

Review Article

Understanding the Hereditary Factors in Cancer- Recent Insights and Developments: An Updated Review

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Abstract

Background: Although cancer (Ca) etiology can be multifactorial, it is nearly universally intertwined with genetic mutations that instigate tumor genesis or progression. This updated review aims at describing if this dispute remains meaningful based on a thorough literature survey.

Methodology: This updated review was conducted over the last 2.5 decades using 3 (three) search engines: Web of Science (WoS), Pubmed and Science direct that encompassed all associated information and hypothetical considerations, globally, utilizing information from 1998 through 2022. All such, concepts, logically deduced explanations and scientifically assumed points if Ca remains hereditary is the main focus of this review.

Results/ Findings: This appraisal on cancer, though yielded some instances of hereditariness in origin, mostly remains of genetic origin. Reportedly, cancers can be passed down from one family member to another through genes, and, may cause by genetic mutation present in eggs or sperms cell during fertilization which are actually considered as hereditary cancer, like breast, colon, and prostate cancer, as well as less common cancers, viz., pancreatic and ovarian cancer.

Therefore, understanding the hereditary factors of Ca is critical not only for assessing the genetic contribution to cancer, but also for designing preventive and therapeutic strategies. It allows identifying people who are at a higher risk due to family history and/or genetic makeup, allow early detection through improved surveillance and, more importantly, for tailored therapeutic modality. By addressing recent advancement, this review will provide an overview on the hereditary factors of cancers and/or raising awareness on significant role of development in Ca genetics.

Keywords: Cancer, BRCA1, BRCA2; Genetic factors; Hereditariness; Public health.

Introduction

Cancer is a complex disease marked by the uncontrolled spread of abnormal cells, which can infiltrate nearby tissues and potentially metastasize to other parts of the body.¹ According to world health organization (WHO) fact sheets, Ca is the second leading cause of death globally,² accounting for an estimated 9.96 million deaths, or 1 in 6 deaths, in 2020.^{3,4}

The loss of life years is not only causing harm and damages to the society but also poses economic consequences. As an example, productivity losses linked to premature Ca deaths were estimated at €104.6 billion

or 0.62% of the national gross domestic product in Europe,⁵ and at US\$46.3 billion or 0.33% of the combined gross domestic product of the BRICS countries (Brazil, Russia, India, China, and South Africa).⁶

Cancer encompasses a diverse group of malignancies, with common types distinguished by their origin and affected organs such as female breast cancer, lung cancer, colorectal cancer, prostate cancer, stomach cancer, liver cancer, etc. According to Global Cancer Statistics 2020,⁴ female breast Ca stands as the most frequently identified cancer, constituting 11.7% of the total cases, closely followed by lung Ca at 11.4%, colorectal Ca at 10.0%, prostate Ca at 7.3%, and stomach Ca at 5.6%.

While female breast Ca stands as the most frequently identified cancer types, lung Cancer on the other hand is regarded as the leading contributor to cancer-related fatalities globally, accounting for 18.0% of total Ca deaths including man and women, followed by colorectal Ca at 9.4%, liver Ca at 8.3%, stomach Ca at 7.7%, and female breast Ca at 6.9%.⁴

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The development of Ca in human body can be influenced by a range of factors, including but not limited to genetics,^{7,8} lifestyle choices,⁹ and environmental exposures.¹⁰ Considering various factors leading to cancer, 22% of cases result from tobacco use, while 10% stem from factors like an unhealthy diet, obesity, insufficient physical activity, excessive alcohol consumption, and other contributors, including exposure to ionizing radiation, environmental pollutants, and infections.¹¹

Infections such as hepatitis B, hepatitis C, human papillomavirus (HPV), helicobacter pylori, immunodeficiency virus (HIV), and Epstein-Barr virus are responsible for around 15% of all Ca cases worldwide.⁴ In general, about 90% of the cancers are caused by above factors. Along with that, at least 5-10% of Ca cases are caused by inherited genetic mutations Ca also known as hereditary Cancer.¹² Based on causes of cancer, these cases can be divided into three categories such as, sporadic, familial, and hereditary. Figure 1 depicts the distribution of cancer categories.

