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Advances And Insights In Biomarker Research

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ABSTRACT:

Biomarker is an important feature, which is quantified and evaluated objectively as an indicator of the healthful biological process, unhealthy processes, and pharmacological responses to a therapeutic intervention. These biomarkers may be circulating whole blood, serum or plasma, excretions or secretions, which are stool, urine, sputum, or nipple discharge, and are analyzed forever without invasion works. Alternatively, biomarkers are generated from tissue specimens that would, therefore, require biopsy or specific imaging for their evaluation. Inherited genetic biomarkers can be discriminated as a person's entire blood cell, sputum, or buccal cells are sequence-differences that should come from germ line DNA. Somatic genetic biomarkers are identified from mutations within DNA from tumor tissue. A marker of the presence of cancer in the body is referred to in the context of cancer as a biomarker. "In most situations, the biomarker could be a molecule released by a tumour or the body's particular response to the presence of cancer." In a summary, the biomarkers with regard to cancer application for diagnosis, prognosis, and epidemiology should be in genetics, epigenetics, proteomics, and imaging. Nonetheless, few numbers of cancer biomarkers can be highly sensitive and specific for detecting cancer. : These biomarkers are not generally ready for use due to the difficulty currently experienced in the clinical validation to improve patient's long-term survival by determining early disease detection, diagnostic, and monitoring of disease.

Keywords: biomarker, cancer; diagnosis; prognosis, pathophysiology, Healthful biological proces, Inherited genetic biomarkers, Somatic genetic biomarkers.

1. INTRODUTION OF BIOMARKER:

• According to Hulka and colleagues, biological markers (biomarkers) are "cellular, biochemical, or molecular abnormalities that are quantifiable in biological media such as human tissues, cells, or fluids.

• The concept has lately been expanded to encompass biological properties that can be objectively tested and analysed as indicators of normal biological processes, pathogenic processes, or pharmacological reactions to a therapeutic intervention.

• Biological markers, also known as biomarkers, are used to identify specific biological states in normal and pathological processes, as well as probable therapeutic pharmacologic responses.

• Biomarkers (proteins, hormones, enzymes) are inappropriately created or whose expression is altered by changes in the gene expression of diseased cells in a patient's blood, body fluids, cells, or tissues during the occurrence and progression of the disease. As a result, biomarkers play a critical role in identifying certain physiological and pathological states in all living creatures. Biomarkers are becoming more prevalent in clinical medicine, as well as bench and bedside research. Biomarkers are primarily employed in clinical settings for diagnosis, prognosis, and risk prediction.

• A biomarker is "a biological molecule present in blood, other body fluids, or tissues that is a sign of a normal or aberrant process, or of a condition or disease such as cancer," according to the National Cancer Institute. Biomarkers are used to distinguish between patients who have the disease and those who do not. A variety of mechanisms might cause the changes, including germ line or somatic mutations, transcriptional changes, and post-translational modifications. Biomarkers come in a wide range of forms, including proteins (such as an enzyme or receptor), nucleic acids (such as a microRNA or other non-coding RNA), antibodies, and peptides, among others. A biomarker can also b e a group of changes, such a s gene expression, proteomic signatures, and metabolomic signatures.

• Biomarkers can be found in the circulation (whole blood, serum, or plasma) or excretions or secretions (stool, urine, sputum, or nipple discharge), making them non-invasive and serially assessable, or they can be tissue-derived, necessitating biopsy or specific imaging for evaluation. Inherited genetic biomarkers can be discovered as sequence differences in germ line t DNA recovered from whole blood, sputum, or buccal cells, or somatic genetic biomarkers can be identified as mutations in DNA derived from tumour tissue.

• Genomic variation accounts for over 80% of the variability in therapeutic efficacy and side effects, posing significant issues in prescription selection and dosing.

• The expression of drug targets, drug metabolising enzymes, and other proteins engaged in pathophysiological mechanisms relevant to the medication's pharmacodynamic and pharmacokinetic processes i s affected by genomic composition, which i s a n essential factor for individual response to therapy. Pharmacogenomics (PGx) is a component of precision medicine that uses genomic profiling to uncover biomarkers based on relevant genotype-phenotype relationships that might predict drug response and the likelihood of adverse drug responses for a specific patient.

• Biomarkers for lung cancer could be used in a variety of clinical settings. They can be utilized for risk stratification, early detection of lung cancer, treatment selection, prognostication, and recurrence monitoring.

2 TYPES OF BIOMARKERS:

1]Diagnostic biomarkers:

To confirm the presence of a disease (and subtypes) or medical condition.

2] Monitoring biomarkers:

To asses presence, status or extent of a disease or medical conditions; to evaluate the response to the intervention.

3] Pharmacodynamic/Response biomarkers:

To evaluate the response to a medical conditions or clinical intervention.

4] Predictive biomarkers:

To identify the probability of develop a clinical event (positive or negative) after the exposure to a medical product or environmental agent.

5] Prognostic biomarkers:

To identify the like hood of clinical event, disease recurrence or progression in patients diagnosed with a disease or having a medical condition.

6] Susceptibility/Risk biomarkers:

To measure the risk of an individual to develop a disease or medical conditions in patients without disease or medical condition.

7] Safety biomarkers:

To predict toxic adverse events induced by drug, medical intervention or environmental agent exposure.

3 APPROACHES OF BIOMARKERS:

• The purpose of this study is to describe the application of proteomics techniques and approaches to develop accurate biomarkers for the diagnosis of various diseases from various types of material. Blood samples, tissue samples, tissue interstitial fluid samples, saliva and urine predisposition biomarkers, diagnostic biomarkers, and prognosis samples are among the samples collected from patients.

