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Cancer Biomarker Molecules

Velázquez Domínguez José Antonio, Rodríguez Céspedez Samantha and y Alavez Pérez Noé Santiago*

Escuela Nacional de Medicina y Homeopatía, Av. Guillermo Massieu Helguera 239, La Escalera Ticomán, Gustavo A. Madero, 07320 Ciudad de México, Mexico

***Corresponding author:** y Alavez Pérez Noé Santiago, Escuela Nacional de Medicina y Homeopatía, Av. Guillermo Massieu Helguera 239, La Escalera Ticomán, Gustavo A. Madero, 07320 Ciudad de México, Mexico

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ABSTRACT

Introduction: Cancer is a disease characterized by the transformation of normal cells into cells with uncontrolled growth due to genetic mutations. These mutations can be inherited or acquired and primarily affect DNA, which is crucial in tumor development. This process involves genetic and epigenetic alterations that allow cells to survive, replicate, and evade apoptosis. Key genes include proto-oncogenes, tumor suppressor genes, DNA repair genes, and genes that regulate programmed cell death. Mutations in these genes can cause genomic instability, promoting uncontrolled cell proliferation and the formation of metastases.

Objective: To identify biomarker molecules in cancer events and their association with other cellular events.

Method: A search and selection of literature on oncogenic events that described the role of biomolecules in cancer events was conducted.

Conclusion: To date, several biomolecules have been described that are involved in genetic alterations and mechanisms that drive tumor genesis. Together, these molecules are involved in biological processes such as cancer development and progression. This knowledge highlights the interconnectedness of the molecular mechanisms underlying different tumor types, opening the door to new avenues for targeted treatments and more effective therapeutic strategies.

Keywords: Genetic Mutations; Proto-Oncogenes; Tumor Suppressor Genes; Genomic Instability; Metastasis; Cell Signaling Pathways

Introduction

Cancer is a disease characterized by the generation of mutations that cause uncontrolled cell growth. This entire process involves genetic and epigenetic alterations that compromise the stability of genetic material, triggering unstable events and leading to proliferation and even metastatic events. Once the biological processes related to these genes are understood, the role of molecular biomarkers in cancer can be better understood. These molecules reflect the genetic and cellular alterations associated with tumor progression. A biomarker can be linked to several types of cancer because mutations affect common cellular pathways in different tissues. For example, mutations in KRAS can alter signaling pathways essential for cell proliferation and angiogenesis, affecting multiple organs. Genomic instability in cancer favors the accumulation of mutations, activating common biomarkers in various types of tumors. Cancer arises when normal cells transform into cells that cannot control their growth due to mutations in their genetic material. These mutations can be hereditary or acquired and primarily affect DNA, which is essential for tumor genesis and the target of oncological drugs [1,2]. The complexity of cancer development lies in the accumulation of mutations over time, which also allows for metastasis, where the primary tumor implants in other organs [1-3]. The development of cancer involves genetic and epigenetic alterations that allow cells to survive, replicate, evade apoptosis, and cell cycle disruption [3].

These alterations primarily affect tumor suppressor genes, proto-oncogenes, genes regulating programmed cell death, and DNA repair genes. Mutations can be sporadic or inherited, affecting all cells or only tumor cells [4]. At the nucleotide level, these mutations can be substitutions, additions, or deletions, which alter cell physiology and cause cell transformation [5]. Some of the changes made to the DNA sequence can be acquired and remain only in tumor cells. These types of changes can be sporadic or inherited, depending on both intrinsic and external factors of the tumor, and genetic alterations in the signaling pathways that control the cell cycle [6-8]. The vast majority of cancers originate from a single cell, requiring 5-10 cumulative mutations to acquire a malignant phenotype. This process can be considered

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Darwinian microevolution, where each mutation confers growth advantages to cells, promoting their predominance in the tissue [9,10]. Mutations required for oncogene activation include mechanisms such as activating mutation, fusion, amplification, deletion, point mutation, chromosomal instability, and cancer tumor syndromes. Changes in genetic material are specific to each tumor, but they present common characteristics that highlight the complexity of cancer and its development from the interaction of multiple genetic and environmental factors [10-12].

Cancer Epidemiology Worldwide

Cancer is one of the leading causes of death worldwide, and its incidence varies according to socioeconomic context. The highest rates of this disease are recorded in countries with higher life expectancies and higher education levels. However, for certain types of cancer, such as cervical cancer, an inverse trend is observed, with higher incidence in countries with low levels of these measures. This relationship highlights how socioeconomic factors influence cancer prevalence and detection [13]. Globally, in 2020, nearly 10 million deaths were attributed to some type of cancer. This year is known to have been one of the most significant, due to a massive increase in the number of cases and deaths resulting from this disease. Breast cancer and lung cancer were the most common worldwide, accounting for 11.7% and 11.4% of the total new cases detected, respectively. Colorectal cancer, accounting for 10% of cases, had the third highest incidence worldwide this year (Figure 1A), and was the cause of the largest number of deaths this year alone (Figure 1B) [13]. In 2022, Mexico recorded 847,716 deaths, of which 10.6% (89,574) were due to malignant tumors. The death rate from this cause increased from 62.04 per 100,000 people in 2012 to 68.92 in 2022 [14], demonstrating a steady increase in cancer mortality in the country (Figure 1C). In 2020, more than 2.26 million new cases of breast cancer were detected worldwide. With this figure, it becomes the most prevalent cancer among the global population and is expected to remain at the top of the ranking even in 2040 (Figure 2A).

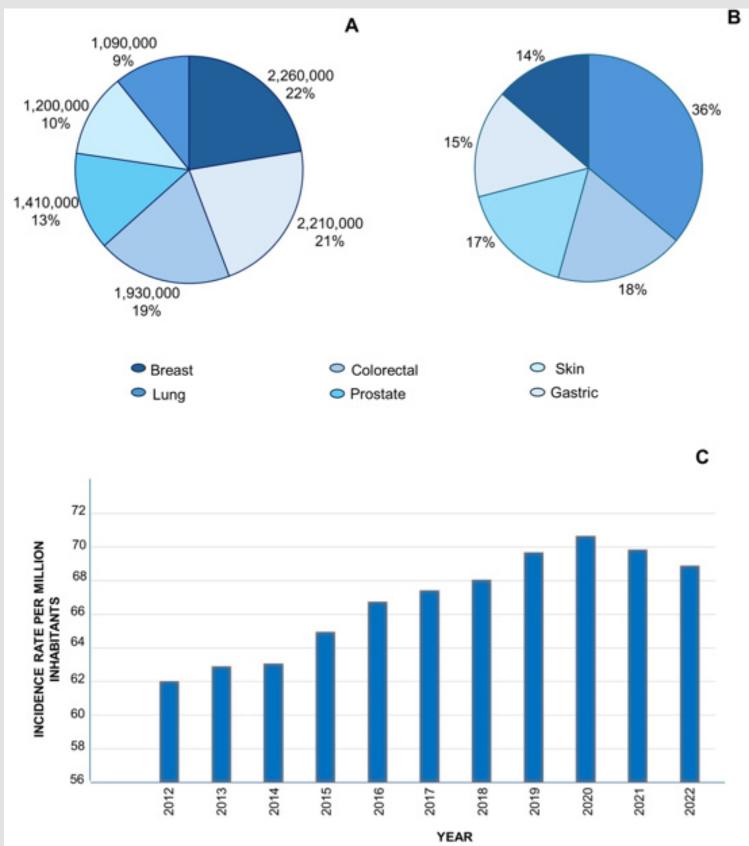

Figure 1: Frequency of cancer types worldwide.