Sporadic cancers are the cancers occurs by chance or due to environmental and lifestyle factors. Familial cancers and hereditary cancers are distinct from one another. The term "familial cancer" accounts for 15-20% of all cancer cases refers to a situation in which more members of a specific family are diagnosed with a particular type of Ca than would be statistically predicted, but it is unknown why this is the case;^{13,14} hereditary and lifestyle factors may individually or jointly contribute to the high incidence in the family.¹⁵

On the other hand, familial tumors with a known genetic basis or genetic mutations are referred to as having "inherited cancer".¹⁶ These mutations confer an increased susceptibility to specific Ca types and are typically inherited from one's parents. Hereditary Ca syndromes often manifest as autosomal dominant inheritance patterns, meaning that a single mutated allele is sufficient to confer an elevated Cancer risk.¹⁷

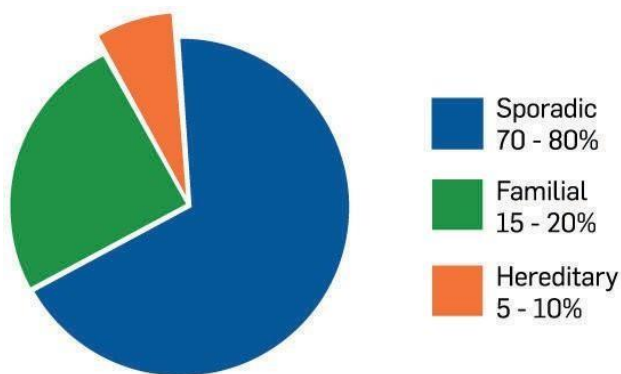


Figure 1: Distribution of cancer categories.

The genetic mutations underlying hereditary Ca syndromes typically involve critical tumor suppressor genes or oncogenes, which perturb cellular homeostasis and regulatory mechanisms, thus fostering carcinogenesis.

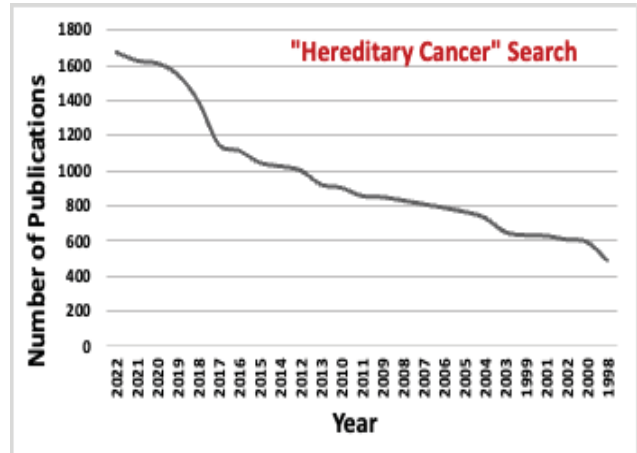


Figure 2: Record of growing interest among scientific community regarding the hereditary factors in cancer. (source: Web of Science data based)

Recently, there has been a growing interest among the scientific community regarding the hereditary factor in Ca as presented in Figure 2 (searched under the keyword "hereditary cancer"). According to the past 25 years of publication statistics, the number of publications related to understanding the hereditary factors, treatment, remedies has increased in ever year, showing the importance of this factor for Ca and interest towards its understanding.

However, the accumulation of the knowledge available in various research based on recent insight may play key role on the understanding of the hereditary factors in Ca among the young researchers. To the best of our knowledge, the accumulated knowledge addressing the recent insight is missing, hence this study focused on the understanding of the basics of hereditary factors in Ca including the molecular mechanisms, global perspective, well-known genetic mutations that passes on to children from the parents and the hereditary factor on different common Ca types.

This study and the topic are particularly important as it provides education for healthcare professionals, enabling individuals to make informed health choices and equipping medical practitioners to deliver superior care. On a global scale, it will contribute to the public health strategies, addressing genetic mutations and their implications in hereditary Ca among diverse populations.