• To discover a biomarker in a certain condition, there are three key processes in pro biomarkers and predictive biomarkers proteomics analysis. These steps include the following:

(1) Protein extraction and separation

(2) Protein identification

(3) Protein verification

The following are the final steps: I database searching

(ii) study of protein-protein interactions (PPIs)

(iii) statistical analysis.

3.1 CATEGORIES OF BIOMARKERBASED ON PATHOPHYSIOLOGY:

• The biomarkers of sepsis can be divided into seven categories based on pathophysiology:

(1) acute phase reactants, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin;

(2) proinflammatory cytokines, such a s interleukin, tumour necrosis factor (TNF), and monocyte chemoattractant protein;

(3) activated neutrophil and monocyte biomarkers, such as cluster of differentiation (CD), presepsin, and receptor for advanced glycation end products;

(4) Infectious organisms and related proteins, such as high-mobility group box 1 and myeloid-related protein;

(5) receptors, such as toll-like receptors, TNF receptors, and triggering receptor expressed on myeloid cell 1 (TREM-1);

(6) anti-inflammatory markers, such as monocyte human leukocyte antigen-DR expression and cytotoxic T-lymphocyte-associated protein 4,

(7) biomarkers for organ dysfunction, such as liver function tests, coagulation tests, and renal function tests.

4. CANCER BIOMARKER

4.1 PATHOPHYSIOLOGY OF CANCER:

• How does cancer work? Pain is a complex pathological process involving cellular, tissue, and systemic alterations that occur as a result of cancer's proliferation, invasion, and metastasis. Cancer cells, the peripheral and central neurological systems, and the immune system.

All interact to cause it. Pain in cancer patients is caused by a variety of factors, including:

- A tumor's existence, or the advent and/or growth of a metastasis

- Anticancer treatment (diagnostic procedures, surgical interventions, radiotherapy, chemotherapy, immunotherapy, hormone and molecular therapy)

- Indirectly related mechanisms to cancer and its treatment (infections, metabolic imbalance, myofascial

- Mechanisms that are unrelated to cancer or its treatment (migraine, painful diabetic neuropathy, low-backpain).

4.2INTRODUTION OF CANCER BIOMARKER:

• Cancer is one of the world's top causes of death. In recent years, major advancements in tumor identification and therapy have been made. Early identification, on the other hand, is crucial for improving cancer patient outcomes and minimizing recurrence and mortality. Early diagnosis is hampered by the lack of evident symptoms and insufficiently sensitive biomarkers in the early stages of cancer.

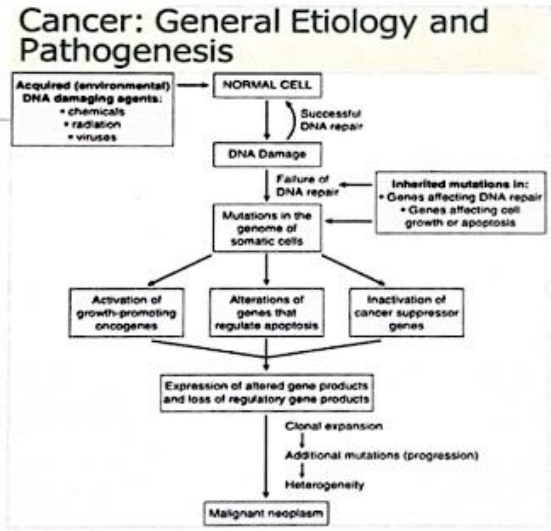
• While biopsy and imaging examination as gold standards considerably improve detection rates, their uses are limited by their respective invasive or radiation-related characteristics.

Cancer poses a significant threat to our lives. According to the American Cancer Society, 1,762,450 new cancer cases and 606,880 cancer deaths are expected in the United States year 2019.

In other words, every day, around 4,829 individuals are diagnosed with cancer, and approximately 1,663 people die from cancer. Early detection and treatment strategies that are effective can significantly reduce cancer incidence and mortality. X-ray, computerised tomography (CT), magnetic resonance imaging (MRI), positron emission tomography, endoscopy, sonography, thermography, cytology, and biopsy are among the complicated clinical scenarios used to diagnose tumours today.

•Molecular tools based on genomic and proteomic data, such as polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunohistochemistry (IHC), and flow cytometry, are also becoming more widely employed.

A cancer biomarker assesses the likelihood of developing, progressing, or responding to a certain treatment.



•Biomarkers offer a wide range of potential uses in cancer, including risk assessment, screening, differential diagnosis, prognosis, therapy response prediction, and disease progression tracking. Because biomarkers are so important at all stages of disease, it's critical that they go through a rigorous evaluation process that includes analytical validation, clinical validation, and clinical utility assessment before being used in normal clinical care.

• In this study, we look at critical processes in the development of biomarkers, such as how to prevent introducing bias and reporting criteria for biomarker studies.

• Cancer cells have a wide range of genetic changes, including as gene rearrangements, point mutations, and gene amplifications, which disrupt molecular pathways that control cell growth, survival, and metastasis. When such alterations occur in a large number of patients with a specific type of tumour

• Biomarkers were used for detection and development of targeted therapeutics, as well as predicting therapy responses.

• Several biomarkers can be measured using genetics, genomics, proteomics, and a variety of non-invasive imaging techniques and other technologies.