A. Cancers with the highest number of cases reported worldwide in 2020.
B. Cancer types with the highest mortality rate in 2020.
C. Cancer deaths over the past 10 years.

Between 2012 and 2022, cancer deaths increased, peaking in 2020, with a slight decline in subsequent years. In 2020, breast cancer was the most commonly diagnosed cancer, accounting for 22% of all cancers, while lung cancer was the most deadly, accounting for 36% of cancer deaths worldwide.

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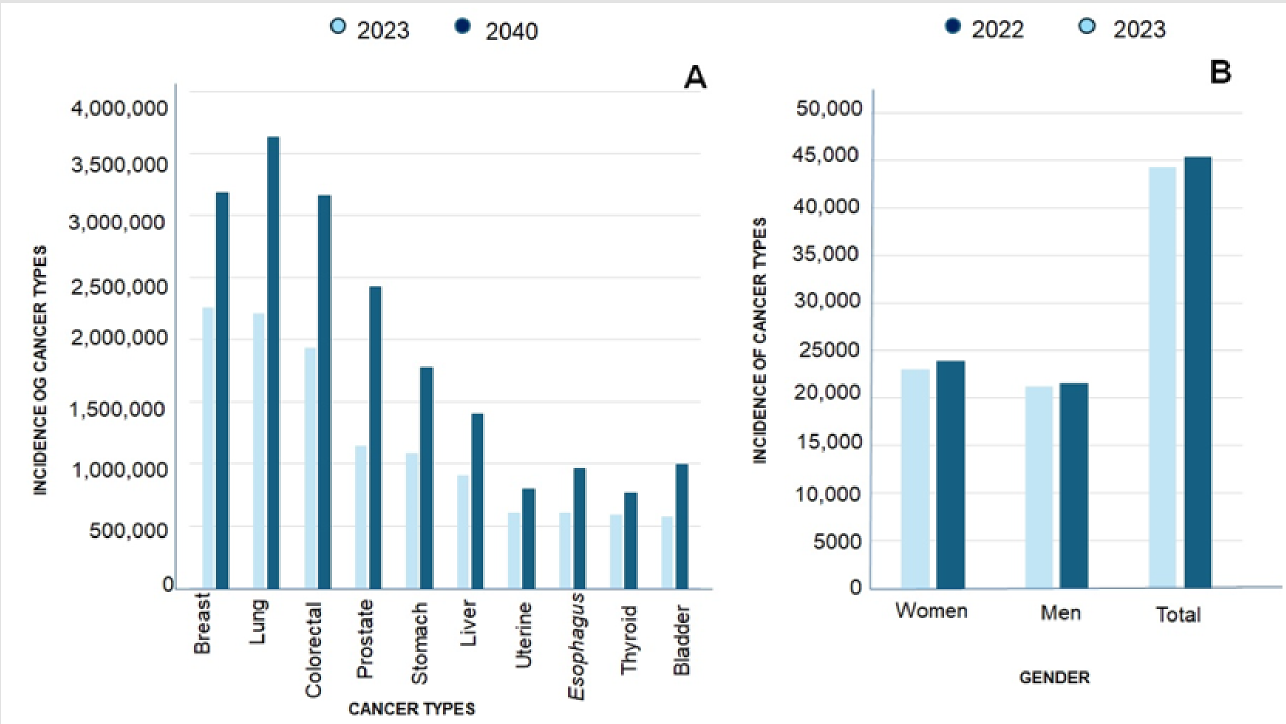

Figure 2: Cancer on the rise.
A. Alarming projections for various types of cancer toward 2040.
B. Cancer incidence by gender in 2022/2023.
In 2023, an overall increase in cancer cases was observed, with a higher incidence in women than in men. Globally, it is estimated that by 2040, cancer cases could increase by 47%, rising from 19.3 million in 2020 to 28.4 million, reflecting a worrying upward trend.

China is the country with the highest number of cancer deaths recorded worldwide in 2020, followed by India, the latter with more than 850,000 cases. According to the Global Cancer Observatory (GCO), this trend will continue over the next two decades, and in China, the death toll could increase by 68.9% by 2040 [15,16]. By 2022, 20 million new cases of cancer and 9.7 million deaths will be recorded worldwide. By 2040, the number of new annual cases is expected to increase to 29.9 million and cancer-related deaths to 15.3 million. The cancer mortality rate is higher in men (173.2/100,000) than in women (126.4/100,000). When analyzing mortality by race and sex, non-Hispanic black men have the highest rate (208.3/100,000), while the lowest is found in non-Hispanic Asian or Pacific Islander women (82.6/100,000). This highlights disparities in cancer mortality by sex and ethnicity [17,18].

Cancer Incidence in Mexico

Although it is classified as a medium-risk area in cancer incidence and mortality compared to high-income countries, neoplasia represents a serious public health problem. Each year, more than 200,000 new cases of cancer and approximately 90,000 deaths are recorded. It is estimated that there are nearly 200,000 prevalent cases over a five-year period. Given the high prevalence of the disease, an organized social response to its prevention and control in the country is crucial [18]. In 2022, the 10 leading causes of death were recorded, among which cancer was the third leading cause with 44,322 cases, 21,266 of which were men and 23,056 women. In 2023, cancer remained at the same level, with 45,409 cases, of which 21,529 were men and 23,880 were women, indicating an increase in both sexes compared to the previous year [14] (Figure 2B). In 2022, the states with the highest rates of deaths from malignant tumors were Mexico City, Sonora, Veracruz, Colima, Morelos, and Chihuahua, with rates ranging from 76.39 to 95.96 deaths per 100,000 inhabitants. On the other hand, the lowest rates were found in Quintana Roo, Guerrero, Chiapas, Tlaxcala, Puebla, and Aguascalientes, with rates ranging from 47.39 to 59.62 deaths per 100,000 inhabitants [14] (Figure 3A). Beginning at age 50, the death rate from malignant tumors increases in both sexes. However, beginning at age 60, the rate is higher in men compared to women.

This highlights the importance of cancer surveillance and prevention in older adults [19]. The most common cancers in Mexico are breast, lung, colorectal, prostate, and cervical cancers [20,21] (Figure 3B).

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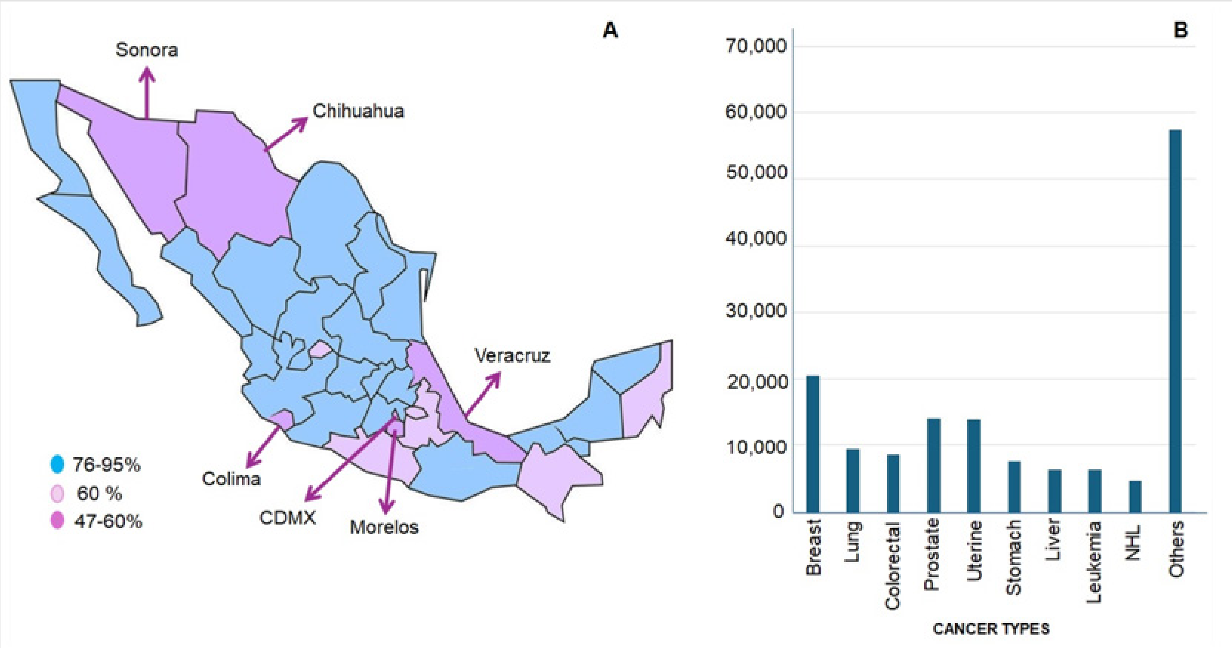

