition, omental adipocytes induce the calcium-dependent activation and .autophosphorylation of SIK2 in ovarian cancer cells and activate cancer cell proliferation through the PI3K/AKT pathway. SIK2 can increase ovarian cancer cell fatty acid oxidation by augmenting AMPK-induced ACC phosphorylation and activating CPT1 during peritoneal disseminated metastasis. Thus, the highly orchestrated crosstalk between ovarian cancer cells and omental adipocytes induces metabolic synergies by reprogramming fatty acidmetabolism and tumor-promoting signaling pathways that enhance theproliferation, invasion, and metastatic progression of ovarian cancer cells with specific metastatic tropism for the omentum.

Adipocytes and metabolic tumor microenvironment:

Adipocytes are the most important and abundant cellular component of omental and peritoneal tissue (Fig. 1). As the master regulator of lipid storage and through the production of a panel of adipokines and endocrine molecules, adipocytes contribute to a variety of biological functions, including cellular metabolism, inflammation, and cancer development, under both physiological and pathological circumstances .Emerging evidence has indicated that bidirectional interactions between cancer cells and adipocytes cause the reprogramming of adipocytes into "cancer-associated adipocytes,"and these activated adipocytes are able to release large amounts of lipids, adipokines, tumor-promoting factors, and hormones, which represent a major part of the metabolic tumor microenvironment and promote aggressive.

In recent years, researchers have started to identify the molecular basis for the establishment of the intraperitoneal metastatic tumor microenvironment associated with the interplay between ovarian cancer cells and adipocytes, as well as the metastatic tropism for the omentum . Nieman et al. showed that omental adipocytes are intimately associated with the ovarian cancer metastatic cascade, including invasion, migration, and homing to omental tissue. After undergoing coevolution with ovarian cancer cells, activated

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omental adipocytes increase the secretion of various types of adipokines, such as interleukin-6 (IL-6), IL-8, monocyte chemoattractant protein-1 (MCP-1), tissue inhibitor of metalloproteinase-1 (TIMP-1), and adiponectine, and these adipokines promote the multistep process of ovarian cancer dissemination with metastatic tropism for the omentum.

Early Detection and Personalized Therapies:

The rationale for early detection of ovarian cancer is compelling. Ovarian cancer confined to the ovaries (stage I) can be cured in up to 90% of patients, and disease confined to the pelvis (Stage II) is associated with a 5-year survival of 70%. However, disease that has spread beyond the pelvis (stage III-IV) has a long-term survival rate of 20% or less. Only 20% of ovarian cancers are currently diagnosed in stage I-II . Computer simulations suggest that detection of preclinical disease at an earlier stage could improve survival by 10–30% and would be cost-effective

Table 1.

Key statistical terminology in the context of population screening tests for ovarian cancer

Characteristic	Synonyms	Definition
Prevalence	Pre-test probability	Proportion of population affected by a condition
Sensitivity	Detection rate; True positive rate (TPR)	Proportion of subjects with cancer who test positive
Specificity	True negative rate (TNR)	Proportion of subjects without cancer who test negative
False positive rate (FPR)	1 - specificity; Type I Error; α	Proportion of subjects without cancer who test positive
False negative rate (FNR)	1 - sensitivity, Type II error; β	Proportion of subjects with cancer who test negative
Positive Predictive Value (PPV)	Positive post-test probability	Probability that a subject with a positive test has cancer
Negative Predictive Value (NPV)	Negative post-test probability	Probability that a subject with a negative test does not have cancer
Positive likelihood ratio (LR+)	TPR / FPR	Ratio between the probability of a positive test result given the presence of the disease and the probability of a positive test result given the absence of the disease
Negative likelihood ratio (LR-)	1 – TPR / specificity	Ratio between the probability of a negative test result given the presence of the disease and the probability of a negative test result given the absence of the disease
Odds Ratio	[TPR / (1 − TPR)] × [(1 − FPR) / FPR]	
Receiver-Operating Characteristic (ROC) Curve		Plot of sensitivity vs. FPR
Area under the ROC Curve (AUC)	C-statistic	A normalized Mann Whitney/Wilcoxon test where the Wilcoxon statistic is divided by the product of the number of individuals in the two groups measured

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Characteristic	Synonyms	Definition
Accuracy		Overall probability that a subject will be correctly classified

Biomarker Tests for Early Detection of Ovarian Cancer

1. CA-125 (Cancer Antigen 125)

- Most widely used blood test.
- Elevated in about 80% of women with advanced ovarian cancer.
- Limitation: Can also be elevated in non-cancerous conditions (like menstruation, endometriosis, or pregnancy), and it may be normal in early-stage cancer.

2. HE4 (Human Epididymis Protein 4)

- More specific than CA-125, especially in distinguishing ovarian cancer from benign diseases.
- Often used in combination with CA-125 for better accuracy.

3. ROMA (Risk of Ovarian Malignancy Algorithm)

- Combines CA-125, HE4, and menopausal status to calculate the risk of ovarian cancer.
- Useful in determining which women with pelvic masses should be referred to a gynecologic oncologist.