4.3 TYPES OF CANCER BIOMARKERS:

1. **Cytogenetic and cytokinetic markers:**
   • Chromosomal structural and numerical abnormalities are traditional cancer indicators, as the link between chromosomal aberrations and neoplastic transformation is well recognised
   • While deviations from diploid chromosomal number have been observed in malignant tumours, sister chromatid exchanges and translocations result in structural abnormalities that may be easily scored using various bands techniques.
   • Furthermore, in cancer cells, double minutes and homogeneously coloured patches (indicative of gene amplification) are frequently detected and can be used as marker.
   • Identification of neoplasm from the amount of lesion specific transcriptomes (mRNA of cytokeratin-19, EGFR, MUC 1, etc.) in the blood has been successfully used in some epithelial malignancies, among other genome-based biomarkers.

• One of the most important characteristics of cancer is increased cell proliferation, which may be detected by a variety of histological, biochemical, and flow cytometric techniques.
• Despite its subjective character, histological assessment, which involves counting the number of mitotic cells in a sample, is nevertheless employed as a routine clinical test and even for grading in some cancers, such as breast cancer.
• Identifying S-phase cells (an unmistakable hallmark of proliferation) and examining a variety of different antigenic drivers of proliferation.

2. **Genetic biomarkers: -**

• Cancer is a hereditary disease caused by mutations in genes that control cell proliferation, survival, and other homeostatic processes, such a s oncogenes and tumour suppressors. Oncogenic transformation is primarily caused by the gain or loss of gene function.
• A single point mutation on a chromosome can turn several proto-oncogenes into oncogenes, affecting the amount of their product, protein. Several non-random mutations, a s well as translocations and rearrangements within the regulatory region of the gene, have been linked to specific forms of cancer.
• Genomic material deletion i s critical because the missing DNA segment may carry tumour suppressor activity. Polymerase chain reaction (PCR) using microsatellite probes to various chromosomes and locations is used to find gene deletions. Tumor-suppressor genes, such as p53, Rb, DCC, Brush-1, BRCA-1, and BRCA-2, are hypothesised to play a role in certain tumours.
•Clinical cancer is caused by well-defined indicators and random chromosomal aberrations that are not related with a specific morphological change.
• Adenomatous polyposis coli (APC) gene: The APC gene, which typically suppresses cancer, is deactivated in many tumours; the changed gene has been discovered in 92 percent of patients with oesophageal adenocarcinoma and 50 percent of patients with squamous c e l l c a r c i n o m a o f t h e oesophagus. APC gene mutations are found in 60% of colorectal cancer patients and are regarded to be the first genetic anomalies in the evolution of colorectal cancer.
• The majority of these mutations result in the generation of an unusually short and non-functional APC protein. This short protein is unable to control cellular expansion, which results in the creation of polyps, which can become cancerous.
• In sporadic colorectal cancer, as well as some cancers of the stomach, pancreas, thyroid, ovary, and other primary sites, somatic mutations of the APC gene have been discovered.

3. **Cells as biomarker: -**

4. • As tumours progress, cells begin to appear in the bloodstream, where they can be easily tracked. Advanced clinical practice has successfully exploited tumour and immune cells as a good biomarker of prognosis in specific malignancies, while its utility in other cancers is still being evaluated, circulating tumour cells (CTCs) are a simple yet effective biomarker in oncology.
• CTCS give an early, accurate indication o f disease progression and survival for patients on systemic therapy for metastatic breast cancer at numerous time points over the course of therapy. CTCs have been demonstrated to be more accurate in predicting prognosis than traditional tumour markers.
• T-regulatory cells (CD4, CD25, and Foxp3) are cells that regulate the immune system A number of mechanisms aid the immune system's ability to distinguish self from non-self, making it easier to maintain immunological tolerance to self-antigens while also inducing protective response to alien antigens.
• Anti-FoxP3 antibodies are used to identify regulatory T cells (T-regs), which are predominantly and particularly identified by (transcription factor, FoxP3) investigations. By influencing the immune system's ability to target tumour cells, the presence of FoxP3+ cells within tumours have been demonstrated to predict the prognosis, invasiveness, and metastatic ability of some malignancies. (37)
• Cancer stem cells (CSCS): It has long been known that inside tumours, there are subpopulations of cancer cells that mirror the developmental hierarchy of the normal tissue from which the tumour formed. The cancer stem cell model of carcinogenesis has gotten a lot of interest in recent years. Tumours, according to this hypothesis, are driven and maintained by a small subpopulation of cells
with the ability to self-renew and generate the more differentiated progeny that make up the bulk of the tumour.Various researchers have dubbed the former population cancer stem cells (CSCs), tumorigenic cancer cells, or tumor-initiating cells to signify that only these cells can cause new tumours when transplanted into immuno-deficient mice.

5. **Viral Biomarkers:**

• Hepatocellular carcinoma (HCC), one of the most frequent malignancies worldwide and a primary cause of mortality in developing nations, where over 80% of cases are documented, is one of the most c o m m o n viral-induced tumours.

• Chronic hepatitis infections, primarily caused by the endemic hepatitis B virus (HBV), are a risk factor, with hepatitis C virus (HCV) infection being recorded in a small percentage of HCC patients (12-17%).

• In addition to immuno-inflammatory reactions, HBV can induce carcinogenesis by causing genetic instability due to its widespread integration in host DNA.

• These markers include viral DNA or protein analysis, as well as antibodies created against viral proteins. HBV surface antigen (HBsAg) is the most commonly used test to detect whether a patient has a chronic infection with high or low viral replication, whereas HBeAg is a test to assess whether a patient has a chronic infection with high viral replication.

• Antibody analysis, including detection of anti-HBV core antigen, anti-HBe antigen, and anti- HBAg, are the other primary types of biomarkers employed in HCC investigations.