Figure 3: Cancer mortality incidence by state in 2022.

A. States with the highest cancer mortality in Mexico.

B. Main cancer types with the highest incidence in Mexico.

In 2022, the death rate from malignant tumors in Mexico showed significant regional differences. The states with the highest mortality (76-95%) were concentrated in the north and southeast of the country, while those with the lowest rates (<60%) were mainly located in the center. The most common cancers were breast, lung, colorectal, prostate, and cervical cancer.

Role of Cancer Biomarkers

Cancer, being one of the most common diseases today, has led to the identification of specific biomarker molecules. A biomarker is any molecule that can be measured in the peripheral circulation, such as in blood or other body fluids, as well as in tissues. Its presence can indicate an abnormal process or disease, and are also known as molecular markers, genotypes, or target molecules [21]. These biomarker molecules participate in several key mechanisms, including determining the presence of a disease, assessing the aggressiveness of the pathology, and predicting the body's response to specific treatments [22]. Numerous tumor biomarkers (TBMs) have been identified. These are substances produced by tumor cells or normal cells in response to cancer or benign conditions [23]. However, they can be indicators of normal biological processes, which sometimes makes it difficult to distinguish between benign and malignant processes. These molecules are found in blood, urine, feces, and cancerous tissue, as well as in other tissues and body fluids close to the tumor [24].

Classification of Tumor Biomarkers

Biomarkers are divided into two main types: circulating and tissue-based [24,25]. Circulating BMTs are present in body fluids such as blood, urine, and feces. They are useful for estimating patient prognosis, determining cancer stage, detecting remaining cancer cells after treatment, and evaluating treatment effectiveness. An example is β-2 microglobulin, which helps assess treatment response in cases such as multiple myeloma and chronic lymphocytic leukemia [26]. In contrast, tissue-based BMTs are obtained from biopsies and are essential for diagnosing and classifying cancer. They allow for estimating prognosis and selecting appropriate treatments. An example is programmed cell death ligand 1 (PD-L1), which regulates the immune response and helps determine eligibility for immune checkpoint inhibitor treatments [27,28].

Molecular Basis of Cancer

As mentioned above, cancer biomarker molecules require specific processes to be able to produce responses that result in cellular proliferation with malignant or benign characteristics. The Cell Cycle and its Importance in Carcinogenic Mechanisms To understand the molecular basis of cancer, it is essential to understand two biological processes: the cell cycle and apoptosis. Under normal conditions, there is a balance between cell proliferation and apoptosis, but in cancer, mutations can activate oncogenes, which promote cell proliferation, or inactivate suppressor genes, which inhibit the cell cycle. This causes an imbalance that leads to uncontrolled proliferation and immortalization of the cell line [29]. Mutations that promote angiogenesis, mediated by growth factors such as VEGF and PD-EDGF, and

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those that affect intercellular adhesion, through molecules such as e-cadherins and integrins, are crucial for tumor aggressiveness and metastatic potential [29]. Various proteins, such as cyclins, play a key role in cell cycle regulation. These proteins appear and disappear cyclically and are required for the activity of cyclin-dependent kinases, which form the holoenzyme required to control cell cycle transitions (Figure 4). Cell cycle progression is essential for the proper functioning of the cell and the organism, which requires rigorous regulation. The cyclin-kinase complex is fundamental to this process, as its activity is necessary at the checkpoints that allow transitions between cell cycle phases.

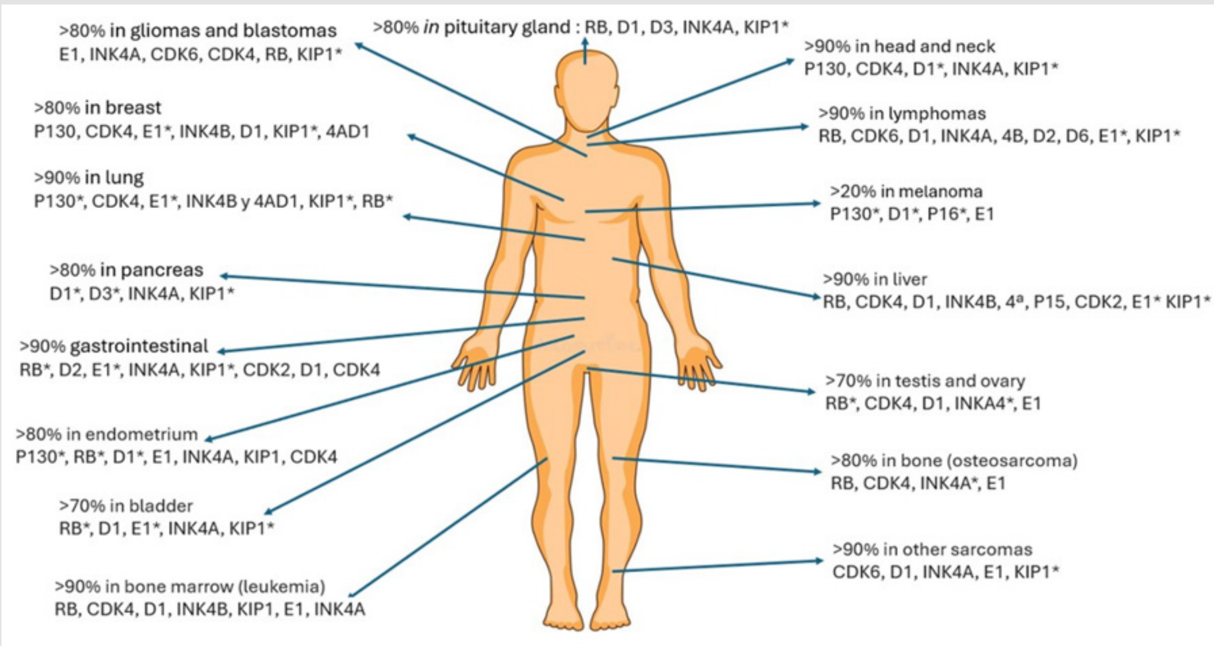

Figure 4: Molecular biomarkers implicated in the presence and development of cancer. Alterations in genes such as RB, CDK4, INK4A, E1, and KIP1, among others, are notable, present in more than 80% of various cancers. KIP/INK: Kinase inhibitors, CDK: Cyclin-dependent kinases, Alterations relevant to tumor prognosis.

