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Breast Cancer: Yesterday, Today, Tomorrow (From the intense probe to targeted therapy)

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Abstract

Since ancient times, humanity's struggle against breast cancer has persisted without pause, and the finding a cure still seems distant. The discovery of the DNA structure marked the beginning of a new era in the exploration of life, establishing this molecule as the central focus of scientific research.

Along the DNA molecule are specialized structures called "genes," in which, through a unique alphabet, the essential blueprint of life is encoded. Intensive research in genetics and molecular biology has opened new horizons, enabling the development and application of innovative cancer treatment methods. The successful treatment of any cancer relies on our ability to accurately identify these specific changes in malignant cells in order to select the most effective therapies to eliminate them.

Breast cancer treatment is becoming increasingly personalized as we learn more about the disease. Today, breast cancer is recognized as a heterogeneous condition with distinct subtypes and different mechanisms of action within the body.

Keywords: Breast cancer, history, targeted therapy

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Breast Cancer: The Most Lethal Serial Killer of Women in Human History

The tragic history of breast cancer and humanity's relentless efforts to overcome it dates back to the earliest foundations of medicine. In the Egyptian Edwin Smith Papyrus, dating to around 1500 BCE and considered the oldest known medical document, eight cases of breast cancer were described for the first time (1).

The document reveals that ancient Egyptians attempted to treat the disease by surgically removing the tumor along with a portion of healthy tissue, using a heated iron instrument known as the "fire drill" a brutal and primitive precursor of the modern electrocautery device (2). Significantly, this surgical approach demonstrates their awareness of one of cancer's most fundamental characteristics: its ability to infiltrate and progressively destroy the healthy tissues surrounding the tumor (3).

Since ancient times, humanity's struggle against breast cancer has known no truce, and its end still seems far from reach. It is estimated that more than 25 million women have died from breast cancer over the centuries, making it one of the most ruthless killers in human history.

The grim reputation of this cancer stems not only from the fear of death but also from the fact that both the disease and its treatments often lead to severe and unacceptable aesthetic and physiological mutilation of an organ that, throughout human history from biblical times to the present has remained a powerful symbol of female beauty and sensuality (4).

The discovery that forever changed our vision of the living world

February 28, 1953 – "DNA Day"

Around noon on February 28, 1953, two young scientists, James Watson (25 years old) and Francis Crick (37 years old), rushed into a small pub called "The Eagle", a popular meeting place for students and academics in the historic university town of Cambridge, England. There, they enthusiastically shared with friends and colleagues the incredible news that they had discovered "the secret of life" (5). This was the first and only time in human history that one of the greatest scientific discoveries was announced outside an academic setting or scientific center.

Approximately two months later, on April 25, 1953, the discovery of the helical structure of the DNA molecule was formally published in the journal Nature (6). It was precisely this magical molecule that holds within it the "secret" of living life and functions as the "command center" or "brain" where every vital activity of living cells is programmed. Along the DNA molecule are specialized structures called "genes," in which, using a unique alphabet, the most important blueprint of life known as the "genetic code" is written (6).

This astonishing code contains all the instructions that direct each cell on what to do and what not to do, in order to ensure its normal function and that of the entire organism as a whole. The fate of every cell and every living organism, including their past, present, and future is encoded in these genes. It quickly became clear that after this

discovery, nothing in our vision of living matter would ever be the same again. The year 1953 was called "the year of miracles" (annus mirabilis), as it marked one of the greatest discoveries of all time (7).

How genetic science has changed our vision of cancer development and its modern treatment methods

The discovery of the DNA marked the beginning of a new era in the exploration of life. From that moment on, the future of scientific research became centered on this molecule (8). Cancer, humanity's most feared disease, was no exception. Advances in genetic sciences made it possible to understand a fundamental principle underlying the initiation of cancerous transformation in the human body. This principle forms the scientific foundation on which every modern strategy for cancer diagnosis and treatment are based. **"All the different types of cancer that arise in human cells result from damage caused by carcinogenic agents to the DNA of the cell nucleus"** (9). In other words, regardless of their type or nature be they chemical substances, radiation, viruses, bacteria, etc. all these agents act on the cell's DNA by "altering" or "deforming" its genetic information. This alteration, referred to in scientific terms as a mutation, represents the ultimate cause of cancer development (9).