5 PROSTATE CANCER BIOMARKER:

5.1 PATHOPYSIOLOGY OF PROSTATE CANCER:

• Androgens are key regulators of both normal prostate cell growth and proliferation, as well as prostate cancer cell growth and proliferation. Prostate cancer cells rely on the androgen receptor as the principal mediator of growth and survival during androgen-dependent development.

When testosterone enters the cell, it is transformed to dihydrotestosterone, a more active hormone with a 5- to 10-fold higher affinity for the androgen receptor, by the enzyme Salpha - reductase.

•Dihydrotestosterone interacts to androgen receptors the cytoplasm, inducing phosphorylation, dimerization, and translocation into the nucleus, where it binds to androgen-response regions within DNA, activating genes important in cell growth and survival.

• Prostate cancer cells develop a multitude of biological pathways to survive and thrive in an androgen deprived environment during androgenic dependent development. Androgen receptor (AR) gene amplification, AR gene mutations, participation of coregulators, ligandin-dependent activation of the androgen receptor, and involvement of tumour stem cells are all hypothesised and verified mechanisms.

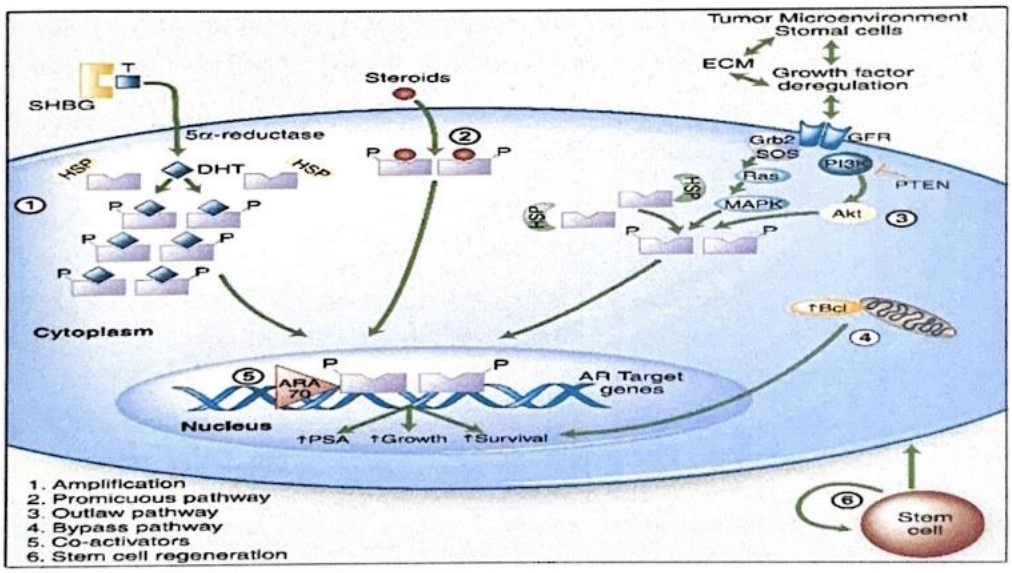


Figure: Mechanisms of androgen independence.

5.2 INTRODUCTION OF PROSTATR CANCER BIOMARKER:

• prostate cancer (PC) continues to be a significant burden on our society, with one out of every nine men obtaining a PC diagnosis at some point in their lives, the hunt for a reliable diagnostic tool is highly justified.

• Prostate specific antigen (PSA) has been the gold standard for PC screening and diagnosis since 1986.

• PSA, PHI, PCA3, and Polaris are biomarkers.

• Prostate cancer (PC) is the second most frequent malignancy in men, accounting for 13.5% of all cancer diagnoses in men around the world.

• PC is classified as an androgen-sensitive illness since it is initiated and progresses in the presence of testosterone.

• Prostate cancer (PC) is the most frequent cancer in males, affecting primarily men over the age of 50, and is the leading cause of cancer-related death in men.

TEST FOR MEN WITH PRIOR NEGATIVE BIOPSIES: -

1) ConfirmMDx:

• ConfirmMDx is a tissue-based gene test that examines a set of epigenetic modifications in a sample of prostate tissue. This method helps risk-stratify males with previous negative biopsies by detecting changes in DNA methylation in key tumour suppressor genes (GSTP1 and APC).

2) Progensa PCA3 Assay:

•In addition, limited data has been gathered on the relationship between PCA3 scores and tumour sizes, as well as the capacity to discern between indolent and serious malignancy. Combinations of various biomarkers are likely to emerge in the near future.

3) ProMark:

•The ProMark test (Metamark, Cambridge, USA) i s a protein-based assay that uses quantitative immunofluorescence to evaluate the levels of proteins in a prostate biopsy sample (DERL1, DPC4, PDSS2, FUS).

•Cell signaling, stress response, and cell proliferation are all aided by these proteins. The idea behind measuring protein levels is-based on t h e fact that PC has alot of intratumoral heterogeneity.

• As a result, a protein-based panel strives to give data generated from the most aggressive cells possible.

• The risk of Gleason score 4 + 3 disease or non-organ confined disease on RP is represented by a score ranging from 0 to 1. Men who are NCCN very-low or low-risk and considering active surveillance should take the test.