This regulation is vital for maintaining the balance between proliferation and apoptosis, so any alteration in these mechanisms can facilitate the development and progression of cancer [29]. These alterations can lead to the development of cancer, where molecular biomarkers associated with these alterations can provide crucial information about the prognosis and aggressiveness of tumors. G1 Phase: Cyclins D and E associate with the kinases CDK4, CDK6, and CDK2; these molecules are directly involved in cell cycle progression.

- **Cyclin D/CDK4, 6:** Phosphorylates the pRb protein, allowing progression from G0 to G1. Its overexpression has been linked to several cancers, such as parathyroid adenoma and lymphomas.
- **Cyclin E/CDK2:** Facilitates the transition from G1 to S. Its overexpression shortens the G1 phase and is associated with a poor prognosis in cancers such as breast adenocarcinoma and prostate and colon carcinomas.
- **S Phase:** Cyclin A plays a crucial role in the transition from G1 to S and in S phase progression, and is required for DNA replication.
- **Cyclin A/CDK2:** Facilitates progression from G1 to S.
- **Cyclin A/CDK1:** Essential for the transition from G2 to M. In addition, it acts as a positive regulator during the S phase and a negative regulator to inhibit E2F family transcription factors [30].

G2-M phase: Cyclin B are required for entry into mitosis, and their degradation is essential for exiting this phase.

- **Cyclin A:** Synthesized in the S phase and degraded during metaphase, just before cyclin B. Mutations in cyclin A can prevent progression from S to M phases. Cyclin A associates with cell growth regulatory proteins, such as the retinoblastoma gene (Rb) and the E1A oncoprotein [31].

Cell Cycle Restriction Points

As mentioned, there is a close association between cellular activation and cell cycle checkpoints, especially during the G1 to S and G2 to M transitions. These checkpoints are essential for protecting cells from DNA damage, which can be caused by both exogenous sources and intrinsic processes, such as gene rearrangement during development and apoptosis. When the damage is intrinsic, checkpoints play a crucial role in preventing the transformation of normal cells into cancerous ones [29]. During the rearrangement of immunoglobulin and T cell receptor genes, DNA breaks are generated, and proteins are present that inhibit cell cycle progression. The genes encoding these proteins are potential targets for mutations that can cause genomic instability, an important factor in the etiology of lymphomas and leukemias. Mutation of genes that control proliferation during apoptosis allows the survival and proliferation of cells with genomic instability that would normally be doomed to die [31]. Regarding the G2 to M transition, it is inhibited by altered DNA damage and replication, with checkpoints that prevent the segregation of defective chromosomes. Although few genes that regulate this transition have been identified, defects in its regulation are significant in tumorigenesis. These alterations in checkpoints and cell cycle regulation underscore the importance of molecular biomarkers in the identification and treatment of various forms of cancer [31,32].

Understanding tumor suppressor genes, proto-oncogenes, programmed cell death regulators, and DNA repair genes is essential for the analysis of cancer biomarker molecules. These molecules provide crucial information about tumor biology and behavior, allowing for better characterization of the disease. By identifying and understanding alterations in these genes, biomarkers can be developed that inform cancer aggressiveness, treatment response, and patient prognosis.

Growth Factors in Cancer Processes

These factors play a crucial role in the development and progression of cancer, regulating essential cellular functions such as proliferation, differentiation, and survival [33] (Table 1). Their importance lies in their participation in:

1. Stimulation of Cell Proliferation: They bind to specific receptors on the cell surface, activating signaling pathways that promote cell division.
2. Angiogenesis: Some factors, such as VEGF, promote the formation of new blood vessels, facilitating tumor growth.
3. Evasion of Apoptosis: They can inhibit signals that induce programmed cell death, allowing cancer cells to survive and multiply.
4. Invasion and Metastasis: They stimulate changes that facilitate invasion into adjacent tissues and spread to other organs.
5. Therapy Resistance: Overexpression or mutation of growth factor receptors, such as EGFR, is associated with resistance to cancer treatments.

Table 1: Growth factors involved in the various types of cancer [34,35].

Factor	Característica
Epidermal growth factor (EGF) family.	Includes transforming growth factor alpha (TGFα), heparin-binding EGF-like growth factor, schwannoma-derived growth factor, amphiregulin, and betacellulin.
Fibroblast growth factor (FGF) family.	They are mitogenic for mesenchymal, neuroectodermal and epidermal cells, and their overexpression can cause malignant transformation.
Hepatocyte growth factor (HGF).	Called hepatotropin or hepatopoietin. It has regenerative activity on liver cells. It is a mitogen for melanocytes, renal tubular cells, endothelial cells, and some epithelial cells.
Insulin-like growth factor (IGF) family.	The functions of IGF I and II were recognized as serum factors that interact with growth hormone to stimulate skeletal tissue.
Neurotrophins.	It is crucial for the survival and differentiation of sympathetic and sensory neurons in the peripheral nervous system. They bind with high affinity to receptors of the tyrosine kinase (TRK) family and the AP75 receptor.
Platelet-derived growth factor (PDGF) family.	PDGF: Key mitogen for connective tissue and glial cells; activates α and β receptors by dimerization. It is associated with tumors such as osteosarcoma, melanoma, and oligodendroglioma. -VEGF: Stimulates endothelial cells, promoting angiogenesis. -PGF: Related to vascular growth.
Growth factors for hematopoietic cells.	- CSF-1: Regulates phagocytes and macrophages; its receptor is encoded by the proto-oncogene c-fos. -CFS: Influences melanogenesis, hematopoiesis, and gametopoiesis; receptor encoded by c-kit.

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Proto-Oncogenes

These are genes that regulate cell growth and division, helping to create new cells and keep them alive. However, when a proto-oncogene is mutated or overproduced, it can be inappropriately activated, becoming an oncogene. This activation can trigger uncontrolled cell growth [34], which contributes to the development of cancer (Table 2). Proto-oncogenes, like growth factors, are essential in regulating cell proliferation and differentiation; their mutated forms can facilitate cell growth even in the absence of normal mitogenic signals [35].

Table 2: Proto-oncogenes associated with cancer development [38,39].

Protooncogene	Function
Abl	Tyrosine kinase controlling cytoskeletal dynamics
Bcl2	Senescence and cell death
c-erbB2	Receptor de membrana para EGF
c-myc (c, l y n), c-myb, c-fos, c-jun	Transcription factors (nuclear proteins)
sos y grb	Adapter molecules (signal cascade)
Raf	Serine-Threonine Kinase (mitogenic signal cascade)
ras (h y K)	GTP-ases (mitogenic signal cascade)
RAR	Nuclear receptor for retinoic acid
Src	Tyrosine kinase signal transduction molecules
Trk	Membrane receptor tyrosine kinase
Sis	PDGF receptor

Oncogenes

Oncogenes originate from proto-oncogenes through three main mechanisms that facilitate cancer development. First, point mutations can constitutively activate the resulting protein, keeping it constantly active without normal regulatory signals, causing uncontrolled cell proliferation. Second, gene amplification leads to an increase in the number of copies of the proto-oncogene, resulting in overproduction of the oncogenic protein and promoting excessive cell growth. Finally, chromosomal rearrangements can place the proto-oncogene near strong promoters, increasing its expression, or fuse the proto-oncogene with another gene, creating proteins with oncogenic properties. These mechanisms together promote the uncontrolled activation of signaling pathways that promote unregulated cell proliferation and resistance to cell death [36]. Like proto-oncogenes, oncogenes are crucial in cancer biology, as their activation significantly contributes to tumor growth and disease progression (Figure 5).