4. OVA1 Test

- Uses a panel of five biomarkers (CA-125, beta-2 microglobulin, transferrin, transthyretin, and apolipoprotein A-1).
- Gives a score to assess the likelihood that a mass is cancerous.
- Approved by the FDA, especially for pre-surgical evaluation.

5. Liquid Biopsies (Emerging Technique)

- Detects circulating tumor DNA (ctDNA), exosomes, or tumor-associated RNA in the blood.
- Still in research phases, but shows promise for earlier and more precise diagnosis.

6. TP53 Autoantibodies

- Studies show some ovarian cancer patients develop autoantibodies to mutated TP53 proteins months before diagnosis.
- Could be part of a future early-detection panel.

7. Other Experimental Biomarkers

- Mesothelin, MMPs, B7-H4, microRNAs (miRNAs) – being studied as potential early detection tools.
- Proteomics and metabolomics approaches are identifying patterns that may help detect cancer earlier

Protein biomarkers.

CA125 remains the most sensitive and specific protein biomarker for detecting early stage disease in apparently healthy populations. CA125 is a high molecular weight (~5 MDa) heavily glycosylated membrane-spanning mucin (MUC16) glycoprotein. The extracellular domain of MUC16 is cleaved near the ovarian cancer cell surface, releasing CA125 into the peri-cellular space and ultimately into the blood where it can be measured with an immunoassay. CA125 levels are elevated in blood from >90% of patients with advanced stage (III-IV) and in 50–60% with stage I ovarian cancer.

Autoantibodies

Autoantibodies to mutant proteins can be stimulated by small volumes of cancer in the ovary or fallopian tube, providing greater sensitivity and earlier detection than CA125 or other assays that detect shed biomarkers. Autologous antibodies can be produced against mutant TP53 protein. Alteration in TP53 is the most common genetic mutation among ovarian cancers, seen in up to 96% of high-grade serous carcinomas [21]. At a specificity of 97%, autoantibodies could be detected in 21–30% of serum samples from ovarian cancer patients from MD Anderson, the Australian Ovarian Cancer Study and the UKCTOCS [22]. Among 164 cases with rising CA125 detected in serial preclinical serum samples with the ROCA, 20.7% had elevated TP53 autoantibody. Of the 34 ovarian cancer cases detected with the ROCA, TP53 autoantibody titers were elevated 8 months before CA125. In the 9 cases missed by the ROCA, TP53 autoantibody was elevated 22.9 months before cancer diagnosis. Consequently, TP53 autoantibody levels provide the first bio-marker with clinically significant lead time over elevation of CA125 or an elevated ROCA value.

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Circulating tumor DNA

Circulating cell-free DNA (cfDNA) in serum and plasma can be distinguished from lymphocyte DNA by size; circulating DNA is fragmented to an average length of 140 to 170 base pairs (bp) Efforts have focused on the fraction of circulating DNA derived from tumors, called circulating tumor DNA (ctDNA) .

DNA methylation

Hypermethylation of tumor suppressor promoters and hypomethylation of oncogenes are frequent genetic events Methylation-specific PCR (MSP) is very sensitive, able to identify 1 methylated allele in 1000 unmethylated alleles. The frequency of promoter hypermethylation increases with advancing disease stage . Using multiplexed MSP to examine cfDNA for seven candidate genes (APC, RASSF1A, CHDH1, RUNX3, TFP12, SFRP 5, and OPCML), Zhang, et al, reported 85% sensitivity at 91% specificity for early stage ovarian cancer compared to a single CA125 value, which produced a sensitivity of 56% at 64% specificity. However, this was based on only 17 early-stage patients

II. CONCLUSION:

In the study of "Genetic Mutations and Ovarian Cancer: Insights into Early Detection and Personalized Therapies," significant strides have been made in understanding how specific genetic mutations contribute to ovarian cancer development. Mutations in genes like BRCA1 and BRCA2, as well as others involved in DNA repair pathways, are linked to higher ovarian cancer risk. These genetic insights allow for the development of early detection methods, such as genetic screening, which can identify at-risk individuals even before symptoms arise.

Early detection, combined with knowledge of a patient's genetic profile, has paved the way for personalized therapies. Targeted treatments, such as PARP inhibitors for BRCA-mutated cancers, have demonstrated effectiveness by exploiting the tumor's genetic vulnerabilities. Furthermore, understanding the tumor microenvironment and immune response associated with these genetic mutations supports the design of immunotherapies and novel drug combinations tailored to the individual.

In conclusion, integrating genetic insights into ovarian cancer research has transformative potential. Early detection and personalized therapies not only improve patient survival rates but also contribute to a more precise and effective approach to managing ovarian cancer. This approach marks a shift from generalized treatment to a personalized model, offering hope for more targeted and successful outcomes.

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[38]. **BRCA1 and BRCA2 Mutations in Ovarian Cancer**

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[40]. **Role of TP53 and KRAS Mutations**

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