4) Oncotype DX:

• Oncotype DX (Genomic Health, Redwood City, USA) is an assay that measures the expression levels of 12 cancer genes and five housekeeping genes using reverse transcriptase-PCR. The 12 cancer genes are involved in four important cellular pathways: proliferation (TPX2), androgen receptor pathway (KLK2, SRDSA2, FAM13C), cellular organisation (FLNC, GSN) and stromal response (AZGP1, KLK2)

• The Genomic Prostate Score (GPS), which runs from 0 to 100, is calculated using the combination of these genes. At the time of prostatectomy, GPS is linked to the likelihood of unfavourable pathology, such as primary grade group and/or non-organ confined disease.

PROSTSTE CANCRE SCREEING TESTS:

• reviewed the various PC screening tests available on the market, including:

i)Blood: Prostate: Health Index (PHI), 4k-score (4-kallikrein panel), and Apifiny;

(ii) Urine: SelectMDx, PCA3, Michigan Prostate Score (MiPS);

iii) Biopsy: ConfirmMDx, Oncotype Dx, Pro-Mark.

6 BREAST CANCER BIOMARKERS:

6.1 PATHOPHYSIOLOGY OF BREAST CANCER:

• Breast cancer is the most prevalent malignant tumour in women and the second leading cause of cancer death. More than 90% of cancer-related deaths are caused by metastatic breast cancer rather than the initial tumour.

• Breast cancer (BC) is the most frequent cancer in women around the world.

• Despite the fact that much research has been devoted to improve disease detection and therapeutic therapy, BC remains the top cause of cancer death in women. Between 20 and 30 percent of BC patients go on to acquire a fatal metastatic disease.

• In breast cancer, there are three stages of cancer immunoediting. The initial stage of cancer immunoediting is elimination. Acute inflammation, such as type 1-polarized macrophages (M1), natural killer (NK), and natural killer T cells (NKT), is activated early in mammary carcinogenesis, resulting in tumour cell death and the development of dendritic cells (DC), which can excite tumor-specific T cells (CD4+ and CD&*). The TME contains soluble factors associated with inflammation, including as IL-2, IFNY, perforin, and TNF. This is followed by either immune-mediated rejection of incipient tumours or tumour cell variant selection, both of which can cause persistent inflammation.

• As a result, the persistent cells reach equilibrium. Finally, the escape phase occurs, resulting in a complex and immune-tolerant composed of suppressive immune cells such as regulatory T cells (Treg), type 2- polarized tumour-associated macrophages (M2), and myeloid-derived suppressor cells (MDSC), as well as inhibitory molecules such as IL-6, galectin, IL-10, and TGF-B, which allow for overt immune escape and tumour progression.

•Prognosis and typical therapies for breast cancer subtypes Based on the expression of ostrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), BC can be divided into four subtypes (HER2). On the basis of molecular markers, targeted and endocrine medications are delivered. Triple-negative breast cancer (ER, PR, HER2) has the worst prognosis and does not respond to endocrine treatments or HER targeting medicines. Chemotherapy is the sole treatment option available.

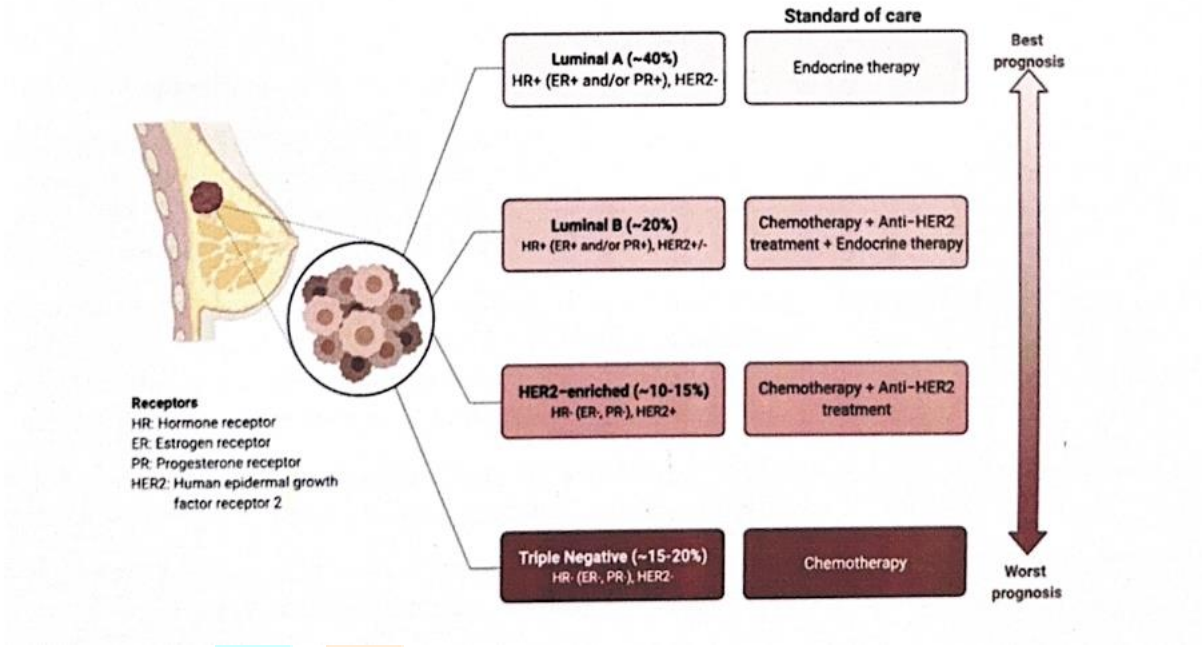


Figure : Breast cancer subtypes.