Table-I
Syndromes of inherited Ca predisposition in clinical oncology syndrome

	Component Tumors	Inheritance Mode	Genes
<u>Hereditary breast cancer syndromes</u>			
Hereditary breast cancer and ovarian cancer Syndrome	Breast cancer	Dominant	BRCA1 BRCA2
	Ovarian cancer		
	Prostate cancer		
	Pancreatic cancer		
Li-Fraumeni Syndrome	Fanconi anemia/medulloblastoma	Recessive	BRCA2
	Soft tissue sarcoma	Dominant	P53 CHEK2
	Breast cancer		
	Osteosarcoma		
	Leukemia		
Brain tumors			
Cowden Syndrome	Adrenocortical carcinoma	Dominant	PTEN
	Breast cancer		
	Thyroid cancer		
Bannayan-Riley-Ruvalcaba syndrome	Endometrial and other cancers	Dominant	PTEN
	Breast cancer		
	Meningioma		
Thyroid follicular cell tumors			
<u>Hereditary gastrointestinal malignancies</u>			
Hereditary gastric cancer	Stomach cancers	Dominant	CDH1
Juvenile polyposis	Gastrointestinal cancers	Dominant	SMAD4/DPC4 BMPR1A
	Pancreatic cancer		
Peutz-Jeghers syndrome	Colon cancer	Dominant	STK11
	Small bowel cancer		
	Breast cancer		
	Ovarian cancer		
	Pancreatic cancer		
Hereditary melanoma pancreatic cancer	Pancreatic cancer	Dominant	CDKN2A/p16
Hereditary pancreatitis	Melanoma	Dominant	PRSS1
	Pancreatic cancer		
Turcot Syndrome	Colon cancer	Dominant	APC MLH1 PMS2
	Basal cell carcinoma		
	Ependymoma		
	Medulloblastoma		
	Glioblastoma		
Familial gastrointestinal stromal tumor	Gastrointestinal stromal tumors		KIT
<u>Genitourinary cancer predisposition syndromes</u>			
Hereditary prostate cancer	Prostate cancer	Dominant	HPC1, HPCX HPC2/ELAC2 PCAP PCBC PRCA
Hereditary bladder cancer	Bladder cancer	Sporadic Unknown	Unknown
Hereditary testicular cancer	Testicular cancer	Possibly x- linked, Possibly recessive	Unknown
<u>Central nervous system/vascular cancer predisposition syndromes</u>			
Hereditary Paraganglioma	Paraganglioma	Dominant	SDHD SDHC SDHB
	Pheochromocytoma		

SDHB(Source: Garber, J. E., & Offit, K. (2005).¹⁶

2. Hereditary cancer genes

Hereditary cancer genes play a pivotal role in our understanding of the genetic basis of cancer susceptibility. These genes are responsible for the transmission of cancer predisposition from one generation to the next within families. Over the past several decades, substantial research efforts have been dedicated to identifying and characterizing these genes.^{16,18} Their discovery has provided valuable insights into the mechanisms underlying cancer development and progression.

Hereditary cancer genes can encompass a wide array of mutations, including those in tumor suppressor genes, oncogenes, and DNA repair genes. The presence of such mutations within an individual's genetic makeup can significantly increase their risk of developing specific types of cancer.

These mutations disrupt cellular equilibrium and regulatory processes, thereby promoting carcinogenesis. A detailed list of syndromes of cancer predisposition is listed in Table 1 with component tumors, the mode of inheritance and corresponding genes. The data underscore key findings from the past two decades, a period marked by the discovery of numerous cancer susceptibility genes.

Epidemiological investigations have uncovered the inherent genetic diversity in even rare tumors. This

means that the predisposition to specific cancers can be ascribed to mutations in various genes which includes but not limited to BRCA2, BRIP1, APC, ATM, BARD1, BRCA1, CDH1, CDKN2A, CDK4, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, SKT11, TP53. While all genes can be responsible for various cancers, BRCA1 and BRCA2 predispose to cause common Ca such as breast, ovarian and pancreatic cancer 18-21 as shown in Figure 3.

Heritable mutations in the mentioned genes, such as lead to different further genetic alterations that are specifically involved in the development of each of these types of breast tumor. BRCA1, BRCA2 are known as high penetrance Ca of which mutations can be found both among men and women.^{18,22}

MLH1, MSH2, and MSH6, which are responsible for most hereditary forms of hereditary nonpolyposis colon cancer (HNPCC) and are associated with up to a 70% chance of endometrial cancer.²³ The APC and MYH genes, which cause the adenomatous polyposis syndromes.²⁴ The RET oncogene, which is responsible for medullary thyroid cancer in patients who have the multiple endocrine neoplasia type 2 syndrome.²⁵

There are several other high penetrance genes responsible for breast cancer are PALB2²⁶, TP53²⁷, PTEN²⁸, CDH1.²⁹ Several moderate penetrance Ca genes