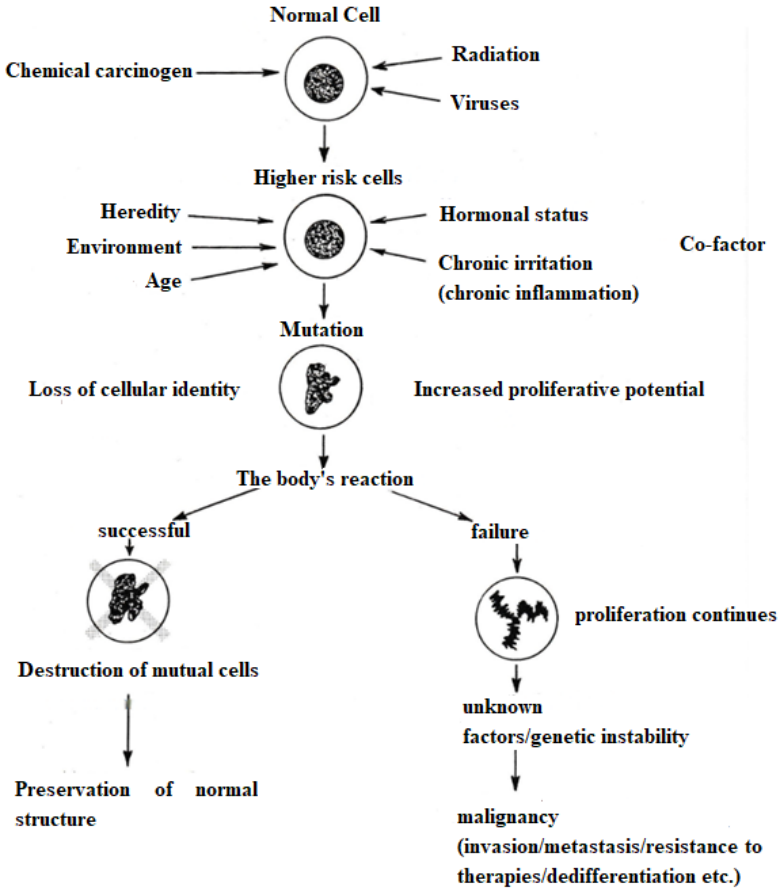

Figure 1. Pathway from normal cell to malignancy.

Summarized in a single sentence, the essence of the malignant transformation of a normal cell into a cancerous cell lies in the fact that the cancer cell is genetically altered, unable to properly interpret the instructions for normal behavior, and as a result, no longer adheres to the fundamental laws of cellular life that maintain the harmony of living nature (10).

Treatment of cancer: where we are and where we hope to go

The importance of this concept relates to the core mechanisms on which the fundamental principles of cancer treatment, and their effectiveness in eliminating malignant cells, are both dependent and guided.

Advanced genetic studies have long highlighted an astonishing feature of the cellular composition of tumors: although every cancer cell may originate from the same initial or "parent" cell of the tissue or organ in which it developed, the cells within a given cancer are not identical to those of another cancer. Each tumor has its own genetic identity, or "fingerprint," determined by the DNA within its cells (10). Thus, two women with breast cancer who share the same age, height, weight, race, and similar medical histories may, in fact, have two biologically and clinically distinct cancers. The only certain and common feature between these two cancers is that they originated from a breast tissue cell (11).

As cancer progresses, new and different types of malignant cells emerge within the same tumor. The cellular composition becomes increasingly complex over time. Therefore, even though every cancer cell originates from the same initial "parent" cell, the cells comprising a tumor are not identical. This concept, that a cancer consists of different types of cells, is called "tumor heterogeneity" (12). By the time a breast cancer tumor reaches a size of one centimeter, the millions of cells forming the tumor mass are already very different from each other.

The successful treatment of any cancer depends on our ability to accurately identify these specific changes in malignant cells so that we can choose the most appropriate treatment to eliminate them. Intensive research in genetics and molecular biology has opened new horizons and enabled the application of many new methods in cancer treatment (13). These methods are collectively referred as "*oriented therapy*" or "*targeted therapy*". The fundamental principle of targeted therapy is based on the new biological concept that "***each person's cancer is genetically unique, and thus, its treatment must also be unique***" (14). This principle represents the key distinction between targeted therapy and traditional chemotherapy or conventional cancer treatment. Targeted therapy aims to ***mark, strike, and destroy only cancerous cells***, while sparing normal cells, effectively replacing the "heavy artillery" of chemotherapy, which destroys everything in its path, with carefully selected sniper-like strikes (15).