6.2 INTRODUCTION BREAT CANCER BIOMARKERS: -

BC biomarkers (glycoproteins: mucin 1 (MUC1), HER2, carcinoembryonic antigen (CEA), epidermal growth factor receptor (EGFR), carbohydrate antigen 15-3 (CA15-3), mammaglobin (MAM); DNA: BRCA1, BRCA2, microRNAs, and circulating tumour cells (CTC); DNA: BRCA1, BRCA2.

• Breast cancer is now the most frequent malignancy in women, as well as the leading cause of cancer- related death. The impact on patients, families, and society is significant, with a projected mortality rate of around 30%. The bulk of these deaths are due to metastatic illness, which has become clinically intractable for existing therapeutic options due to its resistance to standard-of-care medications.

• Breast cancer is classified and managed based on its immunohistochemistry (IC) and molecular subtypes, which can provide prognostic information and predict treatment responses. Tissue-based biomarkers, such as the expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), have proved critical in tumour subtyping, prognosis, and treatment selection.

• Hormone receptor-positive (HR+) breast tumours account for 70-80 percent of all breast cancers and are Molecularly categorized as luminal A or luminal B.

• In the past, BC was divided into histological groups, with invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) being the two most prevalent subtypes. To molecular techniques, this classification has subsequently been of secondary relevance.

• Molecular classifications of BC are more useful for prognosis and therapy strategy guidance. The use of hormone receptor (HR) status staining, specifically estrogen receptor (ER) and progesterone receptor (PR), has resulted in a semistandard method for selecting patients for endocrine therapies such as selective ER modulators (SERM), aromatase inhibitors (Als), and anthracycline and taxane-based chemotherapy, The human epidermal growth factor receptor 2 (HER2) is another commonly tested protein in BO biopsies, and it is used to select therapies such as monoclonal antibodies (mAbs), 85lantibody-drug conjugates (ADCs) 86) tyrosine kinase inhibitors (TKI), poly ADP-ribose polymerase (PARP) inhibitors, and cyclin-dependent kinase (CDK) 4/6 inhibitor, (87]

• Molecular subtyping of BC biomarkers There are up to ten distinct subgroups of molecular BC that have been pro-Posed, although only five of them have clinical significance:

(1) Luminal A: HR positive (HR+) (ER+ and/or PR+) and HER2 negative (HER2);

(2) Luminal B: HR+, and either HER2 positive (HER2+) or HER2;

(3) HER2-enriched BC: HR negative (HR) and HER2+;

(4) Triple-negative Breast cancer (TNBC)/basal-like: HR and HER2;

(5) Normal-like BC, which like luminal A, is HR+, HER2, but it prognosis is slightly worse than luminal A

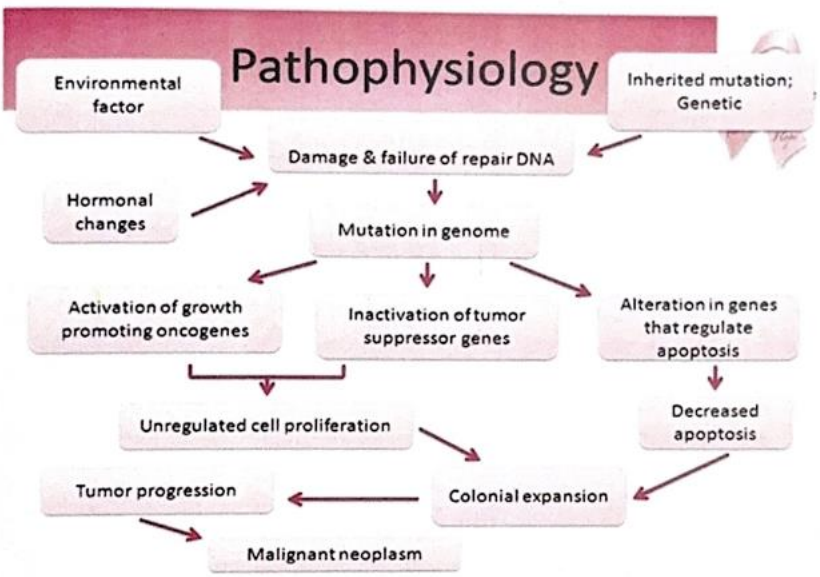


Figure: pathophysiology of breast cancer

DETECTION OF BREAST CANCER:

•A needle or surgical biopsy is frequently used to confirm a diagnosis of breast cancer, which is not only invasive but also unnecessary in most situations when tumours are benign. As a result, the development of non-invasive and more convenient biomarkers that enable for earlier identification of breast cancer has gotten a lot of attention and research. Non-invasive body fluid-based tests, such as circulating carcinoma antigens (CAS), circulating tumour cells (CTCs), circulating cell-free tumour nucleic acids (DNA or RNA), circulating microNAs (miRNAs), circulating extracellular vehicles (EVS) in the peripheral blood, nipple aspirate fluid (NAF), sweat, urine, and tears, and volatile organic compounds (VOCs) in exhaled breath.

7 PANCREATIC CANCRE BIOMARKER:

7.1 PATHOPYSIOLOGY OF PANCERATIC CANCER:

• Patients with pancreatic cancer frequently experience severe abdominal pain, which can be caused by a variety of factors such as tissue destruction, inflammation, ductal blockage, and infiltration, and can be visceral, somatic, or neuropathic in nature.

• Pancreatic cancer (PaCa) is a hard-to-treat disease with a high fatality rate.

• Adenocarcinomas account for over 90% of PaCa cases.

• PaCa mostly affects the pancreas' head and neck.

• As the tumour grows, non-PaCa symptoms emerge, such as jaundice, light-coloured faeces, abdominal pain, weight loss, and exhaustion. Pre-existing diagnostic tests may appear generic, causing individuals in the early stages of the disease to be overlooked.