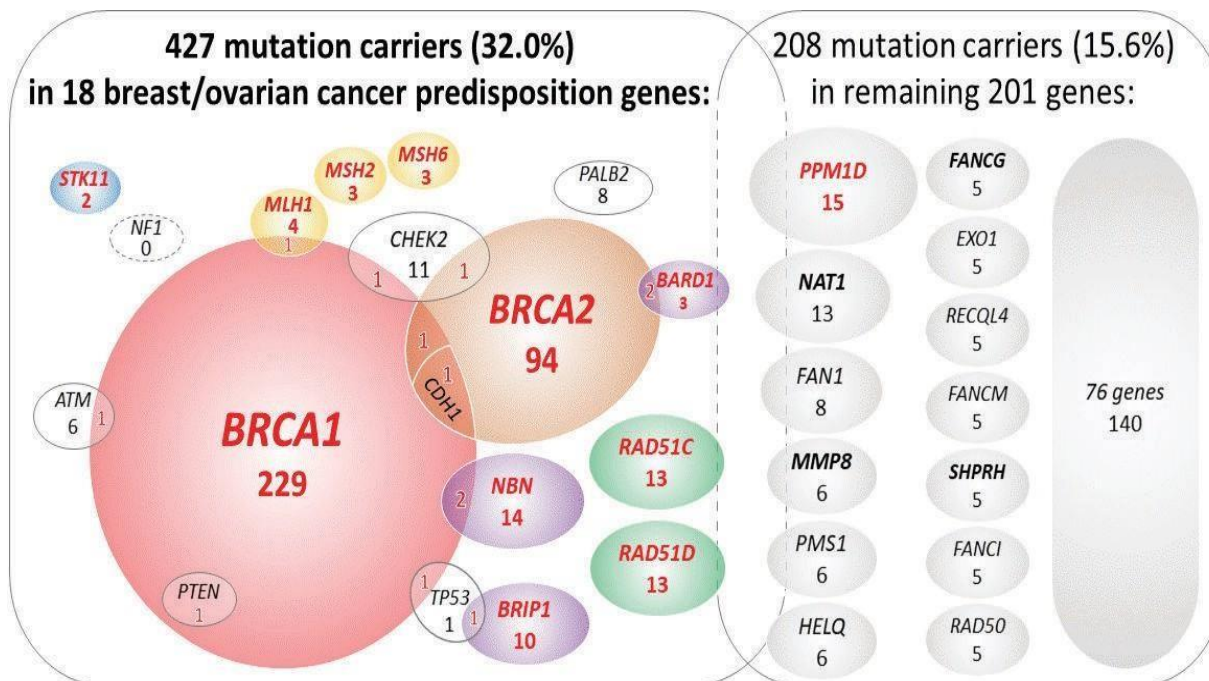


Figure 3: Mutations in 18 known/anticipated hereditary breast and ovarian cancer genes. (Source: Lhotova, K. Et al. (2020)²¹)

such as ATM²⁹, CDKN2A³⁰, BARD1,³¹ were also reported for common cancer types including breast and ovarian cancer.

According to leading medical oncologist and Clinical Director of the Clinical Genetics Service at Memorial Sloan Kettering, moderate-penetrance genes can affect how the medical practitioner counsel and care for patients, particularly if they also have a family history of cancer as patients who have a mutation in a moderate-penetrance gene along with a strong family history of Cancer, being at high risk.³²

Understanding hereditary cancer genes is of critical importance from both clinical and research perspectives. These genes elucidate the genetic predisposition to cancer, facilitating precise risk assessment and stratification. Early detection and intervention strategies are significantly enhanced by this understanding, leading to improved patient outcomes.¹⁶