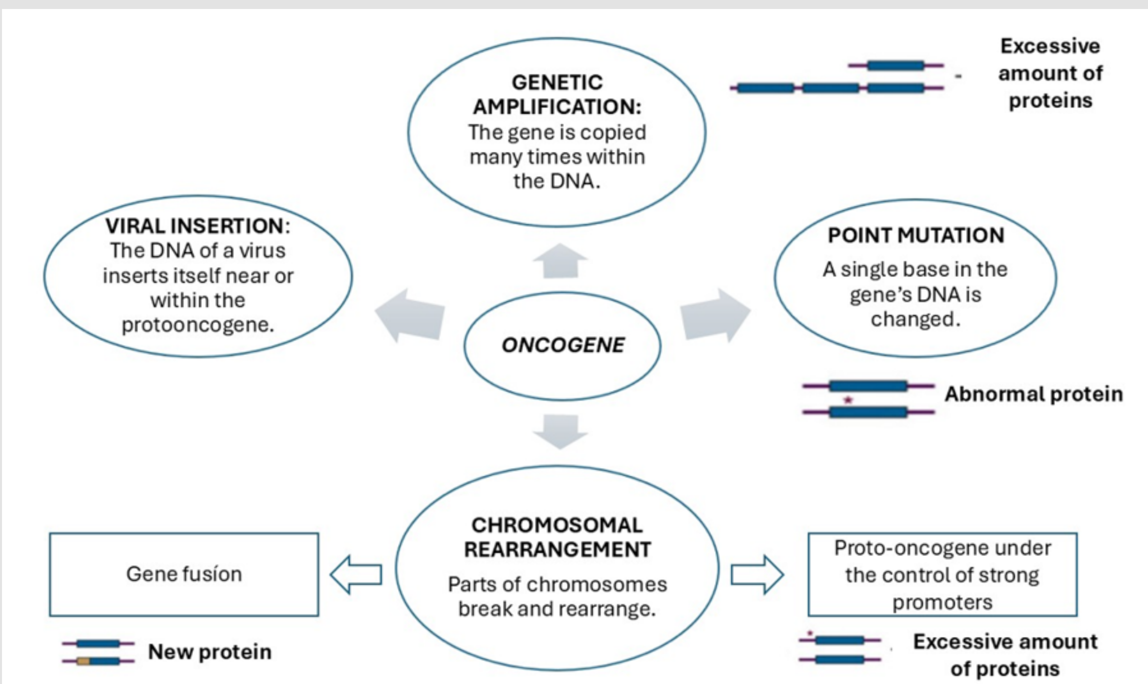

Figure 5: Protoncogene mutations, taken and modified from Verdun JA. Oncogenes and Tumor Suppressor Genes, 2024. They are normal gene that regulate cell growth and division. When abnormally activated (through mutation, amplification, etc.), they become oncogenes that force the cell to divide uncontrollably, causing cancer.

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Tumor Suppressor Genes

These are normal genes that inhibit cell proliferation and regulate apoptosis, that is, they tell cells when to die [37]. When these genes do not function properly, cells can grow uncontrollably, which can lead to cancer. Their inactivation can occur through various mechanisms: point mutations and alternative splicing can alter the DNA sequence, resulting in defective or inactive proteins. Deletions of DNA segments can completely eliminate the gene, while epigenetic silencing, through DNA methylation or histone alterations, can silence the gene without modifying its sequence. Furthermore, post-transcriptional regulatory elements such as miRNAs and lncRNAs can interfere with the expression of the suppressor gene, affecting the translation or stability of messenger RNA. These mechanisms, which can act individually or jointly, contribute to the inactivation of tumor suppressor genes and facilitate cancer development, as does the activation of oncogenes (Figure 6; Table 3).

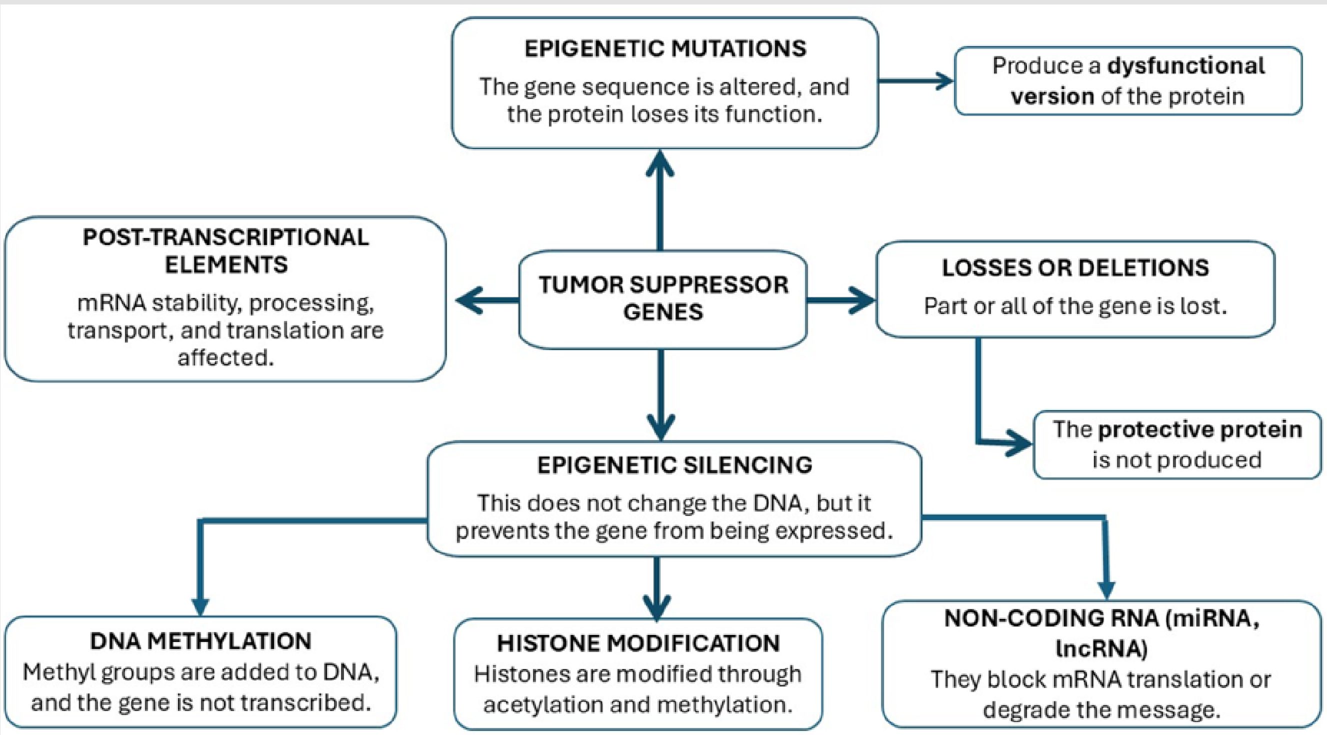

Figure 6: Most common mutations in tumor suppressor genes, taken and modified from Verdun JA. Oncogenes and tumor suppressor genes. These are genes that slow cell growth, repair DNA, or promote apoptosis. When they are inactivated or silenced, the cell loses control of growth, which can lead to cancer.

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Table 3: Tumor suppressor genes and their biological implications [42,43].