• Pancreatic carcinoma majorly originates from lesions associated with pancreatic intraepithelial neoplasia (PanINs), less frequently from intra ductal papillary mucinous neoplasm (IPMN), and rarely from mucinous cystic neoplasm. PanIN is a microscopic lesion of dysplasia from which most PDAC arises. The progression of PanIN to invasive ductal adenocarcinoma is caused by the accumulation of genetic changes and progression of the characteristic microenvironment. (101Jthrough PanIN-2 (atypical hyperplasia, papillary duct lesion with atypia) and PanIN-3 (grade 3 carcinoma in-situ),

7,2 INTRODUCTIONS PANCREATIC CANCRE BIOMARKER:

• Pancreatic cancer is a serious health issue, there are two forms of pancreatic tumours: Endocrine and Exocrine.

1) Endocrine tumours are uncommon and begin in cells that produce hormones.

2) Exocrine pancreatic lesions arise from the cells that make up the pancreas enzyme-producing glands or ducts.

• Pancreatic ductal adenocarcinoma is the most frequent exocrine tumour, accounting for 90-95 percent of all pancreatic cancer cases Pancreatic ductal adenocarcinoma (PDAC)

• Because PDAC patients are detected at an advanced stage, only 10-20 percent of tumours are surgically treatable.

DETECTION OF PANCREATIC CANCER BIOMAEKER:

• Aspects of PDAC tumour formation and potential liquid biopsy diagnostic application areas When people are exposed to risk factors, their bodies begin to change on a molecular level. Relevant pathways are disrupted during carcinogenesis, leading to uncontrolled cell proliferation, invasion, and migration. Many of the molecular alterations that cause this development or result from current processes could be detected and utilised for screening in peripheral blood. After transformation, factors released for niche formation or as part of the tumour microenvironment's molecular communication could circulate in the bloodstream, allowing early diagnosis. Furthermore, such biomarkers may provide useful information for differential diagnosis, such as distinguishing between malignant and benign disorders or allowing therapy monitoring.

8.LIVER CANCER BIOMARKERS: -

INTRODUCTION OF LIVER CANCER:

• Liver cancer is one of the leading causes of cancer-related death globally, with causes including C or B hepatitis, alcohol consumption, smoking, obesity, non-alcoholic fatty liver disease, diabetes, and iron overload, among others.

• There are other types of primary liver cancer, but we'll concentrate on hepatocellular carcinoma (HCC) Hepatocarcinogenesis is linked to a number of cellular signaling pathways, including YAP-HIPPO, Wnt- beta-catenin, and nuclear factor (NEB), all of which are considered novel therapeutic targets.

• The role of peroxisome proliferator activated receptor gamma (PPAR)-mediated lipid metabolism in the development of HCC will also be explored.

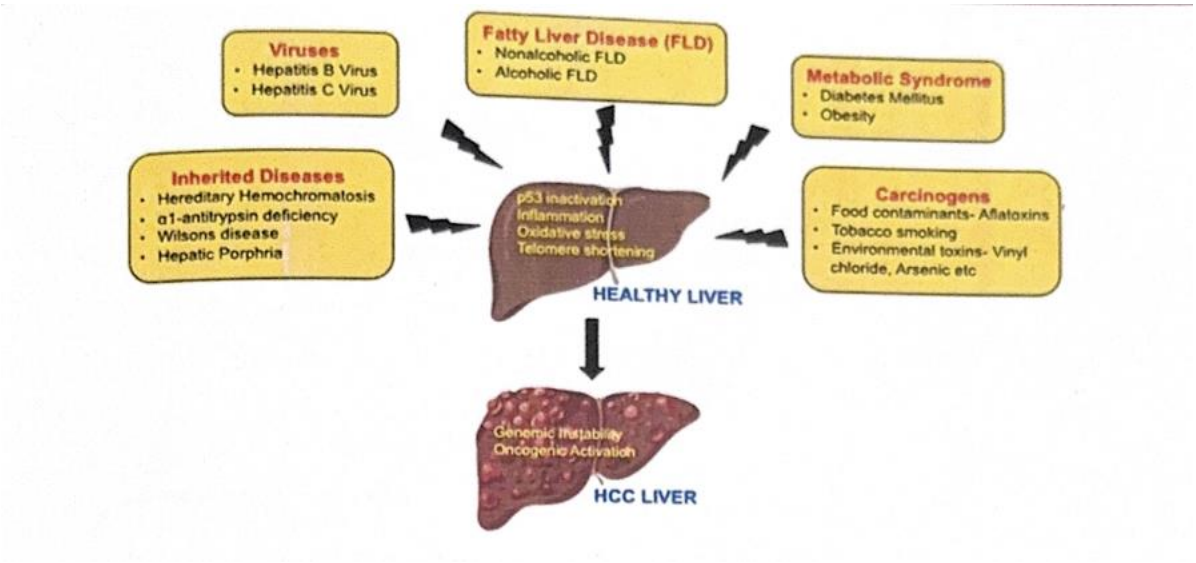


Figure: The etiology of hepatocellular carcinoma.

• Dysregulation of cell cycle and apoptosis, as well as molecular pathways associated to inflammation and fibrogenesis processes, are all involved in the development of liver cancer, and all of these constitute important molecular targets for the development of innovative therapeutic therapies.

• Primary liver cancer is one of the most common malignancies in the world, and it is a deadly disease with a high fatality rate.