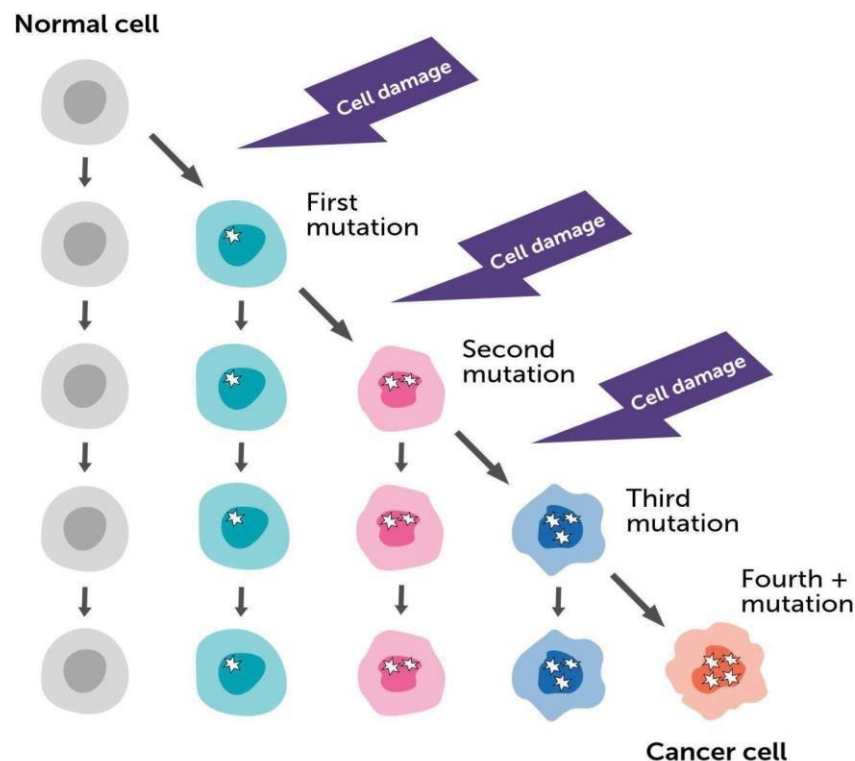
Furthermore, the identification of hereditary cancer genes has a direct impact on therapeutic approaches, enabling the development of tailored treatments that target the specific genetic aberrations associated with each case. It also informs the design of preventive

measures and risk-reduction strategies.^{8,16,17} From research perspective, the study of hereditary cancer genes continues to shed light on the molecular mechanisms underlying cancer initiation and progression, fostering the discovery of novel therapeutic targets, and advancing overall comprehension of cancer genetics.

Molecular mechanisms of hereditary tumor formation

The molecular mechanisms of hereditary tumor formation encompass a complex interplay of genetic factors and cellular processes. These mechanisms often involve mutations in key tumor suppressor genes and oncogenes, disrupting the finely tuned regulatory pathways that maintain cellular homeostasis.^{12,16} Genes exist in pairs, operating synergistically to facilitate the production of proteins. One of these gene alleles is maternally inherited, while the other is paternally inherited. The genesis of tumors primarily arises from dysregulated cell proliferation.

Within the human genome, a multitude of gene variants intricately govern cell growth in a highly precise manner. When these genes harbor errors in their DNA sequences, they may malfunction, giving rise to "altered" or mutated forms.¹²



Adapted from "Understanding Gene Testing" - NIH 1995

Figure 4: Schematic illustration of DNA damage and gene mutations.³³

The cumulative occurrence of numerous mutations across diverse genes within a specific population of cells over an extended period is a prerequisite for the initiation of malignancy or the emergence of cancer cells, as elucidated in Figure 4.³³ In case of hereditary cancers, the initial mutations are inherited and are already present from birth.¹⁶ As time progresses, additional mutations accrue, eventually giving rise to cancerous cells. This stepwise accumulation of mutations is a fundamental process in the development of cancer in individuals with a genetic predisposition to the disease.⁸

It's crucial to understand that the emergence of cancer typically necessitates mutations in multiple genes.¹² The precise triggers for these mutations remain largely mysterious. Nevertheless, mutations can be inherited or acquired. The process of formation of tumors may include mutation in proto-oncogenes, tumor suppressor gene mutations, DNA repair gene mutations, chromosomal aberrations, epigenetic changes and so on.¹⁶

Mutation in Proto-oncogenes: Proto-oncogenes are normal genes that are involved in regulating cell growth and division. When these genes undergo mutations, they can become oncogenes, which promote uncontrolled cell growth. One well-known example is the BCR-ABL fusion gene, which is associated with chronic myeloid leukemia (CML).³⁴

Tumor Suppressor Gene Mutations: Tumor suppressor genes are responsible for preventing the formation of tumors. Mutations in these genes can result in the loss of their function, allowing uncontrolled cell growth. For example, mutations in the TP53 gene are common in various cancers.³⁵

DNA Repair Gene Mutations: DNA repair genes are responsible for fixing errors in DNA replication. Mutations in these genes can lead to the accumulation of genetic mutations, increasing the risk of cancer. For instance, mutations in the BRCA1 and BRCA2 genes are linked to breast and ovarian cancer.³⁶