Localization of Your Products	Tumor Suppressor Gene	Biological Implication
Genes for proteins in cytoplasm	APC	Involved in colon and stomach cancer.
	DPC4	It encodes a molecule in a signaling pathway that inhibits cell division. Involved in pancreatic cancer
	NF-1	It encodes a protein that inhibits a stimulatory protein (Ras). It is implicated in neurofibroma and pheochromocytoma (cancers of the peripheral nervous system) and myeloid leukemia.
	NF-2	Involved in meningioma and ependymoma (brain cancers) and schwannoma (affects the sheath surrounding peripheral nerves).
Genes for proteins in the nucleus	MTS-1	It encodes the p16 protein, a component of the cell cycle clock. It is implicated in a wide range of cancers.
	RB	It encodes the pRB protein, one of the key cell cycle controls. It is implicated in retinoblastoma and cancers of bone, bladder, small cell lung, and breast cancer.
	P53	It encodes the p53 protein, which can halt cell division and induce abnormal cells to kill themselves. It is implicated in a large number of cancers.
	WT1	Involved in Wilm's tumor of the kidney.
Genes for proteins whose cellular localization is not yet clear	BRCA1	Involved in breast and ovarian cancers.
	BRCA2	Involved in breast cancer.
	VHL	Involved in renal cell cancer

Role of the p53 Protein in Cancer Types

The tumor suppressor gene p53 plays a crucial role in cancer prevention by encoding a protein that acts as a transcription factor, regulating genes involved in cell protection. Known as the "guardian of the genome," its main function is to maintain DNA integrity. When cells experience DNA damage due to factors such as radiation or chemicals, the p53 protein is activated and triggers cellular responses to repair the damage. Mutations in the p53 gene are common in several types of carcinoma, such as colon, lung, and ovarian cancers, and the majority of these mutations (87%) result in the loss of production of its functional protein [38,39]. Alteration of p53 not only highlights the importance of this gene in cancer biology but also positions it as a potential molecular biomarker (Figure 7).

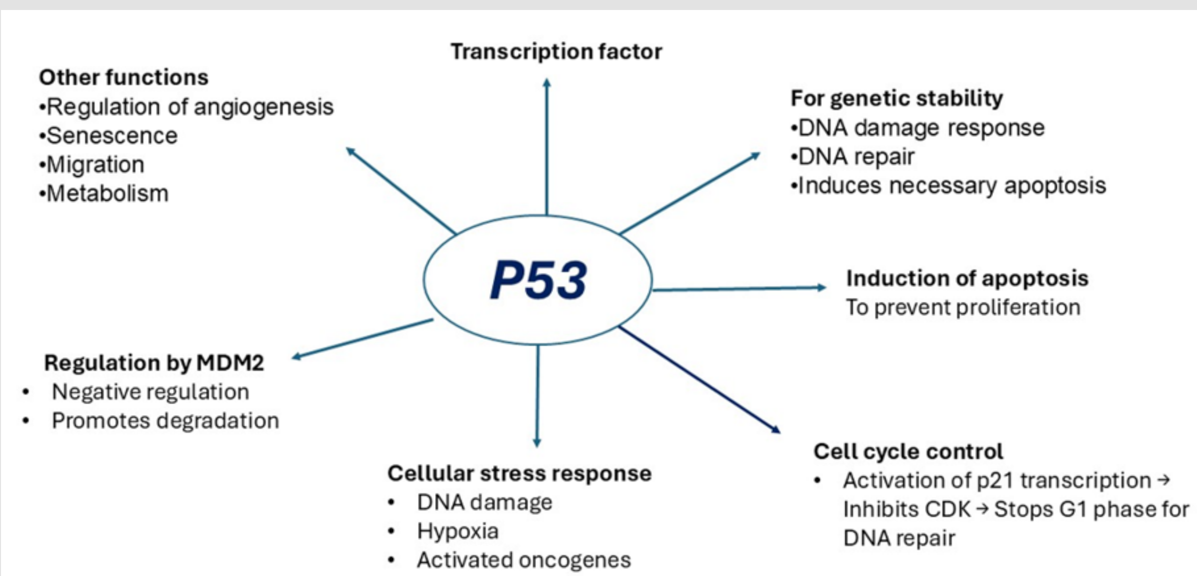

Figure 7: Actions of P53. Known as the "Guardian of the Genome." It arrests the cell cycle and activates DNA repair or apoptosis. Mutated in >50% of cancers.

DNA Repair Genes (Caretakers)

DNA repair genes, known as "caretakers," are essential for correcting DNA errors. If they fail to do so, they induce cell death to prevent further problems. When these genes fail, the mutation rate in the genome increases, which can lead to uncontrolled cell growth. There are several repair mechanisms: homologous recombination repair corrects double-strand breaks using an identical copy of DNA, mediated by genes such as BRCA1 and BRCA2; non-homologous end joining (NHEJ) repairs broken ends less precisely; base excision repair (BER) corrects damage to single bases; nucleotide excision repair (NER) repairs extensive damage, such as that caused by UV radiation; and mismatch repair (MMR) corrects errors in DNA replication [40,41]. These mechanisms work together to prevent the accumulation of mutations that can lead to cancer, highlighting their importance as molecular biomarkers (Figure 8).

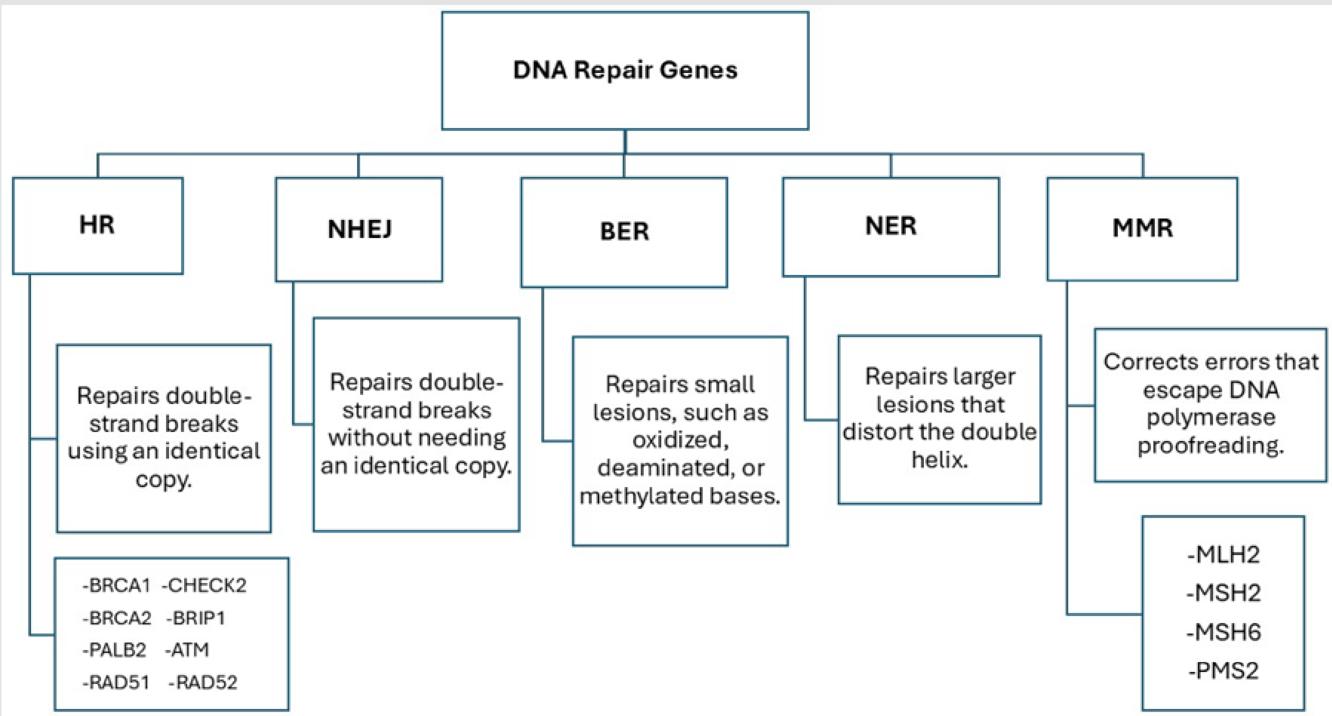

Figure 8: DNA repair genes, taken and modified from Verdun JA. Oncogenes and tumor suppressor genes. These are genes whose function is to maintain genetic stability by correcting errors that occur in DNA during replication or due to environmental damage (UV rays, radiation, chemicals, etc.). NHEJ: Non-homologous end joining; HR: Homologous recombination repair; NER: Nucleotide excision repair; MMR: Mismatch repair mechanism.