• Hepatocellular carcinoma (HOC) and intrahepatic cholangiocarcinoma (ICCA) make up roughly 85% and 1% of all primary liver cancer cases, respectively,

• Liver cancer is the sixth most prevalent cancer diagnosed worldwide and the third leading cause of death from cancer.

• Although an etiology and epidemiology of the two most frequent histological subtypes of primary liver cancer differ, the main risk factors for Hepatocellular carcinoma (HCC) are infection with the Hepatitis B or Hepatitis C viruses.

• Hepatitis B is transmitted from mother to child during childbirth in highly endemic areas, and both hepatitis B and C viruses can be transmitted through hazardous injections and medical procedures, as well as less commonly through sexual contact.

• Heavy alcohol consumption, obesity, diabetes, and Aflatoxins ingestion can all contribute to HCC.

8.2 PATOPHYSIOLOGY OF LIVER CANCER:

> VIRUS AND HCC:

• Traditional risk factors for HCC include chronic infection with the hepatitis B virus (HBV) and hepatitis C virus (HCV) is risk factor that associated with HCC.

• HBV infection is responsible for 75-80% of virus-associated HCC and infects about 240 million persons worldwide.

• Hepatocarcinogenesis is caused by the incorporation of this virus's genetic material into the human genome, which causes p53 inactivation, inflammation, or oxidative stress. Hepatocellular carcinoma's pathogenesis. Hepatitis viruses, carcinogens, hereditary illnesses, metabolic syndrome, and fatty liver disease are just a few of the risk factors linked to the development of Hg.

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• Inactivation of the p53 gene, inflammation, oxidative stress, and telomere shortening all contribute to genomic instability and activation of various oncogenic signaling pathways, which can lead hepatocarcinogenesis.

> Non-Alcoholic Fatty Liver Disease (NAFLD)-Associated HCC:

•NAFLD is characterized by excessive hepatic lipid accumulation (steatosis), which further transitions to steatohepatitis upon the inflammatory insult, to cirrhosis and HCC. It's a pathophysiological condition that is not associated with excess alcohol consumption or other secondary causes such as viral infection and heredity liver diseases.

•NAFLD is classically associated with metabolic disorders such as obesity, hypertension, dyslipidemia, insulin resistance, and type 2 diabetes.

Molecular mechanisms involved in non-alcoholic and alcoholic-associated HCC. High-calorie diet and excessive alcohol consumption is the major risk factor for the development of NAFLD (Non-alcoholic fatty liver disease) and AFLD (Alcoholic Fatty Liver Disease) respectively. Despite the divergent pathogenic origin, the pathological spectra of liver injury in promoting HCC development in NAFLD and AFLD share common molecular pathways.

8.3 INTRODUCTION LIVER CANCER BIOMARKER:

[biomarker include Alpha fetoprotein (AFP)]

• For the past several decades, alpha-fetoprotein (AFP) has been the most extensively utilised biomarker for hepatocellular carcinoma (HCC). The amount of serum AFP drops rapidly after birth and stays low throughout adulthood.

• The Asian Pacific Association for the Study of the Liver has advised the use of AFP as a diagnostic biomarker for early screening of HCC patients, in addition to traditional imaging-based methods such as ultrasonography and computed tomographic (CT) scans.

• Increased blood AFP levels have been linked to an increased risk of HCC in people who have the hepatitis C virus, according to several studies (HCV).

Serum biomarkers:

• Blood biomarkers, which include proteins, cytokines, enzymes, and transcripts of dependent genes, are significant for the early identification of primary liver cancer.

1. AFP Biomarker:

• AFP is a glycoprotein biomarker produced from AFP, which is widely utilised in the diagnosis of liver cancer. However, it may rise in liver cirrhosis and hepatitis, with AFP-L3 rising in 20-30% of early HC cases 13For HC tumours, AFP sensitivity is 25% less than 3 cm in diameter, and combining AFP with additional biomarkers can improve early identification of HC.

2. Des-y-carboxyprothrombin (DCP) Biomarkers:

DCP, a new serological biomarker produced by HC cels, is a new serological biomarker. Folowing abnormalities in carboxylation of prothrombin precursor after translation, DCP is higher in HC patients. DCP was found to be more sensitive than AFP in a study.

3. Golsi protein 73 (GP73) biomarkers:

•GP73 is a trans membrane glycoprotein of type Il Golgi resident that is expressed in epithelial cels from many human organs. In HC patients, GP73 is substantially expressed, but in viral infections and cirrhosis, it is mildly expressed. In comparison to AFP, GP73 expression and sensitivity are significantly higher in HC.

4. fucosidase or AFU biomarker:

•AFU is an enzyme that can degrade fuco - glycoconjugates.

5. Carbohydrate antigen 19-9 (CA19-9) biomarker:

• CA 19-9 is a biomarker that can be used to diagnose several forms of adenocarcinomas.

6. Osteopontin (OPN) biomarker:

• OPN is an extracellular phosphorylated protein that binds to integrin. Normal cells and malignancies both express OPN.

CONCLUSIONS: -

Biomarkers factor into the diagnosis and treatment of almost every patient with cancer. When new pharmaceuticals are developed, they are required to pass high levels of scrutiny and be tested in carefully designed, randomized clinical trials prior to governmental approval. Unfortunately, similar requirements are not in place for biomarkers, although they too can significantly influence patient outcomes. Therefore. it i.e. important for clinical, translational, and laboratory-based re searchers to be acutely aware of the issues surrounding appropriate biomarker development, in order to facilitate a try of clinically useful biomarkers into the clinic, while avoiding the introduction of biomarkers that have not been sufficiently evaluated and therefore may be useless or even potentially detrimental to patient care.

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