Chromosomal Aberrations: Large-scale genetic changes, such as chromosomal translocations and amplifications, can lead to the activation of oncogenes or inactivation of tumor suppressor genes. One notable example is the Philadelphia chromosome in chronic myeloid leukemia.³⁷

Epigenetic Changes: While not strictly genetic, epigenetic alterations, such as DNA methylation and histone modifications, can also contribute to Cancer development by silencing tumor suppressor genes.³⁸

4. High risk individuals for hereditary cancer

High-risk individuals for hereditary cancer are those who possess specific genetic mutations or a strong family history of cancer, predisposing them to an elevated risk of developing certain types of cancer.⁸ The risk of hereditary and sporadic cancer is unique due to practical reason as the Sporadic cancer arises from random mutations in somatic cells, often due to environmental factors or chance occurrences during cell division.^{39,40} It typically lacks a significant family history of the disease. In contrast, hereditary cancer is characterized by specific inherited genetic mutations that predispose individuals to cancer as illustrated in Figure 5.

In case of hereditary cancer, a person receives a working copy of the growth control gene from one parent and a copy of the gene with a mutation from the other parent. The altered gene is also known as a "Cancer susceptibility gene." Every cell in the body contains the inherited Cancer susceptibility gene, but only the functional copy of the gene allows each cell to function normally. But if a cell's working copy of the gene is compromised by a mutation, that cell may no longer be able to regulate its own development and develop cancer. As a result, those who inherit a Cancer susceptibility gene have a considerably higher risk of specific types of Cancer. However, not everyone with an inherited Cancer susceptibility gene may not develop cancer.¹⁶

As for example, if father and mother pass any mutated BRCA1 & BRCA2 gene to their offspring the child may remain at higher risk of developing cancer, more like breast, ovarian cancer, and others. Both men and women can be inherited damage Cancer susceptible gene, in of which have a 50% chance to inherit that very Cancer gene, being susceptible to produce cancer. Moreover, the affected child also has a 50% chance of inheriting that Cancer gene through its working copy.

Literature shows risk of Cancer in those children remain risky than general population. Notably, some Cancer susceptible genes only links to Cancer but may not be equally affected between male and female children. Not only that, but parent of the unaffected sex may also still carry and pass on those genes.^{8,16,18}