In other words, the genetic alterations present in the breast cancer cells of one woman (X) are not identical to those found in another woman (Y).

This variation in their genetic profiles explains why the same breast cancer treatment may not produce identical effects in different patients. Conventional cancer therapies, while effective against malignant cells, also simultaneously damage normal cells. But is it possible to identify in advance the genetic and molecular abnormalities present in different types of cancerous cells, so that we can selectively use drugs that target only cells carrying such abnormalities? In other words, can we now personalize treatment according to the characteristics of a **particular cancer in a particular individual?** Medical science, after long and arduous efforts often reaching ideas, interpretations, and conclusions that bordering the delicate line between established science and science fiction has succeeded, for many cancer types, in predicting whether a particular tumor is sensitive or resistant to a given treatment. In this way, it becomes possible to decide in advance whether or not a particular therapy should be used for a particular patient (16). This philosophy underpins the targeted and personalized therapy, tailored to the unique characteristics of each cancer and each individual patient.

What we expect in the future

Currently, breast cancer is unquestionably the most common cancer among women, with approximately 2 million new cases diagnosed annually, representing about 23% of all cancer worldwide each year. Until recently, it was estimated that around 1 in 3 individuals would develop cancer at some point during their lifetime. In other words, the so-called lifetime risk was approximately 1 in 3 (around 33%) (17). More recent estimates have revised this risk to 1 in 2 (around 50%), indicating a stubborn increase in cancer incidence over the years (18).

Why does the risk of developing cancer increase with age? There is no doubt that the primary factor driving the global rise in cancer incidence is the increasing average age of the population. The longer we live, the more mutations accumulate become “imprinted” in the DNA of our genes, increasing the likelihood that one or more of these defects may initiate the carcinogenic transformation of a normal cell (19). In response to the rising global incidence and the diversity of genetic and molecular features of cancers among individual patients, oncological science has expanded and deepened its objectives. Numerous studies are ongoing to identify the most effective methods for the prevention, early detection, and treatment of breast cancer. Some of these advances have already begun to find application in clinical practice, while others remain under investigation (20).

Some notable recent studies and achievements include research on genetic variations. Scientists are investigating how common genetic variations may influence an individual’s risk of developing breast cancer (21). Research into preventive medications and investigations are ongoing to identify drugs that could help reduce the risk of breast cancer, such as estrogen-blocking

medications (Tamoxifen and Raloxifene), aromatase inhibitors (Exemestane and Anastrozole), and other non-hormonal drugs (22).

Studies on novel laboratory tests, such as liquid biopsy, focus on circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA). CTCs are cancer cells that have detached from the tumor and circulate in the bloodstream, while ctDNA consists of DNA fragments released into the blood upon cancer cell death. This type of biopsy represent non-invasive techniques for cancer monitoring provides a simpler and more cost-effective alternative to traditional needle-aspiration biopsies (22).

Research into new genetic mutations in tumor cells that might indicate resistance to specific treatments (such as aromatase inhibitors) and help predict the recurrence of cancer in women with early-stage breast cancer (23).

CONCLUSION

The treatment of breast cancer is becoming increasingly personalized as we learn more about the disease. Breast cancer is now recognized as a heterogeneous disease, composed of multiple subtypes with distinct biological behaviors. The ability to identify specific genes to more precisely classify breast cancer represents the foundation for developing more effective and tailored treatment strategies.

Acknowledgment

The authors respectfully dedicate this publication to the memory of Professor Shahin Kadere, a distinguished anatomopathologist whose contributions to the field of pathology and medical education were of exceptional significance.

Professor Kadere was a devoted clinician, researcher, and teacher whose work significantly advanced the discipline of anatomical pathology. His meticulous diagnostic insight, commitment to academic excellence, and mentorship of numerous medical professionals have left an enduring impact on the medical community.

His guidance, integrity, and passion for pathology continue to inspire those who had the privilege of working and learning under his mentorship.

Conflict of Interest Statement: The authors declare that they have no conflict of interest.

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