Genes Regulating Programmed Death

The suppression of apoptosis is crucial in the development and progression of tumors, contributing to treatment resistance and the development of metastasis. Several factors are involved in this process, including decreased expression of death receptors, alterations in signaling pathways, mutations in p53, overexpression of anti-apoptotic proteins, low expression of pro-apoptotic proteins, and reduction of caspases. These elements coordinate intracellular signals that determine whether a cell survives or dies in response to different stimuli.

There are two main pathways of apoptosis: the intrinsic pathway, which involves genes such as BAX, BAK, and PUMA (molecules that promote the release of pro-apoptotic factors from mitochondria), and the extrinsic pathway, which activates death receptors such as FAS and TRAIL-R on the cell surface, contributing to the activation of caspases that dismantle the cell in an orderly manner. These mechanisms are essential for eliminating damaged cells and maintaining homeostasis, preventing uncontrolled cell proliferation that can result in tumors. The interaction of apoptosis suppression with DNA repair genes and oncogenes highlights the complexity of cancer and the importance of these processes in identifying molecular biomarkers for cancer diagnosis and treatment.

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Cancer Biomarker Molecules

Once we understand the biological processes related to tumor suppressor genes, proto-oncogenes, DNA repair mechanisms, and apoptosis suppression, we can better understand the role of cancer biomarker molecules. These molecules reflect the genetic and cellular alterations associated with cancer progression. A single biomarker can be associated with multiple cancer types because mutations affect common cellular pathways in various tissues [42]. For example, mutations in genes such as KRAS can activate or suppress signaling pathways essential for functions such as cell proliferation and angiogenesis, affecting various organs [43]. Genomic instability, a hallmark of cancer, favors the accumulation of mutations in various pathways, which contributes to the activation of common biomarkers in different types of cancer (Table 4).

Table 4: Biomarkers present in different types of cáncer (taken from: 50-57).

Type of Cancer	Biomarker Molecule	Description
Breast Cancer	HER2/neu	The gene encodes a tyrosine kinase receptor. Overexpression or amplification of HER2 activates signaling pathways that promote uncontrolled cell growth.
	CA 15-3	Glycoproteins produced by tumor cells. Both molecules activate processes such as cell proliferation and tumor invasion.
	CA 27.29	
	BRCA1	Tumor suppressor genes that help repair damaged DNA. Mutations in BRCA1 and BRCA2 prevent effective repair of DNA damage, leading to the accumulation of mutations.
	BRCA2	
	Estrogen Receptor (ER)	Hormone receptors that, when present, indicate that tumor growth may be influenced by hormones.
	Progesterone Receptor (PR)	
Prostate Cancer	PCA3	Non-coding RNA overexpressed in prostate cancer cells.
	Prostatic Acid Phosphatase (PAP)	Enzyme produced by the prostate.
	Human kallikrein 2 (hK2)	PSA-like protein, produced by the prostate.
	A lpha-Methylacyl-CoA Racemase (AMACR)	Enzyme involved in fatty acid metabolism. Overexpression of AMACR facilitates uncontrolled cell proliferation.
Colon Cáncer	CEA	Glycoprotein involved in cell adhesion, it is related to tumor dissemination and the activation of cell invasion mechanisms.
	CA 19-9	Glycoprotein involved in cell adhesion and migration, essential processes for tumor invasion.
	KRAS	A gene that encodes a protein involved in cell signaling, particularly the MAPK/ERK pathway. Mutations in KRAS constitute an aberrant activation of this signaling pathway, which promotes uncontrolled cell proliferation and survival.
	BRAF	Gene that encodes a protein involved in cell signaling. Mutations in BRAF, especially the V600E mutation, are associated with a more aggressive course of cancer.
	MSI (Inestabilidad de Microsatélites)	An indicator of defects in DNA repair. Microsatellite instability indicates a dysfunction in the DNA repair system, which favors the accumulation of mutations and tumor development.
Lung Cancer	EGFR	Membrane protein that regulates cell growth. Its alteration leads to constitutive activation of the receptor, promoting cell proliferation.
	ALK	Tyrosine kinase receptor involved in cell growth. When fused with other genes (such as EML4), it causes abnormal activation of cell signaling, facilitating cell proliferation and invasion.
	KRAS	A gene that encodes a protein involved in cell signaling. Its mutation results in uncontrolled activation of the MAPK signaling pathway and promotes cell proliferation and metastasis.
	PD-L1	Protein that inhibits the immune response. Its overexpression allows the tumor to evade the immune response, facilitating tumor growth.
Ovarian cancer	CA 125	Glycoprotein produced by cells of the ovarian epithelium.
	HE4	Protein expressed in the ovarian epithelium.
	CA 19-9	Glycoprotein associated with cancer of the gastrointestinal tract.
	CA 15-3	Glycoprotein produced by tumor cells.
	CEA	Glycoprotein involved in cell adhesion.

Liver cancer	AFP	Fetal protein produced by the liver.
	Des-Gamma-Carboxy Prothrombin (DCP)	Abnormal form of prothrombin produced in liver cancer.
	Glycoprotein 3 (GPC3)	Membrane protein overexpressed in liver cancer cells.
	Alpha-L-Fucosidase (AFU)	Lysosomal enzyme.
	Protein Induced by Vitamin K Absence or Antagonist II (PIVKA-II)	Protein Induced by Vitamin K Absence or Antagonist II (PIVKA-II)
Pancreatic Cancer	CA 19-9	Glycoprotein associated with gastrointestinal cancer
	CEA	Glycoprotein involved in cell adhesion.
	CA 125	Glycoprotein produced by cells of the ovarian epithelium.
	MUC1	Cell surface glycoprotein.
Gastric Cancer	CEA	Glycoprotein involved in cell adhesion.
	CA CA 72-4	Cancer-associated glycoprotein.
	CA 19-9	Glycoprotein associated with cancer of the gastrointestinal tract.
	CA 50	Cancer-related glycoprotein.
	CA 125	Glycoprotein produced by cells of the ovarian epithelium.
Melanoma	S100B	Calcium-binding protein.
	LDH	Enzyme involved in energy metabolism.
	MIA (Melanoma Inhibitory Antigen)	Protein secreted by melanoma cells.
	Tyrosinase	Key enzyme in the production of melanin.
	HMB-45	Antibody that reacts with a glycoprotein present in melanoma cells.

The Relationship of Biomarkers with Other Cancer Types

It has been proposed that a single molecular biomarker may be implicated in several types of cancer due to the existence of many genetic alterations that affect common cellular pathways, such as cell proliferation, DNA repair, and apoptosis evasion. Biomarkers such as KRAS and TP53 regulate processes shared by different cell types, which explains their presence in various cancer types. For example, mutations in KRAS are found in lung, colon, and pancreatic cancers, while TP53, responsible for DNA repair and cell cycle regulation, is implicated in a wide variety of tumors, including breast, colon, and lung cancers. This highlights how alterations in key biological processes can impact different cancer types (Table 5).