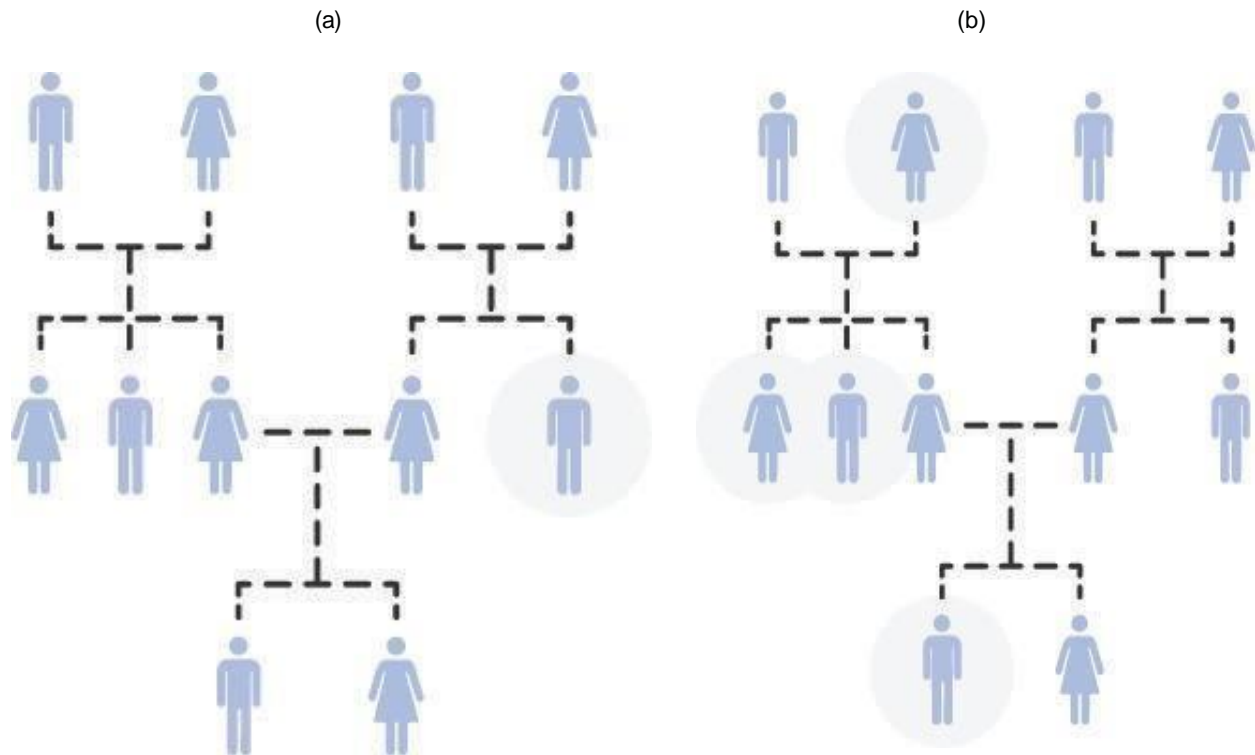


Figure 5: Illustration of high-risk individuals for (a) sporadic and (b) hereditary cancer.

Hereditary cancers typically lack significant distinguishing features when compared to non-hereditary cancers. The distinction arises from familial patterns of occurrence. Key signs suggestive of hereditary Cancer encompass:

- Presence of two or more family members afflicted by the same Cancer type, particularly on the same side of the family lineage, the persistence of this pattern across multiple generations,
- Manifestation of Cancer at an early age,
- Occurrence of multiple primary cancers in an individual, the coexistence of genetically linked cancers within a family, such as breast and ovarian Cancer or colon and uterine cancer,
- The identification of physical attributes associated with hereditary cancer, such as the presence of moles and melanoma or polyps and colon cancer, and the emergence of specific rare Cancer types within the familial context.⁴¹

Global perspectives on hereditary cancer research

More than a century ago, investigators made clinical observations on the hereditary characteristics of cancer, such as cancers diagnosed in patients at a younger age and in many members of the family. Since then, the

global perspective on hereditary cancer research had witnessed significant advances in the identification of genetic mutations associated with hereditary cancer syndromes, including well-known genes like BRCA1 and BRCA2.^{8,16}

International collaborations among researchers and institutions had been on the rise, fostering the sharing of genetic data and research findings to gain a more comprehensive understanding of hereditary cancers.⁴² Based on multigenerational collaboration and commitment leading to foundational discoveries, in recent years, understanding the germ line defects and related biologic consequences helped scientist to develop effective drugs for some of the common hereditary syndromes.⁴³

Among these drugs, HIF2 α inhibitors were specifically developed for treating von Hippel-Lindau syndrome, while anti-PD-1 pembrolizumab was designed to target high microsatellite instability/mismatch repair deficient colorectal cancer and various solid tumors. PARP inhibitors, on the other hand, have shown promise in addressing breast and pancreatic cancer.

The development of these medications for hereditary cancer syndromes represents the culmination of over a century's worth of collective efforts from dedicated

physicians and scientists. Their contributions have been instrumental in establishing clinical diagnostic methods and uncovering the underlying biological mechanisms of these diseases, ultimately paving the way for the recent advancements in novel drug development for hereditary cancer syndromes.⁴⁴

It's important to emphasize that hereditary cancer syndromes make up less than 5% of all cancer cases. However, the valuable biologic and clinical insights obtained during the development of drugs for these genetic disorders have had a broader impact. The investigation and utilization of these agents have expanded to encompass sporadic cancers that share similar underlying mechanisms.

This cross-application of knowledge and treatments derived from hereditary cancer research has significantly benefited the understanding and management of a wider range of malignancies beyond the hereditary context.¹⁸

Apart from drugs, globally the cancer research field has developed significantly through use of new equipment and technology of which hereditary cancer. One example of new technology is Next-Generation Sequencing (NGS). Also known as high-throughput sequencing. Along with that, liquid biopsy, also known as fluid biopsy or fluid phase biopsy has gain momentum in detecting cancers.^{18,44}

Conclusion

Recent insights and in-depth progress on the understanding of hereditary factors of cancer, though yielded a multifactorial etiology, it mostly entangled with genetic origin. Cancer is passed down to family descendants via genes or causing genetic mutation present in eggs or sperms cell during fertilization, considered to be hereditary cancer (breast, colon, prostate, pancreas, ovary).

Understanding Cancer-hereditariness remains critical not only to assess genetic pathways but also to design preventive &/or therapeutic strategies, and also, allows identifying risky group of people having family history and/or genetic makeup. Early detection through improved surveillance and it is important to tailor therapeutic modality.

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