Table 5: Most important biomarkers and in which type of cancer they participate [58-67].

Tumor Biomarker	Mutation or Main Characteristic	Associated Cancer	Common Signs and Symptoms
P53 (TP53)	Mutations in the TP53 gene (p53)	Breast cancer, lung cancer (non-small cell), colon cancer, esophagus cancer, ovary cancer, liver cancer, prostate cancer, and leukemia.	Fatigue, weight loss, pain, palpable masses, abnormal bleeding
BRCA1/ BRCA2	Point mutations, insertion, or deletion in BRCA1 or BRCA2	Breast, ovarian, prostate, and pancreatic cancer (in some cases)	Breast pain, breast lumps, abnormal vaginal bleeding.
HER2/neu (ERBB2)	Mutations in BRCA1 or BRCA2	Breast, esophageal, gastric and ovarian cancer.	Breast pain or tenderness, breast lumps, skin edema.
KRAS	Point mutations in the KRAS gene.	Colon, lung, pancreas and esophageal cancer.	Abdominal pain, jaundice, persistent cough, shortness of breath.
EGFR	Mutations in the EGFR gene.	Non-small cell lung, head and neck, and esophageal cancer.	Persistent cough, dyspnea, chest pain, weight loss.
BRAF	Point mutation in BRAF V600E.	Melanoma, thyroid and colon cancer.	Changes in the color or size of a mole, thyroid nodules.
ALK	ALK genetic rearrangement.	Non-small cell lung cancer and anaplastic lymphoma.	Cough, shortness of breath, weight loss, chest pain.
PD-L1	PD-L1 overexpression.	Melanoma, lung, breast, kidney and bladder cancer.	Fatigue, weight loss, localized pain depending on the type of cancer.

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Signaling Pathways of Biomarkers Associated with Cancer Events

The role of signaling pathways is crucial for the development of all types of cancer, so the aforementioned biomarkers alter various cellular signaling pathways. As is the case with TP53, which participates in the apoptosis pathway, regulating cell death, and its mutation impedes DNA repair, promoting tumor growth in several cancers. BRCA1/BRCA2 are involved in the DNA repair pathway (homologous recombination), and their mutations increase the risk of breast and ovarian cancer by compromising DNA repair [44-47]. Meanwhile, HER2/neu, EGFR, and ALK are associated with the RTK (receptor tyrosine kinase) pathway, which regulates cell growth. HER2 overexpression and EGFR amplification activate this pathway, promoting proliferation in breast and lung cancer, while ALK gene fusions have the same effect in lung cancer [48-50]. KRAS and BRAF are involved in the MAPK/ERK and PI3K/Akt pathways, which control cell proliferation and survival. Mutations in KRAS and BRAF constitutively activate these pathways, promoting uncontrolled cell growth in cancers such as lung, colon, and pancreatic cancers [51-53]. Finally, PD-L1 participates in the immune response pathway, inhibiting T cell function and allowing tumors to evade the immune response, promoting growth in cancers such as lung cancer and melanoma (90,91) [54-74]. In summary, biomarkers alter common signaling pathways, such as: MAPK/ERK, PI3K/Akt, RTK, and apoptosis, which contribute to cancer development and progression (Figure 9).

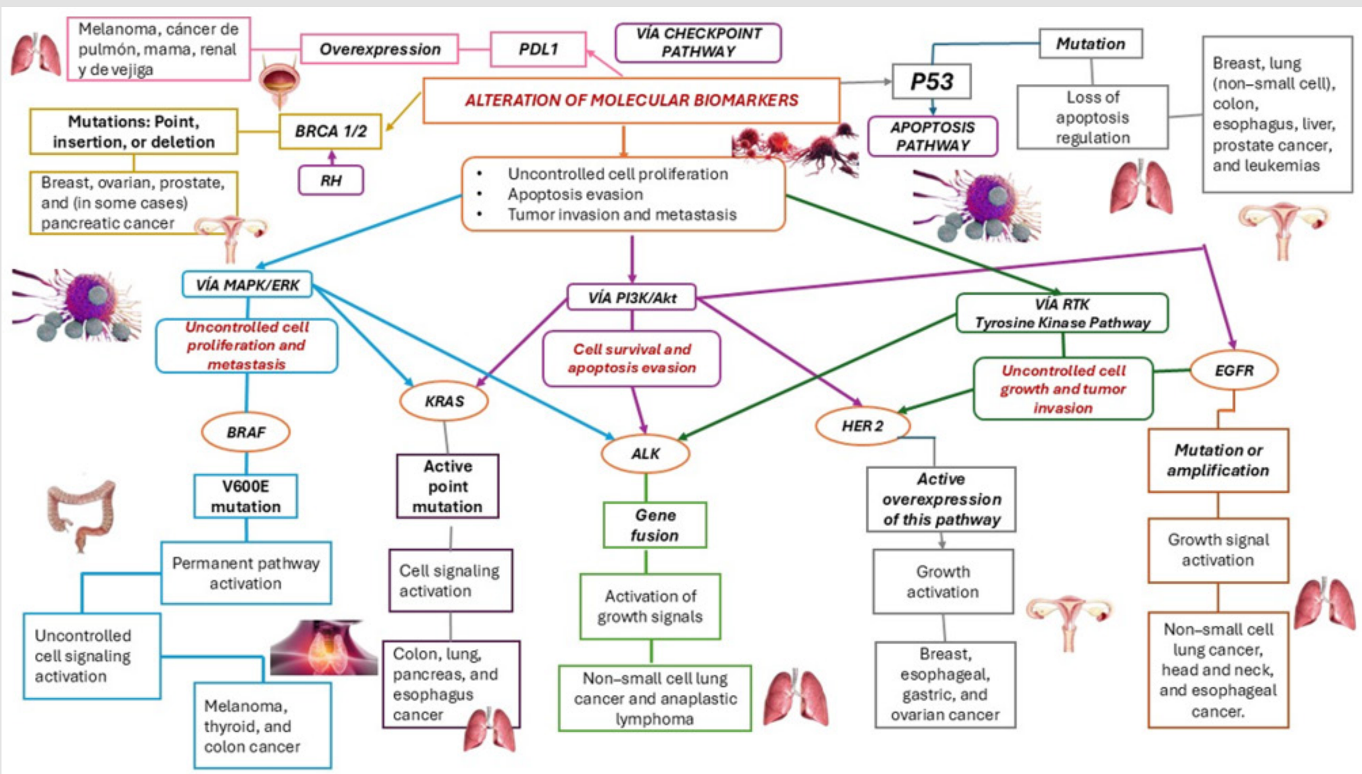

Figure 9: Signaling pathways used by biomarkers. Cancer biomarkers are linked to critical cell signaling pathways that control growth, differentiation, apoptosis, and DNA repair. Activated oncogenes → accelerate these pathways (e.g., EGFR, KRAS, PI3K). Inactivated suppressor genes lose their brakes (e.g., TP53, PTEN, APC).

Conclusion

Biomarkers are molecules involved in fundamental biological processes, such as cell proliferation and apoptosis evasion, mechanisms essential for cancer development and progression. The fact that a single biomarker can be linked to multiple cancer types highlights the importance of understanding the common genetic and molecular alterations that drive tumor genesis. This knowledge highlights the interconnectedness of the underlying mechanisms in different tumor types, some of which are very common in the population, such as breast, prostate, and lung cancers, opening up new possibilities for targeted treatments and more effective therapeutic strategies.

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